

Supporting Information

A Rapid Injection NMR Study of the Reaction of Organolithium Reagents with Esters, Amides and Ketones

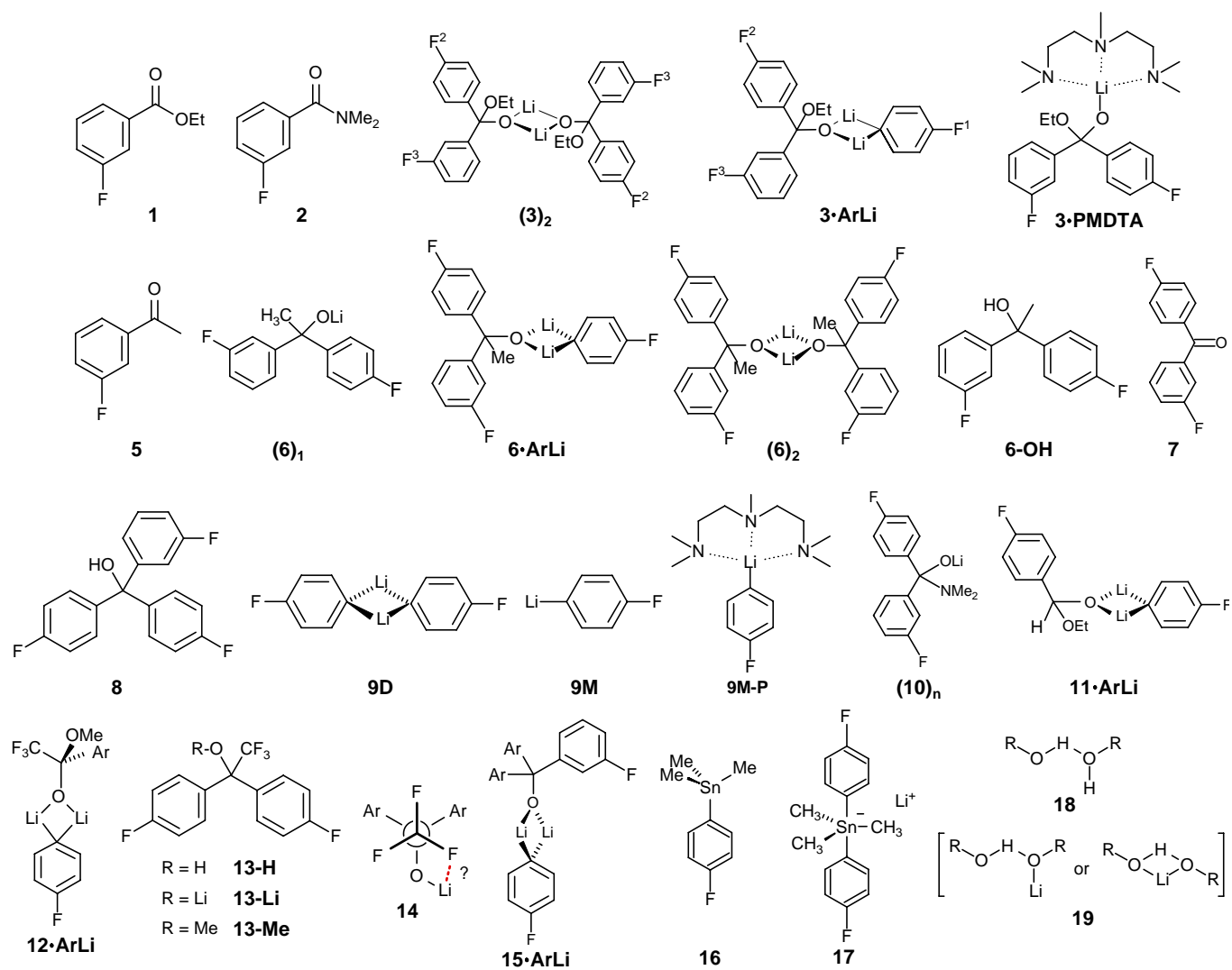
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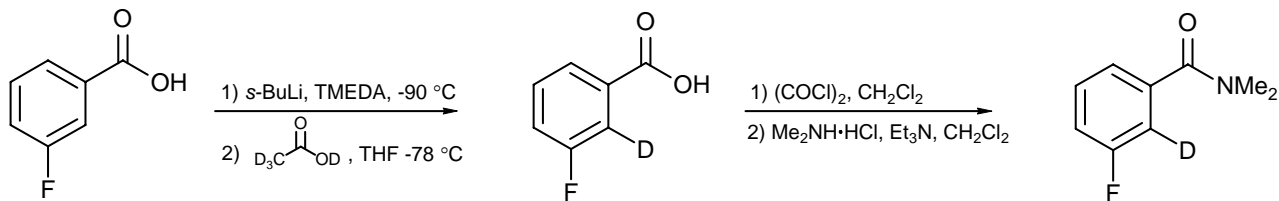


S1. General Experimental.

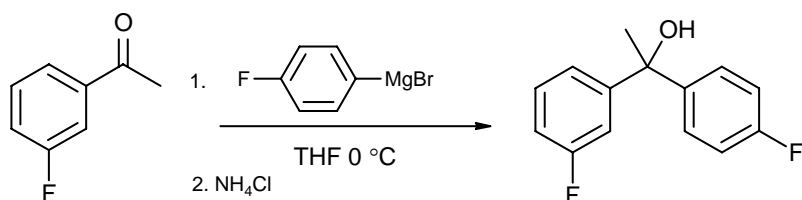
Concentration values of lithium species in experimental procedures are expressed as monomer equivalents independent of the state of aggregation (which is not always known), except in concentration vs time graphs for kinetics experiments, where actual molarities of species indicated are presented (monomer, dimer or tetramer) .

All reactions requiring a dry atmosphere were performed in glassware flame-dried or dried overnight in a 110 °C oven, sealed with septa and flushed with dry N₂. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were freshly distilled from sodium benzophenone ketyl under N₂. Dimethyl ether (Me₂O) was distilled via cannula from a graduated conical cylinder containing *n*-BuLi (for drying). Commercially available starting materials and reagents included: *n*-butyllithium, *s*-butyllithium, methylolithium, phenyllithium, 4-fluorobromobenzene, ethyl 3-fluorobenzoate, 3-fluorobenzoic acid, acetone, ethyl formate, methyl trifluoroacetate and 4-fluorophenylacetylene. Low-temperature NMR spectra were acquired on a spectrometer using a 10 mm broadband probe at the following frequencies: 360.131 MHz (¹H), 90.556 MHz (¹³C), 338.827 MHz (¹⁹F), 139.96 (⁷Li), and 52.99 MHz (⁶Li). All spectra were taken with the spectrometer unlocked. ¹³C NMR spectra were referenced internally to the C-O carbon of THF (δ 67.96), Et₂O (δ 66.57) or Me₂O (δ 60.25). Lorentzian multiplication (LB) of 2-6 Hz was applied to ¹³C NMR spectra. RINMR ¹⁹F NMR spectra and spectra for characterization were acquired without proton decoupling, ¹⁹F NMR spectra for competition experiments proton decoupled. Spectra were referenced internally to 1,3-dimethyl-2-fluorobenzene (δ -122.6) or 4-fluorotoluene (δ -118.85). ⁷Li and ⁶Li spectra were referenced externally to 0.3 M LiCl/MeOH standard (δ 0.00 ppm). Probe temperatures were measured internally with the ¹³C chemical shift thermometer: 10% ¹³C enriched (Me₃Si)₃CH. ^[S1a]

S2. Synthesis



***N,N*-Dimethyl 2-Deutero-3-fluorobenzamide.** *s*-BuLi (33.6 mL, 47.1 mmol, 1.4M in cyclohexane) was added dropwise to a solution of 3-fluorobenzoic acid (3.0 g, 21.4 mmol) and TMEDA (7.3 mL, 49.2 mmol) in THF (100 mL) at $-90\text{ }^{\circ}\text{C}$.^[S2] After stirring for 1.5 h the reaction was warmed to $-78\text{ }^{\circ}\text{C}$ for 30 min before being quenched with acetic acid- d_4 . After stirring for 15 min the reaction was warmed to room temperature and aqueous NH_4Cl was added. The aqueous layer was extracted with 1:1 Et_2O :Hexanes (3 x 50 mL). The combined organic layers were washed with brine, dried (MgSO_4), and the solvent removed under reduced pressure. The resulting off-white solid was dissolved in CH_2Cl_2 (100 mL) and cooled to $0\text{ }^{\circ}\text{C}$. Five drops of DMF was added followed by dropwise addition of oxalyl chloride (2.7 mL, 32.1 mmol) and the reaction warmed to room temperature. After gas evolution ceased (~ 1 h) the reaction was cooled to $0\text{ }^{\circ}\text{C}$ and dimethylamine hydrochloride (5.23 g, 64.2 mmol) and triethylamine (15 mL, 107 mmol) were added. The reaction was stirred for 16 hours before being quenched with NH_4Cl . The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (MgSO_4), and the solvent removed under reduced pressure. The product was purified by column chromatography (7:3 EtOAc :Hexane) to give the product as a colorless oil (2.4 g, 14.3 mmol). The compound was 98% deuterated at C-2. ^1H NMR (CDCl_3 , 300 MHz) δ 7.38 (ddd, $J = 8.3, 7.7, 5.6$ Hz, 1H), 7.19 (dd, $J = 7.6, 1.0$ Hz, 1H), 7.11 (td, $J = 8.6, 1.0$ Hz, 1H), 2.98 (s, 3H), 3.11 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.28 (d, $J = 2.5$ Hz), 162.58 (d, $J = 247.8$ Hz), 138.44 (d, $J = 6.8$ Hz), 130.33 (d, $J = 8.0$ Hz), 122.88 (d, $J = 3.2$ Hz), 116.72 (d, $J = 21.0$ Hz), 114.25 (dd, $J = 48.5, 23.5$ Hz), 39.64, 35.53. ^{19}F NMR (377 MHz, CDCl_3) δ -114.2 (dd, $J = 9.0, 5.3$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_9\text{H}_7\text{DFNO}$ (M^+) 169.0869; found 169.0874.



1-(3-Fluorophenyl)-1-(4-fluorophenyl)ethan-1-ol. Under nitrogen, 3-fluoroacetophenone (5.1 g, 7.2 mmol) was added to a round bottom flask containing THF (20 mL) and cooled to $0\text{ }^{\circ}\text{C}$. 4-Fluorophenylmagnesium bromide (8.6 mL, 8.6 mmol, 1.0 M in THF) was added and allowed to react for 30 min and then warmed to room temperature for 30 min. The reaction was quenched with aqueous NH_4Cl . The mixture was extracted with diethyl ether twice. The organic layer was washed with water and brine, dried with MgSO_4 and the solvent removed *in vacuo*. The product was purified via flash chromatography (30% Et_2O in hexanes) with 87% isolated yield. ^1H NMR (CDCl_3 , 300 MHz) δ 1.93 (s, 3H), 6.94 (tdd, $J = 8.2, 2.9, 0.9$ Hz, 1H), 7.00 (t, $J = 8.25$ Hz, 2H), 7.14 (d, $J = 7.6$ Hz, 2H), 7.27 (m, 1H), 7.37 (dd, $J = 9.0, 5.5$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz) δ 31.15 (CH_3), 75.77 (C), 113.21 (d, $^2J_{^{13}\text{C}-^{19}\text{F}} = 22.3$ Hz, CH), 114.13 (d, $J = 21.2$ Hz, CH), 115.25 (d, $J = 21.2$ Hz, CH), 121.60 (d, $J = 2.2$ Hz, CH), 127.80 (d, $J = 8.3$ Hz, CH), 129.94 (d, $J = 8.3$ Hz, CH), 143.41 (d, $^4J = 3.3$ Hz, C), 150.75 (d, $J = 6.7$ Hz, C), 162.10 (d, $J = 245.4$ Hz, C), 162.99 (d, $J = 245.4$ Hz, C). ^{19}F NMR (CDCl_3 , 282 MHz) δ -114.37 (tt $J = 8.6, 5.5$ Hz), -117.23 (ddd, $J = 10.8, 8.5, 6.1$ Hz). HRMS (EI) (m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{F}_2\text{O}$ (M^+) = 234.0851; found 234.0854.

General Tertiary Alcohol Synthesis. To a solution of ethyl 3-fluorobenzoate (1, 0.15 mL, 1 mmol) in THF (3.3 mL) at $-78\text{ }^{\circ}\text{C}$ was added the organolithium reagent (2.2 equiv) dropwise. After stirring for 1 h the reaction was quenched with aqueous NH_4Cl . The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried (MgSO_4), and the solvent removed under reduced pressure. The product was purified by column chromatography.

General Ketone Synthesis. To a solution of *N*-methoxy-*N*-methyl 3-fluorobenzamide (0.12 mL, 1 mmol) in 3.3 mL of THF at $-78\text{ }^{\circ}\text{C}$ was added the organolithium reagent (1.0 equiv) dropwise. After stirring for 1 h the reaction

was quenched with aqueous NH_4Cl . The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried (MgSO_4), and the solvent removed under reduced pressure. The product was purified by column chromatography.

1-(3-Fluorophenyl)pentan-1-one. Synthesized from *N*-methoxy-*N*-methyl 3-fluorobenzamide and *n*-BuLi. ^1H NMR (400 MHz, CDCl_3) δ 7.74 (dt, $J = 7.8, 1.2$ Hz, 1H), 7.64 (ddd, $J = 9.5, 2.6, 1.5$ Hz, 1H), 7.44 (td, $J = 8.0, 5.5$ Hz, 1H), 7.25 (tdd, $J = 8.2, 2.7, 1.0$ Hz, 1H), 2.95 (t, $J = 7.4$ Hz, 2H), 1.82 – 1.63 (m, 2H), 1.49 – 1.34 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 199.22 (d, $J = 2.1$ Hz), 163.07 (d, $J = 247.6$ Hz), 139.20 (d, $J = 6.1$ Hz), 130.21 (d, $J = 7.6$ Hz), 123.79 (d, $J = 3.0$ Hz), 119.87 (d, $J = 21.5$ Hz), 114.79 (d, $J = 22.2$ Hz), 38.49, 26.33, 22.44, 13.93. ^{19}F NMR (377 MHz, CDCl_3) δ -113.90 (ddd, $J = 9.4, 8.2, 5.6$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_{11}\text{H}_{13}\text{FO}$ (M+) 180.0945; found 180.0944.

5-(3-Fluorophenyl)nonan-5-ol. Synthesized from ethyl 3-fluorobenzoate (**1**) and *n*-BuLi. ^1H NMR (400 MHz, CDCl_3) δ 7.20 (td, $J = 7.9, 5.9$ Hz, 1H), 7.09 – 6.97 (m, 2H), 6.83 (td, $J = 8.5, 2.1$ Hz, 1H), 1.85 – 1.66 (m, 4H), 1.65 (d, $J = 2.2$ Hz, 1H), 1.25 – 1.08 (m, 6H), 1.00 – 0.86 (m, 2H), 0.76 (t, $J = 7.1$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 161.90 (d, $J = 244.6$ Hz), 148.50 (d, $J = 6.4$ Hz), 128.37 (d, $J = 8.1$ Hz), 119.83 (d, $J = 2.8$ Hz), 111.76 (dd, $J = 38.8, 21.8$ Hz), 41.74, 24.51, 22.01, 12.97. ^{19}F NMR (377 MHz, CDCl_3) δ -115.6 (ddd, $J = 11.0, 8.7, 6.2$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_{15}\text{H}_{23}\text{FO}$ (M+) 238.1728; found 238.1718.

1-(3-Fluorophenyl)ethanone (5). Commercially available from Sigma Aldrich.

2-(3-Fluorophenyl)propan-2-ol. Synthesized from ethyl 3-fluorobenzoate (**1**) and MeLi. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.14 (m, 3H), 7.01 – 6.87 (m, 1H), 1.58 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.88 (d, $J = 245.1$ Hz), 151.94 (d, $J = 6.6$ Hz), 129.71 (d, $J = 8.1$ Hz), 128.35, 120.01 (d, $J = 2.9$ Hz), 113.47 (d, $J = 21.2$ Hz), 111.75 (d, $J = 22.4$ Hz), 72.36, 31.74. ^{19}F NMR (377 MHz, CDCl_3) δ -115.1 (ddd, $J = 10.4, 8.5, 5.8$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_9\text{H}_{11}\text{FO}$ (M+) 154.0789; found 174.0781.

(3-Fluorophenyl)(phenyl)methanone. Known.^[S3]

(3-Fluorophenyl)diphenylmethanol. Known.^[S4]

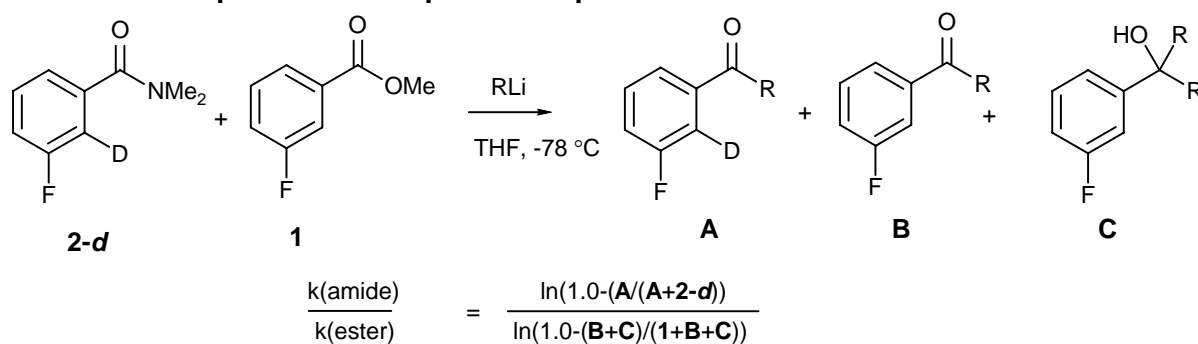
(3-Fluorophenyl)(4-fluorophenyl)methanone (7). Synthesized by reaction of *N*-methoxy-*N*-methyl 3-fluorobenzamide with 4-fluorophenyllithium (prepared from (4-fluorophenyl)trimethyltin and *n*-BuLi). ^1H NMR (400 MHz, CDCl_3) δ 7.85 (dd, $J = 8.8, 5.4$ Hz, 2H), 7.54 (dt, $J = 7.8, 1.3$ Hz, 1H), 7.51 – 7.45 (m, 2H), 7.30 (tdd, $J = 8.3, 2.6, 1.1$ Hz, 1H), 7.18 (t, $J = 8.6$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 194.02, 165.79 (d, $J = 255.0$ Hz), 162.71 (d, $J = 248.7$ Hz), 139.75 (d, $J = 6.4$ Hz), 133.46 (d, $J = 3.3$ Hz), 132.88 (d, $J = 9.2$ Hz), 130.28 (d, $J = 7.7$ Hz), 125.83 (d, $J = 3.2$ Hz), 119.70 (d, $J = 21.4$ Hz), 116.83 (d, $J = 22.6$ Hz), 115.86 (d, $J = 21.9$ Hz). ^{19}F NMR (377 MHz, CDCl_3) δ -107.02 (tt, $J = 8.4, 5.4$ Hz), -113.57 (ddd, $J = 8.9, 8.5, 5.4$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_{13}\text{H}_8\text{F}_2\text{O}$ (M+) 218.0538; found 218.0530.

(3-Fluorophenyl)bis(4-fluorophenyl)methanol (8). Synthesized from ethyl 3-fluorobenzoate and 4-fluorophenyllithium prepared from (4-fluorophenyl)trimethyltin and *n*-BuLi. ^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.18 (m, 6H), 7.04 – 6.97 (m, 6H), 2.75 (s, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 162.61 (d, $J = 246.3$ Hz), 162.12 (d, $J = 247.3$ Hz), 149.12 (d, $J = 6.3$ Hz), 142.02 (d, $J = 3.2$ Hz), 129.61 (d, $J = 7.9$ Hz), 123.41 (d, $J = 3.0$ Hz), 115.01 (d, $J = 21.4$ Hz), 114.92 (d, $J = 22.4$ Hz), 114.48 (d, $J = 21.1$ Hz), 81.00. ^{19}F NMR (377 MHz, CDCl_3) δ -113.6 (ddd, $J = 10.7, 8.4, 5.9$ Hz), -115.91 (tt, $J = 8.4, 5.3$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{O}$ (M+) 314.0913; found 314.0923.

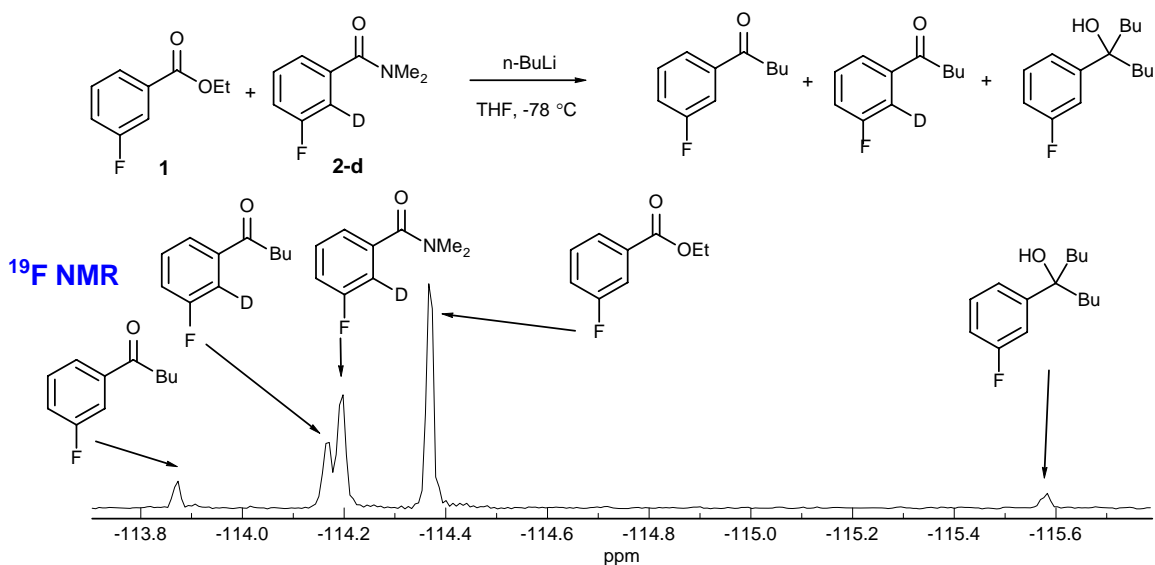
1-(3-Fluorophenyl)-3-(4-fluorophenyl)prop-2-yn-1-one. Synthesized from *N*-methoxy-*N*-methyl 3-fluorobenzamide and ((4-fluorophenyl)ethynyl)lithium (prepared from 4-fluorophenylacetylene and *n*-BuLi). ^1H NMR (400 MHz, CDCl_3) δ 8.01 (dt, $J = 7.7, 1.3$ Hz, 1H), 7.86 (dt, $J = 9.2, 2.0$ Hz, 1H), 7.70 (dd, $J = 8.6, 5.5$ Hz, 2H), 7.51 (td, $J = 8.0, 5.4$ Hz, 1H), 7.34 (td, $J = 8.3, 2.6$ Hz, 1H), 7.14 (t, $J = 8.6$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 176.48 (d, $J = 2.8$ Hz), 164.19 (d, $J = 254.3$ Hz), 162.77 (d, $J = 248.4$ Hz), 138.85 (d, $J = 6.7$ Hz), 135.51 (d, $J = 8.9$ Hz), 130.39 (d, $J = 7.7$ Hz), 125.41 (d, $J = 3.0$ Hz), 121.24 (d, $J = 21.6$ Hz), 116.36 (d, $J = 22.4$ Hz), 115.96 (d, $J = 22.8$ Hz), 115.96 (d, $J = 3.6$ Hz), 92.62, 86.54. ^{19}F NMR (377 MHz, CDCl_3) δ -107.36 (tt, $J = 8.3, 5.3$ Hz), -113.44 (ddd, $J = 9.0, 8.1, 5.4$ Hz). HRMS (EI) (m/z): calcd. for $\text{C}_{15}\text{H}_8\text{F}_2\text{O}$ (M+) 242.0538; found 242.0539.

3-(3-Fluorophenyl)-1,5-bis(4-fluorophenyl)penta-1,4-diyne-3-ol. Synthesized from ethyl 3-fluorobenzoate (**1**) and (4-fluorophenyl)ethynyllithium (prepared from 4-fluorophenylethyne and *n*-BuLi) ¹H NMR (400 MHz, CDCl₃) δ 7.69 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.61 (dt, *J* = 10.0, 2.1 Hz, 1H), 7.47 (dd, *J* = 8.7, 5.4 Hz, 4H), 7.39 (td, *J* = 8.0, 6.0 Hz, 1H), 7.06 (td, *J* = 8.3, 2.2 Hz, 1H) 7.01 (t, *J* = 8.7 Hz, 4H), 3.39 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 162.97 (d, *J* = 250.7 Hz), 162.76 (d, *J* = 246.4 Hz), 144.42 (d, *J* = 7.0 Hz), 133.92 (d, *J* = 8.5 Hz), 130.15 (d, *J* = 8.1 Hz), 121.60 (d, *J* = 3.0 Hz), 117.81 (d, *J* = 3.6 Hz), 115.74 (d, *J* = 22.0 Hz), 113.30 (d, *J* = 23.6 Hz), 88.30 (d, *J* = 1.6 Hz), 84.44, 65.35 (d, *J* = 2.2 Hz). ¹⁹F NMR (377 MHz, CDCl₃) δ -111.81 (tt, *J* = 8.5, 5.4 Hz), -114.40 (ddd, *J* = 9.7, 8.5, 5.9 Hz). HRMS (EI) (m/z): calcd. for C₂₃H₁₃F₃O (M⁺) 362.0913; found 362.0913.

S3. NMR Data and Spectra for Competition Experiments



Competition Experiments of R-Li with ester 1 and Amide 2. To a solution of amide **2-d** (50 mg, 0.3 mmol) and ester **1** (50 mg, 0.3 mmol) in 3 mL of THF at -78 °C (0 °C for 4-fluorophenylethynyllithium) was added the organolithium reagent (0.15 mmol) dropwise. After 30 min the reaction was quenched with 1M propionic acid in ether (0.15 mL, 0.15 mmol) and the reaction warmed to room temperature. 4-Fluoroacetophenone (0.012 mL, 0.1 mmol) was added as an internal standard and an aliquot was removed for ^{19}F NMR analysis. No work up was performed, as this tended to result in some loss of **2**. The relative rates were calculated using the standard competition experiment equation shown. The results are shown in Figures S-1 to S-5.



	Ester	H-Ketone	H-alcohol	D-Amide	D-Ketone	D-alcohol	$k(\text{amide})/k(\text{ester})$
Trial 1	7.86	1	0.73	3.96	2.73	0	2.64
Trial 2	9.17	1	0.89	6.41	3.18	0	2.15
Trial 3	8.72	1	0.48	4.17	1.99	0	2.49
BuLi average							<u>2.42</u>

Figure S-1. *n*-BuLi competition experiment (THF, -78 °C). The numbers are scaled relative to a peak area of 1 for the H-ketone.

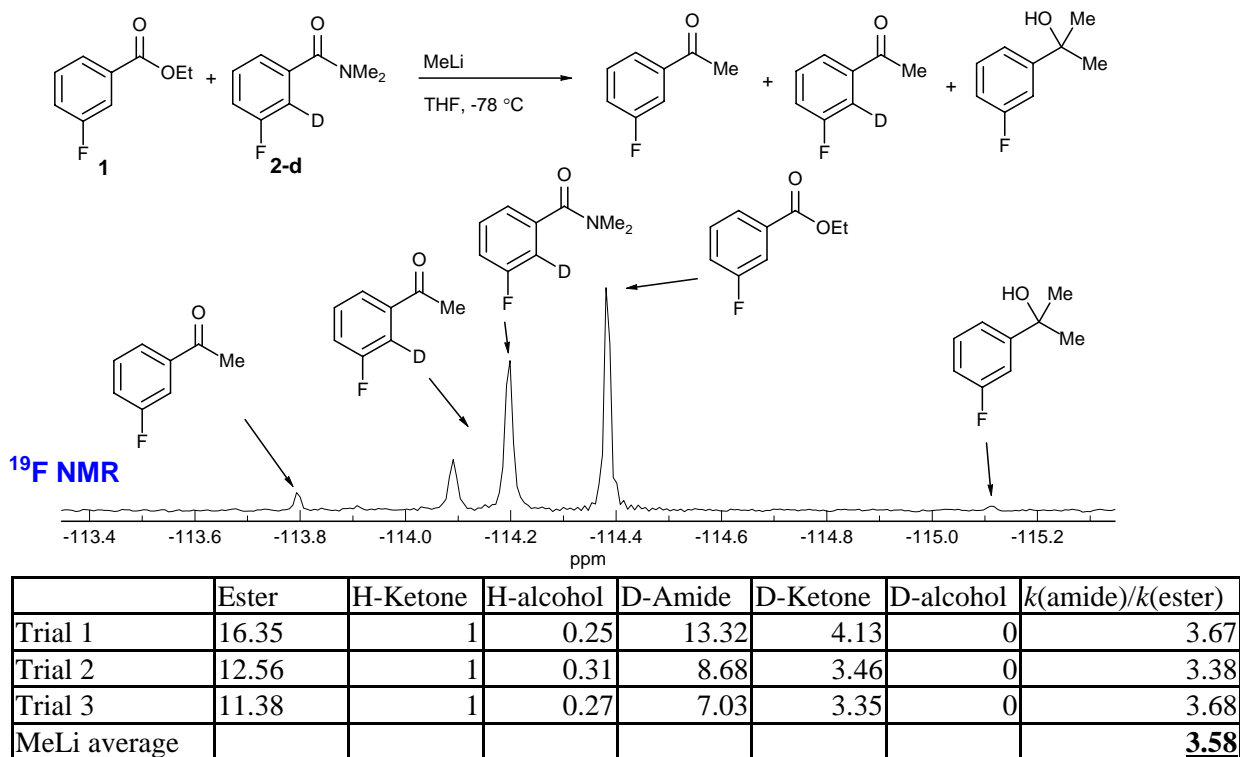


Figure S-2. Methylithium competition experiment (THF, -78 °C). The numbers are scaled relative to a peak area of 1 for the H-ketone.

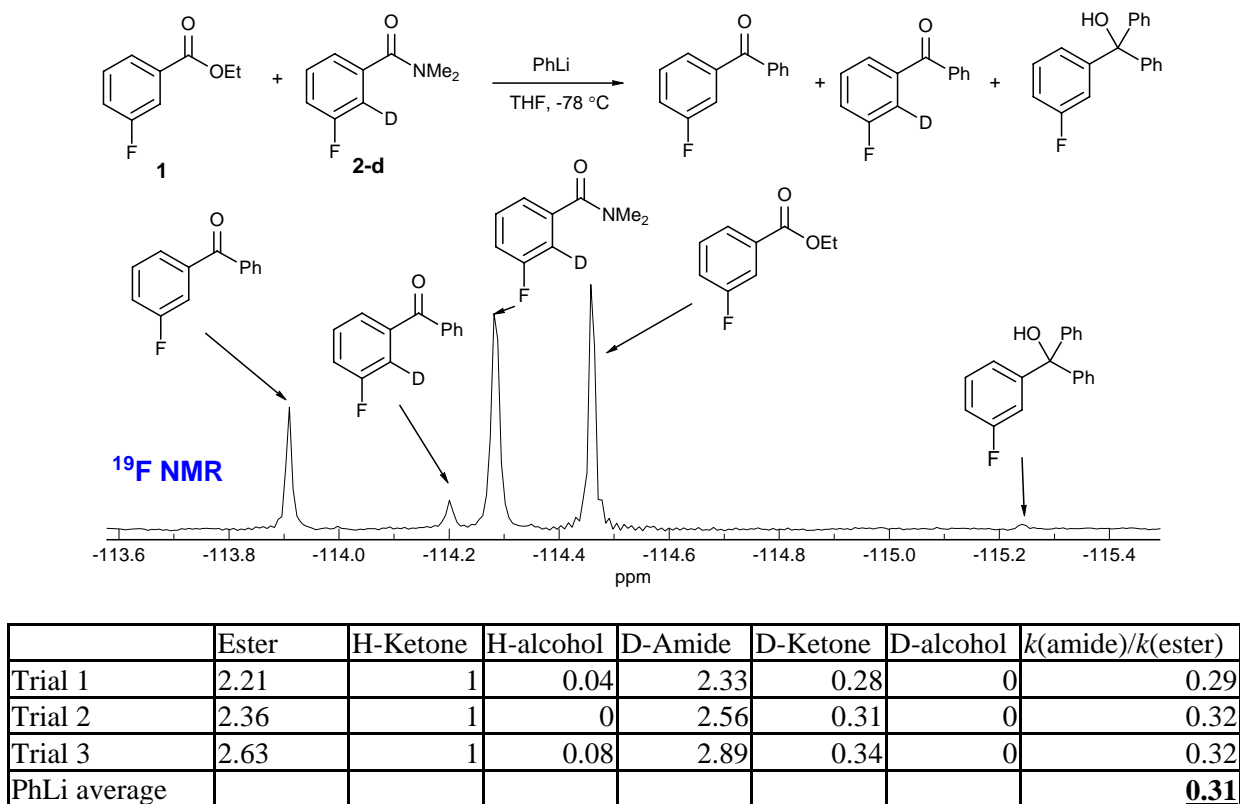
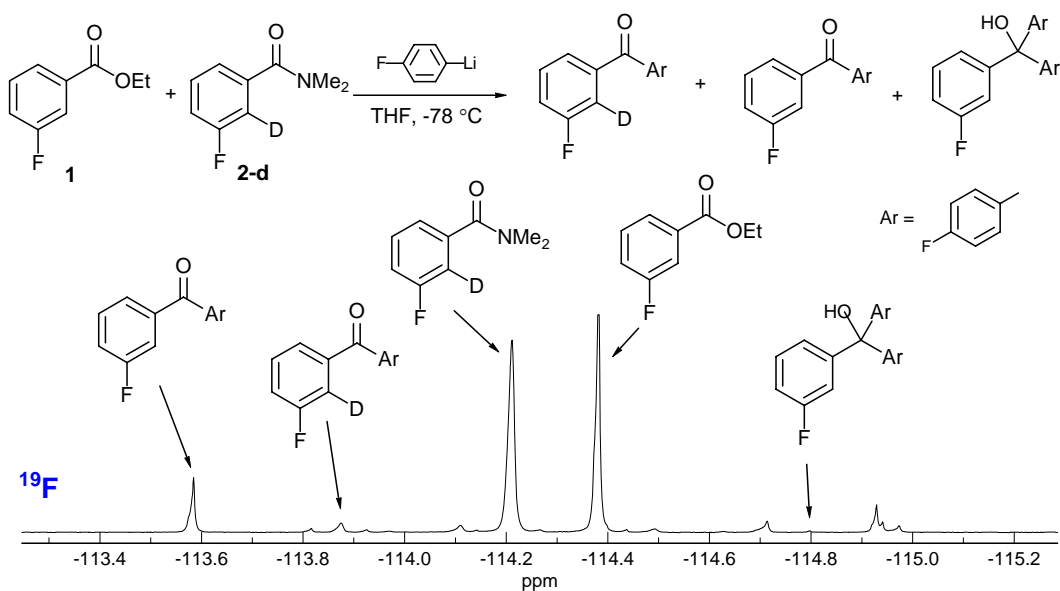
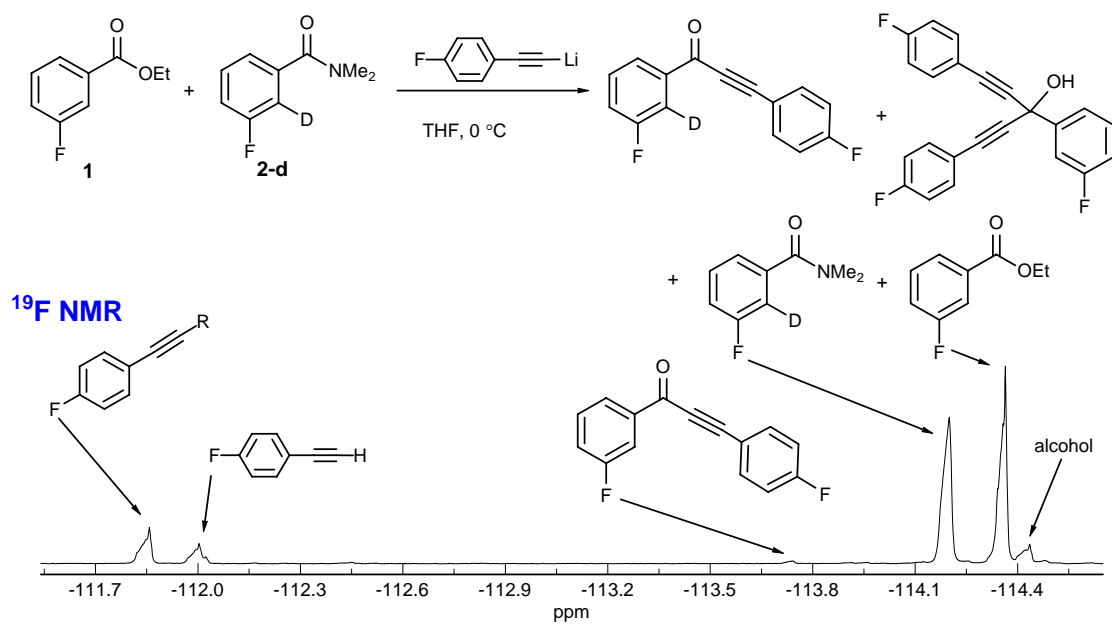


Figure S-3. Phenyllithium competition experiment (THF, -78 °C). The numbers are scaled relative to a peak area of 1 for the H-ketone.



	Ester	H-Ketone	H-alcohol	D-Amide	D-Ketone	D-alcohol	$k(\text{amide})/k(\text{ester})$
Trial 1	5.18	1	0.03	5.8	0.26	0	0.24
Trial 2	4.44	1	0.02	4.81	0.23	0	0.23
4-F-PhLi Average							0.23

Figure S-4. 4-Fluorophenyllithium competition experiment (THF, -78 °C). The numbers are scaled relative to a peak area of 1 for the H-ketone.



	Ester	H-Ketone	H-alcohol	D-Amide	D-Ketone	D-alcohol	$k(\text{amide})/k(\text{ester})$
Trial 1	6.69	0	1	6.81	0.09	0	0.09
Trial 2	7.08	0	1	6.98	0.11	0	0.12
LiAcetylide Avrg							0.11

Figure S-5. 4-Fluorophenylethynyllithium competition experiment (THF, 0 °C). The numbers are scaled relative to a peak area of 1 for the H-alcohol.

S4. 4-Fluorophenyllithium

Synthesis of 4-Fluorophenyllithium (9) by Lithium/Tin Exchange (KNP3021). A 10 mm NMR tube was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added to the NMR tube and cooled in a dry ice/acetone bath and Me₂O (~3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). The ¹³C chemical shift thermometer (10% ¹³C labeled *tris*(trimethylsilyl)methane, 2 μL), an internal standard for concentrations (4-fluorotoluene, 1 μL), 0.114 mL of (4-fluorophenyl)trimethyltin (0.6 mmol) and *n*-BuLi (0.24 mL, 0.6 mmol, 2.5 M/hexane) were added to the NMR tube at -78 °C. The sample was inserted into a precooled NMR spectrometer and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. ⁷Li, ¹³C (1536 scans), ¹⁹F, and ¹H NMR were obtained at -119 °C.

-119 °C, 0.14 M

3:1 Me₂O:THF

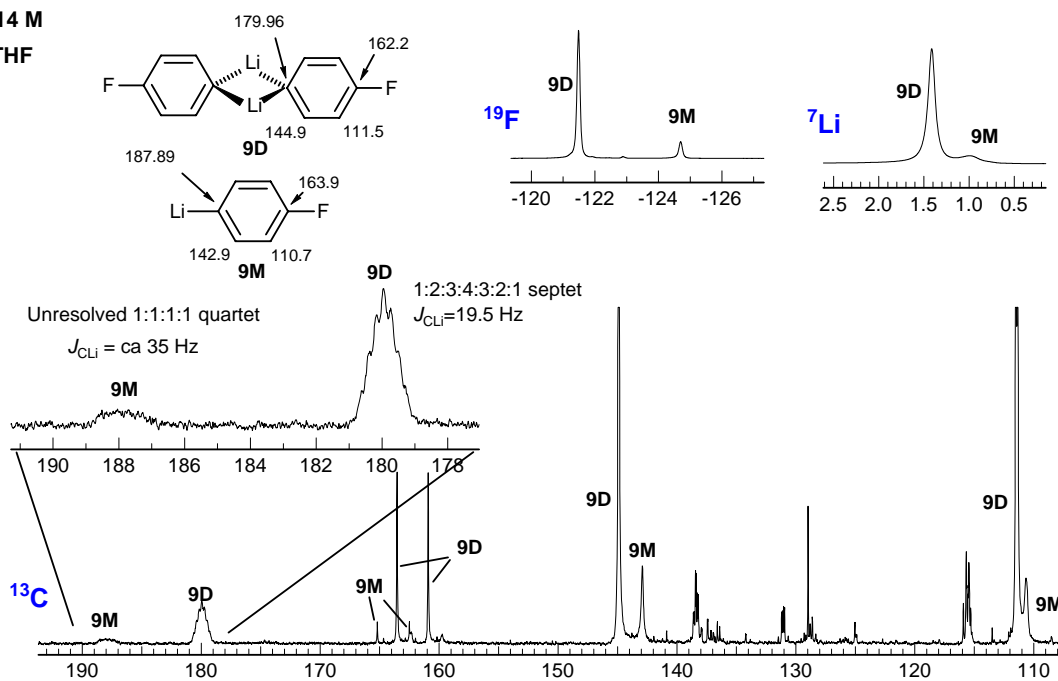


Figure S-6. ¹⁹F, ⁷Li, and ¹³C NMR spectroscopy of **9M** and **9D** prepared by lithium/tin exchange at -119 °C in 3:1 Me₂O/THF.

Variable Temperature NMR Experiment of 4-Fluorophenyllithium: **9D** and **9M** Interconversion.

(KNP3175) A 10 mm NMR tube was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added to the NMR tube and cooled in a dry ice/acetone bath and Me₂O (3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). The ¹³C chemical shift thermometer (10% ¹³C labeled *tris*(trimethylsilyl)methane, 2 μL),^[S1] an internal standard for concentrations (4-fluorotoluene, 1 μL), 0.063 mL of 4-fluorophenyltrimethyltin (0.33 mmol) and *n*-BuLi (0.018 mL, 0.33 mmol) were added to the NMR tube at -78 °C. The sample was inserted into a precooled NMR spectrometer and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. ⁷Li, ¹³C, ¹⁹F and ¹H NMR were obtained at -123, -117, -110, -104, -97, -92, -75 and -72 °C until coalescence of the fluorine signals was observed (Figure S-7). A linear least squares fit to the rates obtained by simulation of ¹⁹F NMR with WINDNMR^[S5] yields enthalpy and entropy of activation values of $\Delta H^\ddagger = 6.4$ kcal/mol and $\Delta S^\ddagger = -7.0$ eu for k_{DM} and $\Delta H^\ddagger = 6.4$ kcal/mol and $\Delta S^\ddagger = -3.3$ eu for k_{MD} (Table S-1).

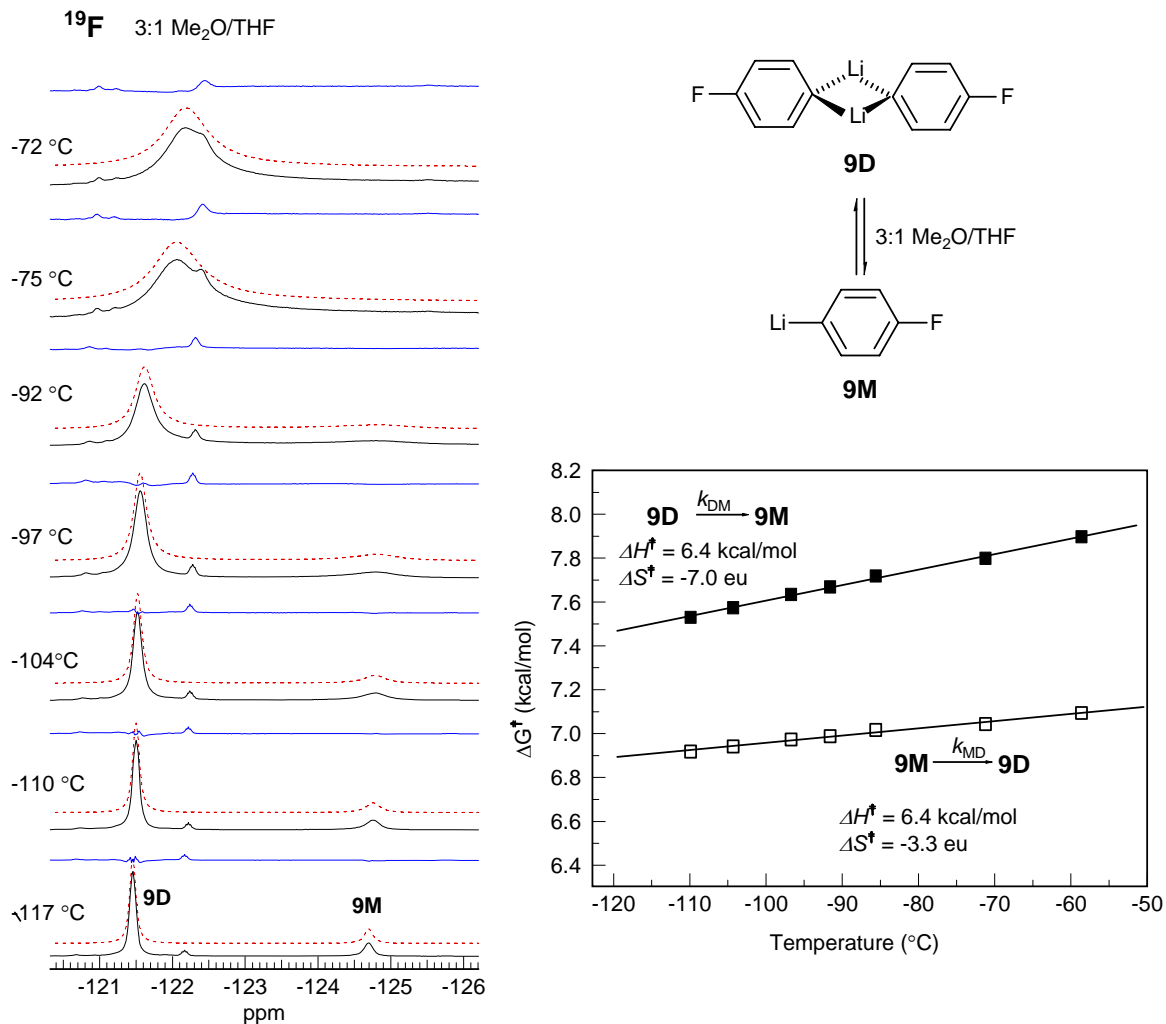


Figure S-7. (KNP3175) Variable Temperature ¹⁹F NMR experiment of **9M** and **9D** in 3:1 Me₂O/THF. Rates were determined by simulation with WINDNMR using the 2-spin simulation.^[S5] Black spectra are measured, red dashed are simulated and blue are the difference spectra.

Table S-1. Numeric data for the line shape simulation of Figure S-7 (D = dimer, M = monomer).

Temperature / °C	-117	-110	-104	-97	-92	-75	-72
ν_D / Hz	32702.2	32687.3	32680.3	32670.9	32652.6	32649.1	32615.4
ν_M / Hz	31603.8	31583	31571.6	31553.3	31528.7	31499.0	31456.0
$k_{DM} + k_{MD}/\text{sec}^{-1}$	47	174	341	793	1367	7497	9397
W_D /Hz	23	19	19	19	19	19	19
W_M /Hz	28	28	28	28	28	28	28
Fraction Dimer	0.81	0.81	0.81	0.81	0.81	0.81	0.81
k_{DM}/sec^{-1}	38.1	140.9	276.2	642.3	1107	6073	7612
ΔG_{DM}^\ddagger /kcal/mol	7.61	7.53	7.57	7.63	7.69	7.71	7.80
k_{MD}/sec^{-1}	8.9	33.1	64.8	151	260	1424	1785
ΔG_{MD}^\ddagger /kcal/mol	7.02	6.92	6.94	6.97	6.99	6.97	7.04

PMDTA Titration of 4-Fluorophenyllithium (9). (KNP3192) A 10 mm NMR tube was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added, the tube was cooled in a dry ice/acetone bath and Me₂O (3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). The ¹³C chemical shift thermometer (10% ¹³C labeled *tris*(trimethylsilyl)methane, 0.002 mL),^[S11] an internal standard for concentrations (4-fluorotoluene, 0.002 mL), 0.050 mL of (4-fluorophenyl)trimethyltin (0.3 mmol) and *n*-BuLi (0.12 mL, 0.3 mmol, 2.5 M in hexanes) were added to the NMR tube at -78 °C. The sample was inserted into a precooled NMR spectrometer and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. ⁷Li, ¹³C, ¹⁹F and ¹H NMR spectra were obtained at -115 °C with 0, 0.33, 0.66, and 1.0 equivalents PMDTA (neat) (Figure S-8).

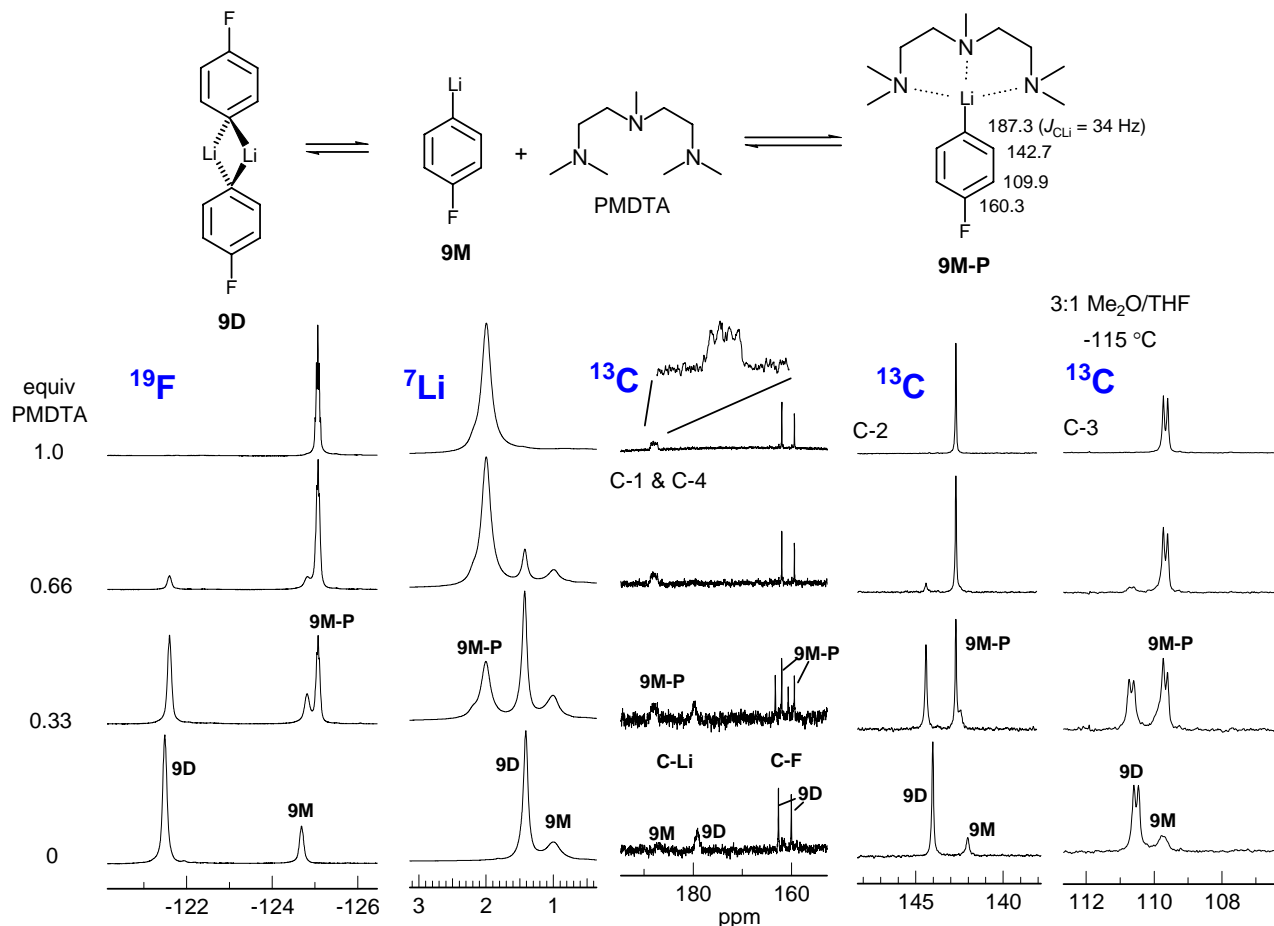


Figure S-8 ¹⁹F, ⁷Li and ¹³C NMR spectra of a PMDTA titration of **9** in 3:1 Me₂O/THF at -115 °C.

^{13}C NMR of 9M-P with Excess PMDTA. (KNP3262) A 10 mm NMR tube was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added to the NMR tube and cooled in a dry ice/acetone bath and Me_2O (3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). An internal standard for concentrations (4-fluorotoluene, 2 μL), (4-fluorophenyl)trimethyltin (50 μL , 0.3 mmol) and *n*-BuLi (0.12 mL, 0.3 mmol, 2.5 M in hexanes) were added to the NMR tube at $-78\text{ }^\circ\text{C}$. The sample was inserted into a precooled NMR spectrometer and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. ^7Li , ^{13}C , ^{19}F and ^1H NMR spectra were obtained at $-115\text{ }^\circ\text{C}$ with 0, 0.44, 0.66 and 0.88 equivalents PMDTA and at $-125\text{ }^\circ\text{C}$ with 1.0, 1.1 and 1.5 equivalents PMDTA (Figure S-9).

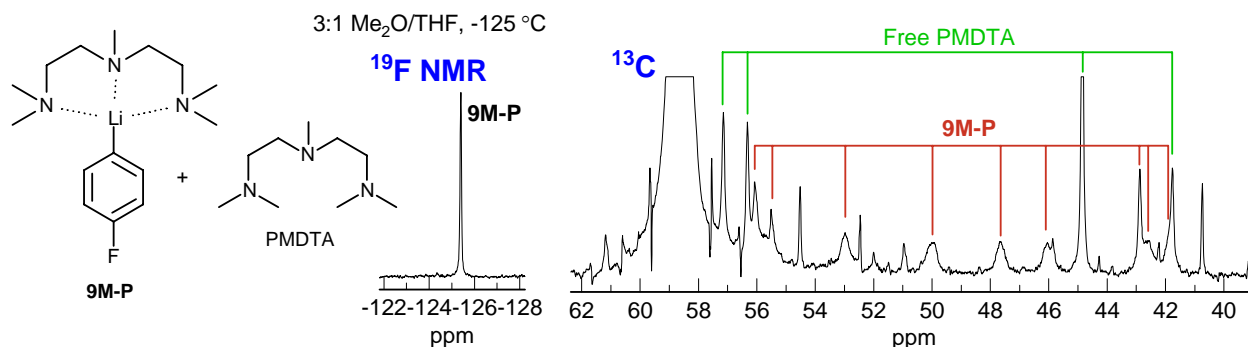


Figure S-9. ^{19}F and ^{13}C NMR spectra of **9M-P** and free PMDTA in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-125\text{ }^\circ\text{C}$ when 1.5 equivalents of PMDTA was added to 4-fluorophenyllithium (**9**). At low temperatures PMDTA complexed to lithium reagents shows all nine carbons non-equivalent, as seen here for **9M-P**. The four signals of free PMDTA are also marked. Neopentyllithium^[S6] and phenyllithium^[S7] show similar desymmetrized signals for PMDTA complexes.

Association Constant of PMDTA with 4-Fluorophenyllithium (K_{eq} of $9M + PMDTA \rightleftharpoons 9M-P$). (KNP3266)
 A 10 mm NMR tube was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added to the NMR tube and cooled in a dry ice/acetone bath and Me₂O (3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). An internal standard for concentrations (4-fluorotoluene, 2 μ L), (4-fluorophenyl)trimethyltin (50 μ L, 0.3 mmol) and *n*-BuLi (0.12 mL, 0.3 mmol, 2.5 M in hexanes) were added to the NMR tube at -78 $^{\circ}$ C. The sample was inserted into a precooled NMR spectrometer and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. ⁷Li, ¹³C, ¹⁹F and ¹H NMR spectra were obtained at -150 $^{\circ}$ C with 0, 0.9 and 1.0 equivalents PMDTA (Figure S-10). ¹³C NMR subtraction spectra were used to calculate the quantity of free PMDTA with 1.0 equivalents. The association constant was calculated as $2.1 \times 10^3 \text{ M}^{-1}$ ($9M + PMDTA \rightleftharpoons 9M-P$).

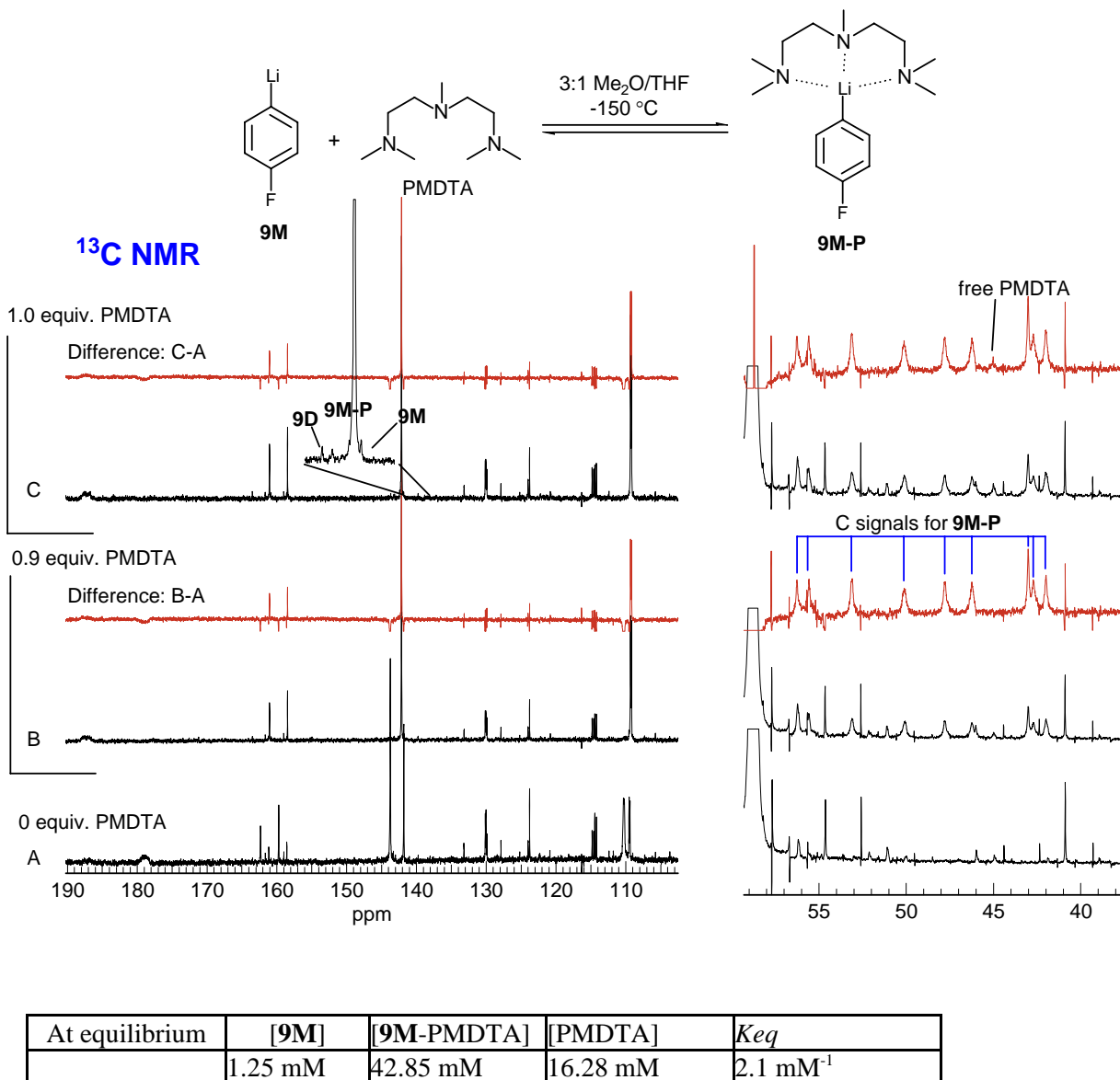


Figure S-10. ¹⁹F and ¹³C NMR spectra of **9** with 0, 0.9 and 1.0 equivalents PMDTA in 3:1 Me₂O/THF at -150 $^{\circ}$ C. Red spectra are the result of the original spectra (0 equiv. PMDTA) subtracted from those with PMDTA (0.9 or 1.0 equiv.).

Variable Temperature NMR Experiment of 9D, 9M and 9M-P. (KNP3197) A 10 mm NMR tube was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added to the NMR tube and cooled in a dry ice/acetone bath and Me₂O (3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). An internal standard for concentrations (4-fluorotoluene, 2 μL), (4-fluorophenyl)trimethyltin (50 μL, 0.3 mmol), *n*-BuLi (0.12 mL, 0.3 mmol, 2.5 M in hexanes) and PMDTA (0.5 eq. 30 uL) were added to the NMR tube at -78 °C. The sample was inserted into a precooled NMR spectrometer and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. ⁷Li, ¹³C, ¹⁹F and ¹H NMR spectra were obtained at -110, -95, -80, -70 and -60 °C (temperatures are estimated) (Figure S-11).

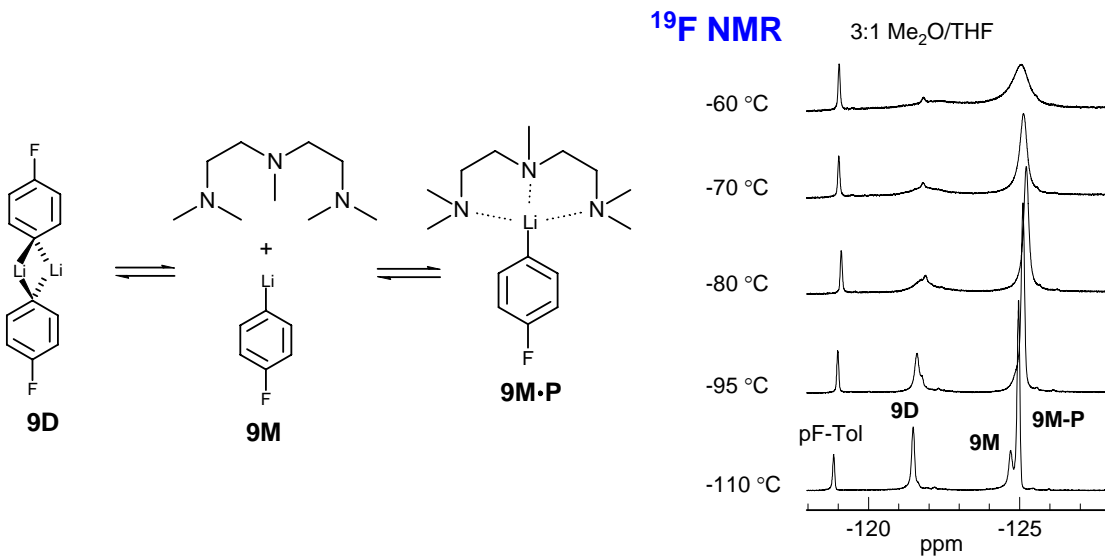


Figure S-11. Variable temperature ¹⁹F NMR experiment of **9D**, **9M** and **9M-P** in 3:1 Me₂O/THF.

S5. Rapid Injection NMR Experiments

General Preparation of RINMR Samples. A 10 mm NMR tube cut to a length of <18 cm was sealed with a septum, grease, and parafilm, and purged with argon. Solvent, 1 mL of freshly distilled THF and 3 mL of Me₂O freshly distilled from n-BuLi, a ¹³C chemical shift thermometer (10% ¹³C labeled *tris*(trimethylsilyl)methane, 0.004 mL),^[S1] and substrate were measured out. 4-Fluorotoluene (0.005 mL) was added as a ¹⁹F NMR standard. The NMR tube was cooled in a dry ice/acetone bath while back-filling with argon, and the final additions to the sample were made. The material to be injected was weighed into a separate, septum-sealed, argon purged flask and dissolved in Et₂O at a concentration appropriate for a standard 0.15 mL injection. The NMR sample (still sealed with a septum) was inserted into the NMR probe, which has been equilibrated to the appropriate temperature, and preliminary spectra were collected to adjust spectrometer tuning, check the quality and concentration of the sample and measure the temperature of the sample using ¹³C NMR.^[S1] The sample was raised, the septum removed, and the open NMR tube was expeditiously lowered into the spectrometer and the apparatus was assembled.

¹⁹F RINMR experiments were performed as follows (a more detailed description of the sequence and apparatus has been given[S8*9]). The pulse program was started, which includes 10 pre-injection scans set to last about 20 to 30 s. Approximately 10 s prior to the injection the spectrometer temperature setting was raised ca 2 °C for every 0.1 mL injected to correct for the warming caused by sample injection.[S8*9] After the pre-injection scans, the automated pulse program lowers the apparatus, starts the stirrer and injects the sample, continues stirring for 0.6 s, stops the stirrer, raises the apparatus and continues collecting spectra. Depending on the length of the experiment, spectra were typically taken at 2 to 3 s intervals (T_1 for 4-fluorophenyl signals was ca 0.3 s at -125 °C) for a few min after which a longer time interval between scans (10-30 s) was selected for the remainder of the experiment (up to 3 h). During the course of an experiment the mass balance (reactants + product) was checked using the internal ¹⁹F NMR standard as well and agreement was found to be within ±5%. At the completion of the experiment, the temperature of the sample was again checked, and post-kinetics analyses of the sample were performed. Post-kinetic analysis included acquisition and analysis of the resulting product(s) NMR spectra and the determination of NMR yields which agreed within 5% to the theoretical yield.

^7Li RINMR of $n\text{-BuLi}$ with Ethyl Formate. (ACJ3010) A RINMR sample was prepared containing $n\text{-BuLi}$ (0.05 mL, 2.5 M/hexane, 0.125 mmol) in 1 mL of THF and 3 mL of Me_2O . A separate flask was prepared containing ethyl formate (1.28 M in Et_2O , 0.25 mmol). A 0.2 mL injection was done (Figure S-12).

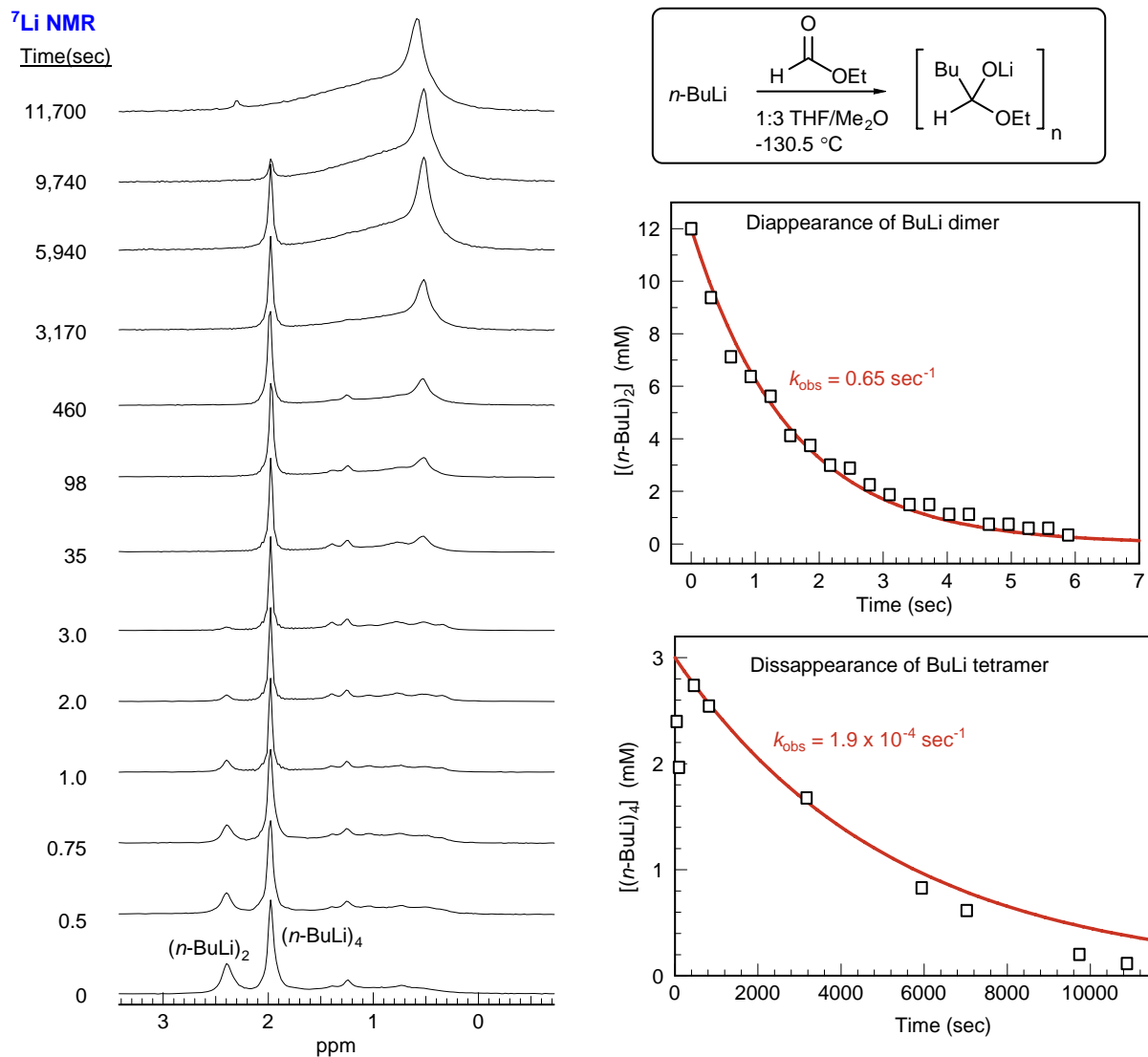


Figure S-12. Injection of ethyl formate into a solution of $n\text{-BuLi}$ (0.03 M total BuLi) in 1:3 THF/ Me_2O at -130 $^\circ\text{C}$. The graphs show the decay of $(n\text{-BuLi})_2$ and $(n\text{-BuLi})_4$ as a function of time. The lines are first order decays with the rate constant shown.

Products from RINMR of *n*-BuLi with Ethyl Formate. A RINMR sample was prepared containing *n*-BuLi (2.5 M in hexanes, 0.12 mL, 0.3 mmol). Ethyl formate (0.024 mL, 0.3 mmol) in 0.175 mL of THF was injected at -135 °C. After 30 seconds all of the dimer had reacted and the reaction was quenched with propionic acid (0.029 mL, 0.39 mmol 1.3 equiv) at -135 °C. ⁷Li spectrum showed no *n*-BuLi left. The sample was warmed to 25 °C to let the Me₂O evaporate. Acetone-*d*₆ (0.10 mL to provide an NMR lock signal) was added, and ¹H and ¹³C NMR spectra were run on a 500 MHz Bruker spectrometer equipped with a DCH cryoprobe (Figure S-13). Only signals corresponding to the aldehyde could be seen. Integration vs the ethyl formate signals in the ¹H spectrum gave a 40% yield of the aldehyde, essentially 100% based in reaction of only (*n*-BuLi)₂ during the 30 sec time period (see Figure S-9). The presence of any secondary alcohol, from double addition of *n*-BuLi was ruled out based on the lack of a significant signal at 72 ppm in the ¹³C NMR spectrum.

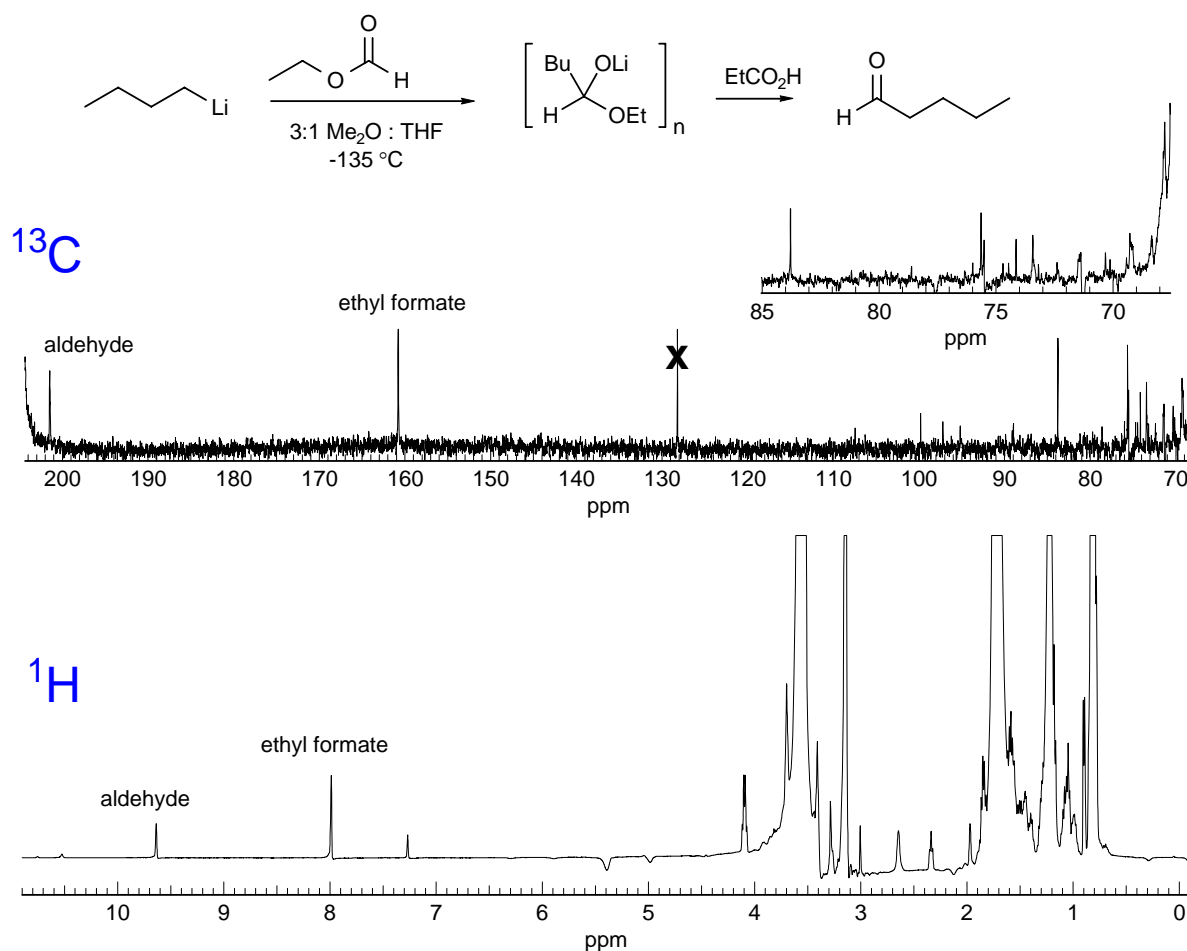


Figure S-13. ¹H and ¹³C spectra of the reaction of (*n*-BuLi)₂ with ethyl formate after propionic acid quench. No significant signal for the secondary alcohol from double addition (nonan-5-ol) at 72 ppm was detected in the ¹³C NMR spectrum.

^7Li RINMR of $n\text{-BuLi}$ with Acetone (ACJ4184). A RINMR sample was prepared containing $n\text{-BuLi}$ (0.1 mL, 2.5 M/hexane, 0.25 mmol) in 1 mL of THF and 3 mL of Me_2O . A separate flask was prepared containing acetone (0.40 mL, 5.5 mmol) and 1.2 mL each of THF and ether for a 2.3 M solution. A 0.24 mL injection (0.55 mmol) was done (Figure S-14).

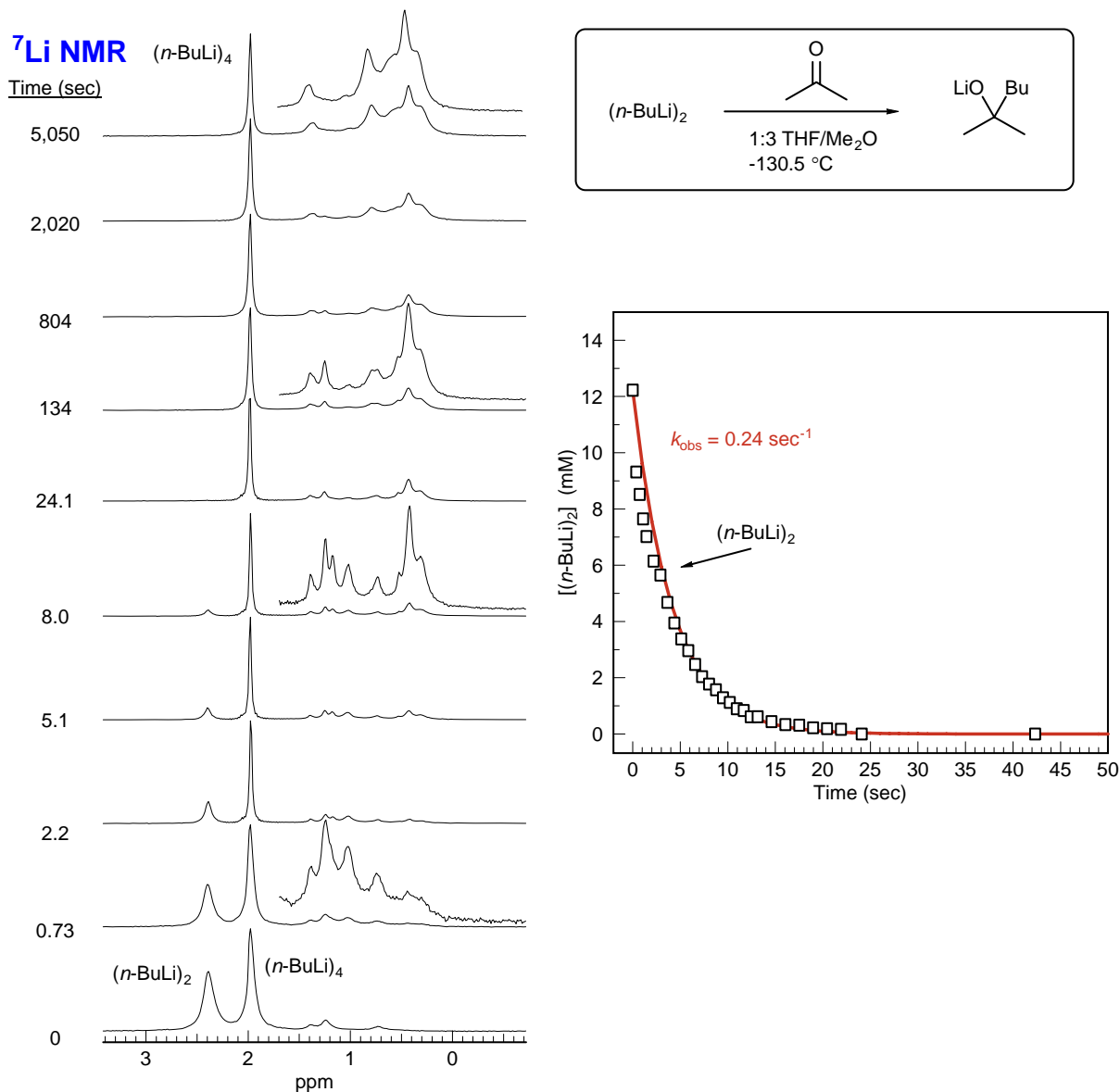


Figure S-14. Injection of acetone into a solution of $n\text{-BuLi}$ (0.07 M) in 1:3 THF/ Me_2O at -135°C . Several intermediate product ^7Li signals were present, presumably various mixed aggregates between $n\text{-BuLi}$ and the alkoxide product, but these were not identified. The graph shows the decay of $(n\text{-BuLi})_2$ as a function of time. The line is first order decay with the rate constant shown.

^7Li RINMR of $n\text{-BuLi}$ with 3-Methoxyacetophenone (ACJ7188). A RINMR sample was prepared containing $n\text{-BuLi}$ (0.05 mL, 2.5 M/hexane, 0.125 mmol) in 1 mL of THF and 3 mL of Me_2O with PhSiMe_3 (0.037 g, 0.23 mmol). A separate flask was prepared containing 3-methoxyacetophenone (0.13 mL, 0.95 mmol) and 435 μL each of THF and ether for a 0.95 M solution. A 0.2 mL injection (0.19 mmol) was done (Figure S-15).

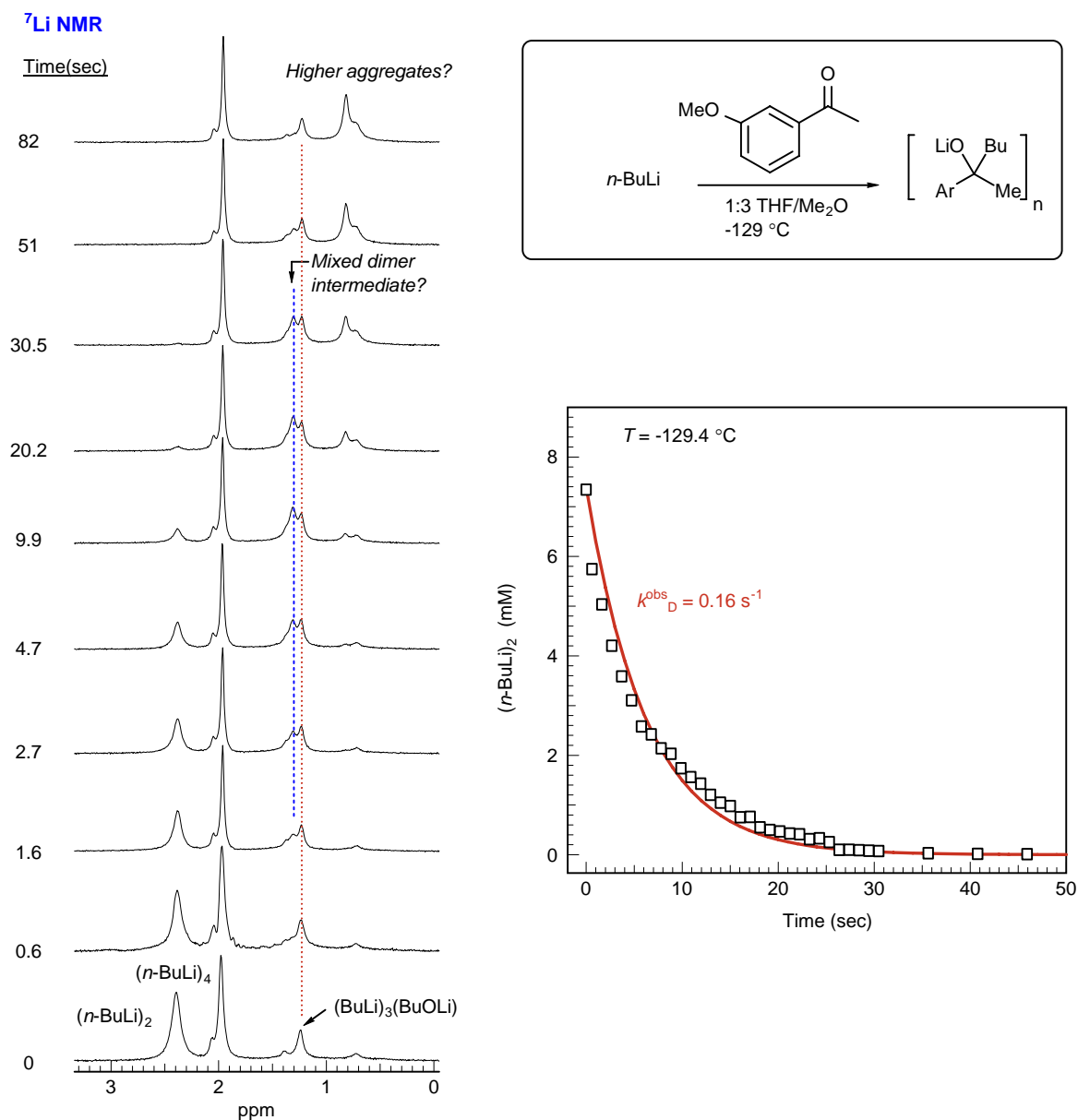


Figure S-15. Injection of 3-methoxyacetophenone into a solution of $n\text{-BuLi}$ (0.03 M) in 1:3 THF/ Me_2O at $-135\text{ }^\circ\text{C}$. If the transient peak at δ 1.3 is correctly identified as the mixed dimer $(n\text{-BuLi})(\text{ROLi})$, as seems likely, then it is slightly less reactive towards the ketone than $(n\text{-BuLi})_2$. It is interesting that the signal for $(\text{BuLi})_3(\text{BuOLi})$ at δ 1.2 was unchanged in this time period. Thus $(n\text{-BuLi})_2$ is substantially more reactive towards the ketone than the mixed alkoxide tetramer. The graph shows the decay of $(n\text{-BuLi})_2$ as a function of time. The line is first order decay with the rate constant shown. Note that significant deviations from first order behavior are seen.

^7Li RINMR of *n*-BuLi with *N,N*-Dimethyl 3-Methoxybenzamide. (ACJ6049) A RINMR sample was prepared with *n*-BuLi (0.05 mL, 2.4 M/hexane, 0.12 mol) in 1 mL of THF and 3 mL of Me_2O with $(\text{Me}_3\text{Si})_3\text{CH}$ (10 μL). A separate flask was prepared with *N,N*-dimethyl 3-methoxybenzamide (ca 200 μL liquid) (0.24 g, 1.33 mmol) and 0.4 mL each of THF and ether for a 1.3 M solution. A 0.2 ml injection was done with $\text{AQ} = 0.5$ s for 500 spectra with a delay of 0 s (See Figure S-16). Propionic acid quench and workup gave 3-methoxyphenyl butyl ketone as product.

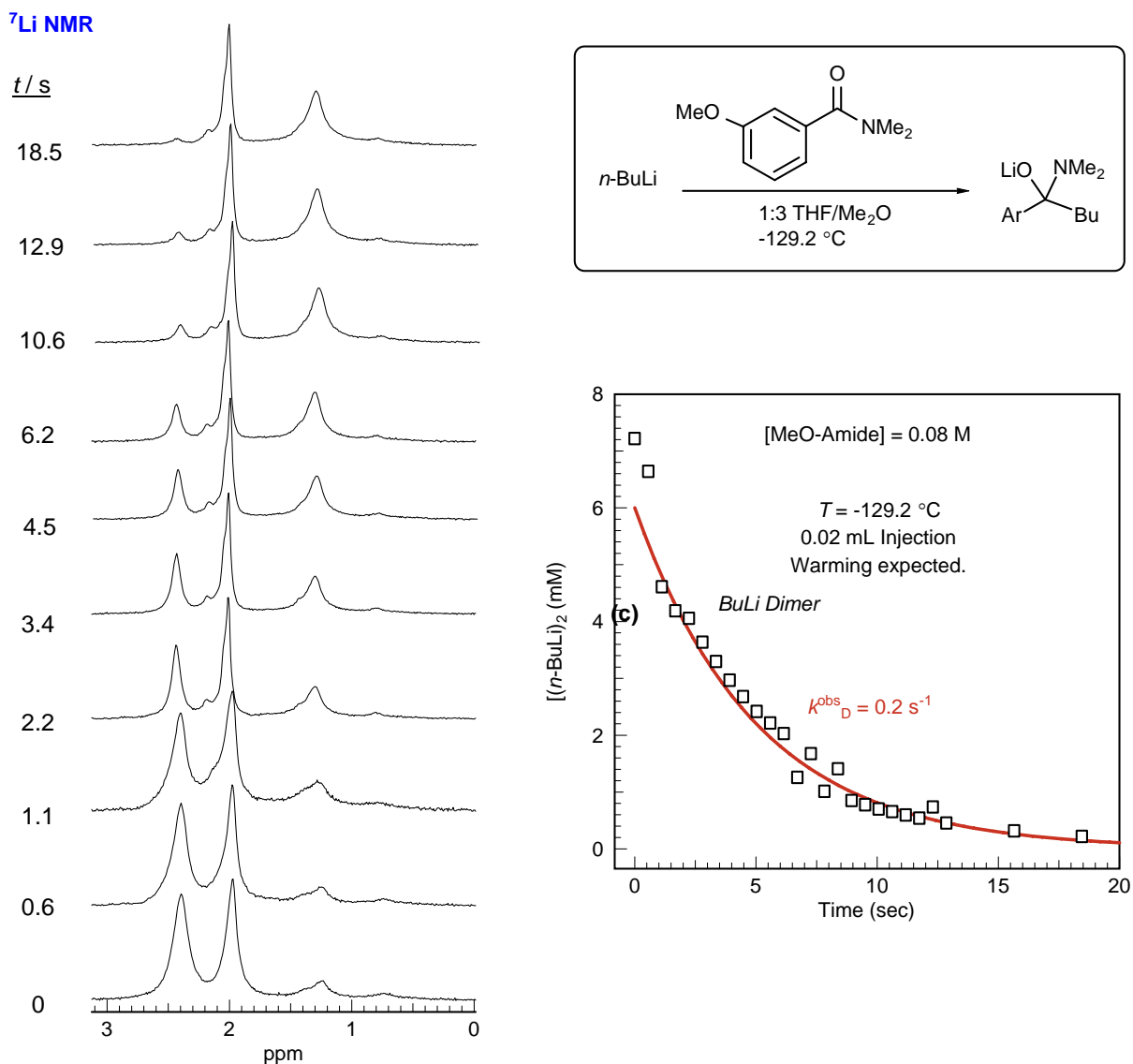


Figure S-16. Injection of *N,N*-dimethyl 3-methoxybenzamide into a solution of *n*-BuLi (0.03 M) in 1:3 THF/ Me_2O at -129 °C. The graph shows the decay of $(n\text{-BuLi})_2$ as a function of time. The line is first order decay with the rate constant shown.

^7Li RINMR of *n*-BuLi with Methyl Benzoate. (ACJ5031) A RINMR sample was prepared with *n*-BuLi (0.08 mL, 2.58 M/hexane, 0.26 mol) in 1 mL of THF and 3 mL of Me₂O with unlabeled (Me₃Si)₃CH (¹³C shift thermometer, ^[51a] 0.010 mL). A separate flask was prepared with methyl benzoate (0.6 mL, 4.8 mmol) and 0.7 mL each of THF and ether for a 2.4 M solution. A 0.21 mL injection was done (Figure S-17). A propionic acid quench at the end of the experiment showed methyl benzoate and valerophenone.

^7Li NMR

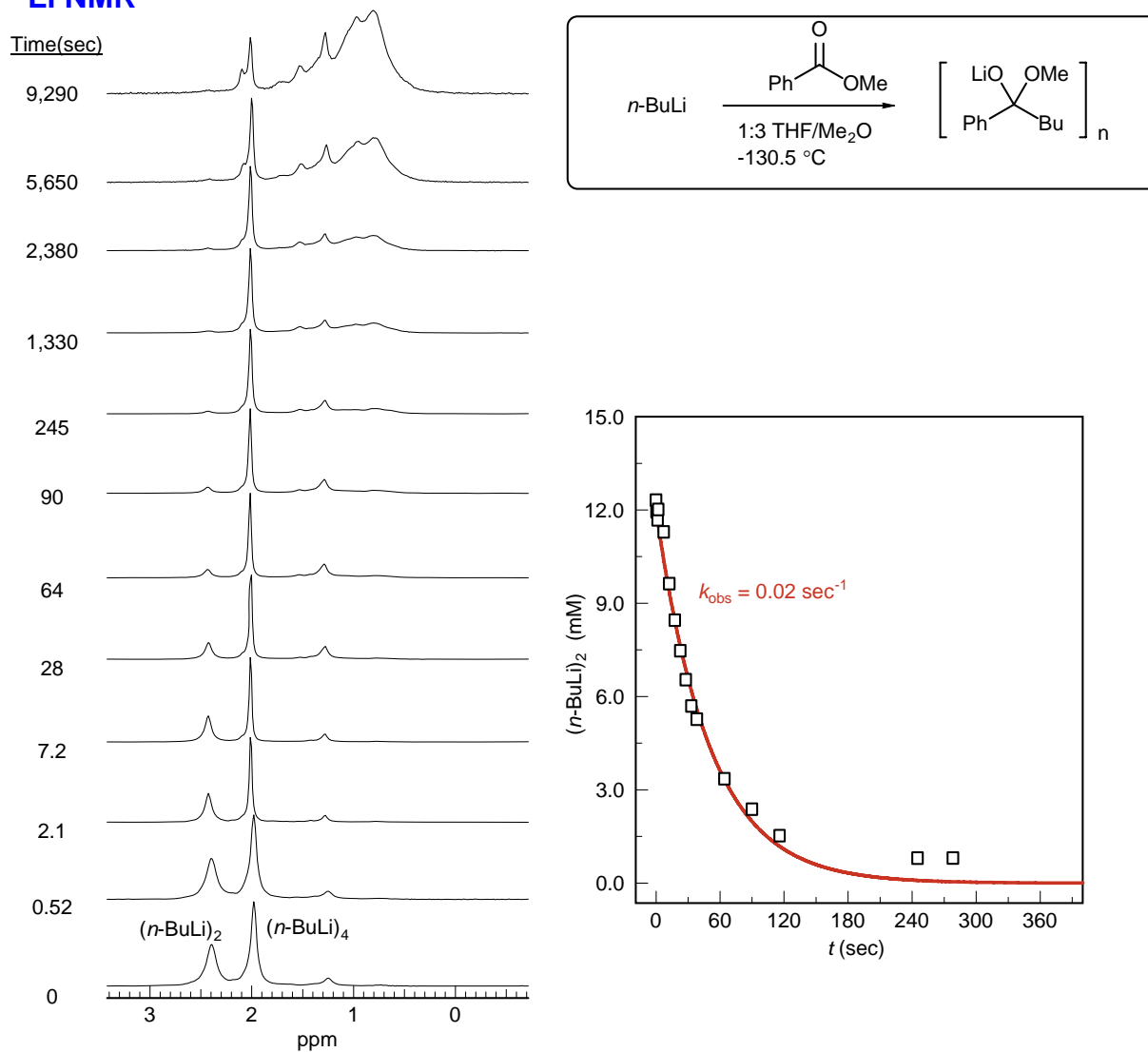


Figure S-17. Selected spectra from injection of methyl benzoate into a solution of *n*-BuLi (0.06 M) in 1:3 THF/Me₂O at -130°C . The graph shows the decay of $(n\text{-BuLi})_2$ as a function of time. The line is first order decay with the rate constant shown.

^{19}F RINMR of 4-Fluorophenyllithium (9**) with Ester **1** at $-110\text{ }^\circ\text{C}$.** (KNP3039) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. Ester **1** (0.2 mL, 1.5 M in THF) was injected into the NMR sample containing **9**. The reaction was monitored with $\text{AQ} = 1\text{ s}$ for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s at $-110\text{ }^\circ\text{C}$. Spectra and concentration traces are shown in Figure S-18. Additional characterization of the intermediates $3\cdot\text{ArLi}$ and $(3)_2$ is shown in Figures S-19. The reaction was quenched with 0.15 mL of propionic acid (3.0 M in THF) using the RINMR apparatus at $-110\text{ }^\circ\text{C}$. ^{19}F , ^7Li , ^{13}C and ^1H NMR spectra were taken of the final solution. Outside the spectrometer, the reaction was quenched with aqueous NH_4Cl . The mixture was extracted with 1:1 ether/hexanes twice. The organic layer was washed with water and brine, dried with MgSO_4 and the solvent removed *in vacuo*, giving 99 % conversion of **9** to ketone **7**.

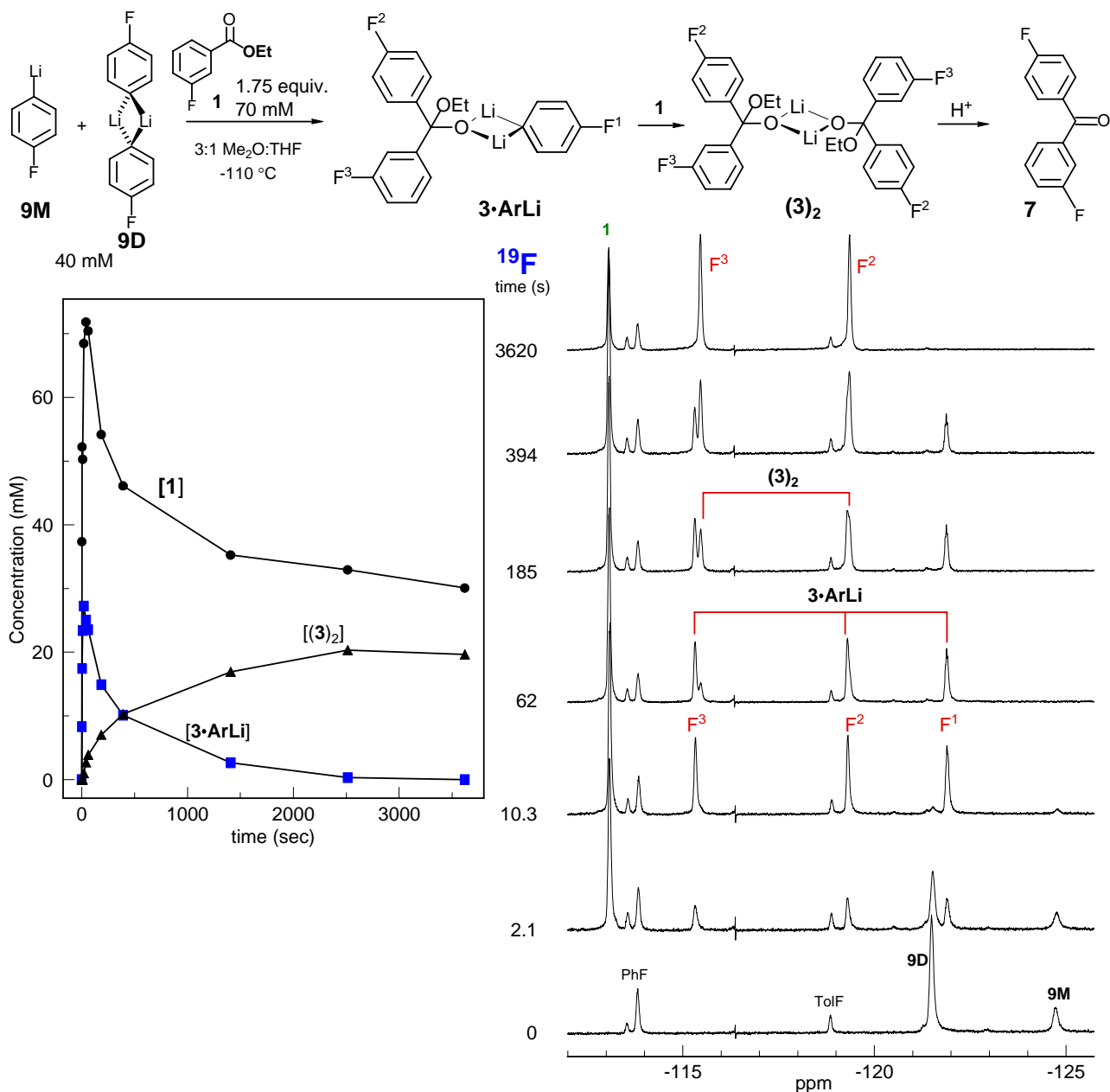


Figure S-18. ^{19}F RINMR experiment of the injection of 1.75 equivalents of ester **1** into a solution of 4-fluorophenyllithium (**9**) in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-110\text{ }^\circ\text{C}$.

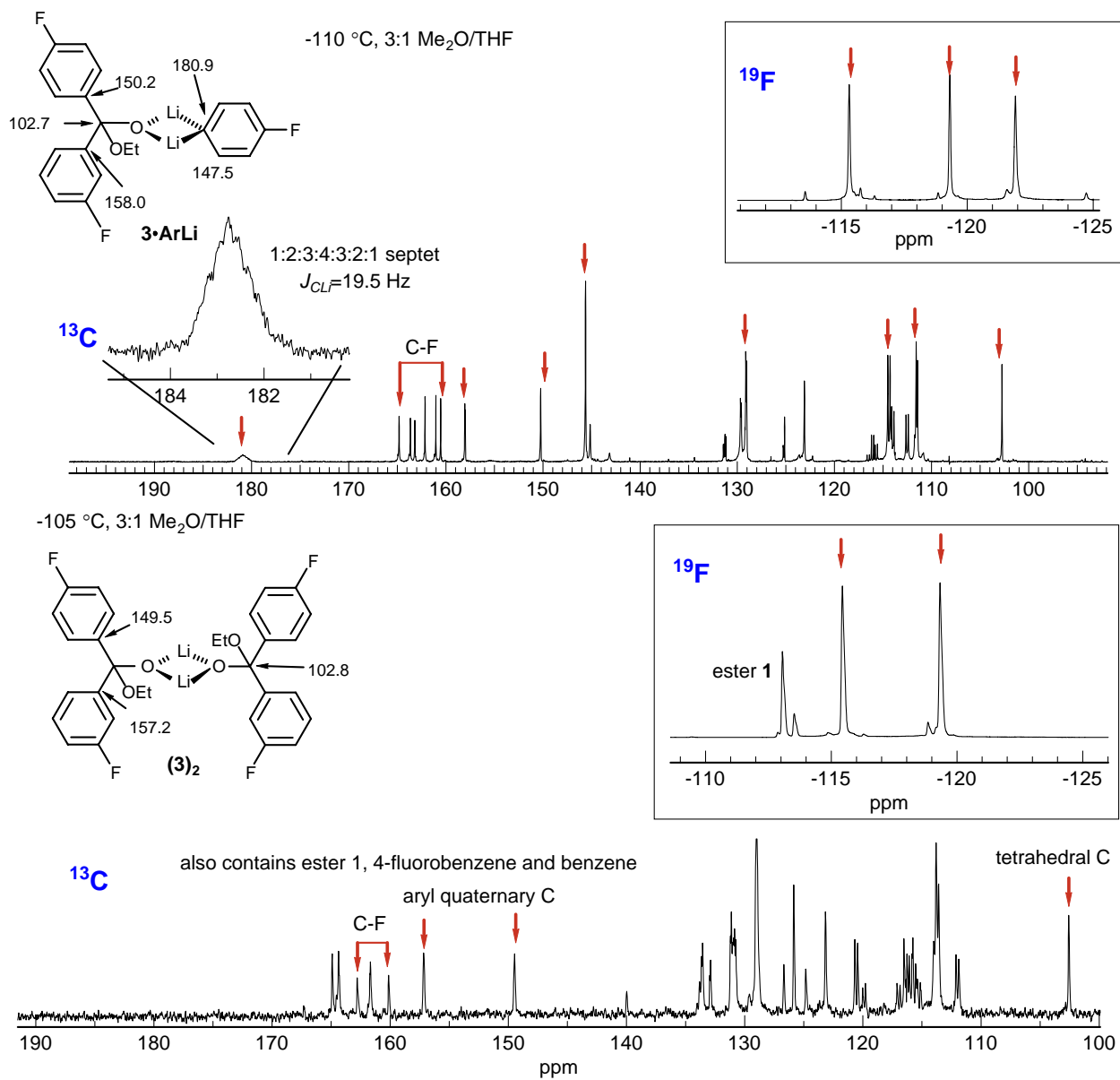


Figure S-19. ¹³C and ¹⁹F NMR spectroscopic characterization of intermediates in the reaction of **1** with 4-fluorophenyllithium (**9**).

^{19}F RINMR of 4-Fluorophenyllithium (9**) with Ester **1** at $-97\text{ }^\circ\text{C}$.** (KNP3271, 3273) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. Ester **1** (1.25 equiv., 44.5 mg in 0.16 mL of THF; 8 equiv., 0.22 g) was injected into the NMR sample containing **9**. The reaction was monitored by ^{19}F NMR with $\text{AQ} = 1\text{ s}$ for 1000 spectra with a delay of 1 s, and 490 spectra with a delay of 180 s at $-97\text{ }^\circ\text{C}$. Sample spectra are shown in Figure S-20, kinetic traces in Figure S-21.

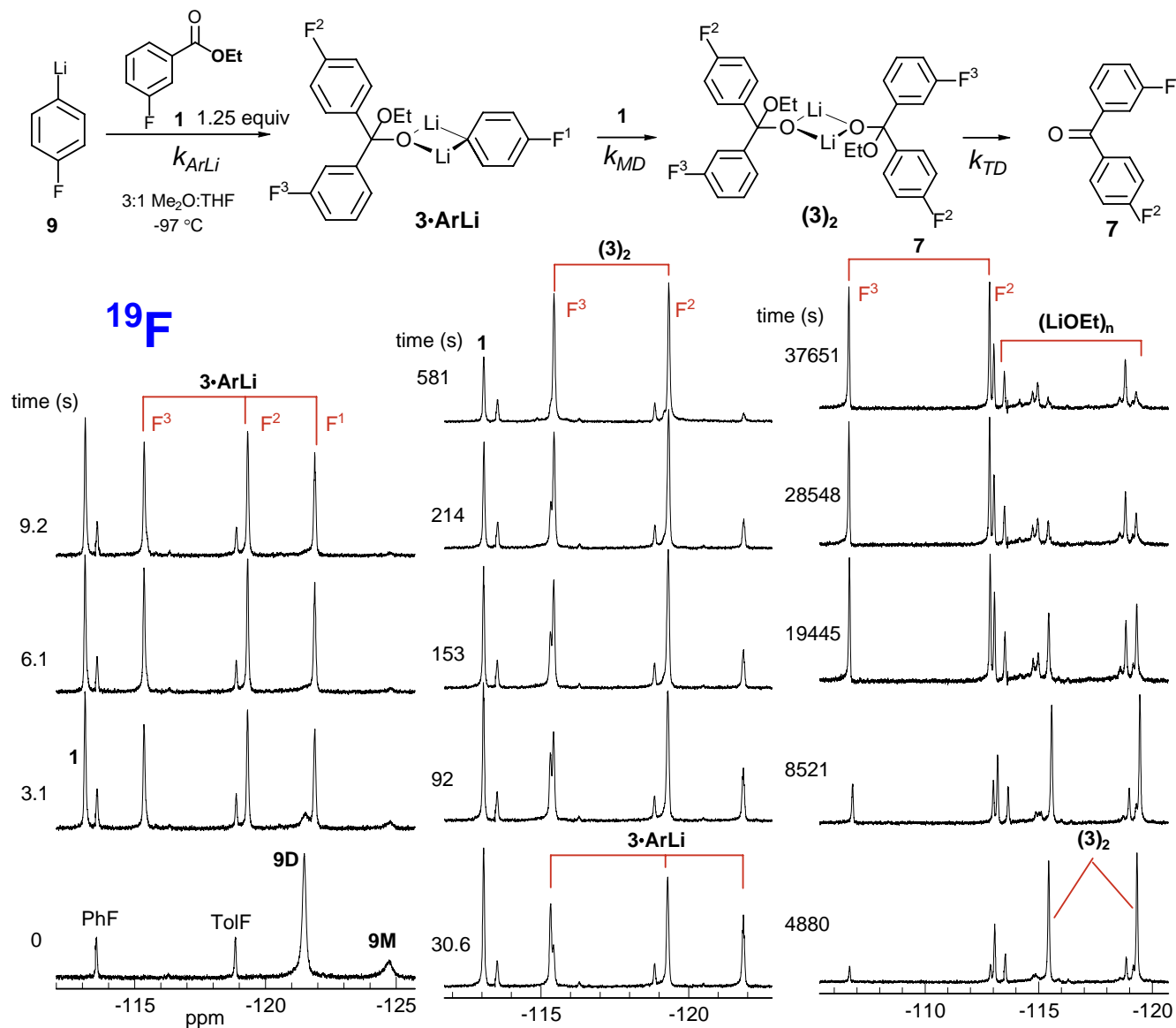
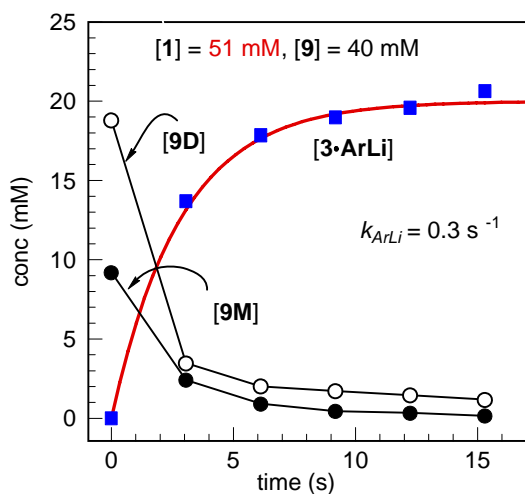
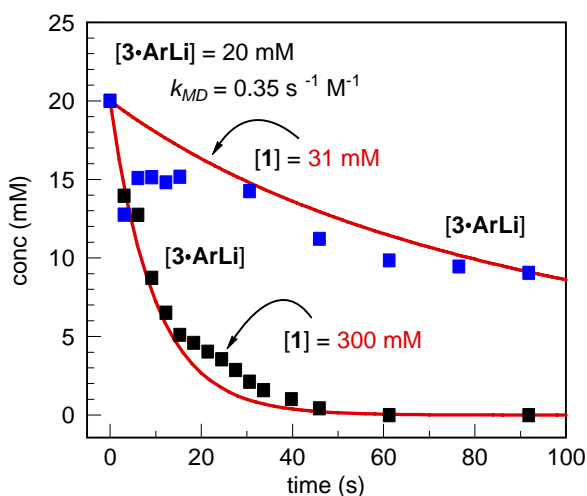


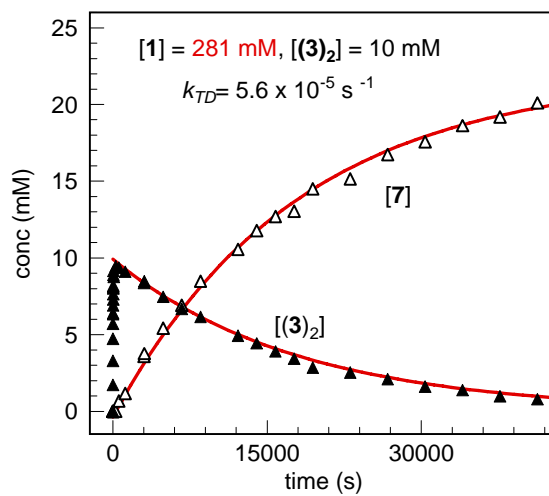
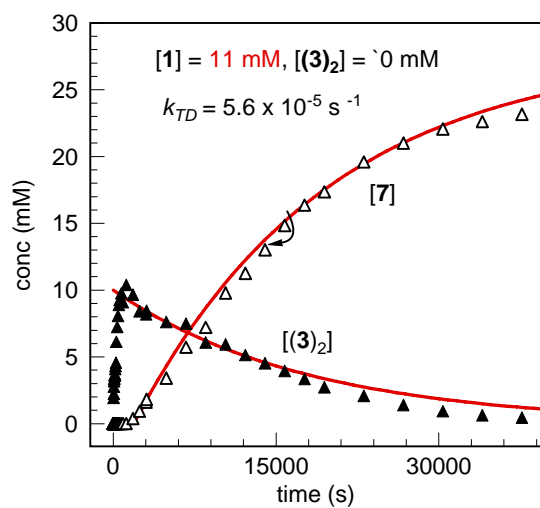
Figure S-20. ^{19}F RINMR of the injection of 1.25 equivalents of ester **1** into a solution of 4-fluorophenyllithium (**9**) in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-97\text{ }^\circ\text{C}$.



(a) First phase (complete in ca 15 s): reaction of ArLi **9** with ester **1** to form **3·ArLi**. The red line is a first order rate simulation of the increase in **3·ArLi** with $k = 0.3 \text{ s}^{-1}$. The rates are too fast and there are not enough data points to determine order in ester, but qualitatively higher ester concentration leads to faster formation of **3·ArLi**.



(b) Second phase (complete in several min): reaction of **3·ArLi** with two different concentrations of ester ($[1] = 31 \text{ mM}$ and $[1] = 300 \text{ mM}$) to form $(\mathbf{3})_2$. The red lines are second order rate simulations with $k = 0.35 \text{ s}^{-1} \text{ M}^{-1}$. The reaction follows approximate second order kinetics.



(c) Third phase (complete in ca 20 hours): decomposition of dimeric tetrahedral intermediate $(\mathbf{3})_2$ to ketone **7** with either 10 mM or 280 mM excess ester **1** present. The red lines correspond to first order decay or increase with $k = 5.6 \times 10^{-5} \text{ s}^{-1}$. Thus decomposition of the tetrahedral intermediate is unimolecular and is not affected by the concentration of ester.

Figure S-21. Concentration plots from RINMR of the injection of 1.25 (See Figure S-20) and 8 equivalents of ester **1** into a solution of **9** in 4 mL of 3:1 Me₂O/THF at -97 °C. Time vs. concentration plots are shown for each reaction separately. The red lines are first (parts a and c) and second (part b) order decay or appearance curves with the rate constants shown. The reaction of **3·ArLi** with **1** is first order in ester. The decomposition of $(\mathbf{3})_2$ to ketone **7** is unaffected by ester concentration.

Diffusion Ordered NMR Spectroscopy (DOSY). DOSY experiments were performed on a Bruker AVANCE DMX-360 equipped with a GRASP II z-axis gradient amplifier and a 5mm BBO probe with z-axis gradients (10mm tubes, and therefore RINMR experiments, were not possible due to the lack of gradients on the 10mm probe). Maximum gradient strength was 40 G/cm. Pulse sequence (DSTE-BP-CC) included stimulated echoes, bipolar sine-shaped gradients, longitudinal eddy current delays and convection compensation.

¹⁹F DOSY of Tetrahedral Intermediate 3·ArLi and (3)_n. (KNP3253) A 5 mm NMR tube was sealed with a septum and parafilm, purged with argon and cooled in a dry ice/acetone bath. Me₂O (0.7 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). 4-Fluorotoluene (2 μL), (4-fluorophenyl)trimethyltin (15 μL, 0.09 mmol) and *n*-BuLi (0.03 mL, 0.07 mmol, 2.5 M in hexanes) were added to the NMR tube at -78 °C. The sample was inserted into a precooled NMR spectrometer (-115 °C) and allowed to equilibrate. Optimization of the shims based on the FID of C-3 of THF was performed. The RINMR apparatus was not available on this spectrometer, so the sample was ejected and frozen with liquid N₂. Under liquid N₂, Et₂O (0.05 mL) and ester **1** (7 mg in 0.05 mL Et₂O) were layered on the sample and immediately frozen. The septa was removed and the sample inserted into a NMR spectrometer precooled to -150 °C manually with low lift air to minimize warming and glass rod to facilitate mixing. The sample was allowed to warm to -115 °C over 1 hour. ¹⁹F DOSY spectra were recorded with varying gradient strength (ns = 64, ds = 4, aq = 2, rg = 300, d1 = 8, d20 = 0.1 s, p30 = 3ms, d16 = 0.1 s). Individual rows of the diffusion sets were phased and baseline corrected. The integrations were plotted vs. gradient strength (Stejskal-Tanner plot, Figure S-22a), and the slope of this line was taken as an estimation of diffusion. A log-log plot of diffusion as a function of formula weight was used to estimate the formula weight of the tetrahedral intermediate **3** and is shown in Figure S-22b.

In DOSY, the diffusion coefficients of molecules in solution are measured by fitting peak areas to the Stejskal-Tanner equation for the pulse sequence (Equation S-1)^[S-9] and can provide their relative particle size. The Stokes-Einstein equation (Equation S-2) theoretically correlates diffusion coefficients and molecular radii. Williard has shown through examination of solid-state X-ray crystal structures that the densities of organolithium aggregates are very similar (about 1.0 g/cm³) and are relatively spherical.^[S-10] Therefore, it is assumed that the volume of the aggregate is proportional to the formula weight. The diffusion coefficient obtained from a DOSY experiment can be related to formula weight (FW) by Equation S-3. Taking the logarithm of both sides yields a linear correlation between measured diffusion coefficients and the formula weight of the aggregates (Equation S-4). A calibration curve can be established from the use of molecules with known formula weight in solution. Extrapolation of the curve allows empirical formula weights of molecules of unknown aggregation state like tetrahedral intermediate (3)_n to be calculated.

$$\ln(I/I_0) = -G^2\gamma^2\delta^2[D + 4\delta/3 + 3\tau/2]D \quad \text{Equation S-1}$$

where *I* = intensity of a given peak, *I*₀ = intensity at a very small gradient value, *G* = gradient strength, γ = gyromagnetic ratio, δ = length of the bipolar gradient pulse, *D* = time between pulses, τ = gradient ringdown delay and *D* = diffusion coefficient

$$D = kT/6\pi\eta r \quad \text{Equation S-2}$$

where *D* = diffusion coefficient, *k* = the Boltzman constant, *T* = temperature in Kelvin, η = the viscosity of the solution and *r* = the radius of the molecular sphere

$$D \approx \text{FW}^a \quad \text{Equation S-3}$$

$$\log(D) = a \log(\text{FW}) + b \quad \text{Equation S-4}$$

While DOSY experiments have been applied to organolithium species with nuclei such as ¹H, ⁶Li, ⁷Li, ¹³C, ³¹P, and ²⁹Si nuclei,^[S-11] ¹⁹F diffusion analysis is more rare^[S-12] but similar to ¹H DOSY pulse sequences due to their similar high natural abundance and gyromagnetic ratio. Previously published DOSY experiments were performed at temperatures at or above -85 °C. However, our studies of reactive intermediates mixed dimer **3·ArLi** and the tetrahedral intermediate **3** must be performed at temperatures below -100 °C to avoid alkoxide elimination to form benzophenone. At these low temperatures, the higher viscosity of the solvent restricts diffusion and convection currents associated with temperature gradients form. To avoid these complications, an ethereal solvent mixture that is largely composed of non-viscous Me₂O (no THF, approx. 1.0:0.1 Me₂O/Et₂O) and a convection compensated pulse program (DSTE-BP-CC) was used.^[S-9]

The ¹⁹F NMR signals of fluorobenzene, 4-fluorotoluene, (4-fluorophenyl)trimethyltin, mixed dimer **3·ArLi**,

and tetrahedral intermediate **3** are well separated. In a series of experiments, the gradient field was incremented with the DSTE-BP-CC ^{19}F pulse program. The peak areas by integration were determined and decay curves (area vs. gradient strength squared) were generated. The decay curves were linearized (Figure S-22a), but the absolute diffusion coefficients were not calculated. Instead, the slopes of the decay curves were used as a relative estimation of diffusion (“ D ”) and plotted as a function of formula weight, as defined by Equation S-4 (Figure S-22b). The correlation between $\log \text{FW}$ and $\log “D”$ of the linear least-squares fit to the molecules of known molecular weight is high ($R^2 = 0.9955$). Formula weights were estimated with minimal solvation using the most polar solvent available to the lithium, Me_2O . Extrapolation of the measured diffusion values to the known line confirms the mixed dimer structure for $\mathbf{3}\cdot\text{ArLi}$ (FW = 464.28 for bis- Me_2O solvate, measured: 512.6) and dimer structures for $(\mathbf{3})_2$ (FW = 632.5 for bis- Me_2O solvate, measured: 559.3).

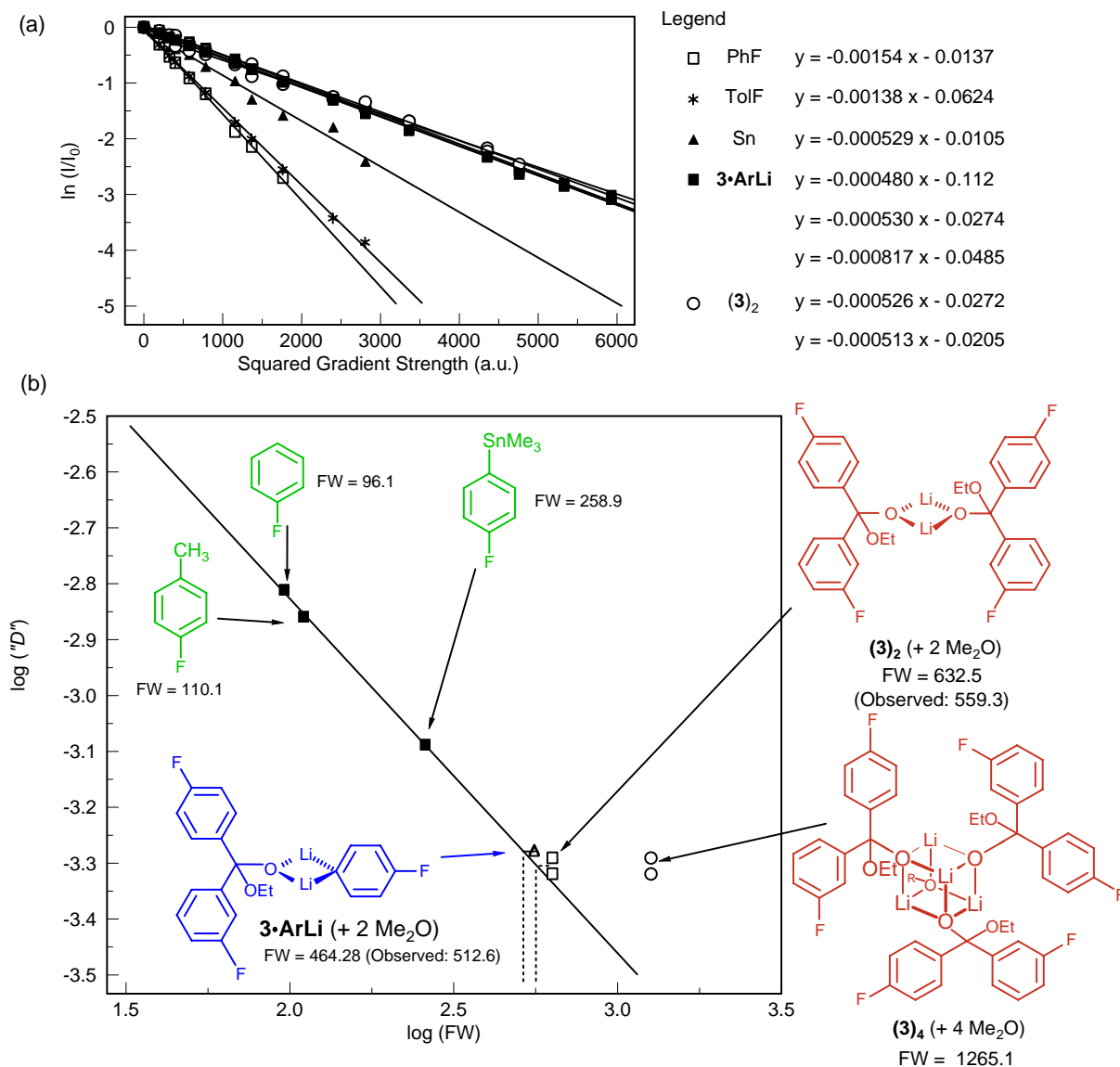


Figure S-22. (KNP3254) Results of ^{19}F DSTE-BP-CC DOSY experiment in 1.0:0.1 $\text{Me}_2\text{O}/\text{Et}_2\text{O}$ at $-115\text{ }^\circ\text{C}$ on $\mathbf{3}\cdot\text{ArLi}$, $(\mathbf{3})_n$ and reference compounds fluorobenzene (PhF), 4-fluorotoluene (TolF), (4-fluorophenyl)trimethyltin (Sn). (a) Stejskal-Tanner plot of experimental peaks and their best fit lines. Three lines and points are shown for $\mathbf{3}\cdot\text{ArLi}$, and two for $\mathbf{3}$ for the behavior of each individual ^{19}F signal. The nearly identical diffusion rates for the multiple fluorines of each product shows that the signals are in the same molecule. (b) Log-log plot of diffusion as a function of formula weight. The diffusion points for $\mathbf{3}$ are also plotted with molecular weights corresponding to both dimer $(\mathbf{3})_2$ and tetramer $(\mathbf{3})_4$.

^{19}F RINMR of 4-Fluorophenyllithium (9**) with Amide **2** at $-110\text{ }^\circ\text{C}$.** (KNP3036) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. A solution of amide **2** (0.2 mL, 1.5 M in THF) was injected into the NMR sample. The reaction was monitored with $\text{AQ} = 1\text{ s}$ for 200 spectra with a delay of 1 s, and 600 spectra with a delay of 10 s at $-110\text{ }^\circ\text{C}$. Data is shown in Figure S-23. The build-up of PhF during the reaction, the greater loss in [**9**] than of [**2**], as well as the complexity of the products suggest that some competing metalation of **2** and/or **10** was occurring during the reaction, but such products were not characterized. Analysis of the final solution after protic quenching showed 60% conversion of **9** to ketone **7**.

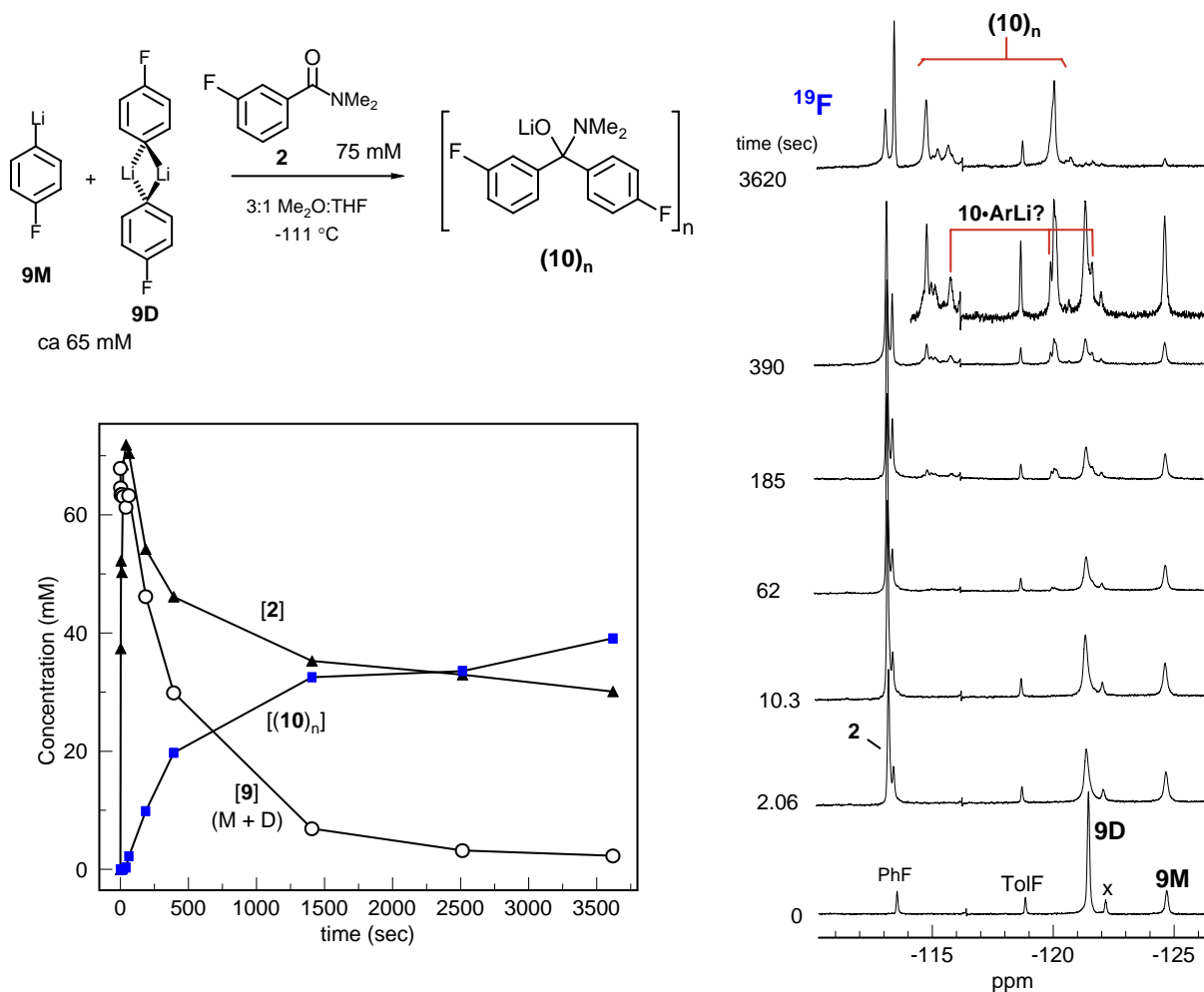


Figure S-23. ^{19}F RINMR experiment of the injection of amide **2** into a solution of 4-fluorophenyllithium (**9**) in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-110\text{ }^\circ\text{C}$. The concentrations of **9** and **10** are given in monomer units (normality). There are several tetrahedral intermediates at the end of the experiment, presumably the major two peaks correspond to the dimer $(\text{10})_2$, as also found for $(\text{3})_2$, and for the crystal structure of a bis-THF-solvate of the bisphenyl analog of **10**.^[S12] Three minor peaks may be the mixed dimer $10\cdot\text{ArLi}$.

¹⁹F RINMR Competition Experiments between Amide 2 and Ester 1. (KNP3061, 3063, 3069, 3071) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 Me₂O/THF using the typical RINMR sample preparation procedure. A pre-mixed solution of amide **2** or **2-d** (0.67 g, 0.4 mmol) and ester **1** or **1-d** (0.67 g, 0.4 mmol) was injected into the NMR sample. The reaction was monitored with AQ = 1 s for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s at -110 °C. The sample was quenched with 0.15 mL of propionic acid (3.0 M in THF) at -110 °C. ¹⁹F, ⁷Li, ¹³C and ¹H NMR spectra were taken of the final solution. Results are shown in Table S-2 and Figure S-24. Outside the spectrometer, the reaction was quenched with aqueous NH₄Cl. The mixture was extracted with 1:1 ether/hexanes twice. The organic layer was washed with water and brine, dried with MgSO₄ and the solvent removed *in vacuo*. The relative ratios of products and remaining starting materials were determined by ¹⁹F{¹H} NMR integration with CDCl₃ as a solvent. Conversion was calculated by dividing the sum of the products by the sum of the products and starting materials.

Table S-2. Results of Competition Experiments of Ester **1** And Amide **2** in Reaction with 4-Fluorophenyllithium

	Ester 1-d	Ketone 7-d	Alcohol 8-d	Amide 2	Ketone 7	k(amide)/k(ester)
KNP3063	271.94	180.00	0.00	100.00	16.67	0.30
KNP3061	171.75	139.75	0.00	88.94	19.46	0.33
	Ester 1	Ketone 7	Alcohol 8	Amide 2-d	Ketone 7-d	k(amide)/k(ester)
KNP3069	20.45	13.94	0.00	20.05	1.97	0.18
KNP3071	4.81	6.14	0.00	8.65	1.00	0.13
Average						0.21

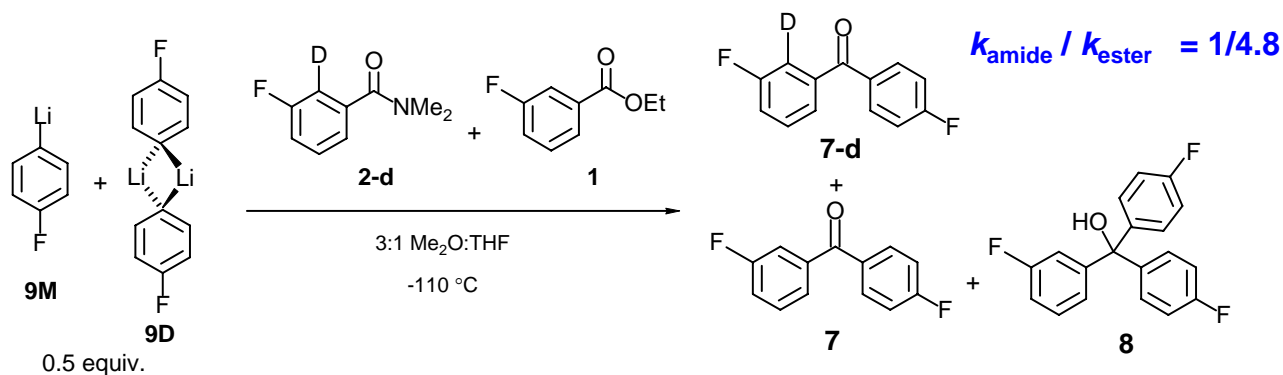


Figure S-24. RINMR competition reaction between amide **2-d** and ester **1** with 0.5 equivalents of 4-fluorophenyllithium (**9**) in 3:1 Me₂O/THF at -110 °C. The numbers are arbitrary peak areas in ¹⁹F NMR spectra.

¹⁹F RINMR of Excess 4-Fluorophenyllithium (9) with Ester 1 at -120 °C. (KNP3097) 4-Fluorophenyllithium (**9**) (0.6 mmol) was prepared in 4 mL of 3:1 Me₂O/THF using the typical RINMR sample preparation procedure. Ester **1** (0.025 mmol, 0.05 mL, 0.5 M in THF) was injected into the NMR sample. The concentrations reported in Figure S-25 are those measured in the actual sample using an internal standard. The reaction was monitored with AQ = 1 s for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s at -120 °C. An equal second portion of ester **1** was injected into the NMR sample. The reaction was monitored with AQ = 1 s for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s at -120 °C.

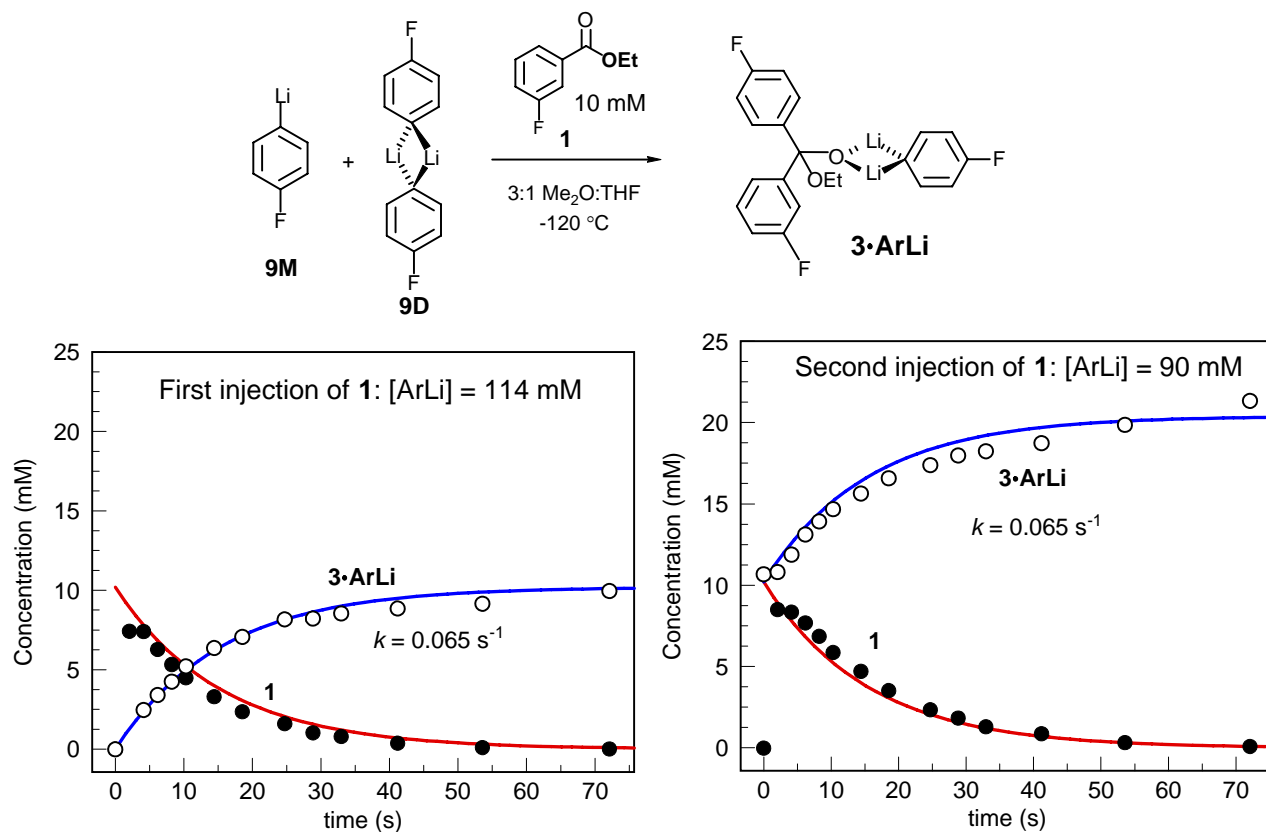


Figure S-25. Time vs. concentration plots for the reaction of 4-fluorophenyllithium (**9**) with two portions of ester **1** in 3:1 Me₂O/THF at -120 °C to form **3·ArLi**. Both rates are identical within experimental error. The Blue and red lines correspond to first-order increase/decrease with $k = 0.065 \text{ s}^{-1}$. Thus the mixed aggregate products do not catalyze or inhibit the reaction between **9** and **1**.

^{19}F RINMR of Excess Mixed Dimer $3\cdot\text{ArLi}$ with Ester **1 at $-120\text{ }^\circ\text{C}$.** (KNP3097) Continuing with sample from above experiment, several portions ester **1** were injected into the NMR sample containing 4-fluorophenyllithium (**9**) at $-120\text{ }^\circ\text{C}$ until conversion to mixed dimer $3\cdot\text{ArLi}$ was complete. Solution concentration of $3\cdot\text{ArLi}$ was measured at 62 mM, and this solution was used for two kinetic experiments to determine the reactivity of the mixed dimer. One portion of ester **1** (0.025 mmol, 0.05 mL, 0.025 M in THF) was injected into the NMR sample. The reaction was monitored with $\text{AQ} = 1\text{ s}$ for 200 spectra with a delay of 1 s, and 390 spectra with a delay of 10 s at $-120\text{ }^\circ\text{C}$. A second equal portion of ester **1** was injected into the NMR sample and the reaction was similarly monitored. Concentrations were measured by comparison of ^{19}F integrations with the internal standard 4-fluorotoluene. Results are reported in Figure S-26.

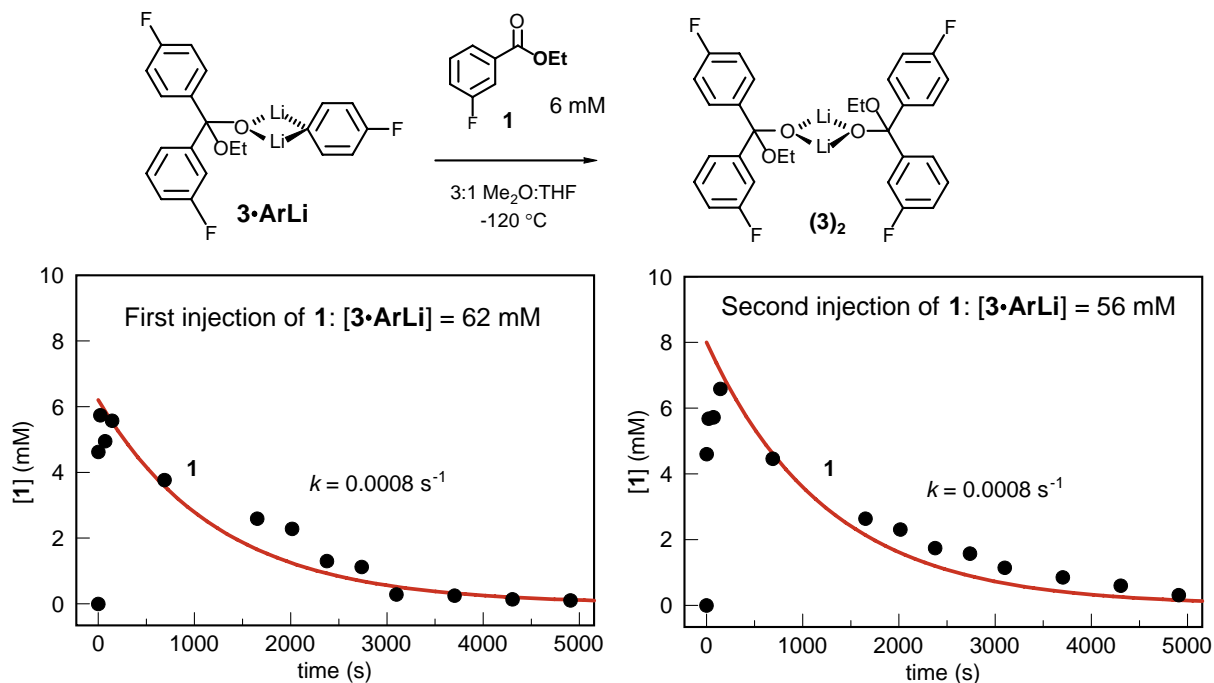


Figure S-26. Time vs. concentration plots for the reaction of preformed mixed dimer $3\cdot\text{ArLi}$ with ester **1** in 3:1 $\text{Me}_2\text{O}:\text{THF}$ at $-120\text{ }^\circ\text{C}$. Two consecutive injections of ester gave the same rate constant within experimental error, so no obvious acceleration or inhibition by the product $(3)_2$.

^{19}F RINMR of Excess 4-Fluorophenyllithium (9**) with Amide **2** at $-120\text{ }^\circ\text{C}$.** (KNP3100) 4-Fluorophenyllithium (**9**) (0.6 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. The concentration of **9** was measured at 124 mM. A solution of amide **2** (0.025 mmol, 0.05 mL, 0.5 M in THF) was injected into the NMR sample. The reaction was monitored with $\text{AQ} = 1\text{ s}$ for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s at $-120\text{ }^\circ\text{C}$. A second equal portion of amide **2** was injected into the NMR sample and the reaction was similarly monitored. Concentrations were measured by comparison of ^{19}F integrations with the internal standard 4-fluorotoluene. Results are reported in Figure S-27.

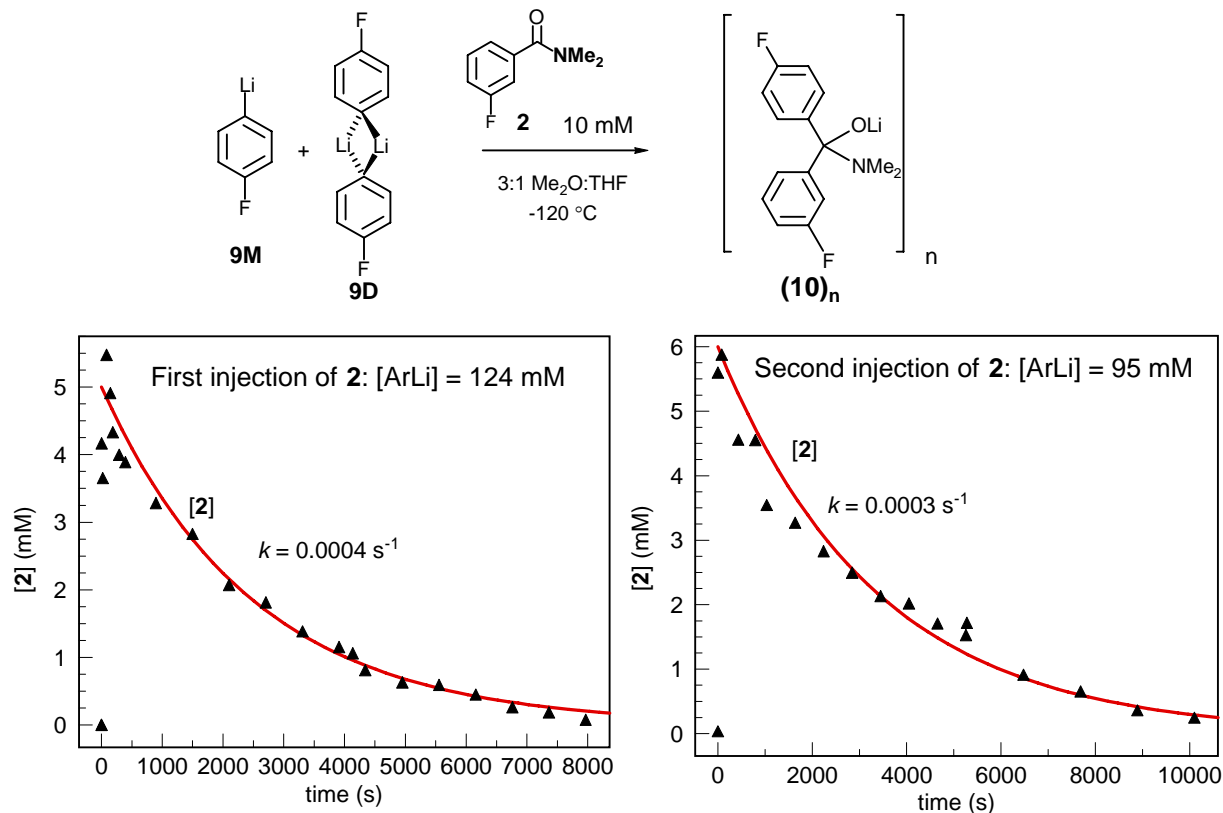


Figure S-27. Time vs. concentration plots for the reaction of 4-fluorophenyllithium (**9**) with two portions of amide **2** in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-120\text{ }^\circ\text{C}$. The red lines are first-order traces with the rate constants shown. No significant inhibition or catalysis of the addition to amide **2** was detected.

¹⁹F RINMR of Excess Mixed Dimer 3·ArLi with Amide 2 at -120 °C. (KNP3102) A solution of 4-fluorophenyllithium (**9**) (ca 0.7 mM) was prepared in 4 mL of 3:1 Me₂O/THF using the typical RINMR sample preparation procedure. Ester **1** was injected in 0.1 mmol increments at -120 °C and the reaction was monitored by ¹⁹F NMR until conversion of ArLi to mixed dimer **3·ArLi** was complete (34 mM, as measured by NMR integration). A solution of amide **2** (0.025 mmol, 0.05 mL, 0.5 M in THF) was injected into the NMR sample. The reaction was monitored with AQ = 1 s for 100 spectra with a delay of 1 s, and 390 spectra with a delay of 10 s at -120 °C. A second equal portion of **2** was injected into the NMR sample. The reaction was monitored with AQ = 1 s for 100 spectra with a delay of 1 s, and 390 spectra with a delay of 10 s at -120 °C. Results are reported in Figure S-28. A summary of the kinetic experiments with **3·ArLi** is shown in Figure S-29.

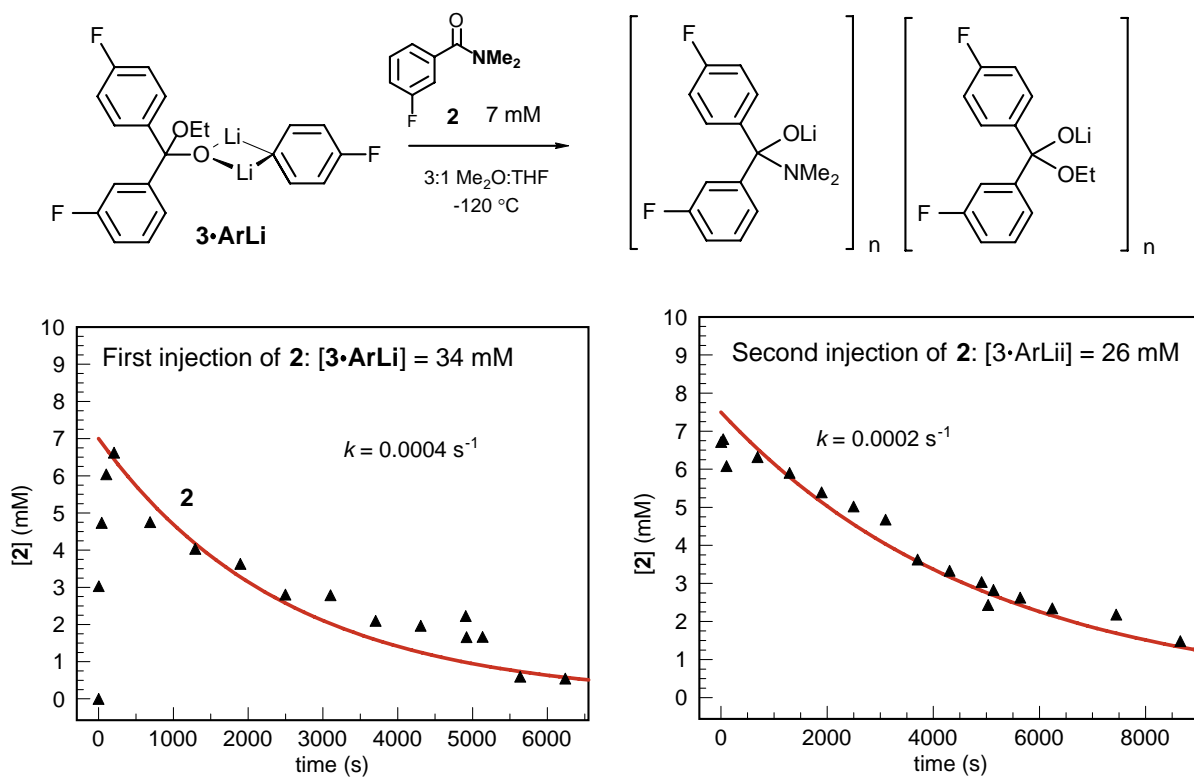


Figure S-28. Time vs. concentration plots for the reaction of mixed dimer **3·ArLi** with two portions of amide **2** in 3:1 Me₂O/THF at -120 °C. The red lines are first-order traces with the rate constants shown. The rate difference in the two injections may be outside experimental error.

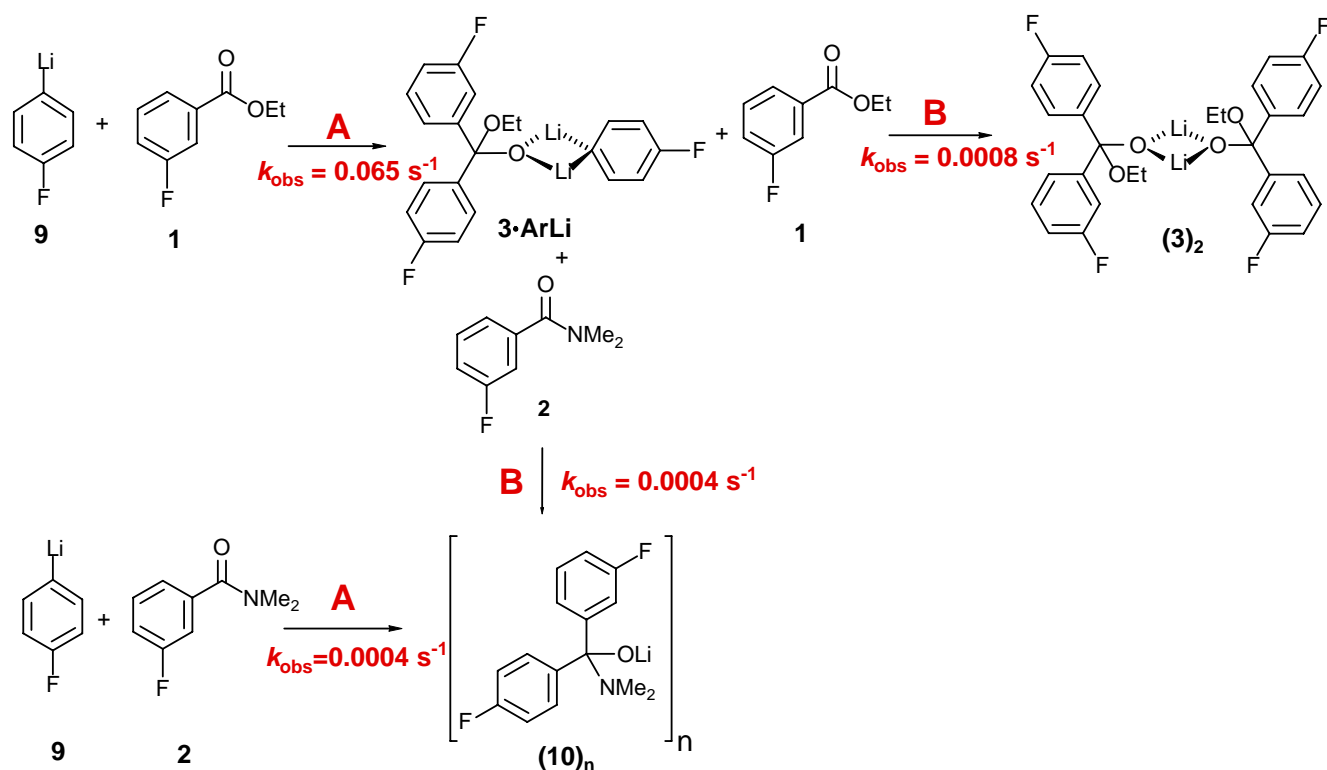


Figure S-29. Scheme detailing reactions occurring in competition experiments between ester **1** and amide **2**. In the initial additions (reactions A: **9** + **1** / **2**) the ester is about 160 times as fast (Figure S-25 and S-27), so when both **1** and **2** are present, more than 99% of the reaction should form **3·ArLi**. In the second phase (reactions B in the scheme: **3·ArLi** + **1** / **2**) the ester is only twice as fast as the amide (Figures S-26 and S-28). Observed rate constants are from ^{19}F RINMR injections of electrophile into lithium reagent at -120°C in 3:1 $\text{Me}_2\text{O}/\text{THF}$.

^{19}F RINMR of PMDTA Complex **9M-P with Ester **1**.** (KNP3209) A solution of PMDTA monomer of 4-fluorophenyllithium (**9M-P**, 0.03 M in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$) was prepared using the typical RINMR sample preparation procedure. Ester **1** (50 mg in 0.2 mL of THF, 0.3 mmol) was injected into the NMR sample containing **9**. The reaction was monitored with $\text{AQ} = 1$ s for 150 spectra with a delay of 1 s, and 340 spectra with a delay of 10 s at -110 °C. ^{19}F , ^7Li , ^{13}C and ^1H NMR spectra were taken of the final solution (94% conversion). Results are reported in Figure S-30.

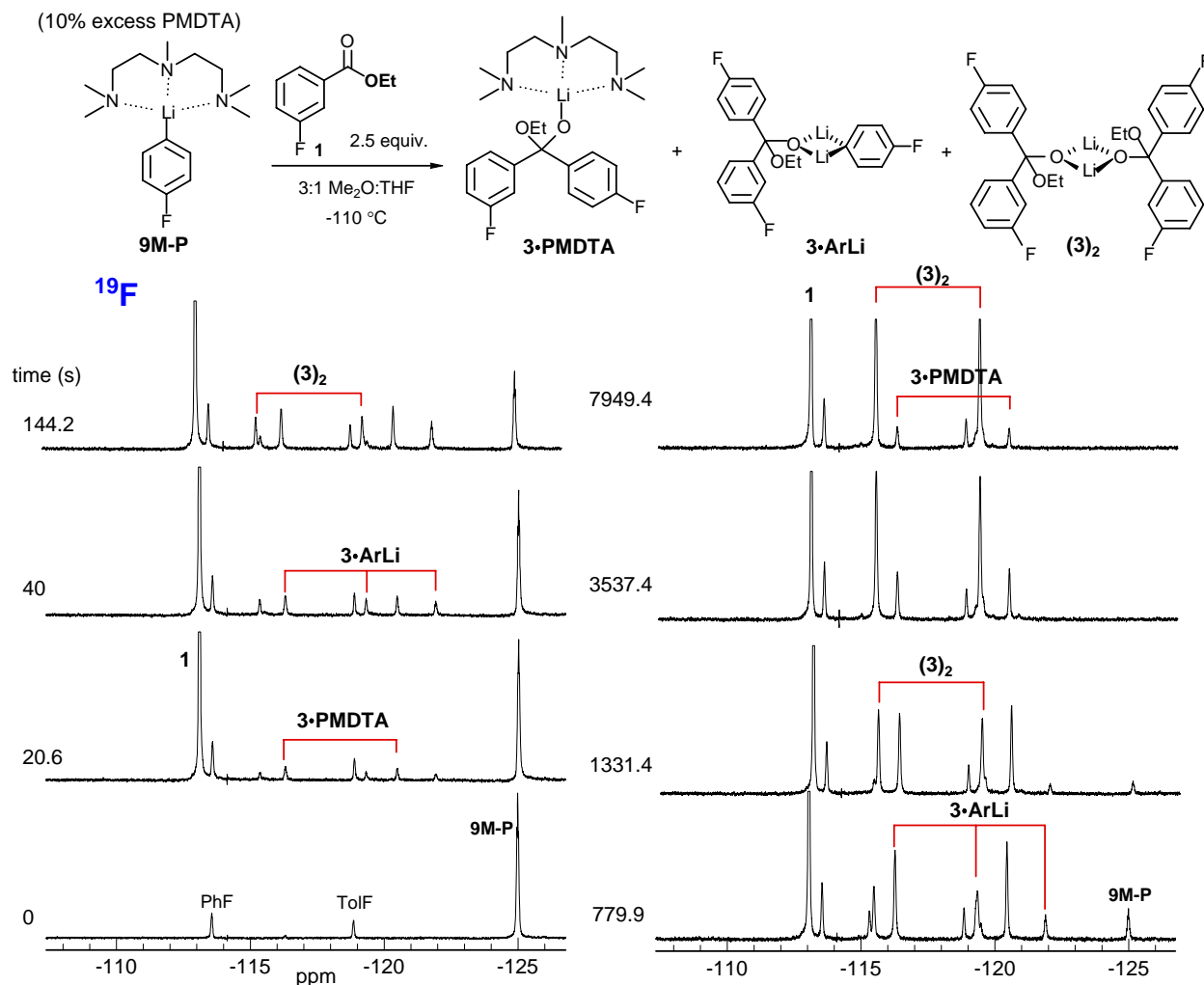


Figure S-30. ^{19}F RINMR of PMDTA monomer **9M-P** with excess ester **1** in the presence of 1.1 equivalents PMDTA in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -110 °C. With a small excess of PMDTA the dissociation of **9M-P** to form THF-solvated **9** is competitive with the reaction of **9M-P** with the ester **1**, leading to a mixture of **3-PMDTA**, **3-ArLi**, and **(3)₂**. Eventually almost all of the PMDTA is expelled to give **(3)₂**.

^{19}F RINMR of PMDTA Complex 9M-P with Ester 1 with excess PMDTA. (KNP3196) A sample of 4-fluorophenyllithium (**9**) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. PMDTA (0.180 mL, 0.9 mmol) was added, the concentration of **9**·PMDTA was measured as 31 mM. A solution of ester **1** (50 mg in 0.2 mL THF, 0.3 mmol) was injected into the NMR sample. The reaction was monitored by ^{19}F NMR with $\text{AQ} = 1$ s for 150 spectra with a delay of 1 s, and 340 spectra with a delay of 10 s at -110°C . Sample spectra and concentration plots are shown in Figure S-31.

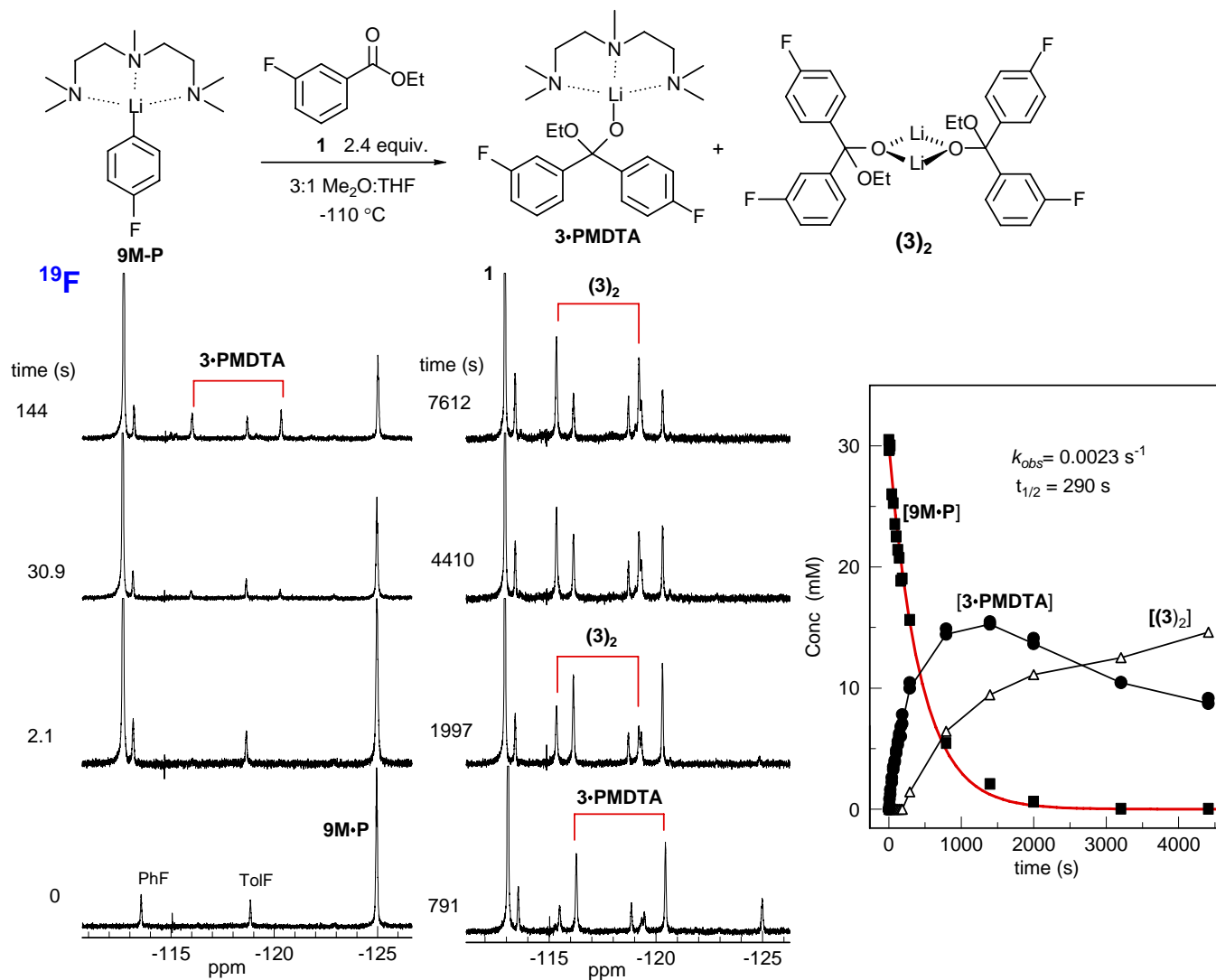


Figure S-31. (KNP3196) ^{19}F RINMR of PMDTA monomer **9M·P** with ester **1** in the presence of ca 6 equivalents of PMDTA in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -110°C . The red line represents first order decay of **9M·P** with $k = 0.0023 \text{ s}^{-1}$.

Long Term Observation of the Reaction of 9M-P with Ester 1. (KNP3226) A solution of 4-fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 Me₂O/THF using the typical RINMR sample preparation procedure. PMDTA (0.18 mL, 0.9 mmol) was added. A solution of ester **1** (50 mg in 0.2 mL THF, 0.3 mmol) was injected into the NMR sample. The reaction was monitored by ¹⁹F NMR with AQ = 1 s for 20 spectra with a delay of 1 s, and 470 spectra with a delay of 180 s at -110 °C. Results are reported in Figure S-32.

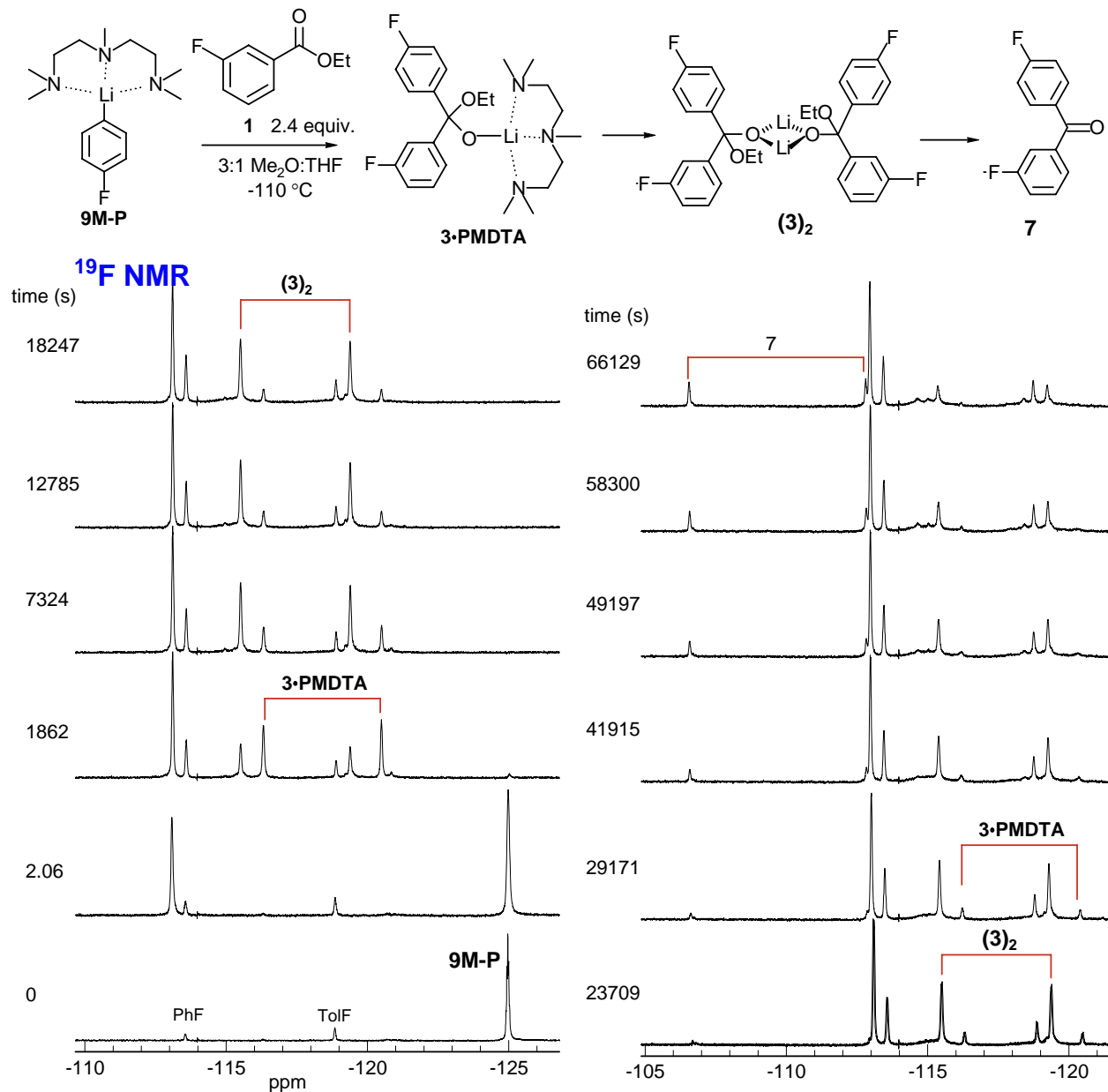


Figure S-32 ¹⁹F RINMR (long term observation) of monomeric PMDTA complex **9M-P** with ester **1** in 3:1 Me₂O/THF at -110 °C in the presence of 200% excess PMDTA. No significant amount of **3·ArLi** was formed. Ketone formation began before equilibrium between **3·PMDTA** and **(3)₂** was reached.

^{19}F RINMR of 4-Fluorophenyllithium (9**) with Ethyl Formate.** (KNP3278a) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. Ethyl formate (40 mg in 0.2 mL THF, 0.5 mmol) was injected into the NMR sample containing **9**. The reaction was monitored with $\text{AQ} = 1$ s for 200 spectra with a delay of 0.3 s, and 290 spectra with a delay of 10 s at -137°C . Results are reported in Figure S-33.

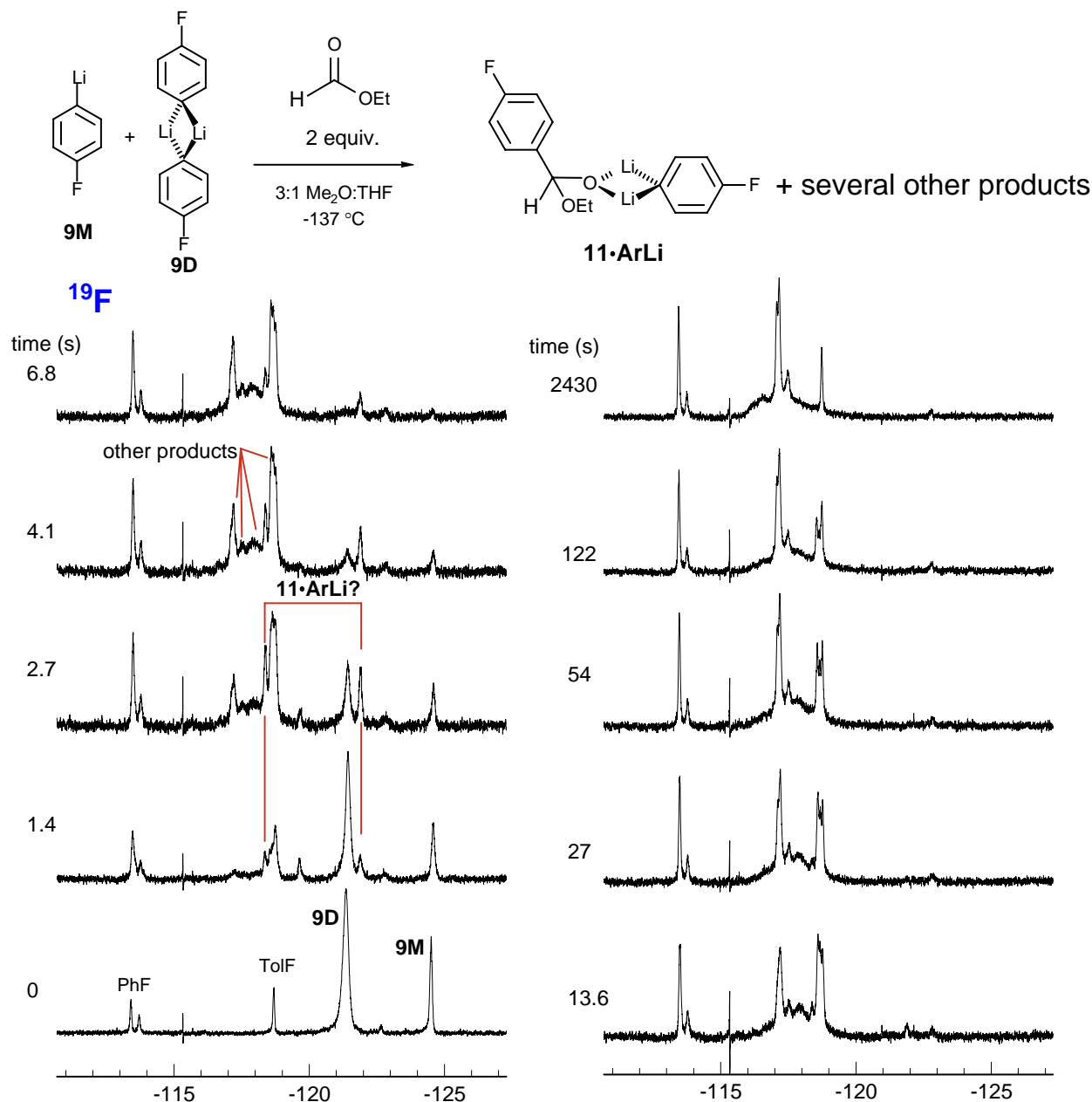


Figure S-33. ^{19}F RINMR of the injection of two equivalents of ethyl formate into a solution of 4-fluorophenyllithium (**9**) in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -137°C (the rate at -137°C is similar to rate of addition to **1** at -110°C). The rate of addition of **9** to ethyl formate is, as expected, faster than addition to ester **1**, but slower than reaction with ketone **5** (Figures S-40 and S-42 below). However, the addition of **9** is slower than interconversion of **9M** and **9D**, so no direct information about which aggregate reacts can be obtained (Curtin-Hammett). The marked peaks were assigned to the mixed dimer **11·ArLi**, which was not further characterized. As was seen with the mixed dimer **3·ArLi**, the proposed **11·ArLi** is also less reactive than is **9**. Several other unidentified intermediates were also formed.

^{19}F RINMR of 4-Fluorophenyllithium (9) with Methyl Trifluoroacetate. (KNP3294, 3185 higher temperature) 4-Fluorophenyllithium (9) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. Methyl trifluoroacetate (45 mg in 0.2 mL 1:1 $\text{Et}_2\text{O}/\text{THF}$) was injected into the NMR sample. The reaction was monitored with $\text{AQ} = 1$ s for 200 spectra with a delay of 0.3 s, and 200 spectra with a delay of 10 s at -130 °C (Figure S-33a). The sample was warmed to -78 °C and ^{19}F , ^6Li , and ^{13}C NMR spectra were taken. The main product was a 1:1 mixture of two tetrahedral intermediates, as shown by the doubling of most peaks in the ^{19}F and ^{13}C NMR spectra (Figure S-34b). The sample was quenched with aqueous NH_4Cl , extracted with ether, dried over MgSO_4 , filtered and rotary evaporated, yielding trifluoromethyl 4-fluorophenyl ketone (95%). Results are reported in Figure S-34.

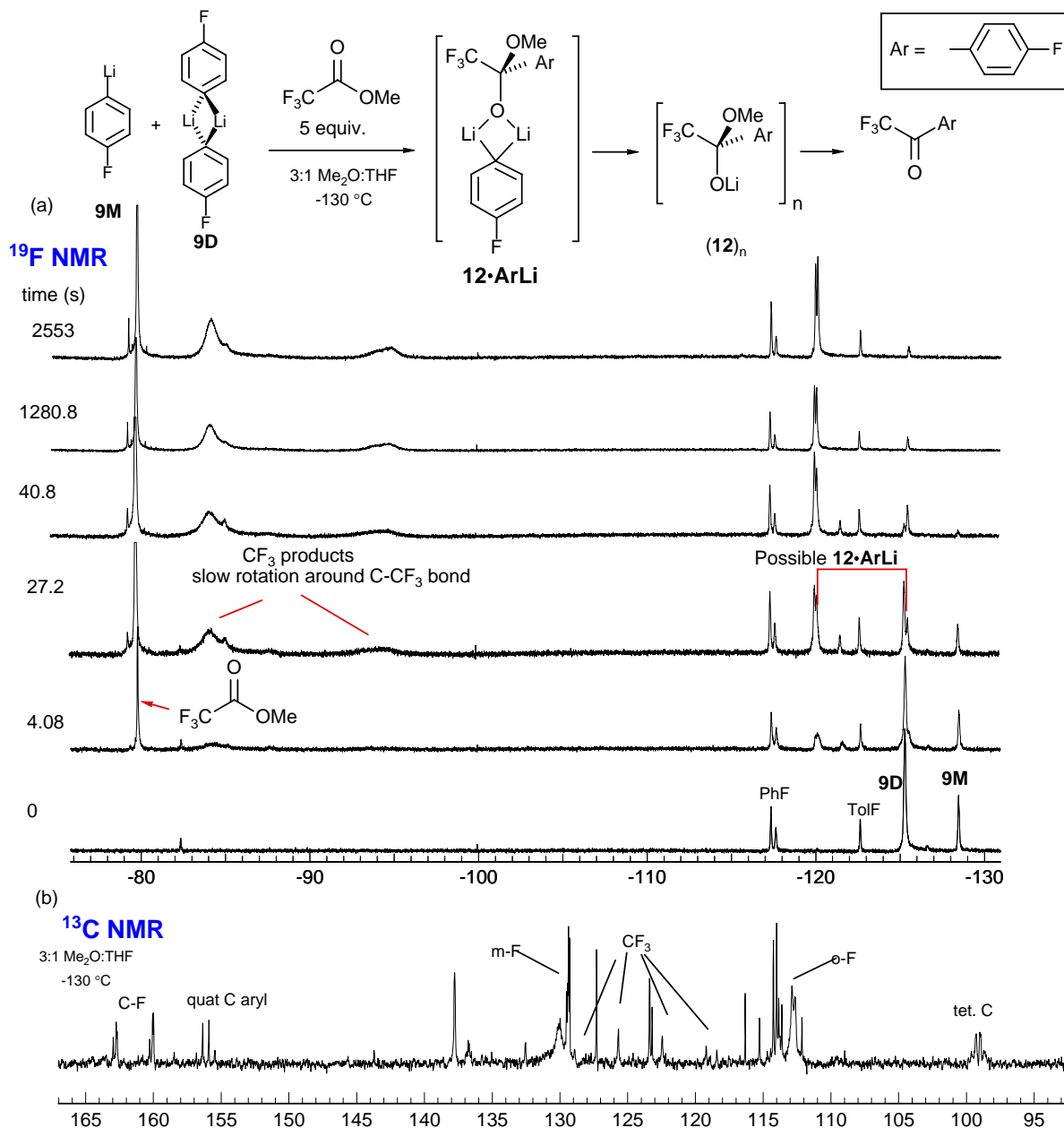
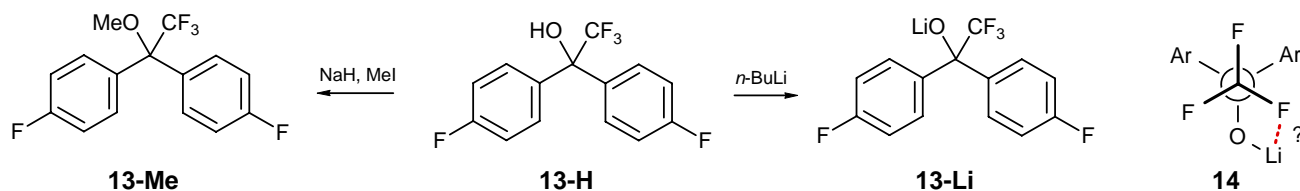


Figure S-34. (a) ^{19}F RINMR of the injection of 5 equivalents of $\text{CF}_3\text{CO}_2\text{Me}$ into 4-fluorophenyllithium (9) in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -130 °C. The CF_3 fluorines in the tetrahedral intermediates are non-equivalent due to slow rotation of the CF_3 group. This is not a special property of the lithium species due to Li-F bonding, since rotation is also slow in the related lithium alkoxide **Q13-Li** (Figure S-35), the alcohol **Q13-H** and the methyl ether **Q13-Me** (Figure S-36). (b) ^{13}C NMR of the reaction solution before the final quench.

Lithium alkoxide of 2,2,2-Trifluoro-1,1-bis(4-fluorophenyl)ethan-1-ol (13-Li). A solution of **13-Li** was prepared by addition of **13-H** (0.05 g, 0.17 mmol) to a 10 mm NMR tube that was sealed with a septum, and parafilm, and purged with argon. Freshly distilled THF (1 mL) was added and the tube was cooled in a dry ice/acetone bath. Me₂O (3 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). The ¹³C chemical shift thermometer (10% ¹³C labeled tris(trimethylsilyl)methane, 0.002 mL),^[S1a] an internal standard for concentrations (2,6-dimethyl-1-fluorobenzene, 0.005 mL), and *n*-BuLi (0.08 mL, 0.2 mmol, 2.5 M/hexane) were added to the NMR tube at -78 °C.

2,2,2-Trifluoro-1,1-bis(4-fluorophenyl)-1-methoxy-ethane (13-Me). NaH (60% dispersion in mineral oil, 180 mg, 4.6 mmol) was added portionwise to a solution of 2,2,2-trifluoro-1,1-bis(4-fluorophenyl)ethan-1-ol (1.2g, 4.16 mmol) in DMF (8 mL) at 0 °C. The solution was warmed to room temperature and stirred for 20 min. Methyl iodide (0.29 mL, 4.6 mmol) was added dropwise and the mixture stirred for 2 h. The mixture was poured into a mixture of Et₂O and H₂O (30 mL each) and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO₄, and the solvent was removed under reduced pressure to give **13-Me** as a colorless oil (1.26 g, 4.16 mmol, 100%) that was used without any further purification.



Restricted Rotation of Trifluoromethyl Group. A variable temperature NMR study of **13-Li** is shown in Figure S-35. The appearance of a 1:2 ratio of doublet and triplet below -100 °C indicates slow rotation around the F₃C-C bond. Below -120 °C the upfield signal begins to split into two signals, most reasonably interpreted in terms of a desymmetrization of the otherwise symmetric structure, perhaps by Li-F interactions with one of the fluorines, as in structure **14**. The upfield signal appears broader, perhaps due to Li-F J-coupling, although no coupling could be resolved at accessible temperatures. Although other explanations are also possible, the relatively sharp Ar-F signal at δ -188 argues against an explanation involving slow exchange between multiple aggregates.

A Li-F interaction is not the principal reason for the slow rotation of the CF₃ group in **Q13-Li**, since the alcohol **Q13-H** also shows decoalescence of the fluorine signals at a similar temperature. A F-H hydrogen bond is not the principal reason for this slow rotation, since the methyl ether **Q13-Me** also shows slow rotation (Figure S-36).

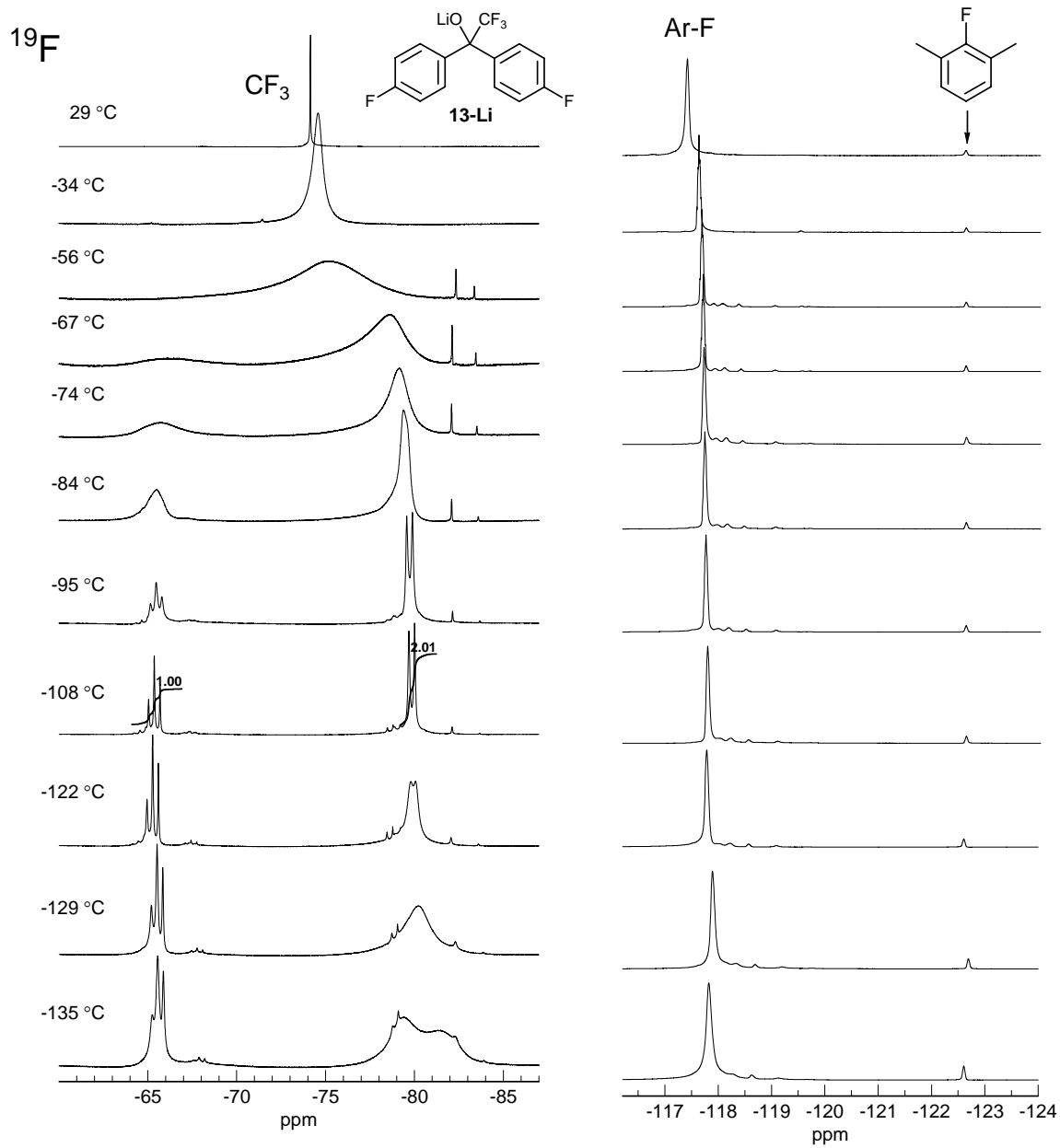


Figure S-35. Variable temperature ^{19}F NMR study of **13-Li** in 3:1 $\text{Me}_2\text{O}:\text{THF}$.

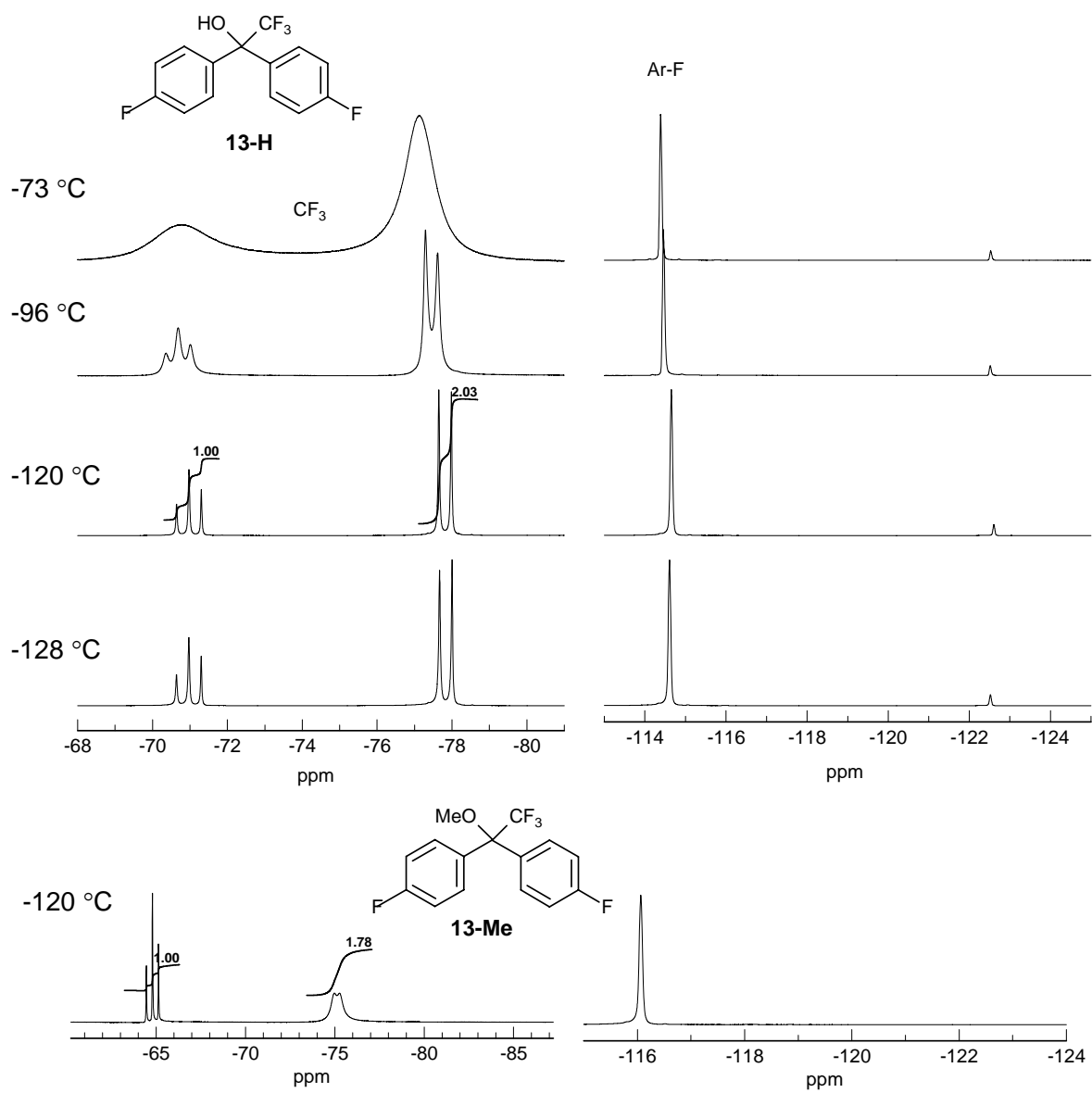


Figure S-36. Low temperature ^{19}F NMR spectra of **Q13-H** and **Q13-Me** in 3:1 $\text{Me}_2\text{O}:\text{THF}$.

^{19}F RINMR of 4-Fluorophenyllithium (9**) with *S*-iso-Propyl 3-Fluorobenzothioate.** (KNP3298) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. *S*-iso-Propyl 3-fluorobenzothioate (45 mg in 0.2 mL THF, 0.45 mmol) was injected into the NMR sample containing **9**. The reaction was monitored with $\text{AQ} = 1$ s for 200 spectra with a delay of 0.3 s, and 290 spectra with a delay of 10 s -130 °C. The sample was stored overnight at -78 °C and ^{19}F NMR spectra were taken. The sample was quenched with aqueous NH_4Cl , extracted with ether, dried over MgSO_4 , filtered and rotary evaporated, yielding the tertiary alcohol (95%). Spectra are shown in Figure S-37.

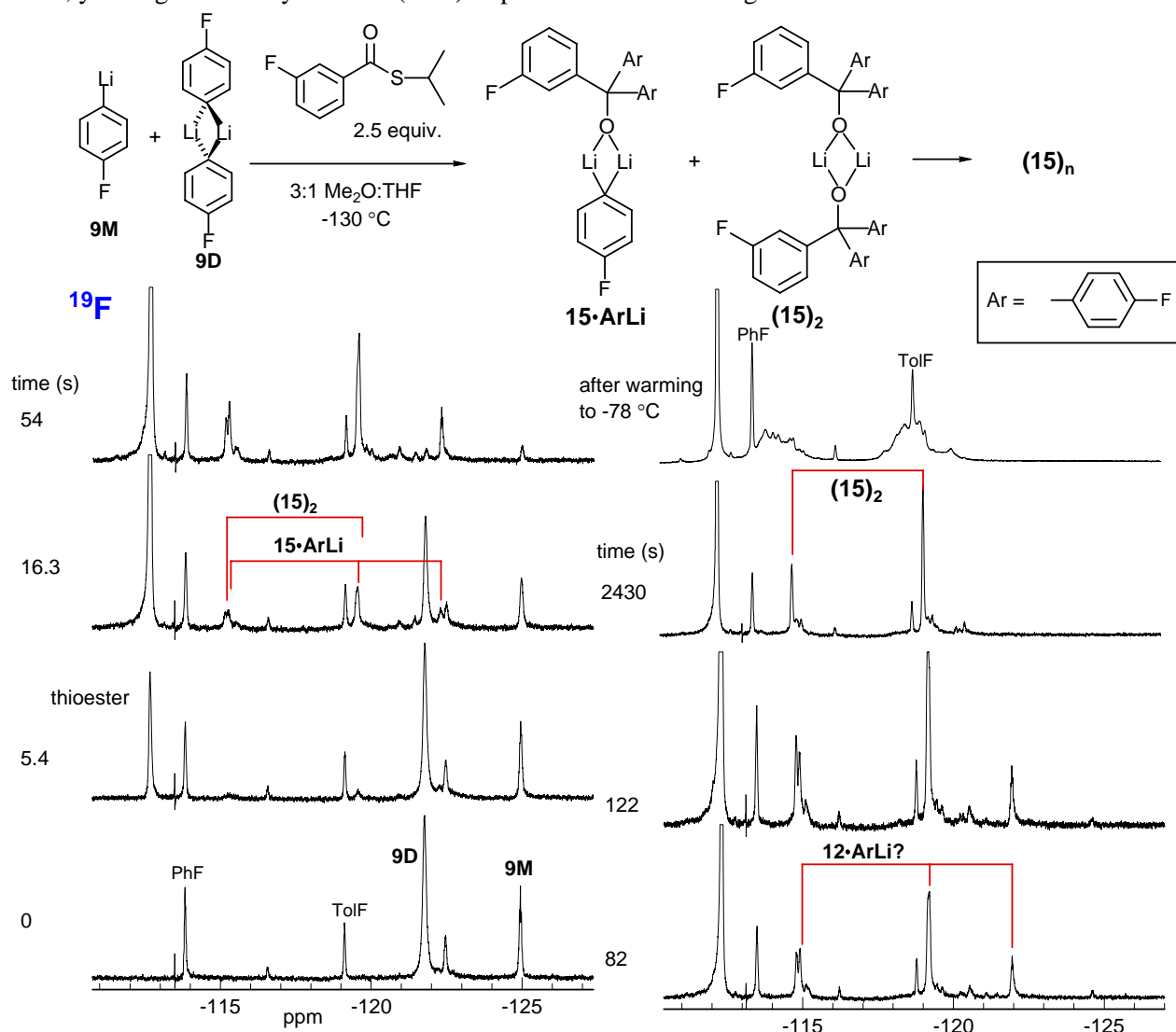


Figure S-37. ^{19}F RINMR of the injection of 1.5 equivalents of *S*-iso-propyl 3-fluorobenzothioate into a solution of **9** in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -130 °C. The two intermediates were identified as the mixed dimer **15·ArLi** (1:2:1 ratio of ^{19}F peaks) and the homodimer **(15)₂** (1:2 ratio of signals) of the tertiary alkoxide **15** formed by double addition of ArLi to the thioester. No tetrahedral intermediates were detected. These assignments were supported by an experiment in which two of the same intermediates (**15·ArLi** and **(15)₂**) were formed by addition of **9** to 3,4'-difluorobenzophenone (**7**) (Figure S-38). Both intermediates are metastable, since they disappeared on warming to -78 °C, being replaced by a complex set of resonances.

^{19}F RINMR of 4-Fluorophenyllithium (9**) with 3,4'-Difluorobenzophenone (**7**).** (KNP3300) 4-Fluorophenyllithium (**9**) (0.15 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. 3,4'-Difluorobenzophenone (31 mg in 0.2 mL 1:1 $\text{Et}_2\text{O}/\text{THF}$, 0.15 mmol) was injected into the NMR sample. The reaction was monitored with $\text{AQ} = 1$ s for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s at -124°C . Results are reported in Figure S-38.

Injection of LiS-i-Pr into the end solution at -124°C formed no new fluorine-containing species, although additional species were formed when the sample was warmed above -90°C .

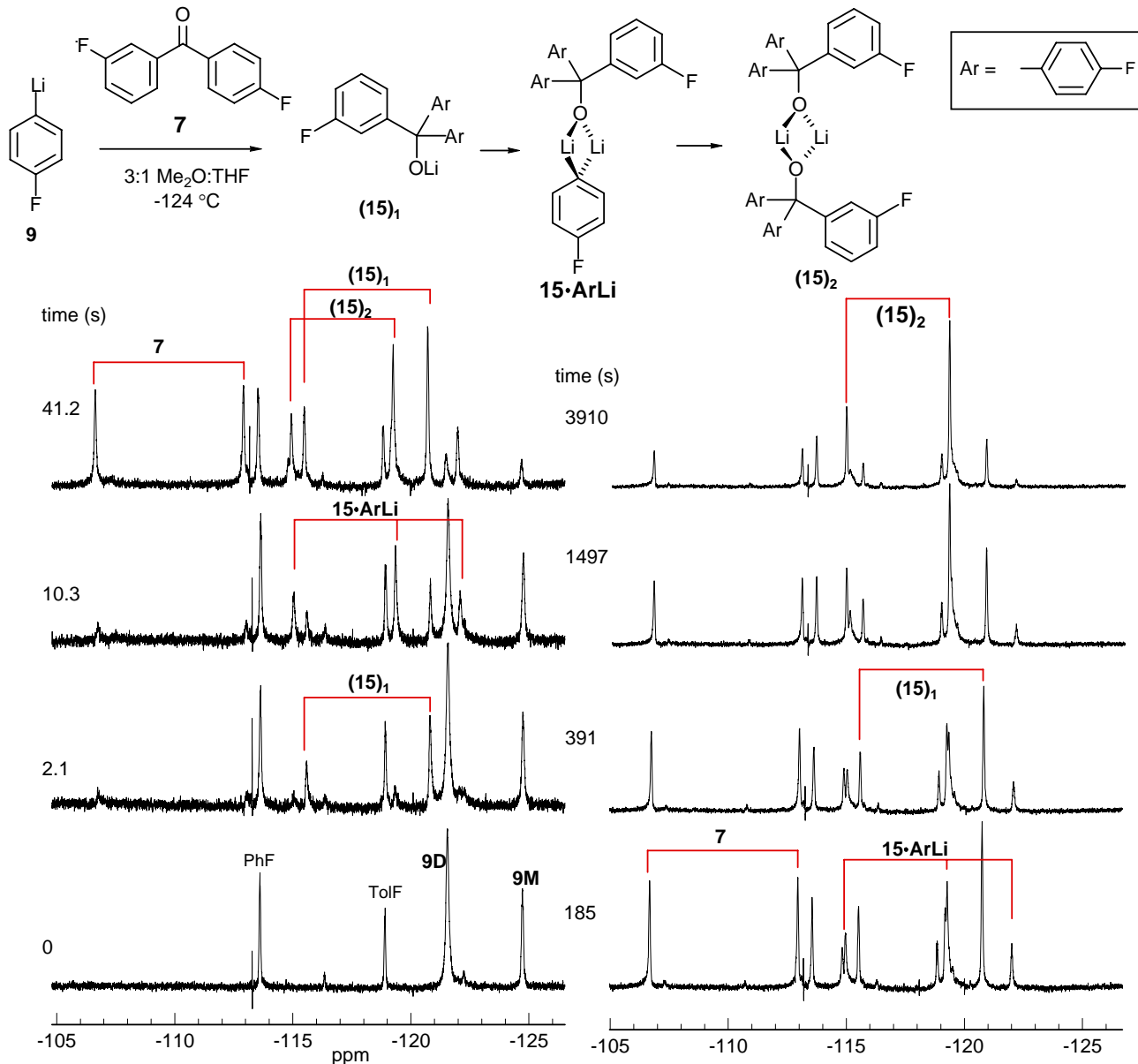


Figure S-38. ^{19}F RINMR of the injection of 3,4'-difluorobenzophenone (**7**) into a solution of **9** in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -124°C . The kinetic product is the alkoxide monomer (**15**)₁ (thus **9M** is probably the reactive ArLi species), which then forms both mixed dimer **15**·ArLi and the homodimer (**15**)₂.

¹⁹F RINMR of 4-Fluorophenyllithium (9) with Excess 3-Fluoroacetophenone (5) at -115 °C.

(KNP3188) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 Me₂O/THF using the typical RINMR sample preparation procedure. 3-Fluoroacetophenone (0.40 g in 0.2 mL THF, 0.6 mmol) was injected into the NMR sample at -115 °C. The reaction was monitored with AQ = 1 s for 100 spectra with a delay of 1 s, and 390 spectra with a delay of 30 s at -115 °C. ¹⁹F, ⁷Li, ¹³C and ¹H NMR spectra were taken of the final solution. Spectra are shown in Figure S-39.

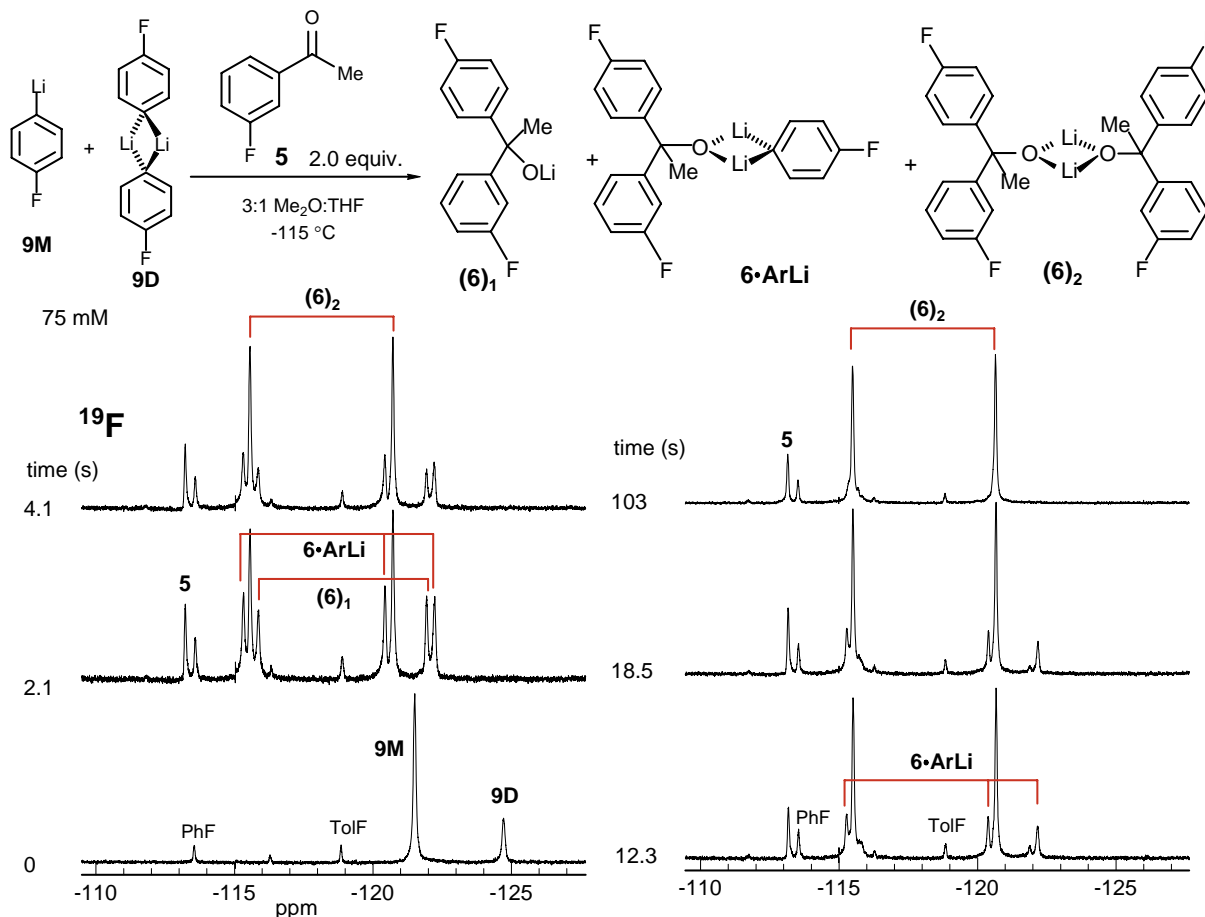


Figure S-39. (KNP3188) ¹⁹F RINMR of 4-fluorophenyllithium (**9**) with 2 equivalents of 3-fluoroacetophenone (**5**) in 3:1 Me₂O/THF at -115 °C. The ArLi is has fully reacted when the first spectrum was measured at 2.1 seconds. The intermediates visible at this point were the mixed dimer **6•ArLi**, and two aggregates of the alkoxide **6**, very likely the monomer and dimer. Thus here also, the mixed dimer **6•ArLi** is substantially less reactive than the ArLi **9** towards **5**. After several minutes only **(6)₂** remained.

^{19}F RINMR of 4-Fluorophenyllithium (9**) with 3-Fluoroacetophenone (**5**) at $-135\text{ }^\circ\text{C}$ (under Curtin Hammett conditions).** (KNP3258) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. 3-Fluoroacetophenone (10 mg in 0.1 mL THF, 0.15 mmol) was injected into the NMR sample at $-135\text{ }^\circ\text{C}$. The reaction was monitored with $\text{AQ} = 1\text{ s}$ for 200 spectra with a delay of 0.3 s, and 290 spectra with a delay of 10 s at $-135\text{ }^\circ\text{C}$. Results are reported in Figure S-40.

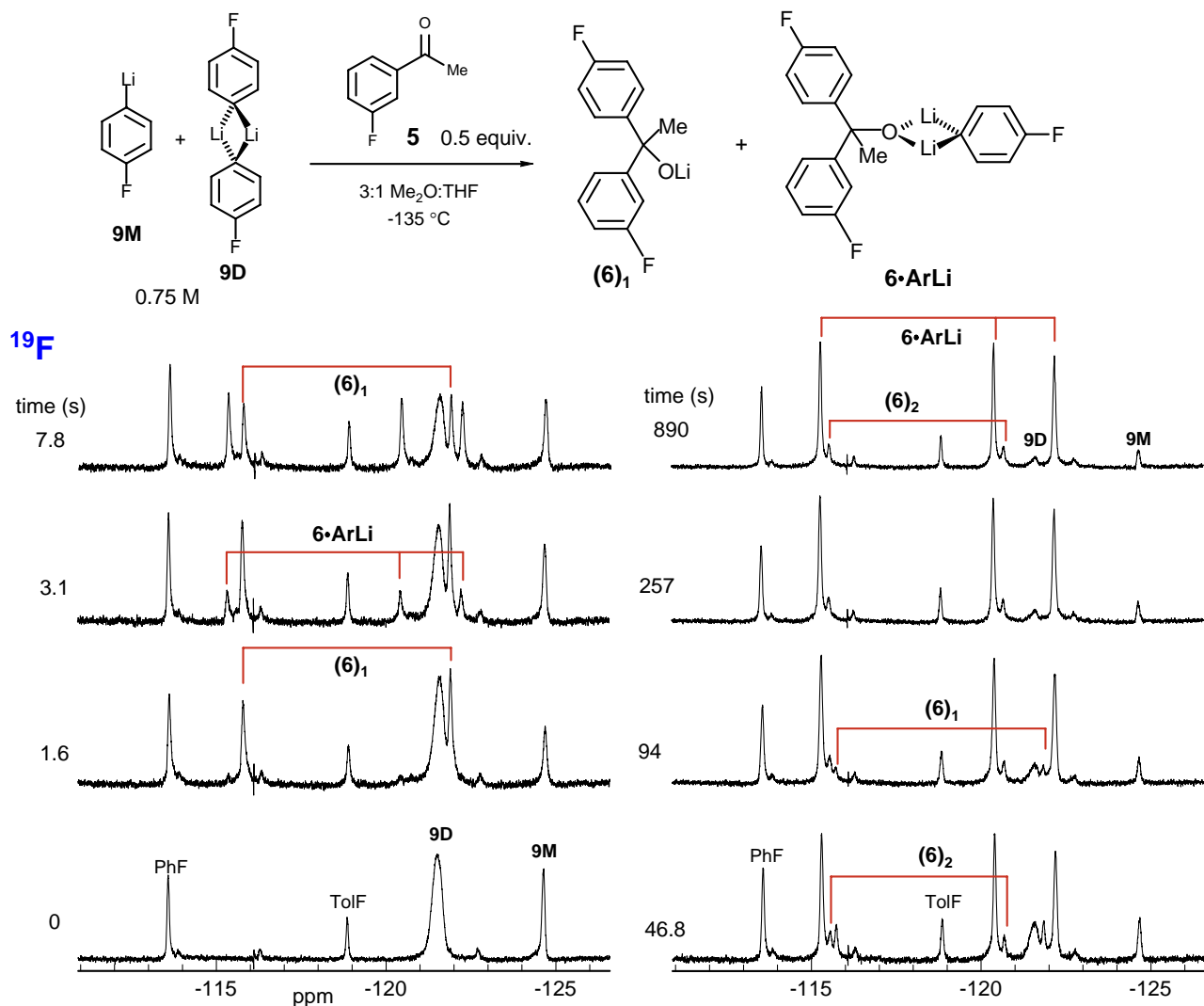


Figure S-40 ^{19}F RINMR spectra of the reaction of 4-fluorophenyllithium (**9**) with 0.5 equivalent of 3-fluoroacetophenone **5** in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-135\text{ }^\circ\text{C}$. In this experiment, carried out at $20\text{ }^\circ\text{C}$ lower temperature than that of Figure S-39 and with excess lithium reagent, the monomeric alkoxide (**6**)₁ is the sole kinetic product. (**6**)₁ then cross dimerizes with **9** to form **6**·ArLi with a half life of ca 7 seconds. Only traces of the homodimer (**6**)₂ is formed at this temperature during this 15-minute experiment. The cross-dimerization to form **6**·ArLi is thus substantially faster than the homodimerization of (**6**)₁.

^{19}F RINMR of the Reaction of 4-Fluorophenyllithium (9**) with 3-Fluoroacetophenone (**5**) at $-140\text{ }^\circ\text{C}$.** (KNP3258) 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. 3-Fluoroacetophenone **5** (25 mg in 0.2 mL of THF, 0.75 mmol) was injected into the NMR sample at $-140\text{ }^\circ\text{C}$. The reaction was monitored with $\text{AQ} = 1\text{ s}$ for 200 spectra with a delay of 0.3 s, and 290 spectra with a delay of 10 s at $-135\text{ }^\circ\text{C}$. Spectra are shown in Figure S-41.

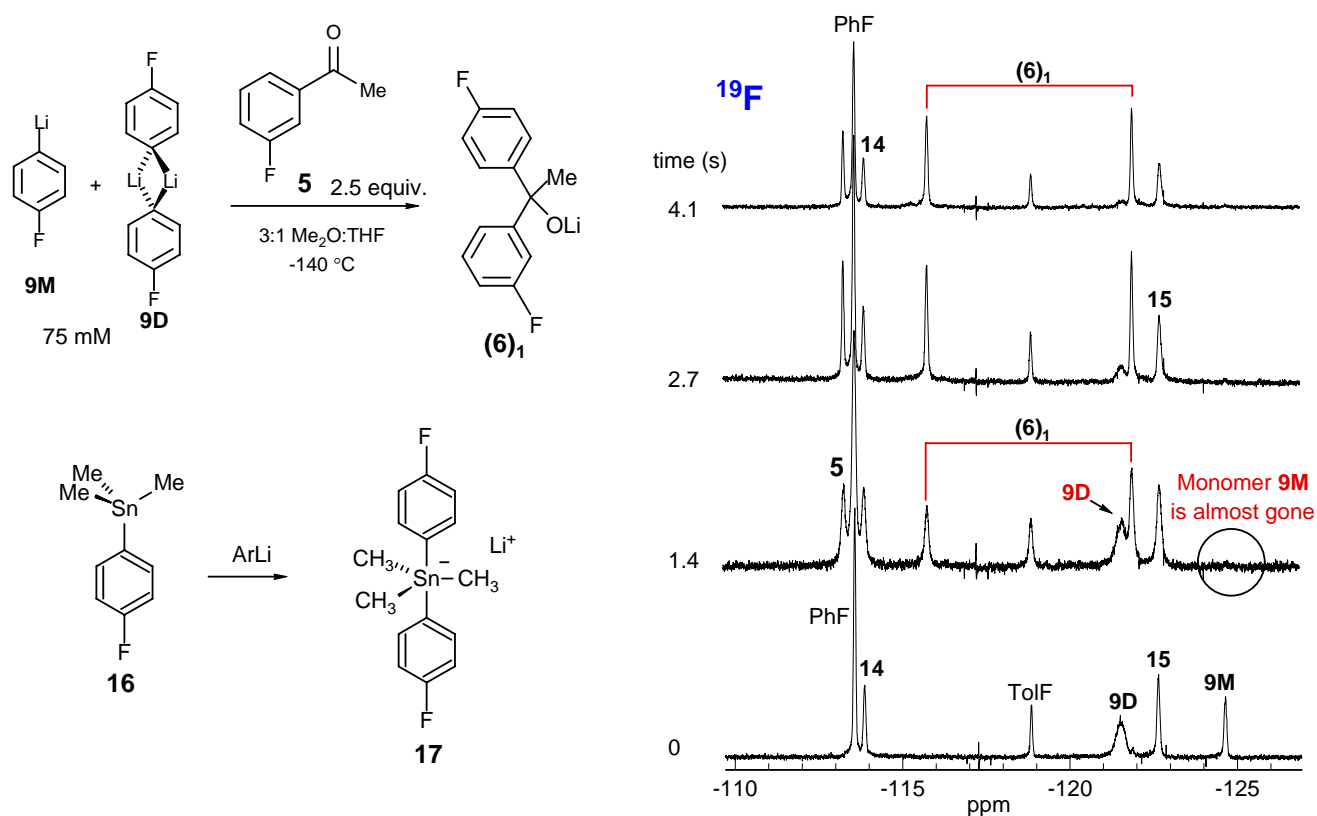


Figure S-41. ^{19}F RINMR of 4-fluorophenyllithium (**9**) with 2.5 equivalents of 3-fluoroacetophenone (**5**) in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at $-140\text{ }^\circ\text{C}$. The almost complete disappearance of the ^{19}F signal for **9M** unambiguously shows that **9M** is more reactive towards ketone **5** than is **9D**. No mixed dimer $\mathbf{6}\cdot\text{ArLi}$ is formed in this experiment because the rate of addition of **9M** to ketone is much faster than either the hetero or homo-dimerization of $(\mathbf{6})_1$. There is a trace of **9M** detectable at 1.4 and 2.7 seconds, indicating that the rate of **9D** going to **9M** is almost competitive with the rate of reaction of **9M** with the ketone. The peak at -122.7 is due to a small amount of tin ate complex $\mathbf{17}^{[\text{S13}]}$ formed as a result of a stoichiometry error (ratio of $n\text{-BuLi}/\mathbf{16}$ was < 1.0). There is a possibility that the lithium counterion of the ate complex could participate in the process as a Lewis acid catalyst for ketone addition. We are operating so close to the practical limits of temperature, ketone solubility, solvent freezing, and time in this experiment that only two out of a total of 5 experiments gave a comparable result, but these appear to be sound. The others showed clear signs of inadequate mixing, probably due to crystallization or gelling of ketone and/or solvent. Even this experiment showed less excess ketone than was injected, presumably some has solidified during the injection and was not visible in the NMR spectrum.

^{19}F RINMR of the Reaction of Alcohol **6-OH with 4-Fluorophenyllithium (**9**).** 4-Fluorophenyllithium (**9**) (0.3 mmol) was prepared in 4 mL of 3:1 $\text{Me}_2\text{O}/\text{THF}$ using the typical RINMR sample preparation procedure. 1-(3'-Fluorophenyl)-1-(4'-fluorophenyl) ethan-1-ol **6-OH** (0.07 g in 0.3 mL THF, 0.3 mmol) was injected into the NMR sample at -110°C . The reaction was monitored with $\text{AQ} = 1$ s for 200 spectra with a delay of 1 s, and 290 spectra with a delay of 10 s. Results are reported in Figure S-42.

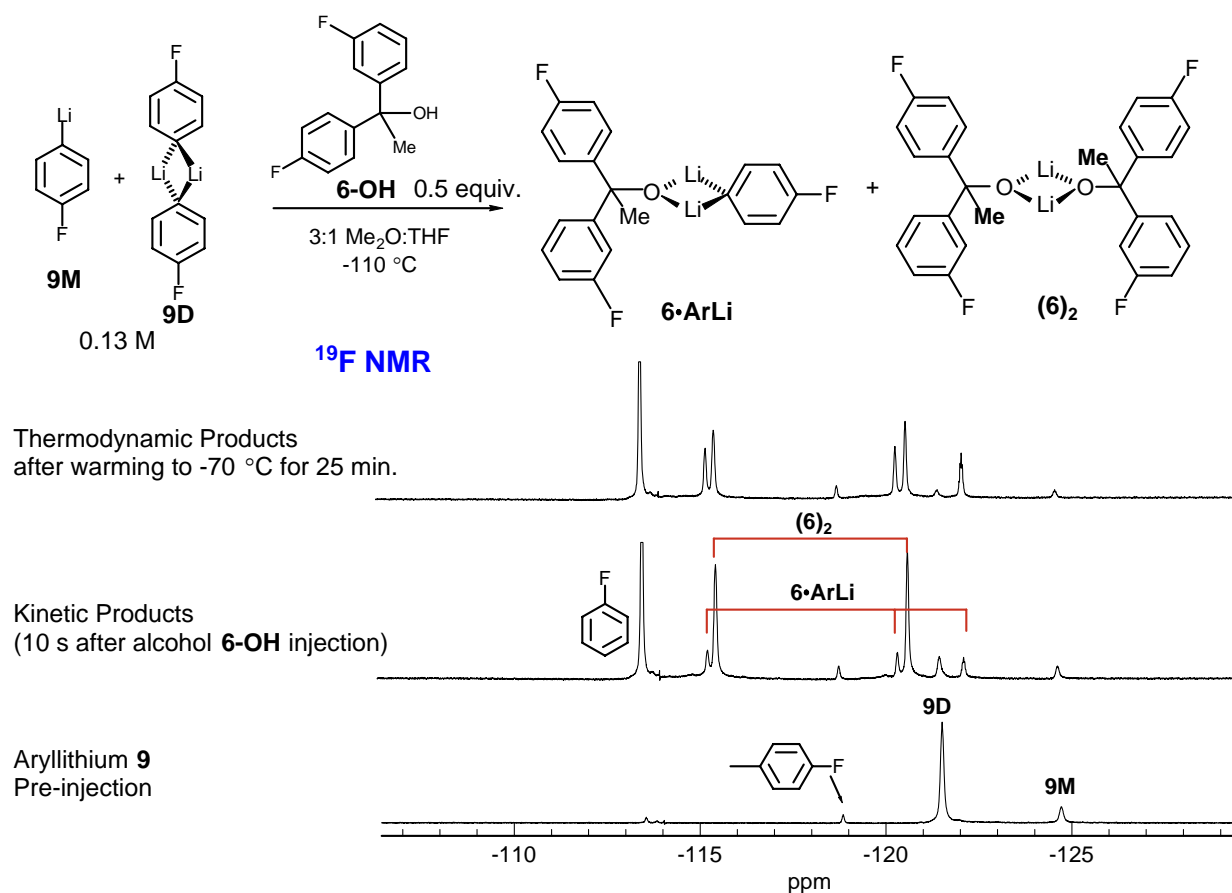
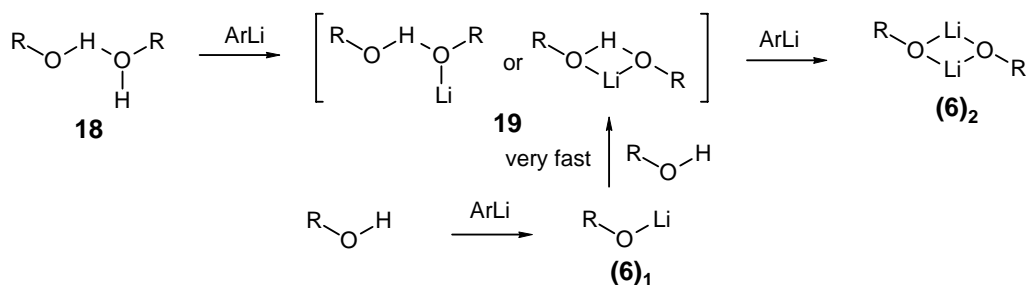


Figure S-42. ^{19}F NMR of kinetic product mixture from injection of 0.5 equivalent of alcohol into a solution of 4-fluorophenyllithium (**9**) in 3:1 $\text{Me}_2\text{O}/\text{THF}$ at -110°C . No alkoxide monomer (**6**)₁ is formed at this temperature, nor at -135°C , where dimerization of (**6**)₁ is known to be slow (see Figure S-40). Our rationalization of this observation is that either the hydrogen bonded dimer **18** which might be present at these low temperatures is deprotonated to directly form **19**, which is deprotonated a second time to form (**6**)₂ without ever forming (**6**)₁, or, perhaps more likely, (**6**)₁ forms a strong hydrogen bonded dimer **19** with alcohol more rapidly than the deprotonation process, and deprotonation by **9M** then leads directly to (**6**)₂.



¹⁹F RINMR of 2,5-Difluorophenyllithium with Ester 1 at -115 °C. 1,3-Dimethyl-2-fluorobenzene (0.005 mL, 0.01M, internal standard) was added to 4 mL of a freshly prepared 3:1 Me₂O/Et₂O solution of 2,5-difluorophenyllithium (prepared from 1,4-difluorobenzene and n-BuLi) in a dried thin-walled 10 mm NMR tube. ¹³C, ¹⁹F and ⁷Li spectra were acquired at -115 °C to check concentration and sample integrity. Following the general RI-NMR procedure, ester 1 (0.06 mL, 0.4 mmol) was injected at -115 °C. Spectra were obtained every 2 sec for 200 spectra followed by every 20 sec for 300 spectra. The concentrations of the reagents were determined from the first scan after injection to be 0.07 M for 2,5-difluorophenyllithium and 0.11 M for the ester. Results are reported in Figure S-43.

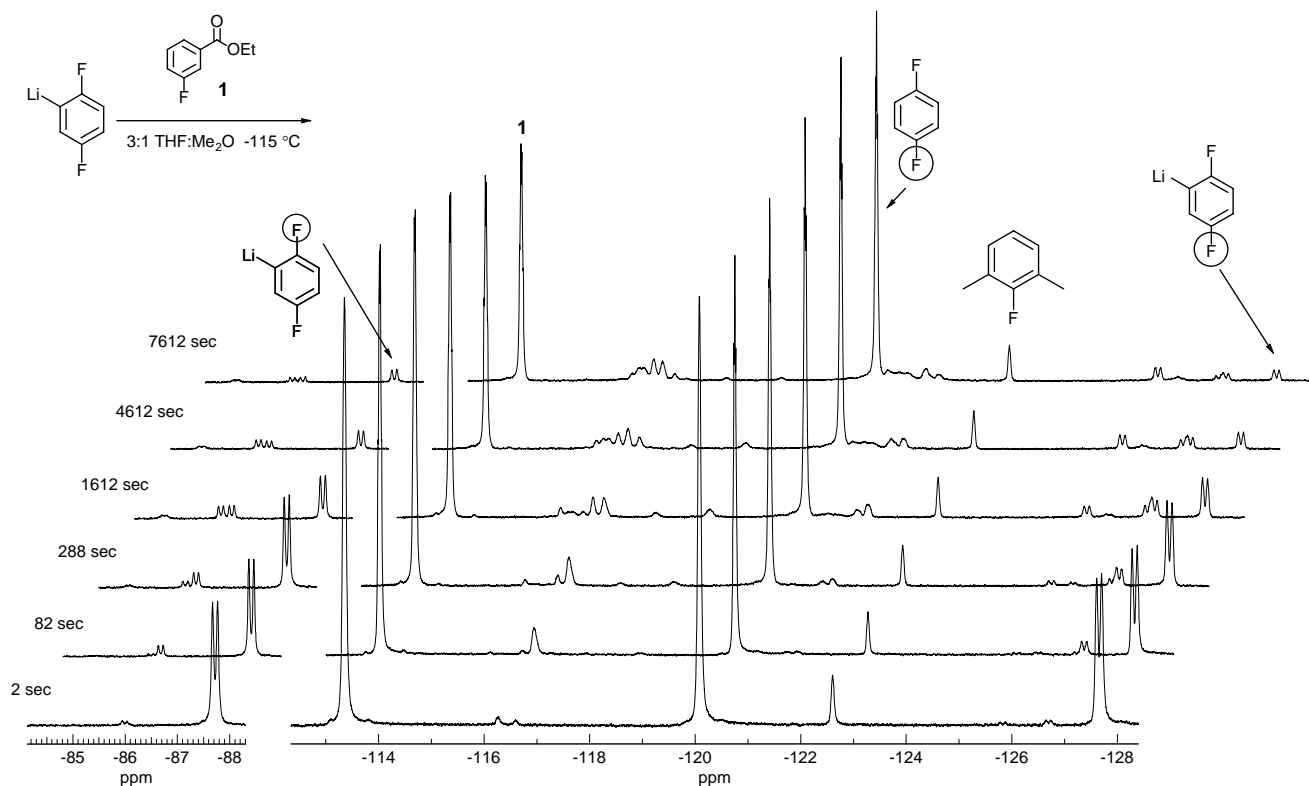


Figure S-43. ¹⁹F RINMR experiment of the injection of 1.6 equivalents of ester **1** into a solution of 2,5-difluorophenyllithium in 4 mL of 3:1 Me₂O/THF at -115 °C. The half life for the disappearance of the lithium reagent is ca 860 sec, thus almost 100 times slower than for 4-fluorophenyllithium (**9**). Thus *E,Z*-isomerization of the starting ester cannot be the rate-determining step for both **9** and 2,5-difluorophenyllithium. This does not rule out rate determining isomerization for reaction of **1** with **9**, but does argue against it.

Lithium Iodide Titration of Amide 2 and Ester 1. (KNP3051) Four 5 mm NMR tubes were sealed with a septa and parafilm, and purged with nitrogen. THF (0.2 mL), methyllithium (0, 0.02 mL, 0.04 mL and 0.14 mL of a 1.4 M solution in ether) and methyl iodide (0, 0.002, 0.004, 0.012 mL, respectively) were added to the NMR tubes at room temperature and cooled in a dry ice/acetone bath to form solutions of anhydrous LiI. Me₂O (~0.7 mL) was distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). 4-Fluorotoluene (0.001 mL) as internal chemical shift standard, 0.06 mL of a 1.5 M solution of amide **2**, and 15 μL of ester **1** was added and ¹⁹F NMR was taken at -80 °C. Spectra are shown in Figure S-44.

HMPA Titration of Amide 2 and Ester 1 with 2.0 Equivalents LiI (KNP3051) A 5 mm NMR tube was sealed with a septa and parafilm, and purged with nitrogen. THF (0.2 mL), methyllithium (0.14 mL of a 1.4 M solution in ether) and methyl iodide (0.012 mL) was added to each NMR tube at room temperature and cooled in a dry ice/acetone bath. Me₂O (~0.7 mL) is distilled via cannula into the NMR tube from a graduated conical cylinder containing *n*-BuLi (for drying). 4-Fluorotoluene (0.001 mL) as internal chemical shift standard, 0.06 mL of a 1.5 M solution of amide **2**, and 15 μL of ester **1** was added. ¹⁹F NMR was taken at -80 °C with 0.5 (0.017 mL), 1.0 (0.034 mL), 2.0 (0.068 mL) equivalents of HMPA and are shown in Figure S-44.

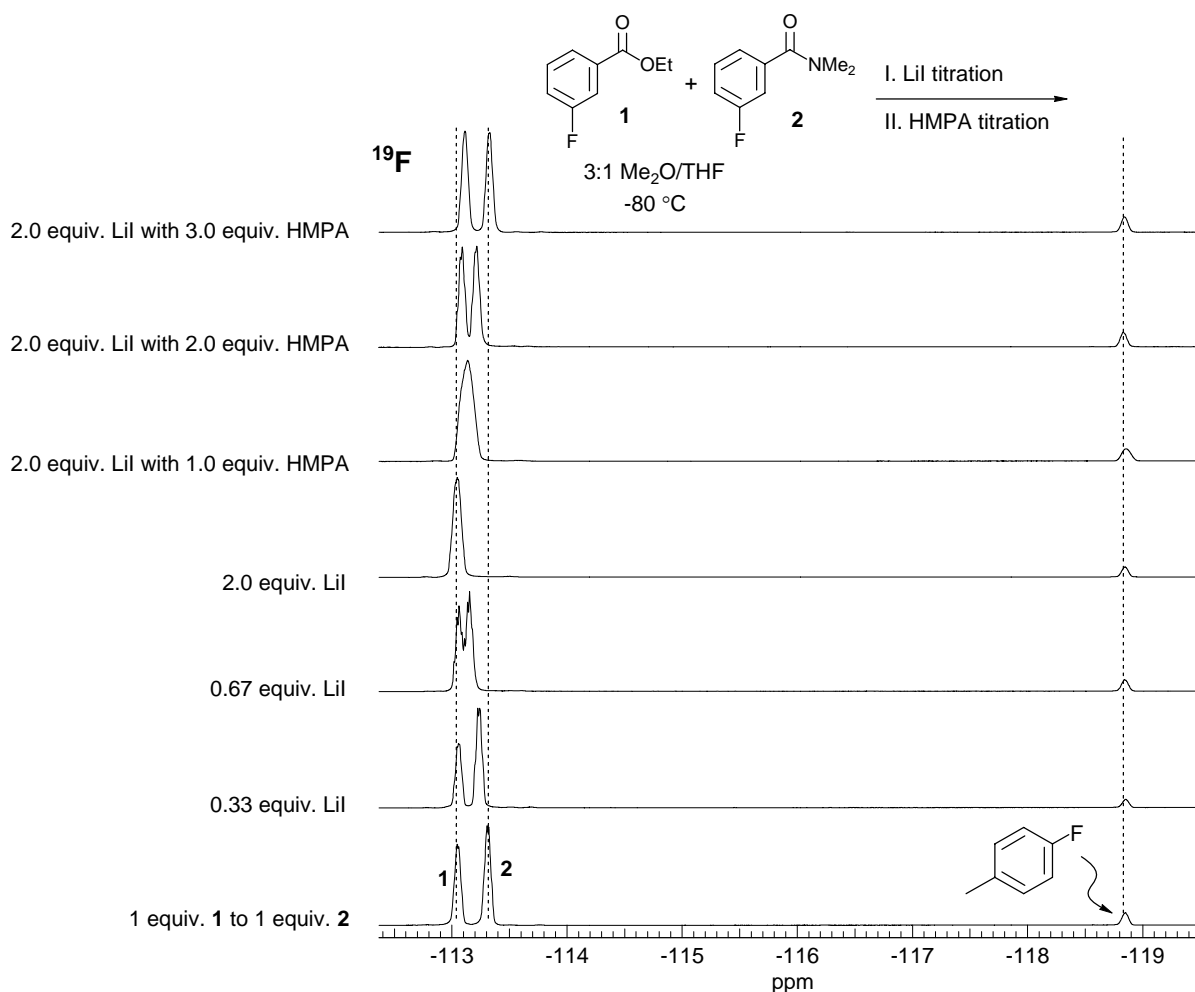
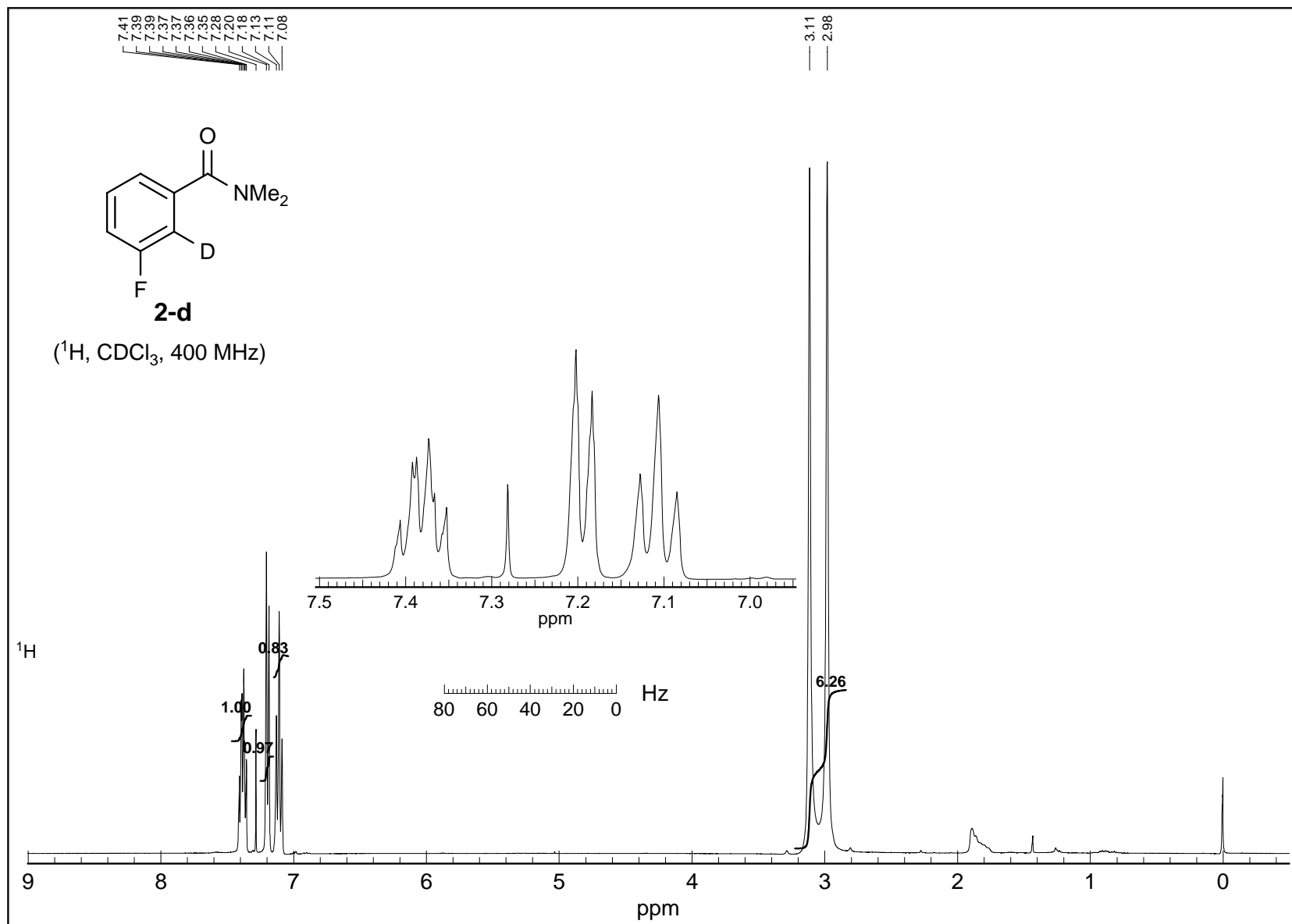
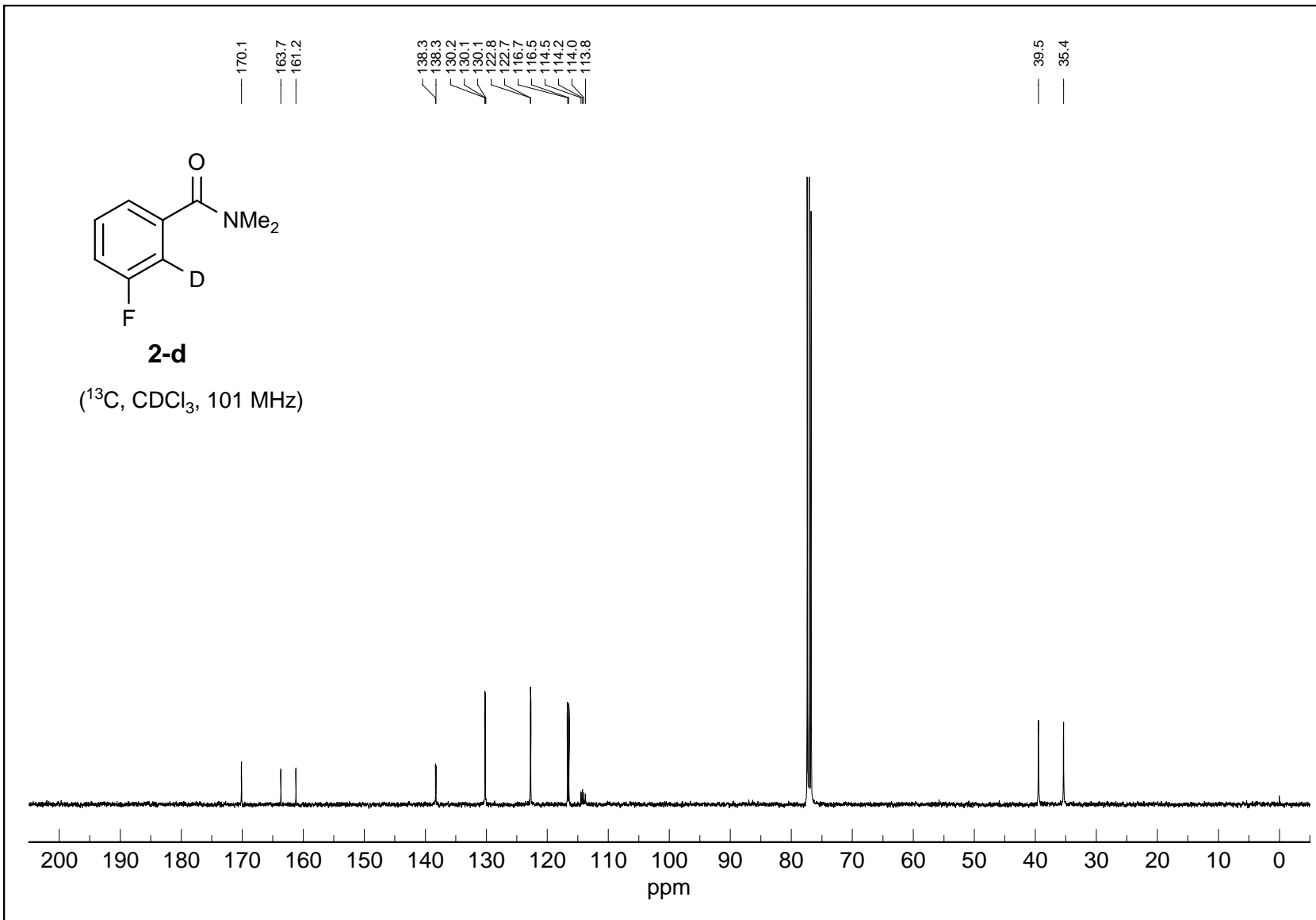
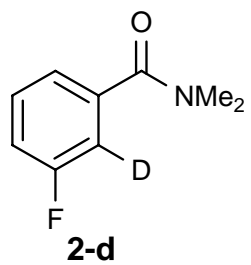


Figure S-44. LiI titration of amide **2** and ester **1**, followed by an HMPA titration to show reversibility. 4-Fluorotoluene was used as an internal chemical shift standard and the dotted lines indicate initial chemical shifts. The amide **2** appears to complex with the LiI. The ester **1** shows no significant effects of added LiI, it is presumably less basic than solvent THF.

S6. NMR Data and Spectra

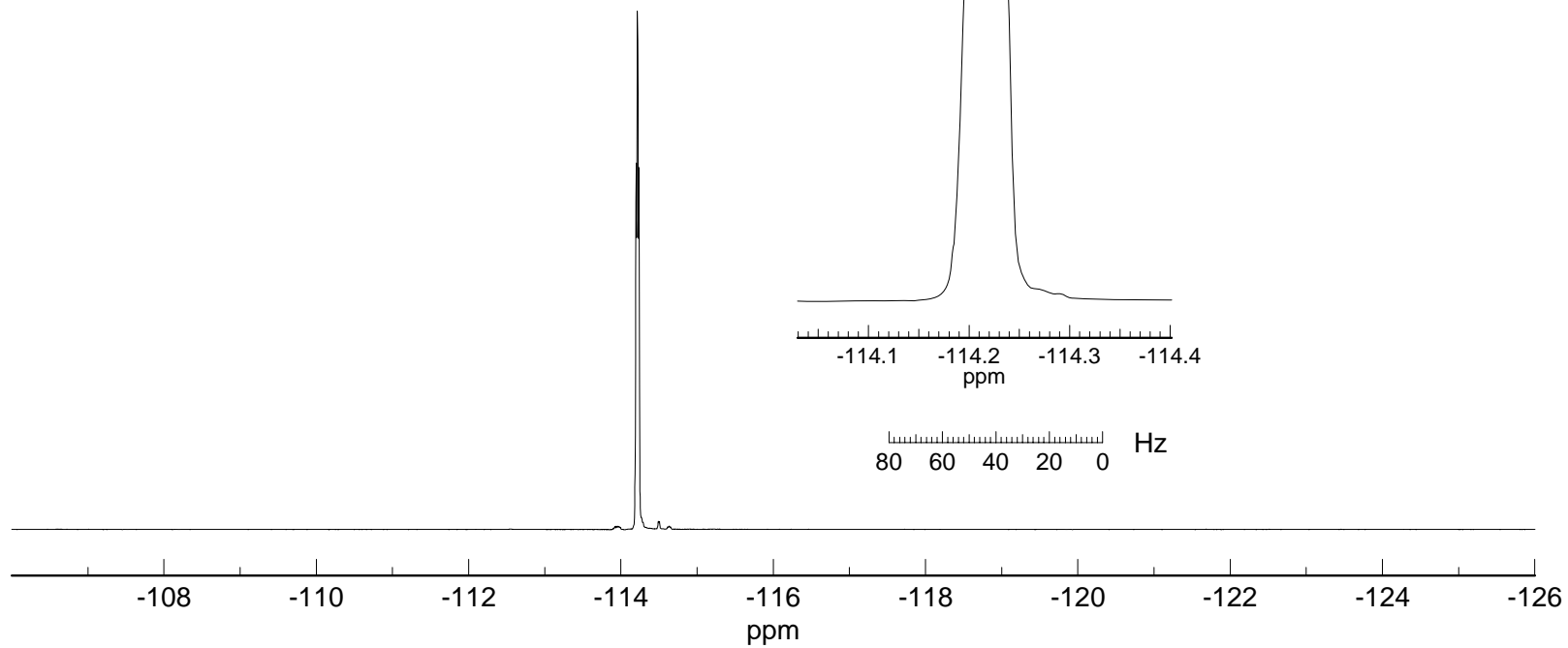


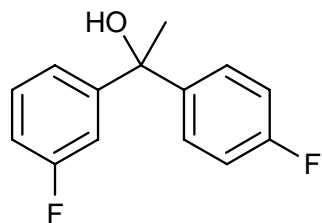




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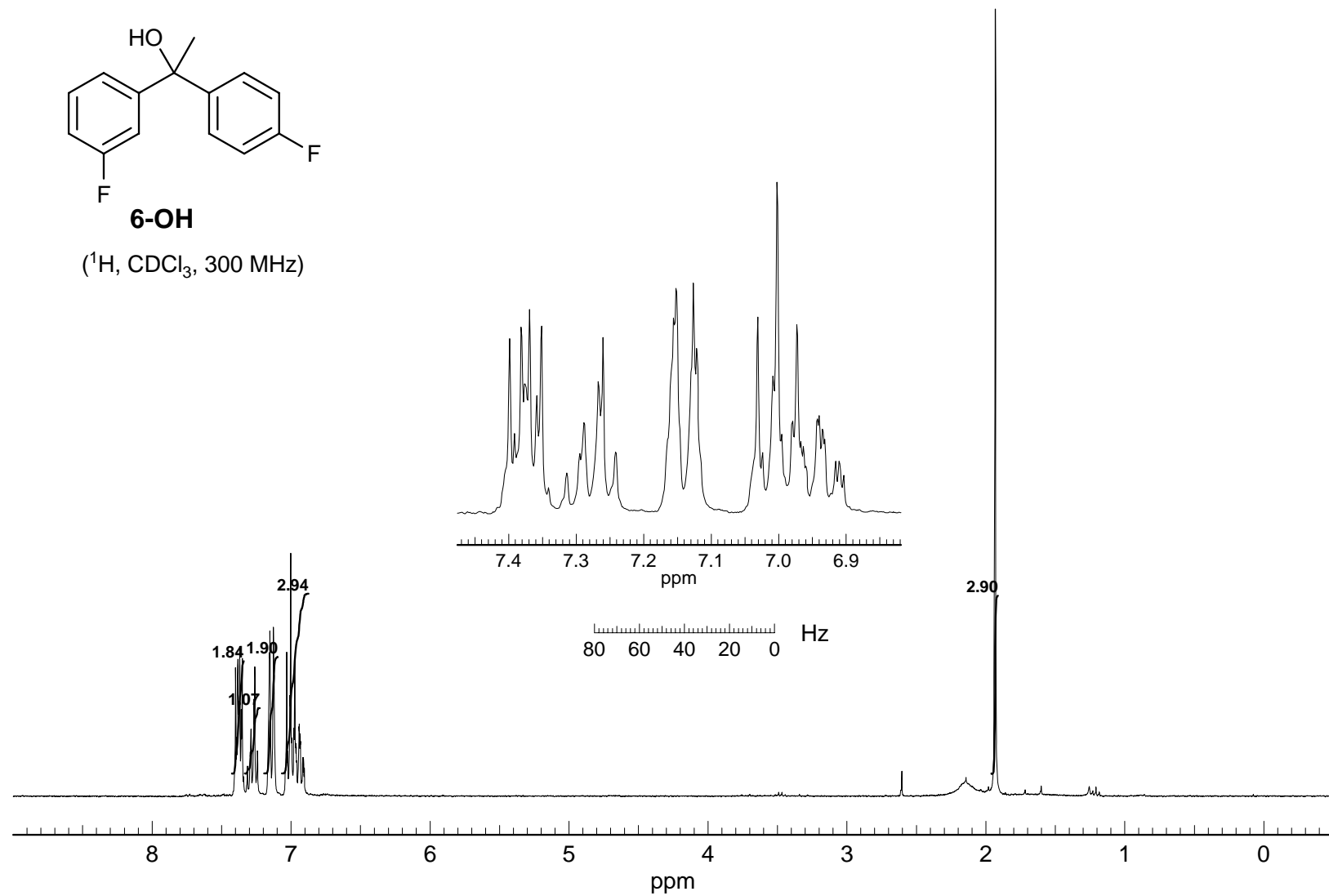
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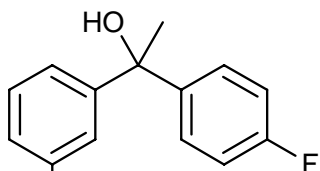




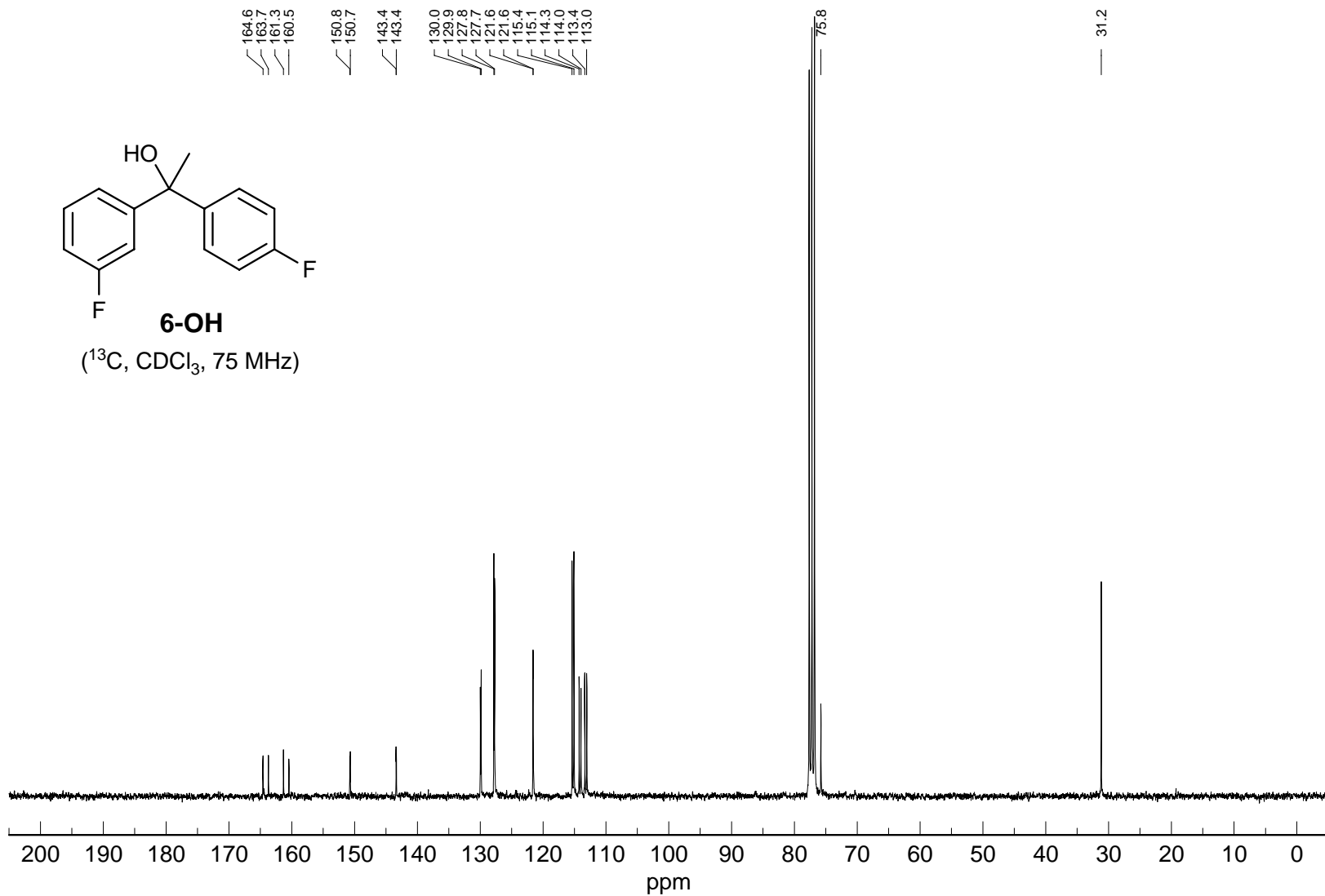
6-OH

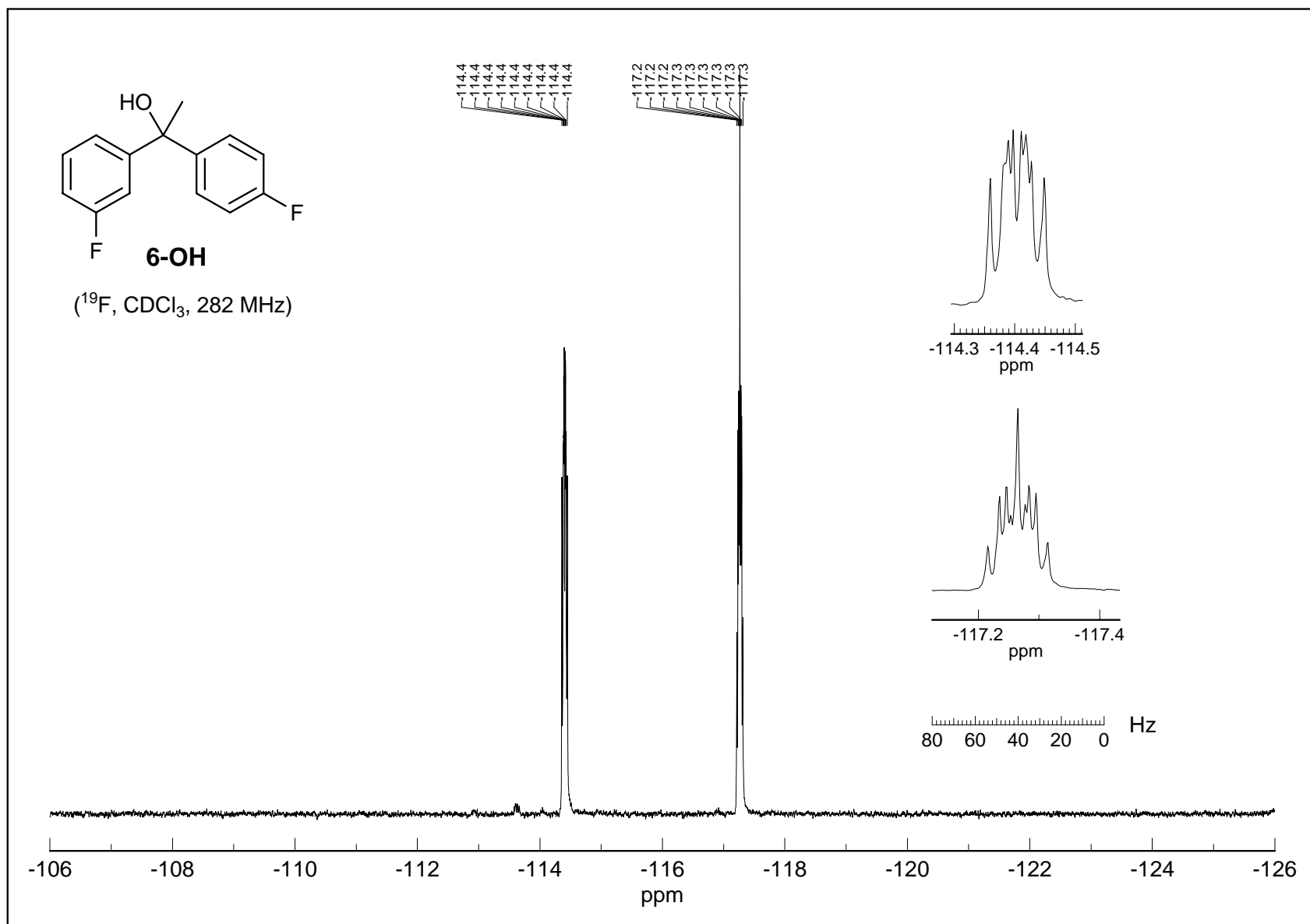
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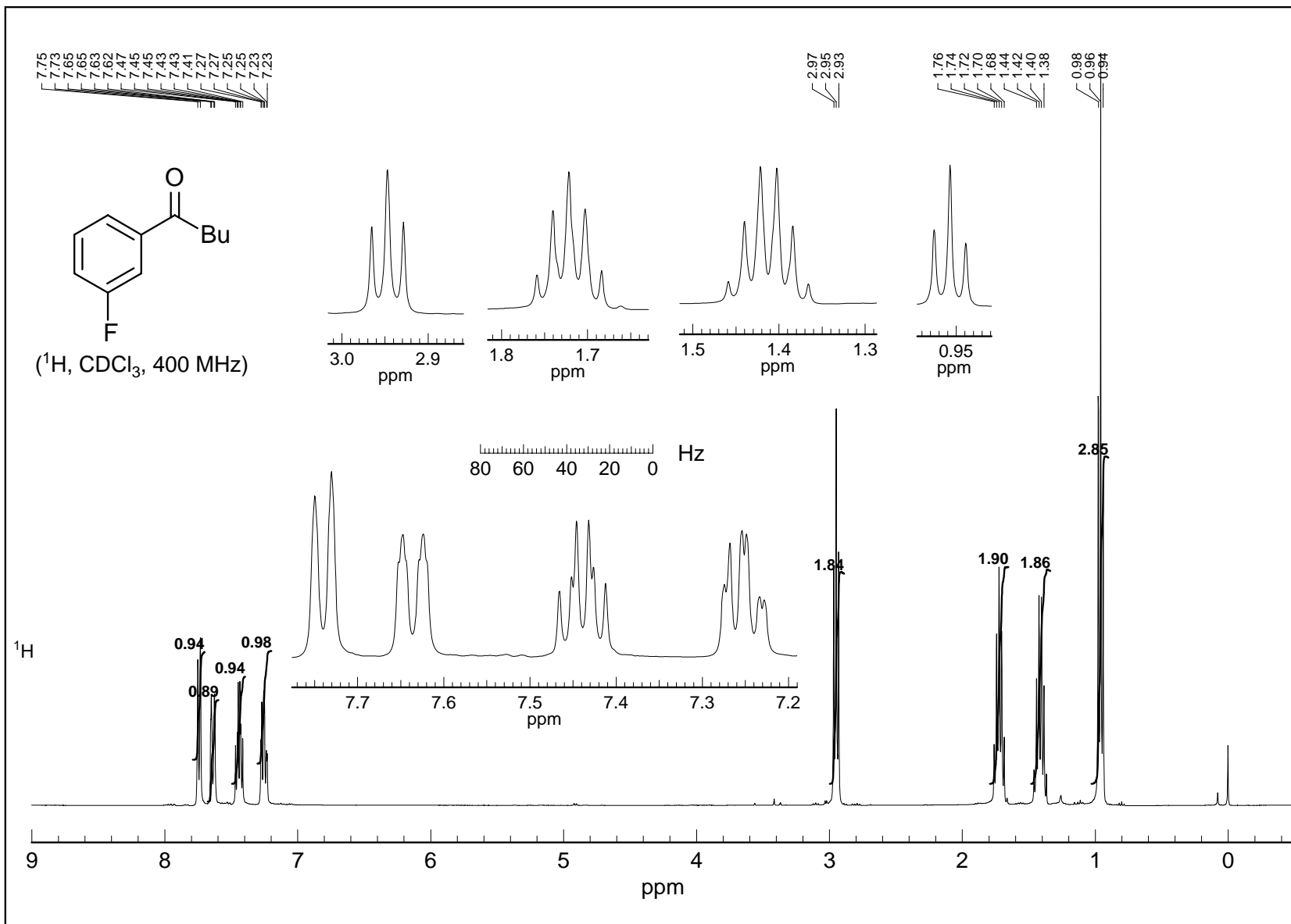


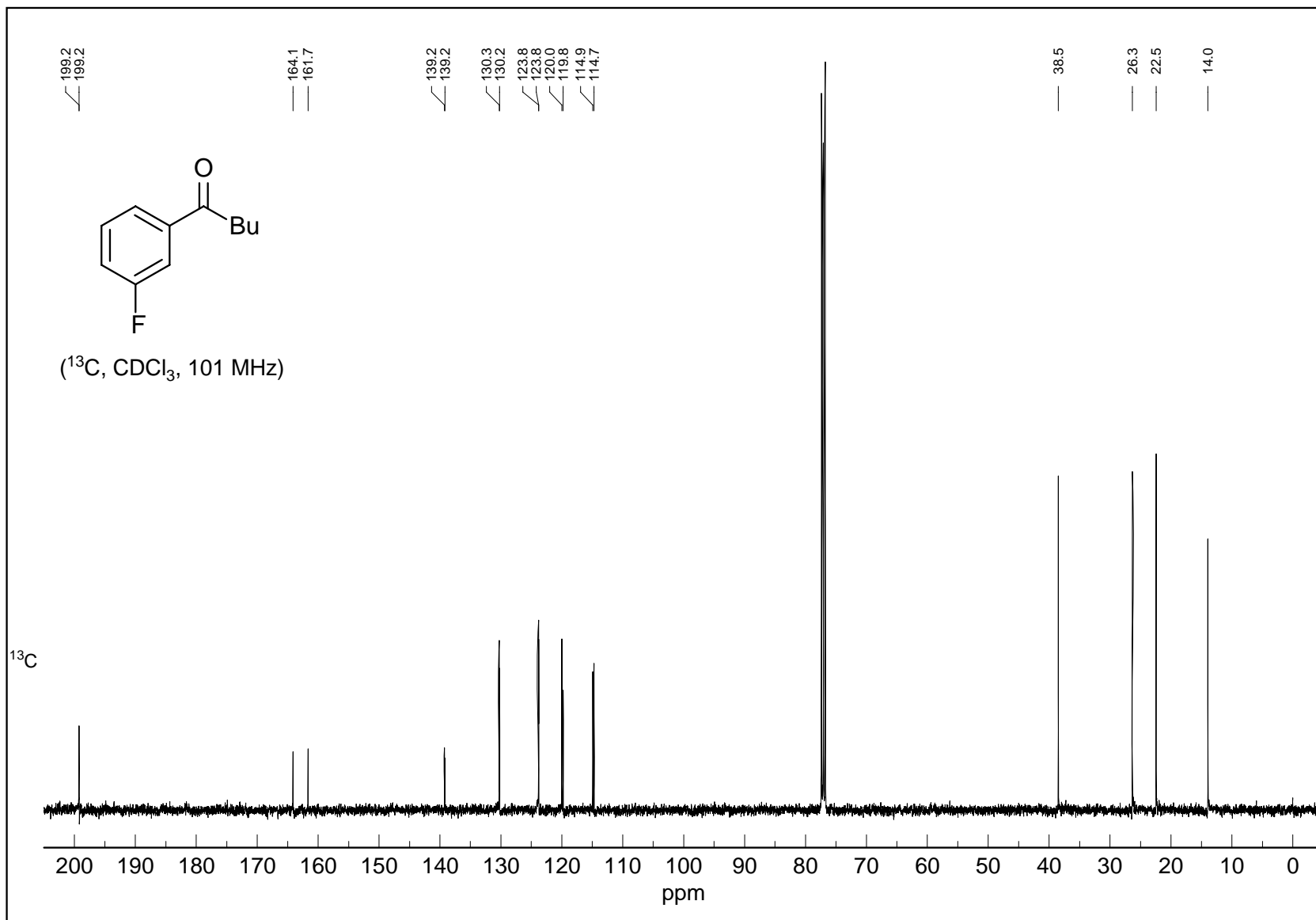


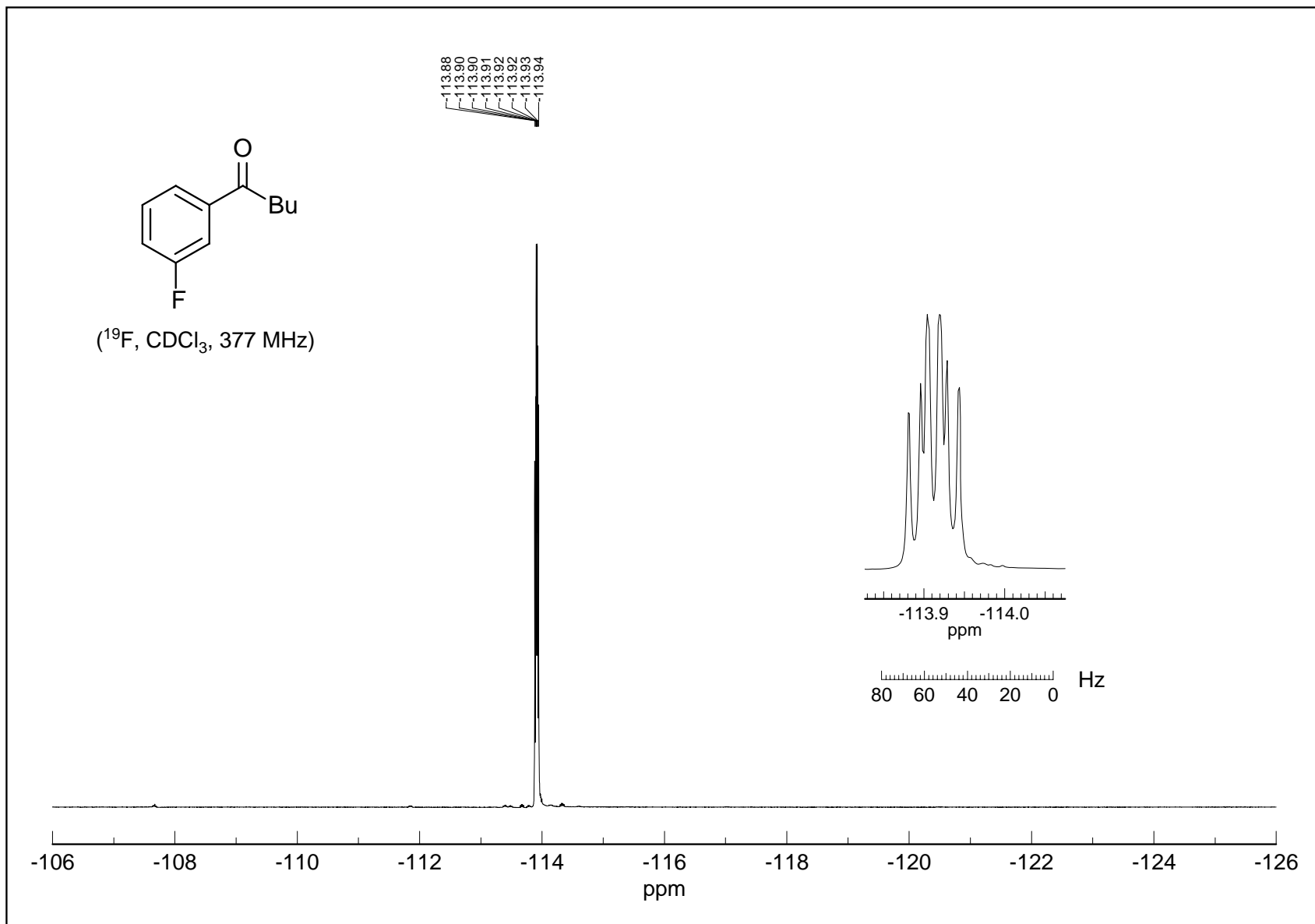
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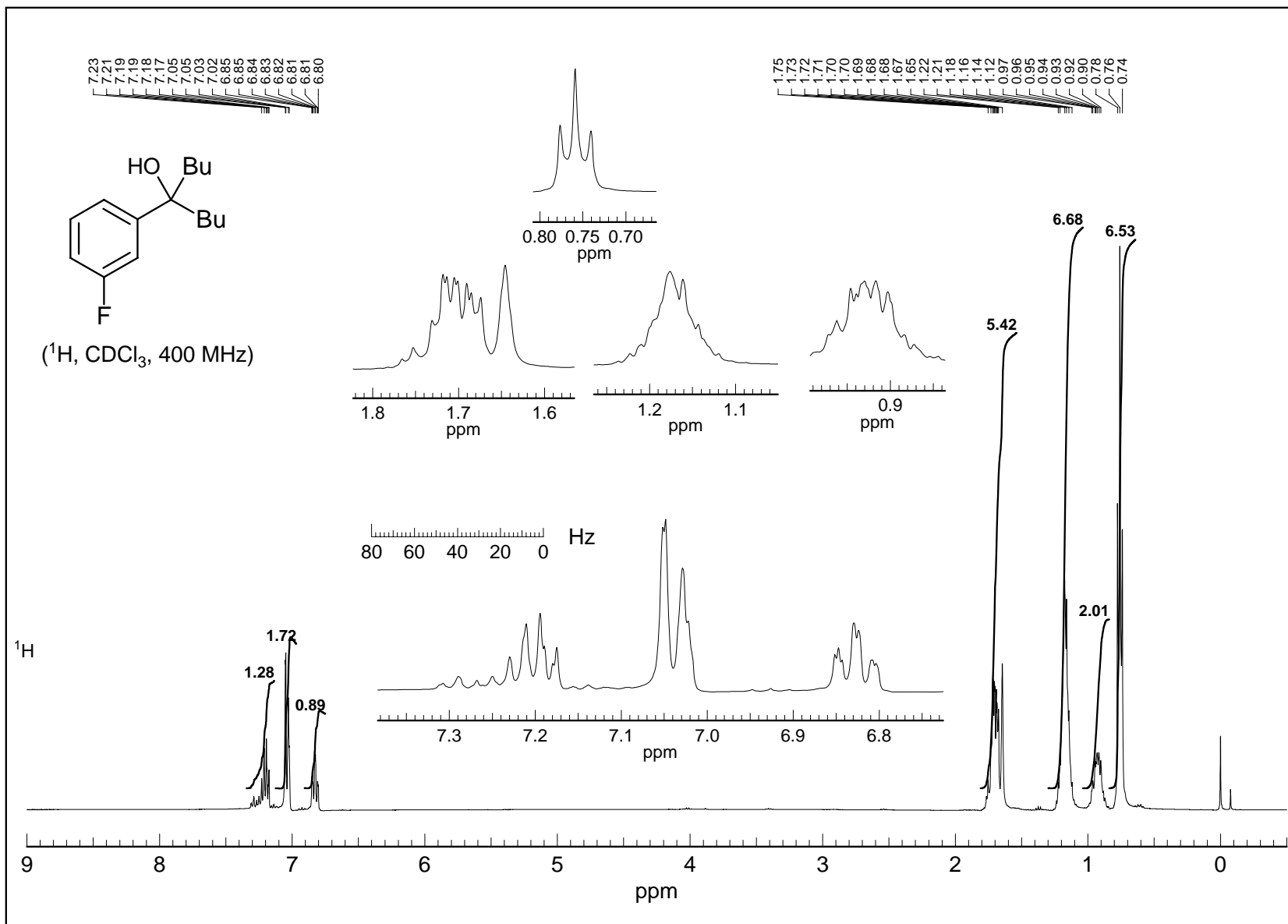


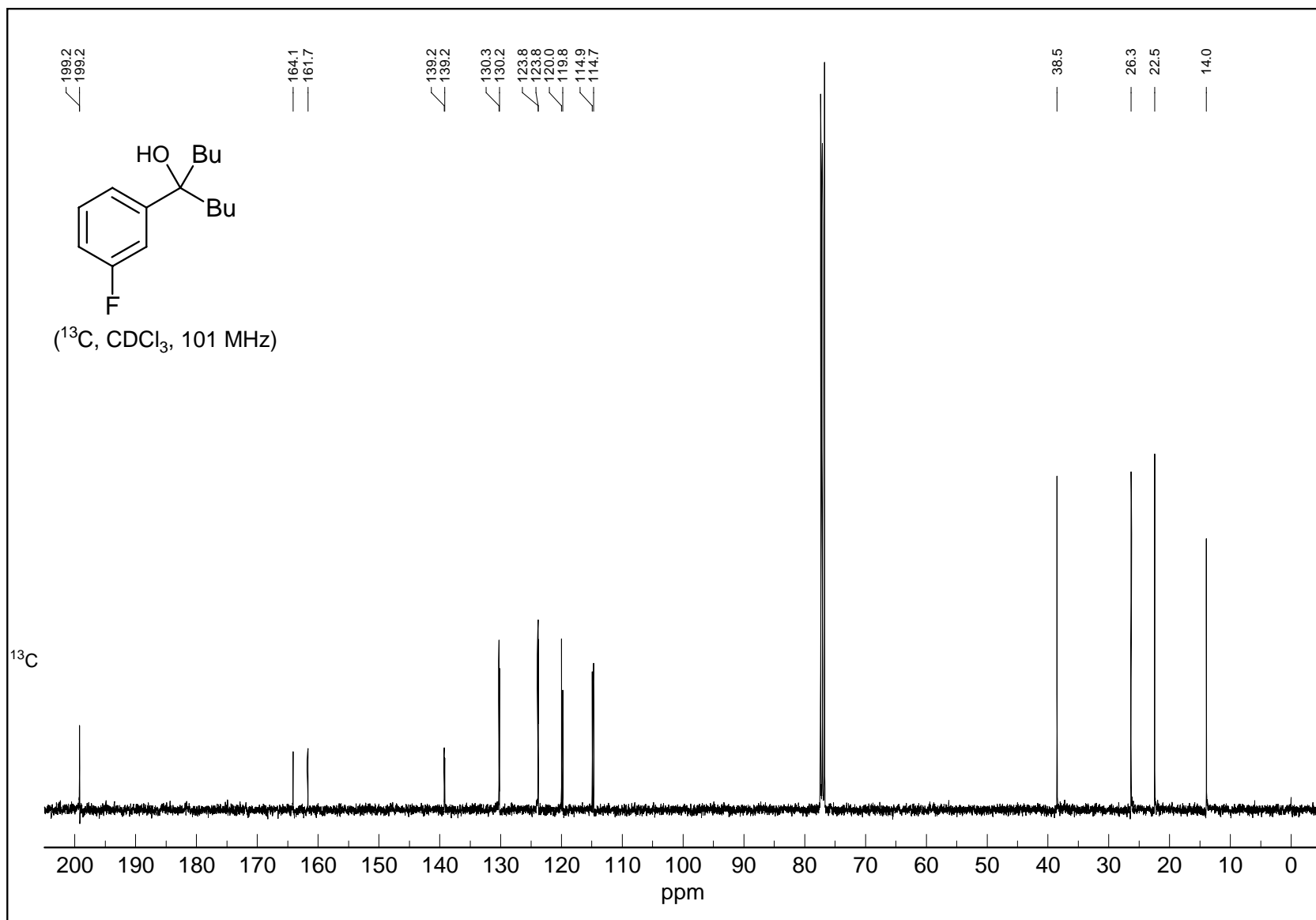


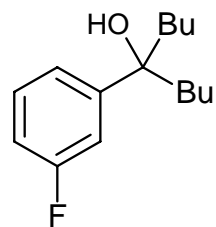




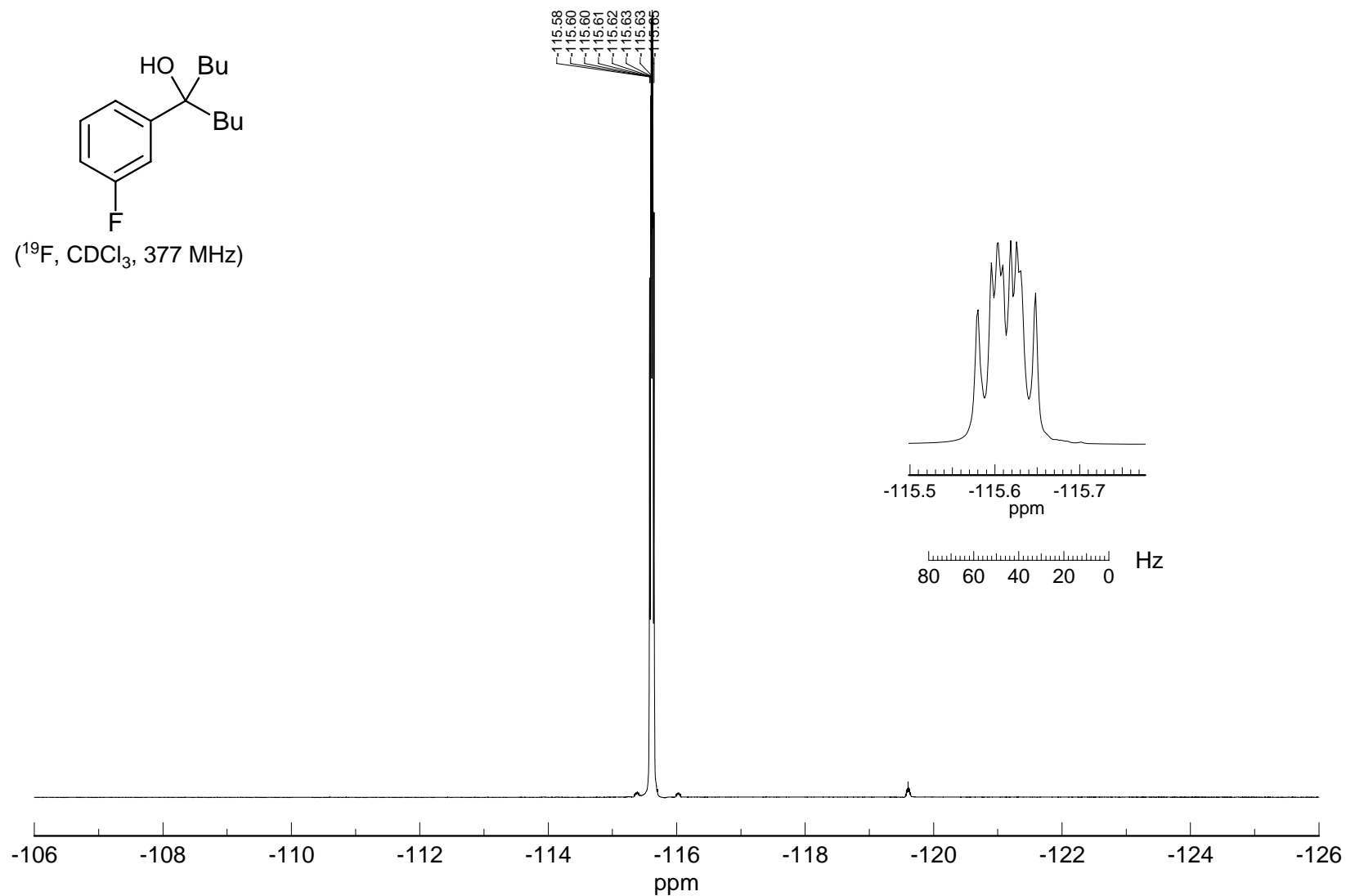




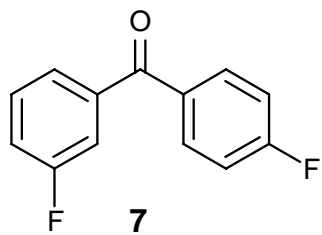




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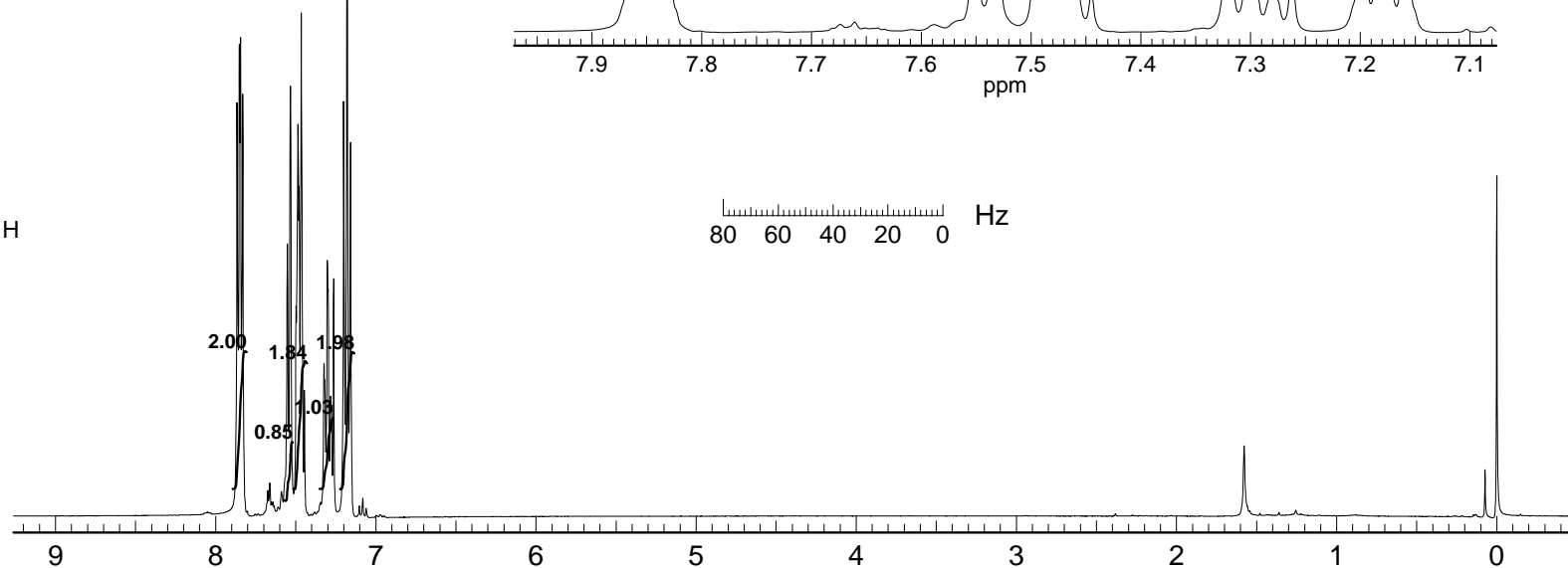


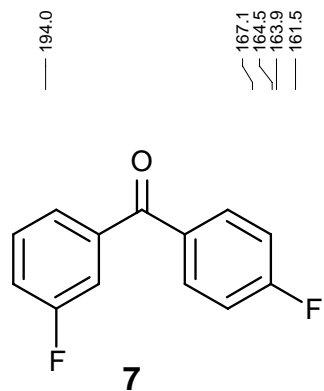
7.87
7.86
7.85
7.84
7.83
7.83
7.56
7.53
7.50
7.49
7.49
7.48
7.46
7.45
7.32
7.30
7.30
7.28
7.20
7.18
7.16



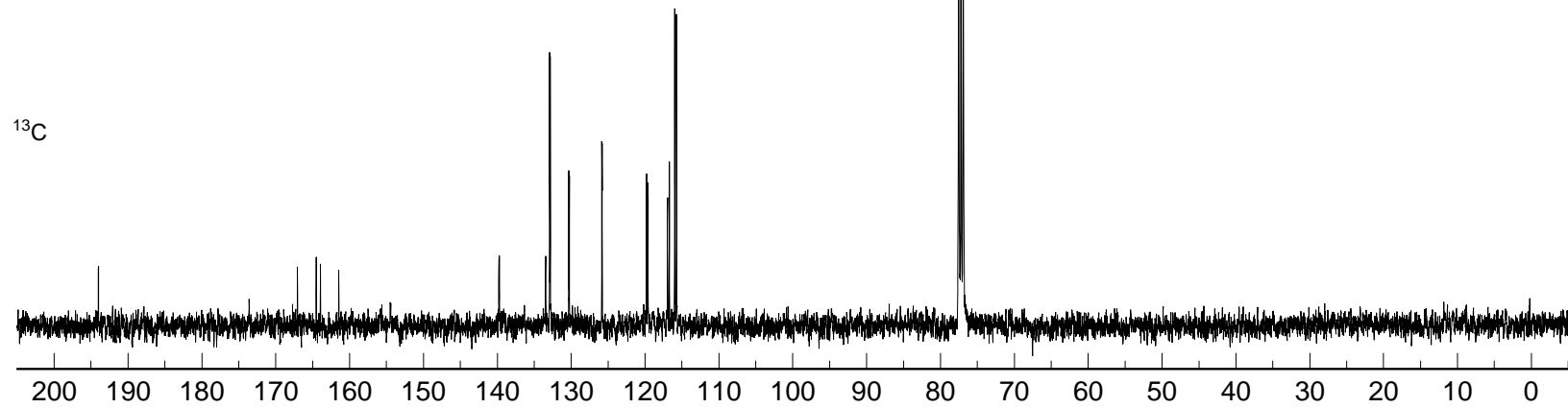
(¹H, CDCl₃, 400 MHz)

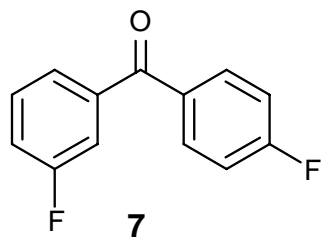
¹H



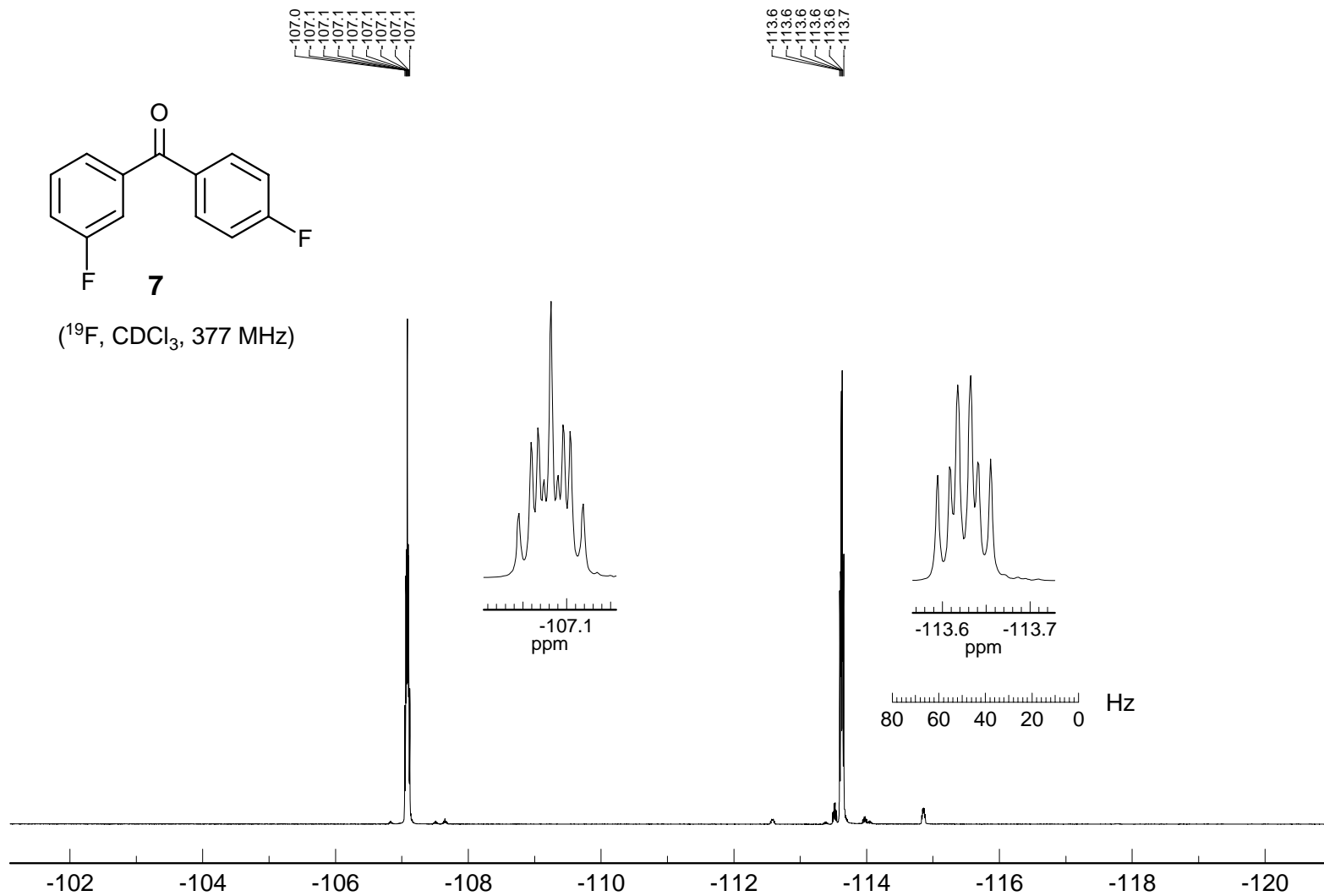


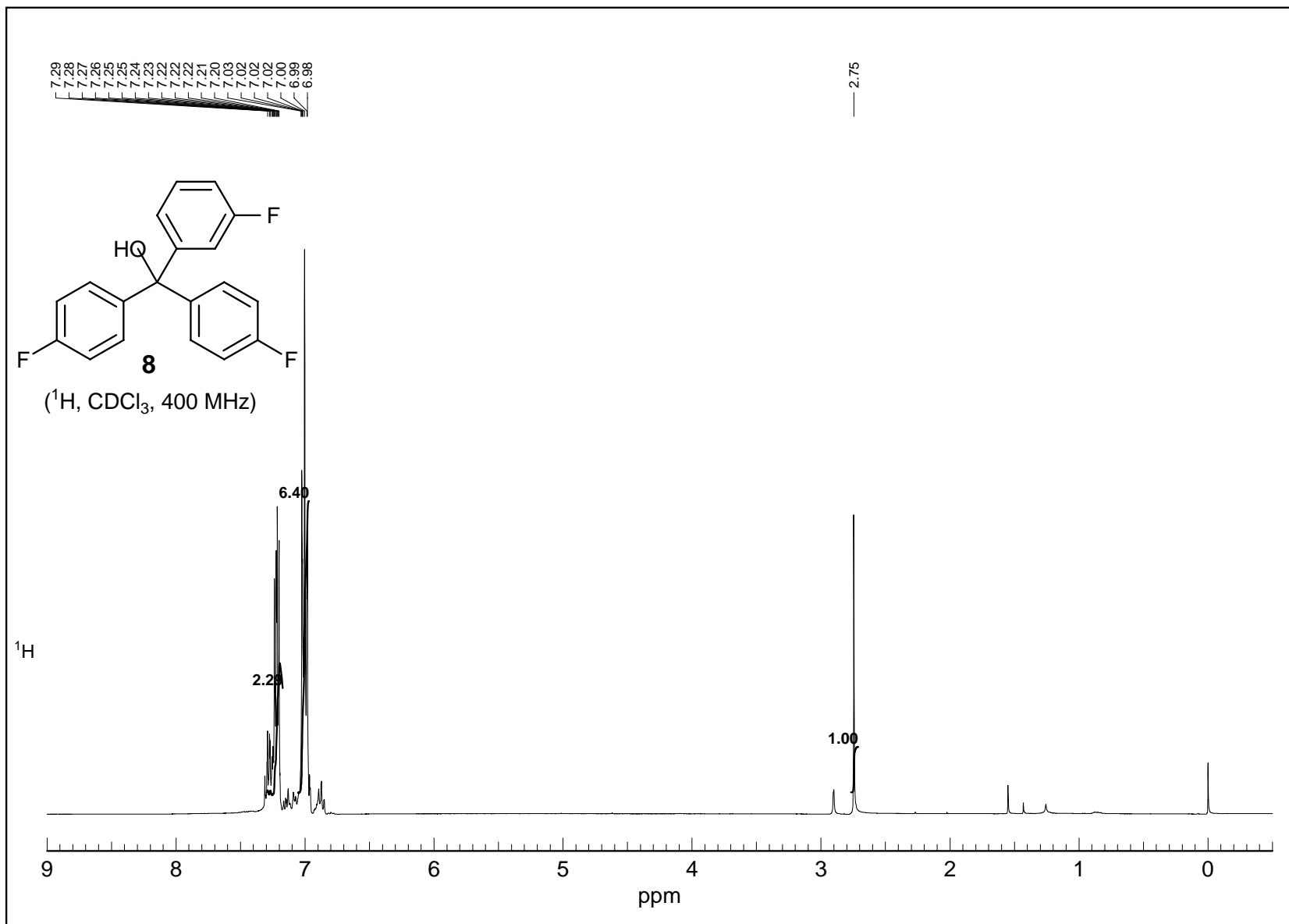
(¹³C, CDCl₃, 101 MHz)

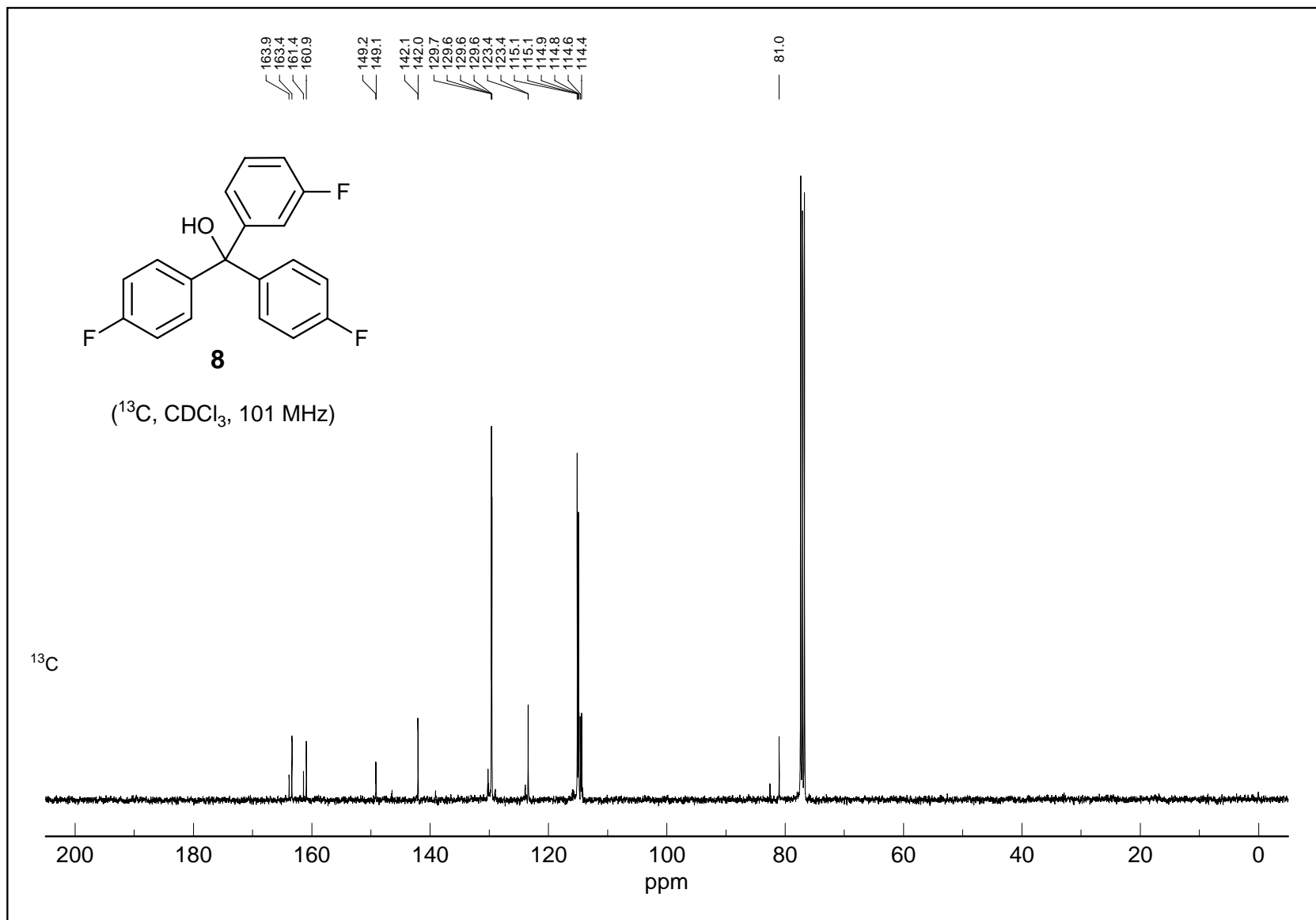


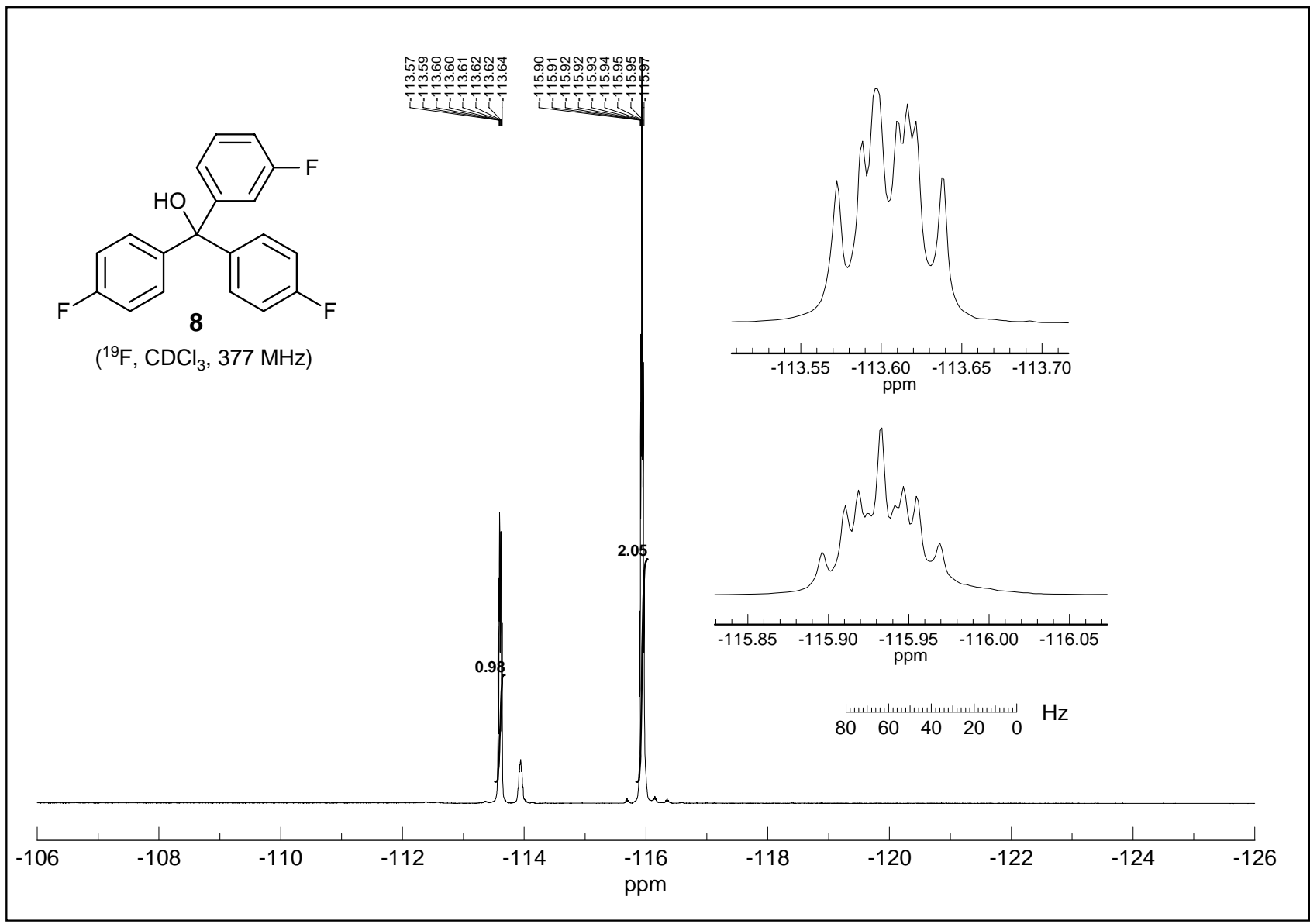


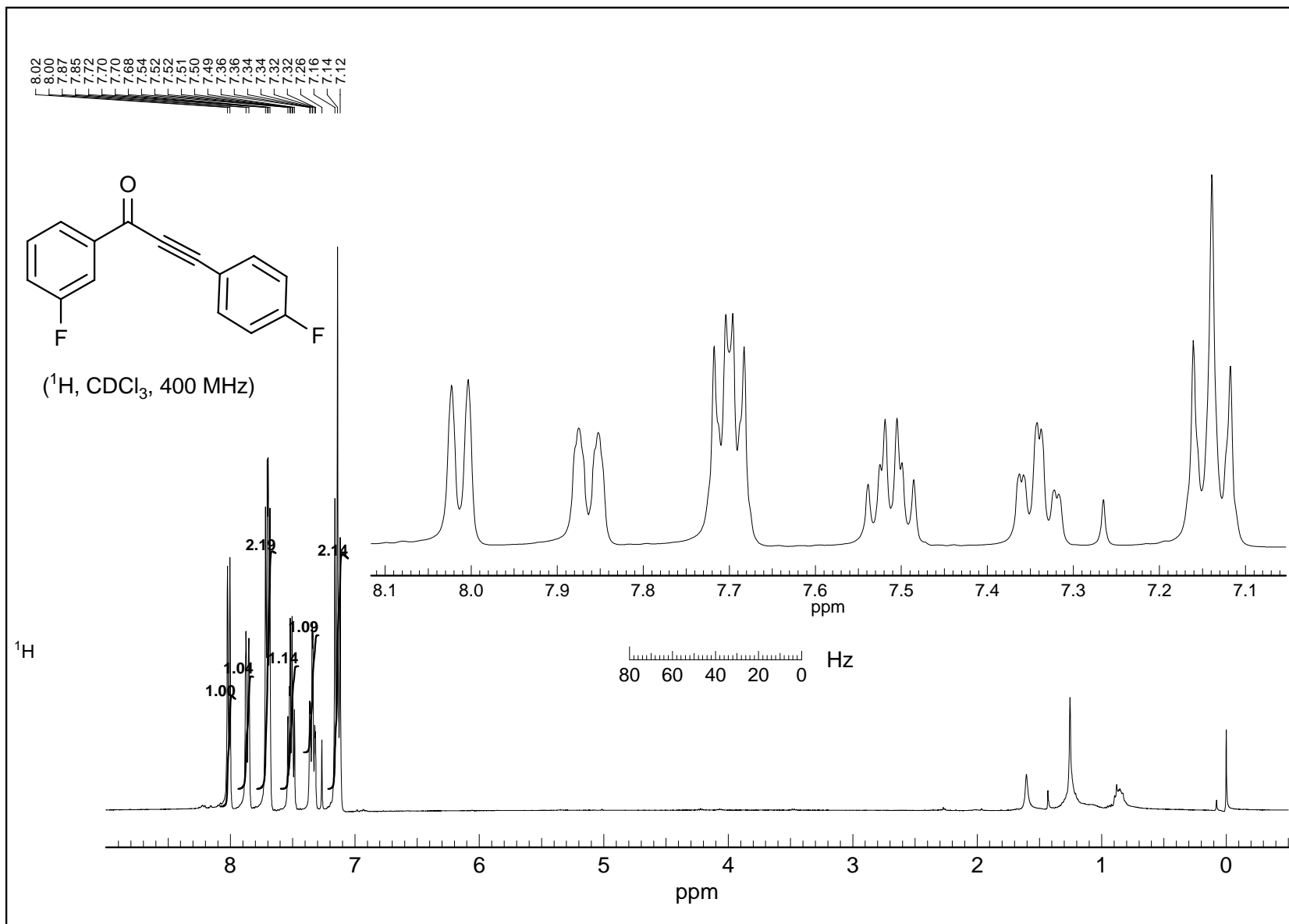
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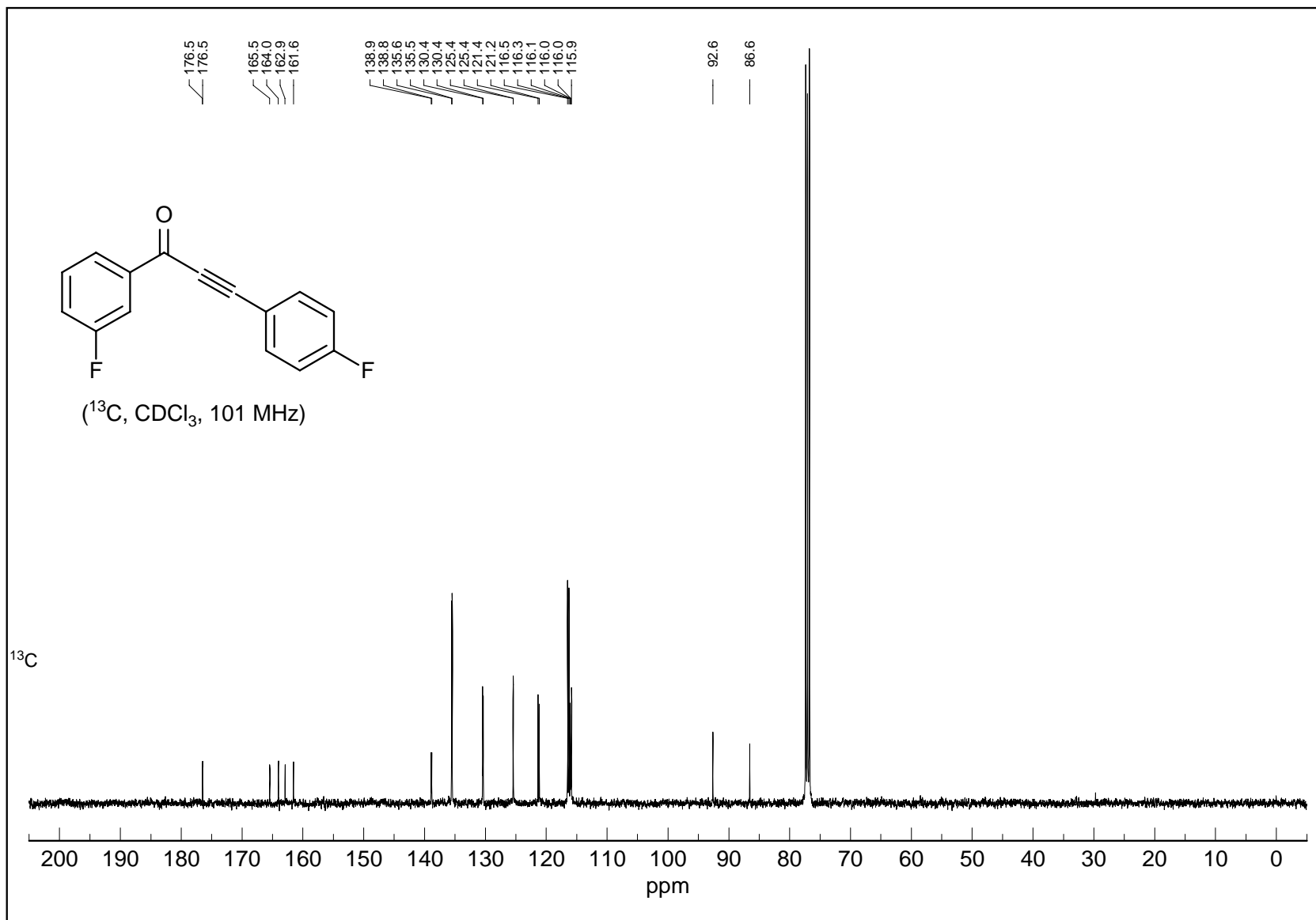


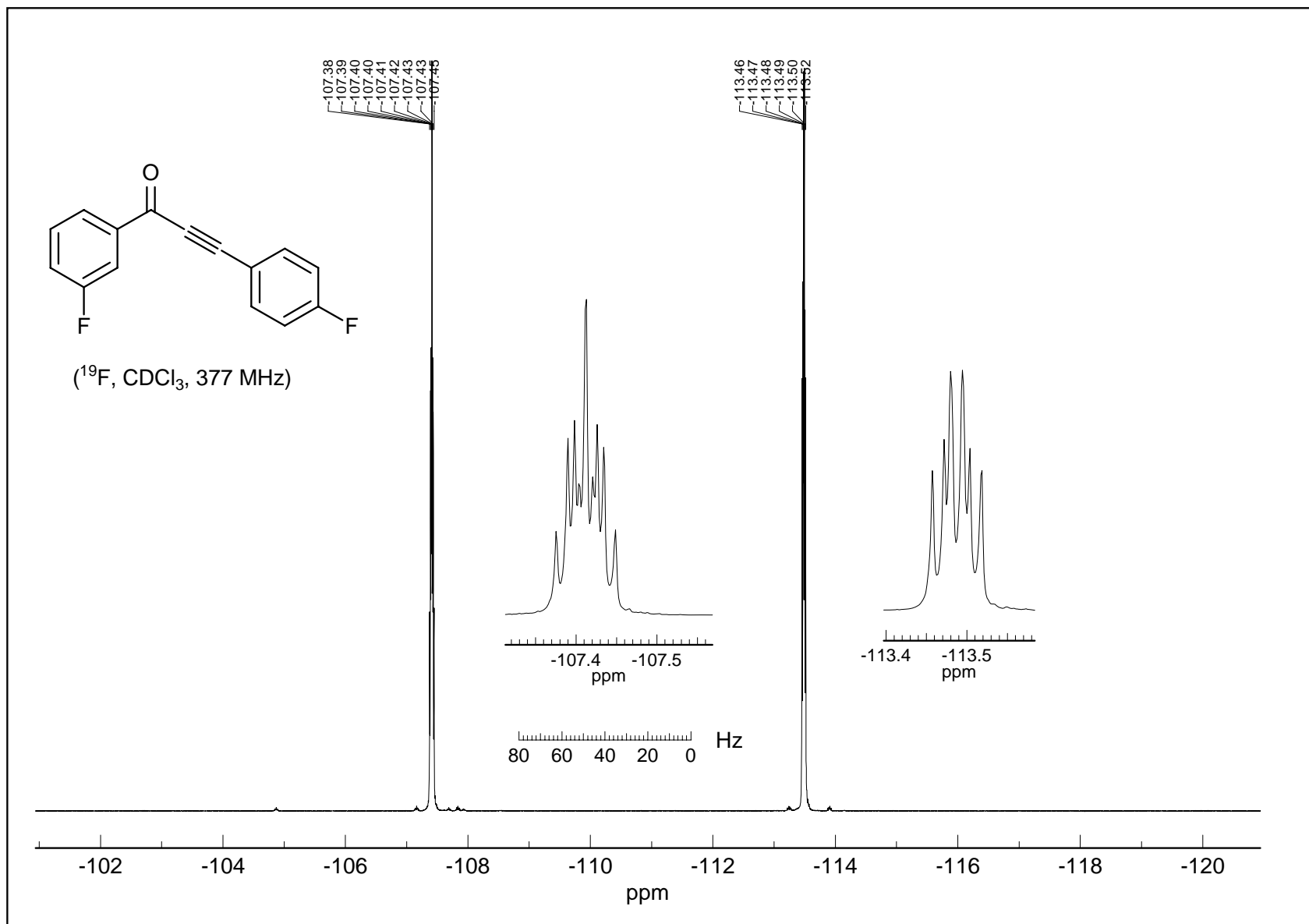


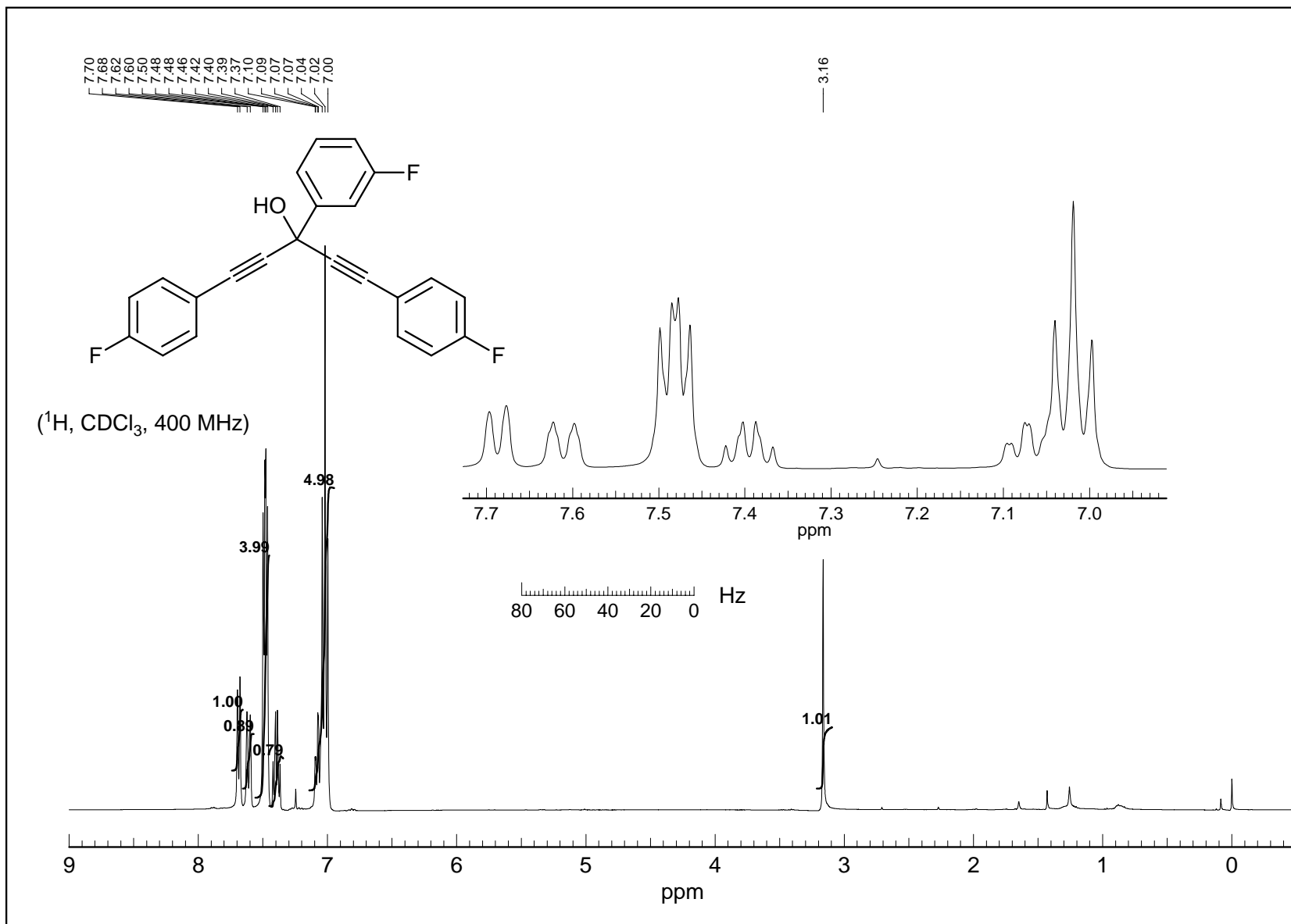


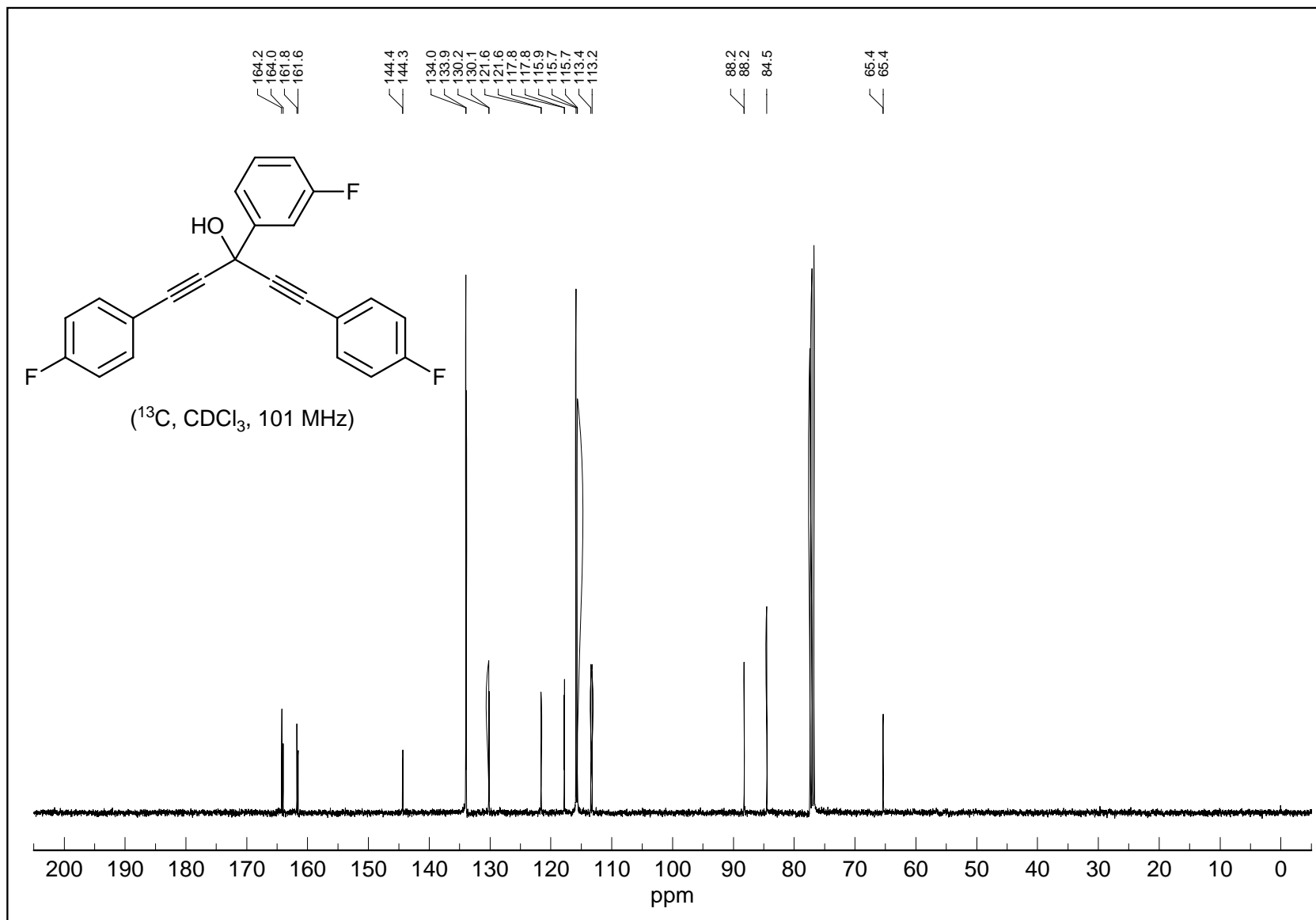


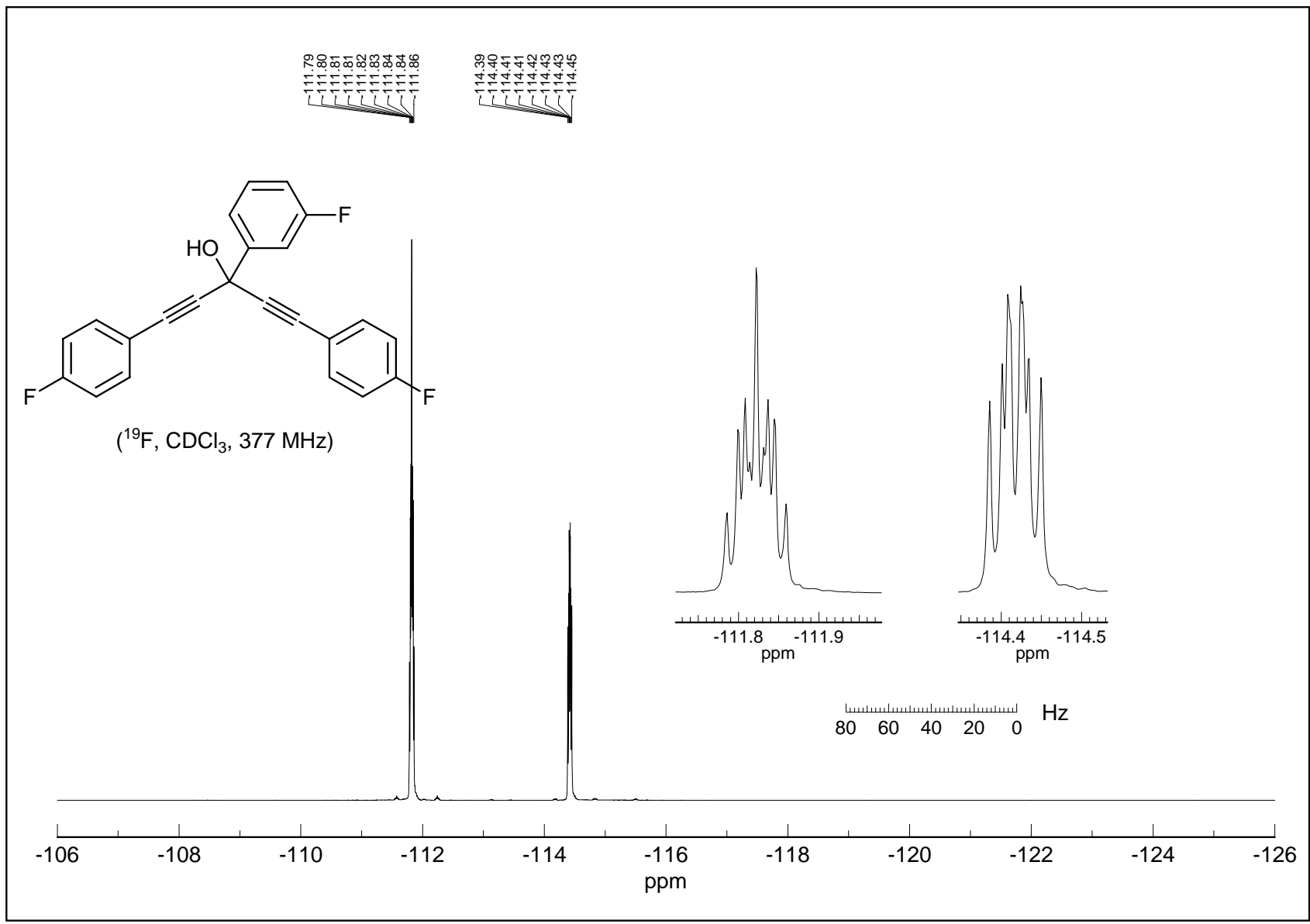


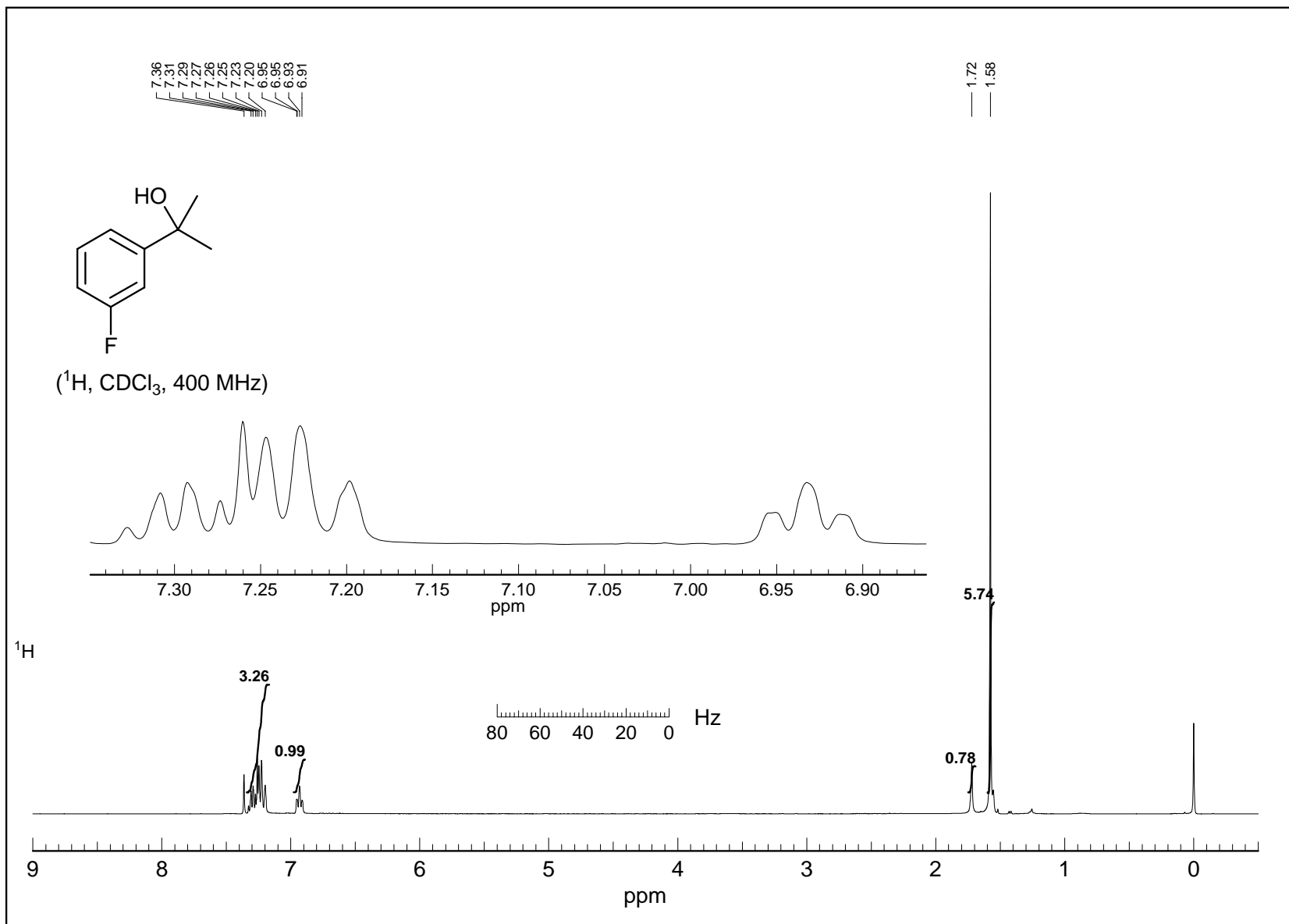


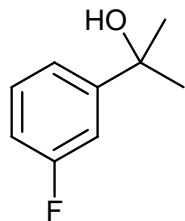




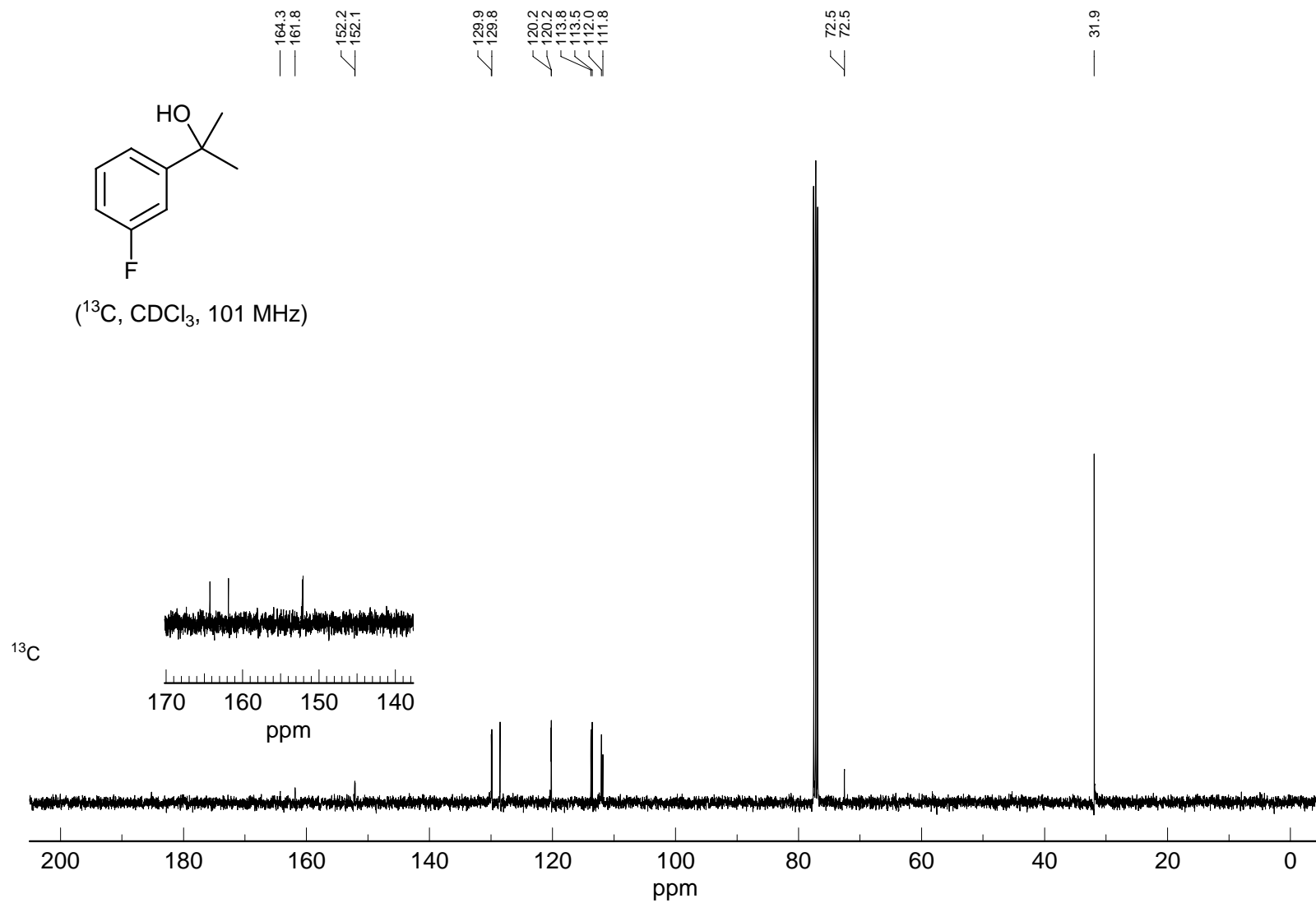


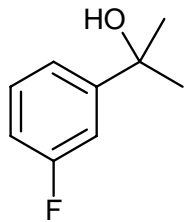




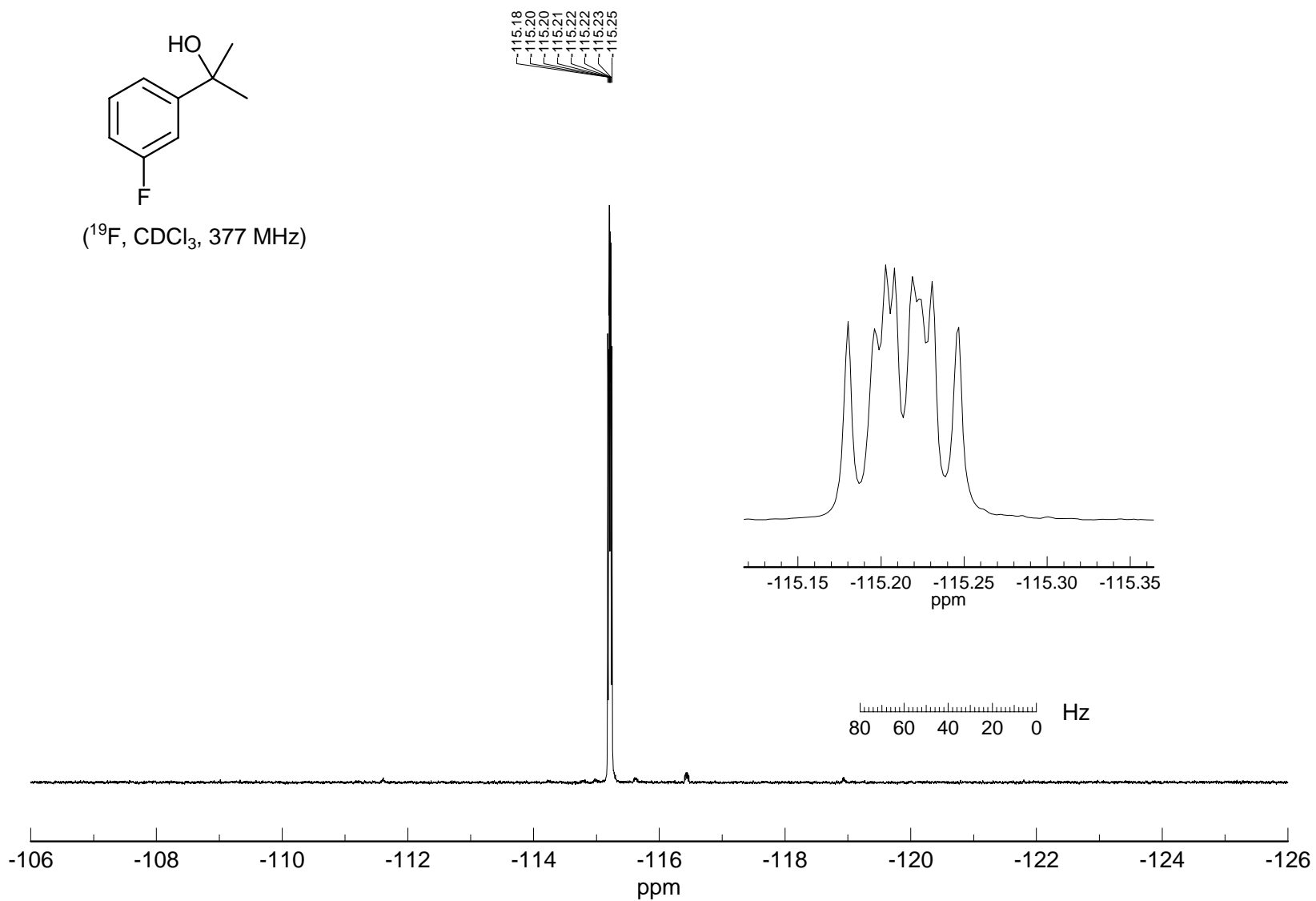


(¹³C, CDCl₃, 101 MHz)





(¹⁹F, CDCl₃, 377 MHz)



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