

## Supporting Information

### Mechanistic Studies of the Lithium Enolate of 4-Fluoroacetophenone: Rapid-Injection NMR Study of Enolate Formation, Dynamics, and Aldol Reactivity

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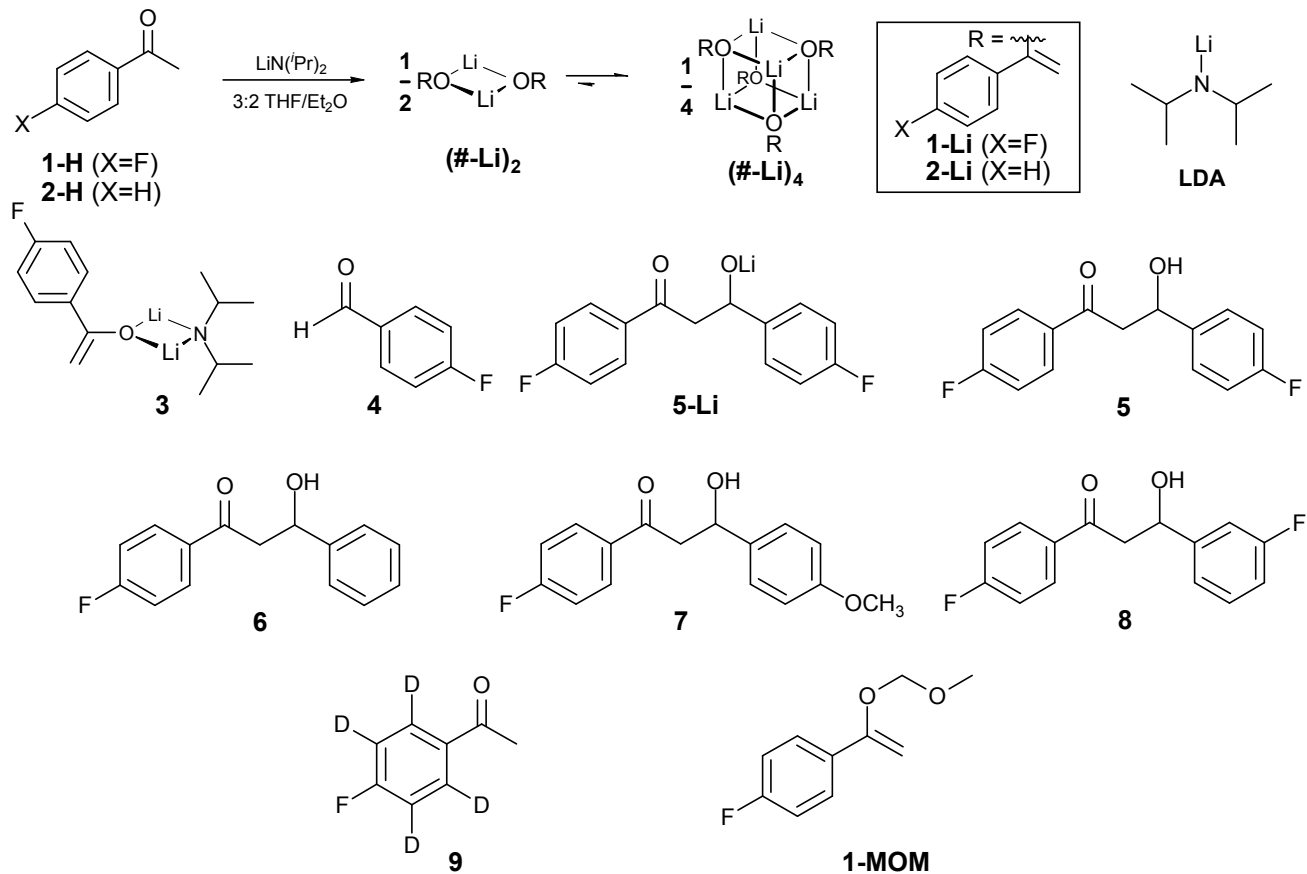
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## S1. General Experimental.

All concentration values in the experimental procedures are expressed as monomer units independent of the state of aggregation (which is not always known). Concentration values presented in the figures were corrected to reflect the aggregation state of the species if known and instances when monomer unit concentrations are presented have been noted on the figure.

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 N<sub>2</sub>. Tetrahydrofuran (THF) and Et<sub>2</sub>O were freshly distilled from sodium benzophenone ketyl under N<sub>2</sub>. Commercially available starting materials and reagents were obtained and included: *n*-butyllithium, diisopropylamine, 4-fluoroacetophenone (**1-H**), acetophenone, benzaldehyde, 4-fluorobenzaldehyde (**4**), 3-fluorobenzaldehyde, and 4-methoxybenzaldehyde. *d*<sub>3</sub>-4-Fluoroacetophenone was prepared according to the previously published procedure.<sup>[S1]</sup> 1-(2,3,5,6-Tetradeutero-4-fluorophenyl)ethanone (**9**) was prepared and utilized to reduce the line width of the <sup>19</sup>F NMR signals.

Low-temperature NMR spectra were acquired on a NMR spectrometer using a 10 mm broadband probe at the following frequencies: 360.131 MHz (<sup>1</sup>H), 90.556 MHz (<sup>13</sup>C), 338.827 MHz (<sup>19</sup>F), 139.96 (<sup>7</sup>Li) and 145.785 MHz (<sup>31</sup>P). All spectra were taken with the spectrometer unlocked. <sup>13</sup>C NMR spectra were referenced internally to the C-O carbon of THF (δ 67.96), Et<sub>2</sub>O (δ 66.57) or Me<sub>2</sub>O (δ 60.25). Lorentzian multiplication (LB) of 2-6 Hz was applied to <sup>13</sup>C NMR spectra. <sup>31</sup>P NMR spectra were referenced externally to 1.0 M PPh<sub>3</sub> in THF (δ -6.00) or internally to free HMPA (δ 26.40). <sup>19</sup>F NMR spectra were acquired without proton decoupling and were referenced internally to CFCl<sub>3</sub> (δ 0.0), 1,3-difluorobenzene (δ -110.8), 1,3-dimethyl-2-fluorobenzene (δ -122.6), or 1,2-difluorobenzene (δ -140). <sup>7</sup>Li spectra were referenced externally to 0.3 M LiCl/MeOH standard (δ 0.00 ppm) or internally to free <sup>+</sup>Li(HMPA)<sub>4</sub> (δ -0.40). Probe temperatures were measured internally with the <sup>13</sup>C chemical shift thermometer: 10% <sup>13</sup>C enriched (Me<sub>3</sub>Si)<sub>3</sub>CH.<sup>[S2]</sup>

## S2. Synthesis

Aldol products were isolated from Rapid-injection NMR experiments by quenching with propionic acid (1 mL of 3 M solution in Et<sub>2</sub>O was added). Samples were poured into a stirring mixture of 10 mL of saturated NaHCO<sub>3</sub> and 10 mL of Et<sub>2</sub>O. The organic layer was separated, washed with saturated NaHCO<sub>3</sub> twice, dried over MgSO<sub>4</sub> and the solvent and remaining starting materials were removed under vacuum. Sample could be purified by chromatography (column or thin layer) using 1:1 hexanes/ethyl acetate. <sup>1</sup>H, <sup>19</sup>F and <sup>13</sup>C NMR and HRMS were then obtained.

**1,3-Bis-(4-fluorophenyl)-3-hydroxypropan-1-one (5):** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ 3.29, 3.32 (ABX, *J*<sub>ab</sub> = 17.7 Hz, *J*<sub>ax</sub> = 1.8 Hz, *J*<sub>bx</sub> = 10.2 Hz, 2H), 3.56 (bs, 1H), 5.32 (apparent triplet (X of ABX), *J* = 6 Hz, 1H), 7.06 (t (AA'BB'X), *J* = 8.6 Hz, 2H), 7.14 (t (AA'BB'X), *J* = 8.6 Hz, 2H), 7.40 (dd (AA'BB'X), *J* = 8.5, 5.5 Hz, 2H), 7.98 (dd (AA'BB'X), *J* = 8.8, 5.5 Hz, 2H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>), δ 47.5 (s), 69.7 (s), 115.3 (d, *J*<sub>CF</sub> = 21 Hz), 116.1 (d, *J*<sub>CF</sub> = 21 Hz), 127.7 (d, *J*<sub>CF</sub> = 8 Hz), 131.1 (d, *J*<sub>CF</sub> = 8 Hz), 133.2 (d, *J*<sub>CF</sub> = 3 Hz), 138.5 (d, *J*<sub>CF</sub> = 3 Hz), 162.5 (d, *J*<sub>CF</sub> = 246 Hz), 166.4 (d, *J*<sub>CF</sub> = 256 Hz), 198.5 (s). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -104.3 (tt, *J*<sub>FH</sub> = 8.6, 5.5 Hz), -115.2 (tt, *J*<sub>FH</sub> = 8.6, 5.5 Hz). HRMS (EI) (m/z): calcd. for C<sub>15</sub>H<sub>12</sub>F<sub>2</sub>O<sub>2</sub> (M<sup>+</sup>) 262.0805; found 262.0796.

**1-(4-Fluorophenyl)-3-phenyl-3-hydroxy-1-propanone (6):** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>), δ 3.24, 3.28 (ABX, *J*<sub>ab</sub> = 17.9 Hz, *J*<sub>ax</sub> = 1.8 Hz, *J*<sub>bx</sub> = 10.3 Hz, 2H), 3.42 (bs, 1H), 5.26 (apparent triplet (X of ABX), *J* = 6 Hz, 1H), 7.06 (t (AA'BB'X), *J* = 8.6 Hz, 2H), 7.16-7.4 (m, 5H), 7.91 (dd (AA'BB'X), *J* = 8.8, 5.5 Hz, 2H). <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>), δ 47.6 (s), 70.2 (s), 116.1 (d, *J*<sub>CF</sub> = 21 Hz), 125.9 (s), 128.0 (s), 128.8 (s), 131.1 (d, *J*<sub>CF</sub> = 8 Hz), 133.2 (d, *J*<sub>CF</sub> = 3 Hz), 143.1 (s), 166.3 (d, *J*<sub>CF</sub> = 256 Hz), 198.7 (s). <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ -104.6 (tt, *J*<sub>FH</sub> = 8.6, 5.5 Hz). HRMS (EI) (m/z): calcd. for C<sub>15</sub>H<sub>13</sub>FO<sub>2</sub> (M<sup>+</sup>Na<sup>+</sup>) 267.0792; found 267.0798.

**1-(4-Fluorophenyl)-3-(4-methoxyphenyl)-3-hydroxy-1-propanone (7):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  3.36, 3.38 (ABX,  $J_{ab}=16.4$ ,  $J_{ax}=9.4$ ,  $J_{bx}=3.2$  Hz, 2H), 3.48 (bs, 1H), 3.82 (s, 3H), 5.30 (dd (X of ABX),  $J=8.3$ , 3.7 Hz, 1H), 6.92 (d, AA'BB',  $J=8.7$  Hz, 2H), 7.14 (tt (AA'BB'X),  $J_{\text{HF}}=8.6$  s, 2 Hz, 2H), 7.36 (d (AA'BB')  $J_{\text{HF}}=8.5$  Hz, 2H), 7.99 (apparent dd (AA'BB'X),  $J=8.9$ , 5.4 Hz, 2H).  $^{13}\text{C}$  NMR (75.4 MHz,  $\text{CDCl}_3$ ),  $\delta$  47.5 (s), 55.6 (s), 69.9 (s), 114.2 (s), 115.9 (s), 116.1 (d,  $J_{\text{CF}}=21$  Hz), 127.2 (s), 131.1 (d,  $J_{\text{CF}}=8$  Hz), 135.3 (s), 136.0 (d,  $J_{\text{CF}}=3$  Hz), 143.1 (s), 162.0 (d,  $J_{\text{CF}}=256$  Hz), 198.8 (s).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CFCl}_3$ ),  $\delta$  -104.74 (tt,  $J=8.4$ , 5.4 Hz, 1F). HRMS (EI) (m/z): calcd. For  $\text{C}_{16}\text{H}_{15}\text{FO}_3$  (M+) 274.1000; found 274.0992.

**1-(4-Fluorophenyl)-3-(3-fluorophenyl)-3-hydroxy-1-propanone (8):**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  3.25, 3.27 (ABX,  $J_{ab}=17.8$ ,  $J_{ax}=9.4$ ,  $J_{bx}=2.7$  Hz, 2H), 3.53 (d,  $J=3.1$  Hz, 1H), 5.27 (apparent dt (X of ABX),  $J=6.1$ , 3.1 Hz, 1H), 6.92 (tdd,  $J=8.3$ , 2.5, 1 Hz, 1H), 7.0-7.13 (overlapping multiplets, 4H), 7.27 (td,  $J=8.3$ , 5.4 Hz, 1H), 7.99 (apparent dd (AA'BB'X),  $J=8.9$ , 5.4 Hz, 2H).  $^{13}\text{C}$  NMR (75.4 MHz,  $\text{CDCl}_3$ ),  $\delta$  47.5 (s), 69.7 (s), 113.1 (d,  $J_{\text{CF}}=22$  Hz), 114.8 (d,  $J_{\text{CF}}=22$  Hz), 116.3 (d,  $J_{\text{CF}}=21$  Hz), 121.6 (d,  $J_{\text{CF}}=2$  Hz), 130.4 (d,  $J_{\text{CF}}=8$  Hz), 131.2 (d,  $J_{\text{CF}}=8$  Hz), 133.3 (d,  $J_{\text{CF}}=2$  Hz), 136.0 (d,  $J_{\text{CF}}=3$  Hz), 145.9 (d,  $J_{\text{CF}}=7$  Hz), 163.3 (d,  $J_{\text{CF}}=256$  Hz), 166.5 (d,  $J_{\text{CF}}=256$  Hz), 201.3 (s).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CFCl}_3$ ),  $\delta$  -104.3 (tt,  $J_{\text{FH}}=8.4$ , 5.4 Hz, 1F), -113.1 (ddd,  $J_{\text{FH}}=10.2$ , 9.2, 5.6 Hz, 1F). HRMS (EI) (m/z): calcd. For  $\text{C}_{15}\text{H}_{12}\text{F}_2\text{O}_2$  (M+) 262.0800; found 262.0811.

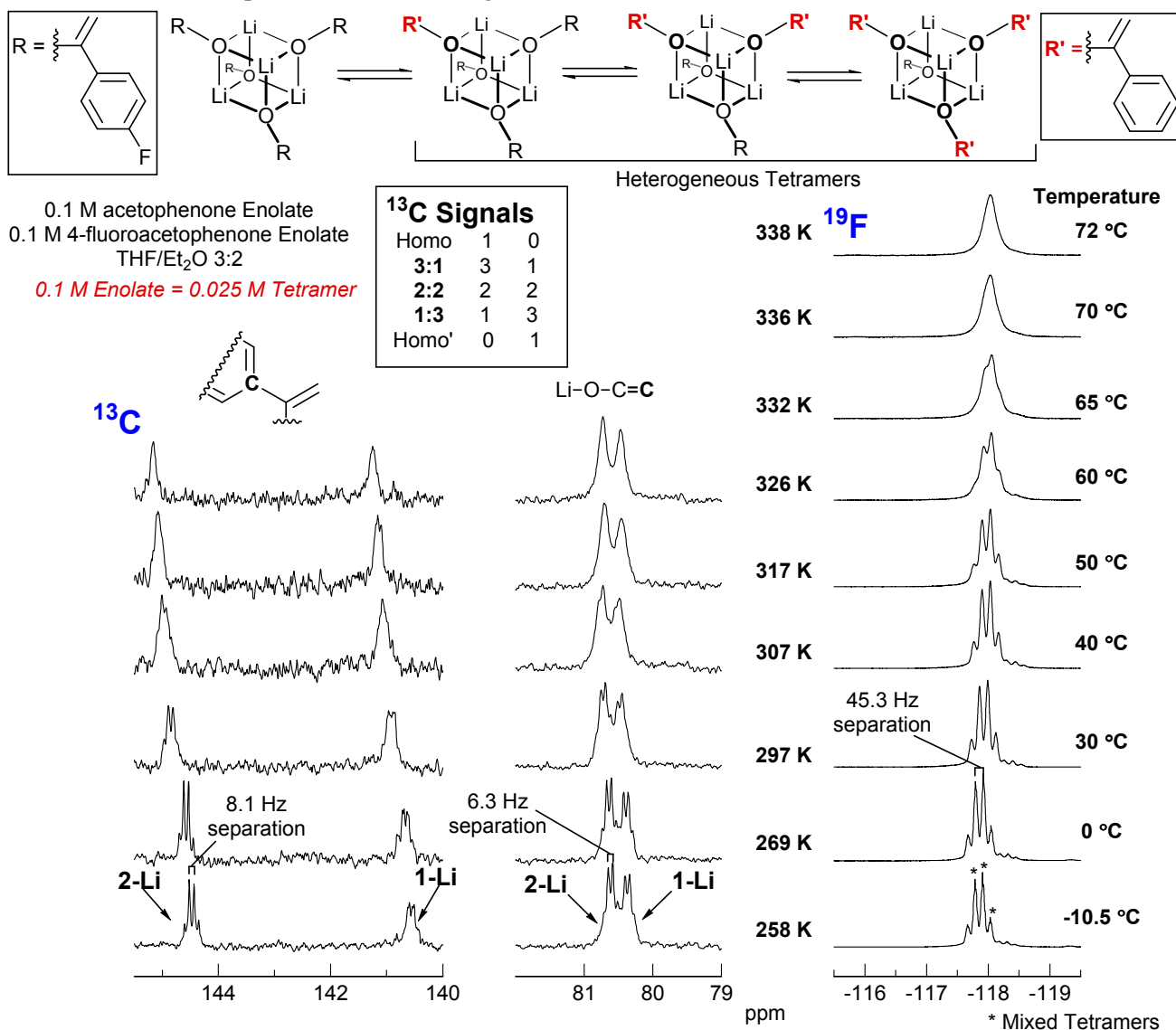
**1-(2,3,5,6-Tetradeutero-4-fluorophenyl)ethanone (9).** A solution of acetyl chloride (1.1 mL, 14.8 mmol) in dichloromethane (2 mL) was added dropwise to a suspension of aluminum trichloride (2.1 g, 15.8 mmol) and fluorobenzene- $d_5$  (1 g, 9.9 mmol) in dichloromethane (6 mL) at 0 °C. The mixture was heated to reflux for one hour then cooled to room temperature. The reaction mixture was poured onto 6M HCl (50 mL) at 0 °C and allowed to stir for 10 min. Brine (10 mL) was added and the mixture was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried with  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The crude material was purified via column chromatography (9:1 Hex:EtOAc) to give the product as a clear oil (1.2 g, 8.5 mmol, 86%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  2.61 (s, 3H).  $^{13}\text{C}$  NMR (75.4 MHz,  $\text{CDCl}_3$ ),  $\delta$  26.7 (s), 115.5 (1:1:1 t of d,  $J=25.6$ , 21.7 Hz), 130.8 (1:1:1 t of d,  $J=25.6$ , 9.5 Hz), 133.6 (s), 165.9 (d,  $J_{\text{CF}}=254.6$  Hz), 196.6 (s).  $^2\text{H}$  NMR (55.3 MHz, 3:2 THF:Et<sub>2</sub>O) 7.11 (s, 2D), 7.95 (s, 2D).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ),  $\delta$  -107.8 (s, 1F). HRMS (EI) (m/z): calcd. For  $\text{C}_8\text{H}_3\text{D}_4\text{FO}$  (M+) 142.0727; found 142.0732.

**1-Fluoro-4-(1-(methoxymethoxy)vinyl)benzene (1-MOM)** - KHMDS (6 mL, 3.0 mmol, 0.5 M in toluene) was added to a solution of 4-fluoroacetophenone (0.3 mL, 2.47 mmol) and 18-crown-6 (1.0 g, 3.7 mmol) in THF (12 mL) at -78 °C. After stirring for 45 min chloromethyl methyl ether (0.38 mL, 4.95 mmol) was added and the reaction stirred for 3 hours at -78 °C. The reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (20 mL) and extracted with Et<sub>2</sub>O (2 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over  $\text{MgSO}_4$ . The solvent was removed under reduced pressure, and column chromatography purification was performed (9:1 Hex:EtOAc) to give the product (0.32 g, 1.73 mmol) as a colorless oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ),  $\delta$  3.51 (s, 3H), 4.51 (d,  $J=2.7$  Hz, 1H), 4.74 (d,  $J=2.7$  Hz, 1H), 5.16 (s, 2H), 7.05 (t (AA'BB'X),  $J=8.7$  Hz, 2H), 7.62 (dd (AA'BB'X),  $J=8.7$ , 5.4 Hz, 2H).  $^{13}\text{C}$  NMR (75.4 MHz,  $\text{CDCl}_3$ ),  $\delta$  56.5 (s), 85.8 (s), 94.4 (s), 115.2 (d,  $J_{\text{CF}}=21$  Hz), 127.4 (d,  $J_{\text{CF}}=8$  Hz), 132.5 (d,  $J_{\text{CF}}=3$  Hz), 157.2 (s), 163.2 (d,  $J_{\text{CF}}=248$  Hz).  $^{19}\text{F}$  NMR (282 MHz,  $\text{CFCl}_3$ ),  $\delta$  -114.42 (tt,  $J=9.0$ , 5.4 Hz, 1F). HRMS (EI) (m/z): calcd. For  $\text{C}_{10}\text{H}_{11}\text{FO}_2$  (M+) 183.0816; found 182.0738 (1.6 ppm).

### S3. NMR Characterization of Enolate Structures

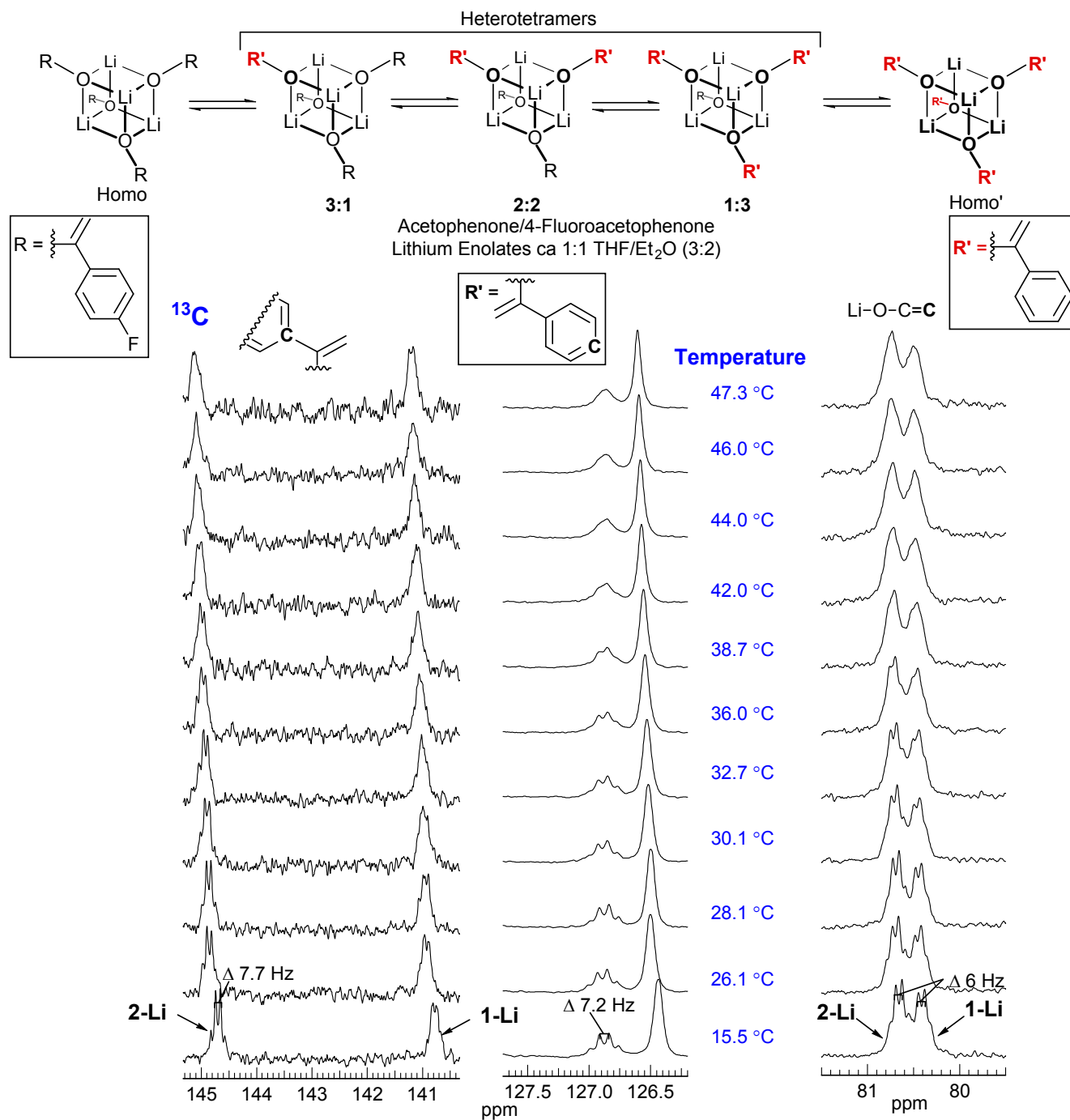
**General Preparation of Enolate Samples for Multinuclear NMR Spectroscopy.** Lithium diisopropylamide was prepared fresh by the following procedure. Solvent was added (typically 1.8 mL of THF and 1.2 mL of Et<sub>2</sub>O) including 1-2  $\mu$ L of 10% <sup>13</sup>C enriched (Me<sub>3</sub>Si)<sub>3</sub>CH as a shift thermometer<sup>[S2]</sup> to a dried thin-walled 10 mm NMR tube that had been stored under vacuum, fitted with septa, and flushed with N<sub>2</sub> or Ar. Silicon grease was applied to the interface between the tube and the septa before securing with parafilm for a better seal, as well as to the top of the septa to seal needle punctures. The NMR tube was cooled to -78 °C under positive N<sub>2</sub> or Ar pressure and diisopropylamine (42  $\mu$ L, 0.30 mmol) and *n*-BuLi (120  $\mu$ L, 2.5 M) were added to the solution. The solution was warmed to 0 °C in an ice bath for 5 min, and then cooled to -78 °C under positive N<sub>2</sub> or Ar pressure. The carbonyl compound was added by syringe either neat or as a solution in a solvent. Samples free of diisopropylamine were prepared from either crystallized enolate or from cleavage of the enol silyl ether with *n*-BuLi (-78 °C to 0 °C). Experiments run using these samples did not differ in chemistry or kinetics from those containing diisopropylamine. Samples were stored at -78 °C. The spectrometer probe was cooled to <-78 °C, the sample was inserted and the probe was shimmed on the <sup>13</sup>C FID of the THF peak. Spectra of NMR active nuclei which usually included <sup>13</sup>C, <sup>31</sup>P, <sup>19</sup>F, <sup>7</sup>Li and <sup>1</sup>H were acquired. At this point, a titration, variable temperature or variable concentration experiment could be performed. In the case of a titration experiment, for each addition the sample was ejected, placed in a -78 °C bath, the silicon grease was removed from the top of the septum, a desired amount of cosolvent was added, silicon grease was reapplied to the top of the septum and the NMR spectra were measured, including a <sup>13</sup>C NMR spectrum to determine the sample temperature.

**Variable Temperature NMR Study of Heterotetramer Exchange.** 4-Fluoroacetophenone (35  $\mu$ L, 0.3 mmol) and acetophenone (35  $\mu$ L, 0.3 mmol) were added at -78  $^{\circ}$ C to 3 mL of a 0.2 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) and 1-2  $\mu$ L of 10% <sup>13</sup>C enriched (Me<sub>3</sub>Si)<sub>3</sub>CH as a shift thermometer<sup>[S2]</sup> was added. <sup>13</sup>C and <sup>19</sup>F spectra were acquired at 258 K, 269 K, 297 K, 307 K, 317 K, 326 K, 332 K, 336 K, and 338 K. Spectra are shown in Figure S-1.

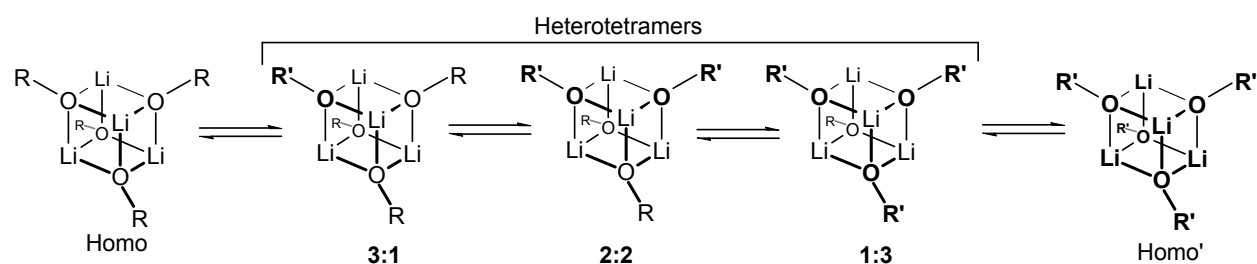


**Figure S-1.** <sup>13</sup>C and <sup>19</sup>F NMR spectra of a mixing experiment of enolates of acetophenone and 4-fluoroacetophenone in 3:2 THF/ether at various temperatures. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate (**1-Li**)<sub>4</sub>; actual concentrations determined based on integration relative to the internal standard.)

**$^{13}\text{C}$  DNMR Study of Heterotetramer Exchange.** 4-Fluoroacetophenone (35  $\mu\text{L}$ , 0.3 mmol) and acetophenone (35  $\mu\text{L}$ , 0.3 mmol) were added at  $-78^\circ\text{C}$  to 3 mL of a 0.2 M solution (3:2 THF/ $\text{Et}_2\text{O}$ ) of freshly prepared LDA.  $(\text{Me}_3\text{Si})_3\text{CH}$  (1-2  $\mu\text{L}$  of 10%  $^{13}\text{C}$  enriched) was added as a shift thermometer.<sup>[S2]</sup>  $^1\text{H}$ ,  $^{13}\text{C}$ , 7Li and  $^{19}\text{F}$  NMR spectra were acquired at 295 K.  $^{13}\text{C}$  NMR spectra were acquired at 290 K, 297 K, 300 K, 303 K, 306 K, 309 K, 312 K, 314 K, 316 K, and 318 K. Spectra are shown in Figure S-2 and Figure S-4. Lineshape analysis was performed using WinDNMR<sup>[S3]</sup> using the exchange matrix in Figure S-3 and spectra with simulated fits are shown in Figure S-4. Simulation data is presented in Table S-1. Figure 1 in the main paper shows an Eyring plot of the data.



**Figure S-2.** Select resonances of the  $^{13}\text{C}$  NMR spectra of a DNMR mixing experiment of enolates of acetophenone (**2-Li**) and 4-fluoroacetophenone (**1-Li**) in 3:2 THF/ether at various temperatures. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate (**1-Li**)<sub>4</sub>.)



4-Nucleus exchange matrix

	A	B	C	D
	T <sub>4,0</sub>	T <sub>3,1</sub>	T <sub>2,2</sub>	T <sub>1,3</sub>
A	T <sub>4,0</sub>	2/4	1/4	0
B	T <sub>3,1</sub>	2/12	4/12	1/12
C	T <sub>2,2</sub>	1/12	4/12	2/12
D	T <sub>1,3</sub>	0	1/4	2/4

Statistical distribution of tetramers:

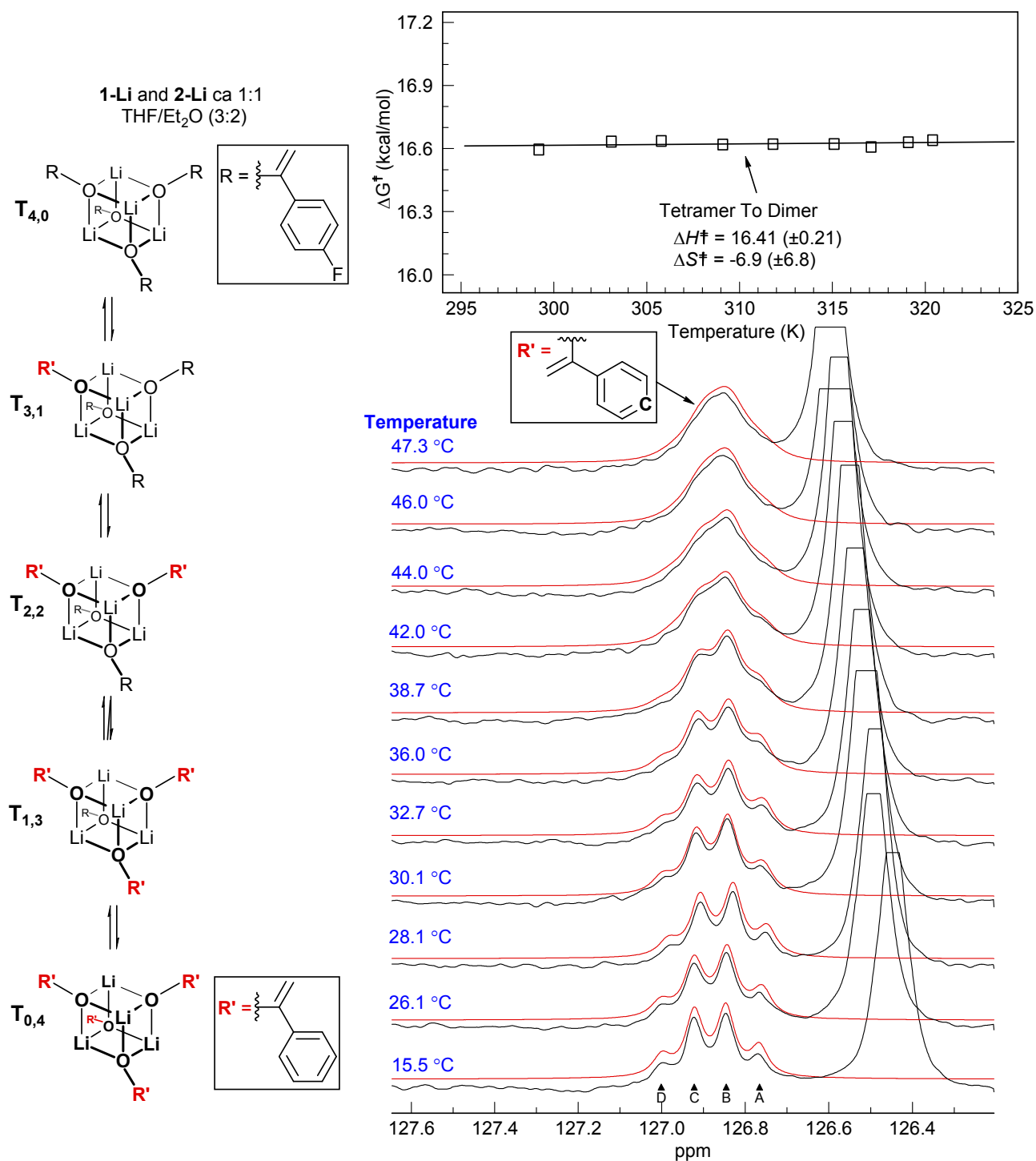
	Pop	#Fs	Signal
T <sub>4,0</sub>	1	4	4
T <sub>3,1</sub>	4	3	12
T <sub>2,2</sub>	6	2	12
T <sub>1,3</sub>	4	1	4
T <sub>0,4</sub>	1	0	0

**Figure S-3.** Four spin exchange matrix for the exchange of the homogenous and heterogenous tetrameric species NMR signals via a dimer based pathway.



**Table S-1.** Simulation data for the  $^{13}\text{C}$  DNMR spectra of the exchange of the homogenous and heterogenous (mixed) tetrameric species of **2-Li** and **1-Li** in 3:2 THF/Et<sub>2</sub>O.

Temp. °C	15.5	26.1	28.1	30	32.7	36	38.7	42	44	46	47.3
$\nu_a$ /Hz	13982	13981.3	13980.2	13981.1	13980.9	13981.4	13981.3	13980.6	13980.2	13980.2	13980.1
$\nu_b$ /Hz	13989.3	13989	13987.7	13988.8	13988.6	13988.6	13988.6	13988.6	13988.2	13988.2	13988.1
$\nu_c$ /Hz	13996.2	13996.3	13995	13995.9	13995.9	13995.9	13995.8	13996	13995.8	13995.8	13995.3
$\nu_d$ /Hz	14003.3	14003.6	14002	14003.3	14003.5	14003.5	14003.8	14003.5	14003.2	14003.2	14002.7
$k$ / sec <sup>-1</sup>	1.7	4.7	5	6.4	8.2	11.4	14.5	19.4	23.6	27	29.7
% a	16.22	17.35	16.9	16.54	19.21	19.69	18.34	17.19	17.12	16.1	17.63
% b	37.15	39.17	39.35	40.01	39.2	37.97	42	42.34	41.89	42.78	39.65
% c	34.98	33.36	33.89	33.17	31.76	32.52	31.77	30.97	31.34	32.13	32.81
% d	11.66	10.12	9.86	10.28	9.83	9.82	7.89	9.5	9.65	8.99	9.91
$W_a^a$ /Hz	4.2	4	3.8	4	3.8	3.6	3.8	4.2	3.7	4	3.7
$W_b^a$ /Hz	4.2	4	3.8	4	3.8	3.6	3.8	4.2	3.7	4	3.7
$W_c^a$ /Hz	4.2	4	3.8	4	3.8	3.6	3.8	4.2	3.7	4	3.7
$W_d^a$ /Hz	4.2	4	3.8	4	3.8	3.6	3.8	4.2	3.7	4	3.7
$\Delta G^\ddagger$ / kcal/mol	16.57	16.59	16.67	16.63	16.64	16.62	16.62	16.62	16.61	16.63	16.64



**Figure S-4.** <sup>13</sup>C DNMR spectra of the exchange of the homogenous and heterogenous (mixed) tetrameric species of 2-Li and 1-Li in 3:2 THF/Et<sub>2</sub>O. The upper (red) lines are simulations using the four spin dimer-based exchange simulation in WINDNMR.<sup>[S3]</sup> (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate (1-Li)<sub>4</sub>.)

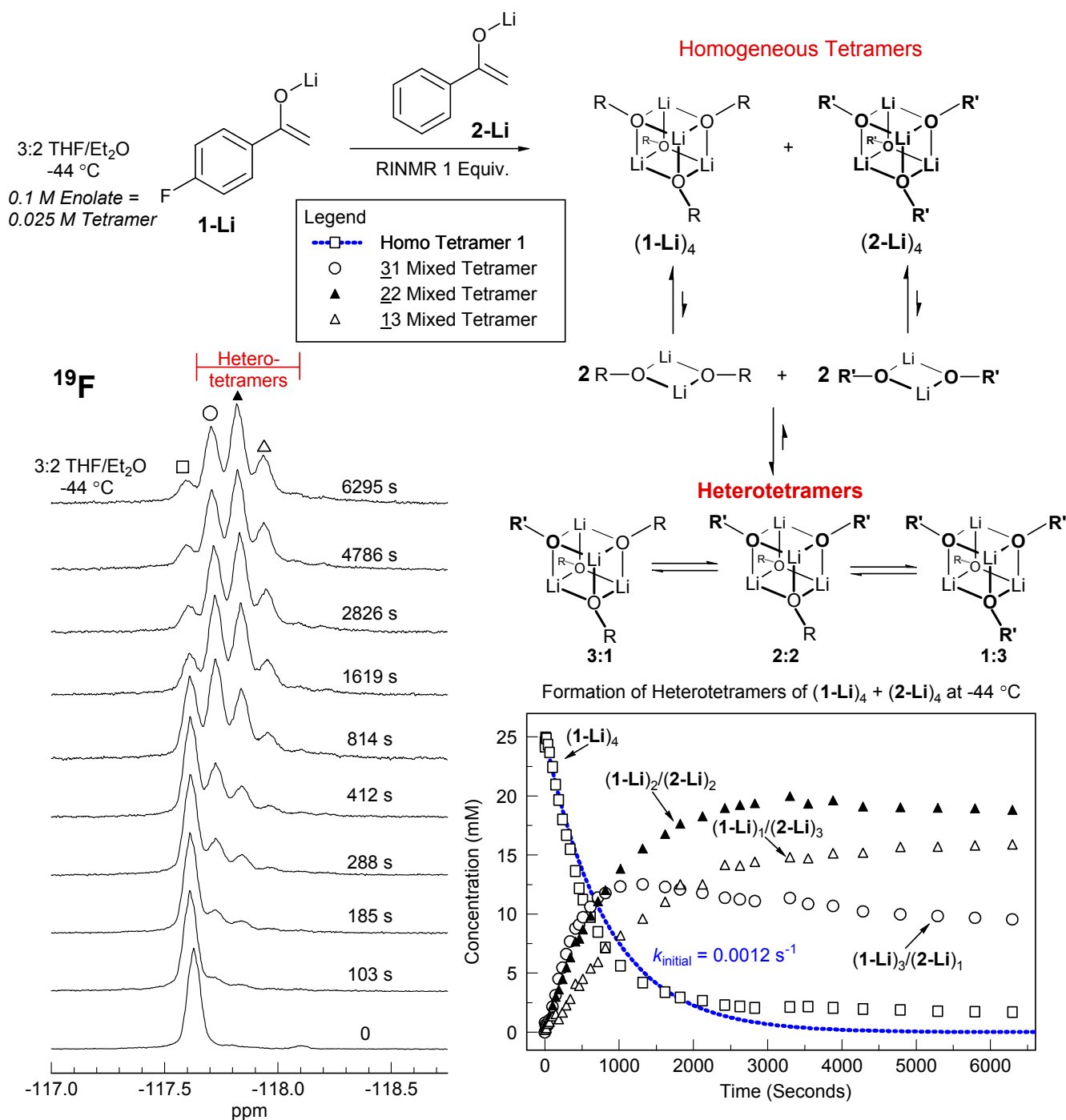
#### S4. Rapid Injection NMR Experiments

**General Preparation of RI-NMR 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, 1.8 mL of freshly distilled THF and 1.2 mL of freshly distilled Et<sub>2</sub>O, a <sup>13</sup>C chemical shift thermometer (10% <sup>13</sup>C labeled *tris*(trimethylsilyl)methane, 0.004 mL),<sup>[S2]</sup> and substrate were measured out. 1,3-Difluorobenzene (0.005 mL) was added as a <sup>19</sup>F 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 are made. The material to be injected was weighed into a separate, septum-sealed, argon purged flask and dissolved in THF/Et<sub>2</sub>O 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 <sup>13</sup>C NMR.<sup>[S2]</sup> The sample was raised, the septum removed, and the open NMR tube was expeditiously lowered into the spectrometer and the apparatus was assembled.

<sup>19</sup>F RI-NMR experiments were performed as follows (a more detailed description of the sequence and apparatus has been given).<sup>[S4]</sup> 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.<sup>[S4]</sup> 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*<sub>1</sub> for 4-fluorophenyl signals was ca 0.3 s at -125 °C) for a few min after which a longer time interval between scans (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 <sup>19</sup>F 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. Quenched products were isolated as outlined in the synthesis section.

##### **Rate of Heterotetramer Formation by Injection of 2-Li into a Solution of 1-Li. 4-**

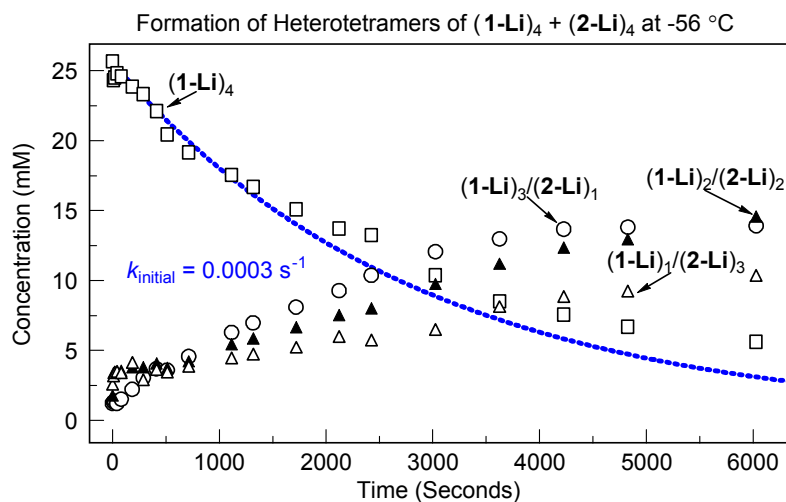
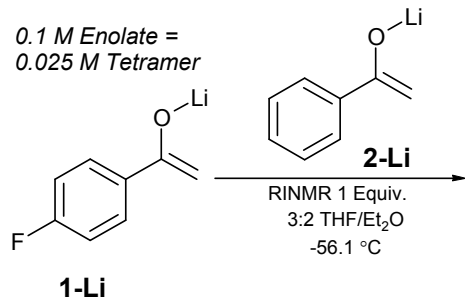
Fluoroacetophenone (35 µL, 0.3 mmol) was added at -78 °C to 3 mL of a freshly prepared solution of 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> in 3:2 THF/Et<sub>2</sub>O. 1,3-Difluorobenzene (5 µL) was added as an internal standard. <sup>1</sup>H, <sup>7</sup>Li, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were obtained at temperature indicated. Following the general RI-NMR procedure 0.3 mL of a 1.0 M solution of **2-Li** in 3:2 THF/ Et<sub>2</sub>O was injected and <sup>19</sup>F spectra were obtained every 2 seconds for 7 minutes after which <sup>19</sup>F spectra were obtained every 10 seconds for 40 minutes. Post kinetic analysis was then performed. Spectra and a concentration versus time graph are shown in Figure S-5 for injection at -44 °C. Concentration versus time graphs are shown in Figures S-6 (-56 °C), S-7 (-18.3 °C), and S-8 (-29.6 °C).



**Figure S-5.** Injection of 2-Li into a solution of 1-Li at -44 °C. Formation of signals corresponding to the heterotetrameric species (2-Li/1-Li) is observed over several minutes. The rate determining step for the formation of heterotetramers (2-Li/1-Li) was assumed to be the dissociation of the homogenous tetramers [(1-Li)<sub>4</sub> ⇌ 2 (1-Li)<sub>2</sub>] followed by fast combination of the dimers to form the more stable tetrameric forms. The dashed line corresponds to a first order fit for the first 10% dissociation of (1-Li)<sub>4</sub> with the rate constant indicated on the graph. Note that the 2:2-heterotetramer does not appear to be the first-formed one, as would be required for a strictly dimer based mechanism. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate (1-Li)<sub>4</sub>.)

### <sup>19</sup>F RINMR Formation of Heterotetramers

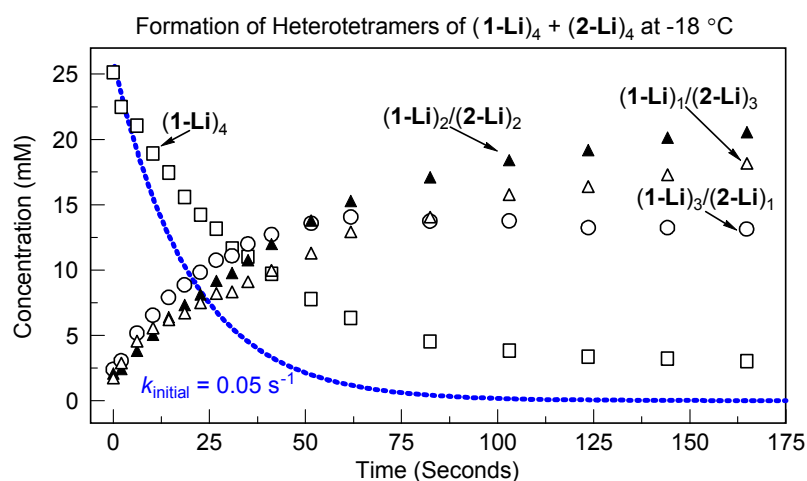
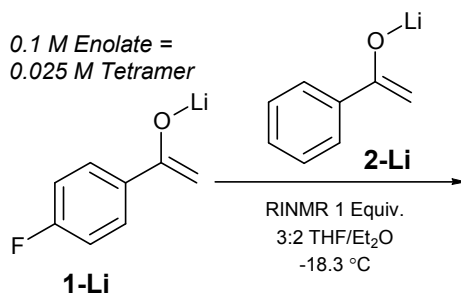
0.1 M Enolate =  
0.025 M Tetramer



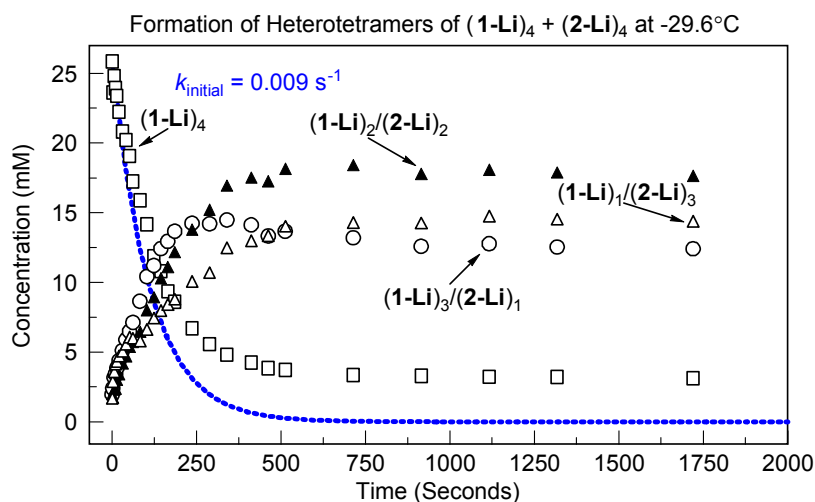
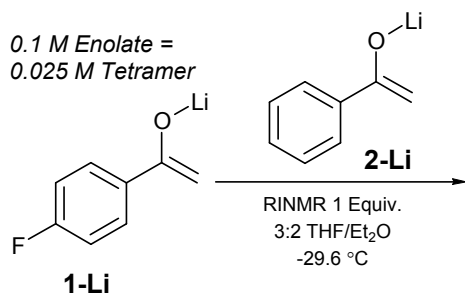
**Figure S-6.** A concentration versus time graph for the injection of **2-Li** into a solution of **1-Li** at -56 °C. The dashed line corresponds to a first order fit for the first 10% dissociation of (1-Li)<sub>4</sub> with the rate constant indicated on the graph. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate (1-Li)<sub>4</sub>.)

### <sup>19</sup>F RINMR Formation of Heterotetramers

0.1 M Enolate =  
0.025 M Tetramer



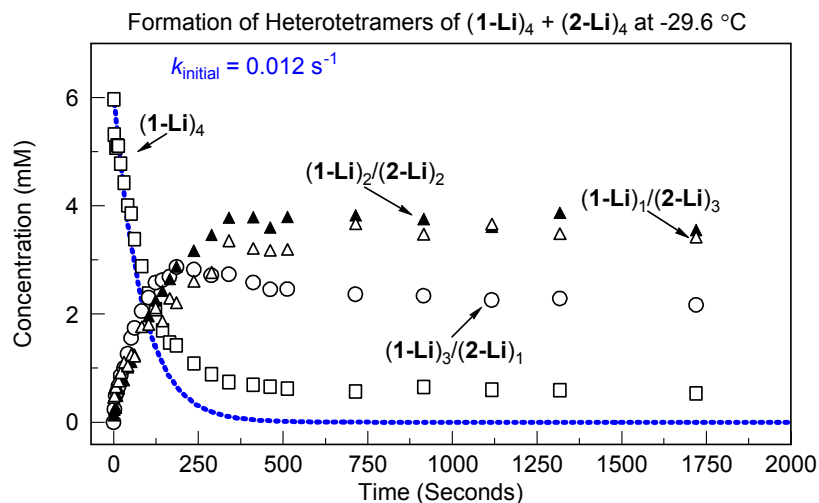
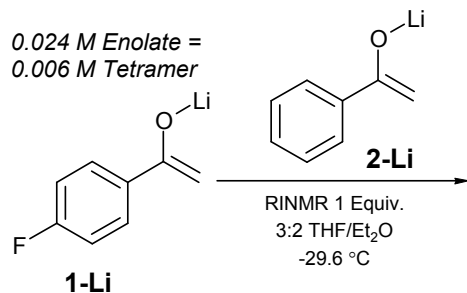
**Figure S-7.** A concentration versus time graph for the injection of **2-Li** into a solution of **1-Li** at -18 °C. The dashed line corresponds to a first order fit for the first 10% dissociation of (1-Li)<sub>4</sub> with the rate constant indicated on the graph. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate (1-Li)<sub>4</sub>.)

**<sup>19</sup>F RINMR Formation of Heterotetramers**

**Figure S-8.** A concentration versus time graph for the injection of **2-Li** into a solution of **1-Li** at -29.6 °C. The dashed line corresponds to a first order fit for the first 10% dissociation of **(1-Li)<sub>4</sub>** with the rate constant indicated on the graph. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate **(1-Li)<sub>4</sub>**.)

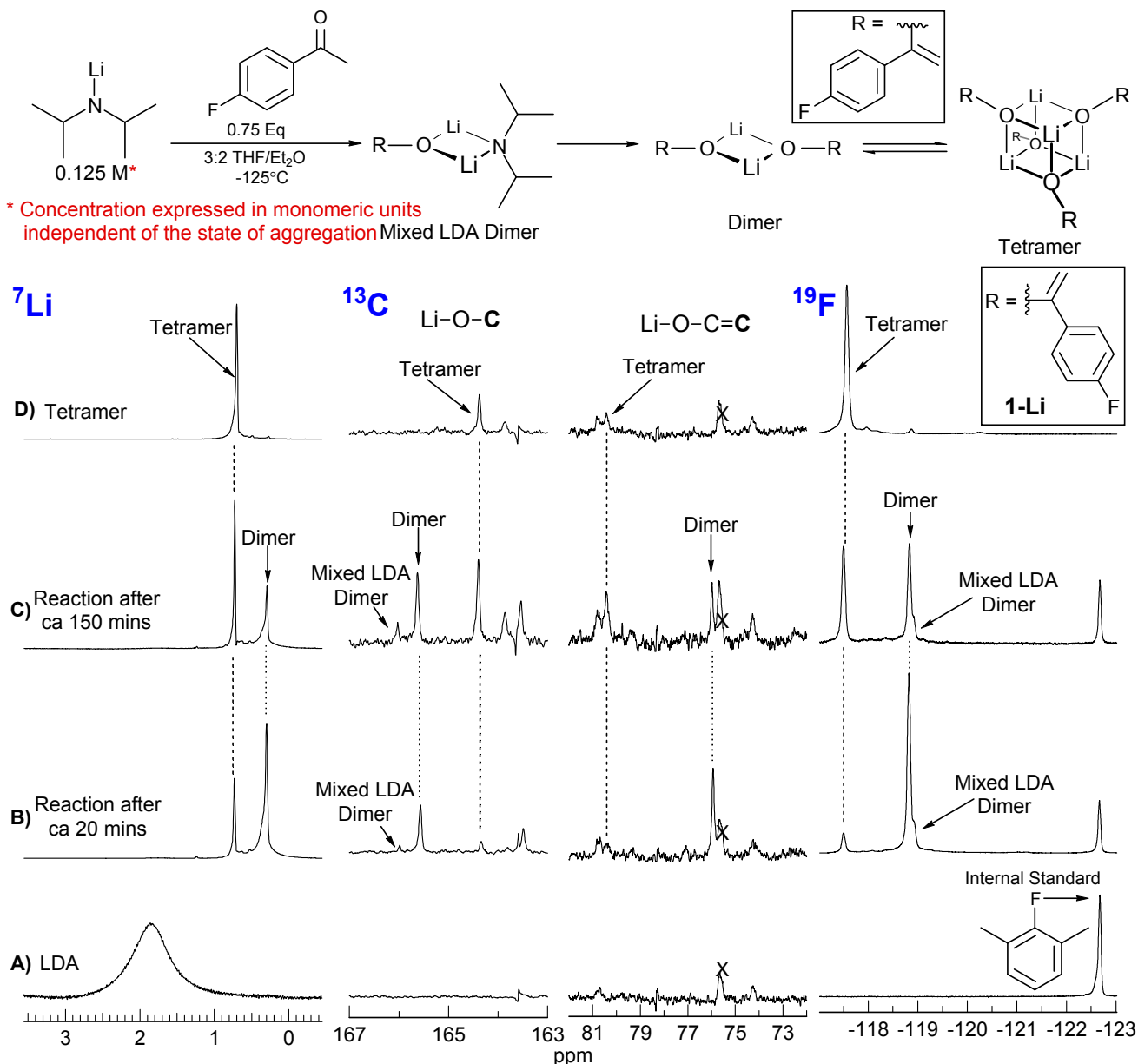
**Rate of Heterotetramer Formation by Injection of 2-Li into a Solution of 1-Li at Reduced**

**Concentration.** 4-Fluoroacetophenone (9  $\mu\text{L}$ , 0.075 mmol) was added at -78 °C to a freshly prepared solution of 0.025 M  $\text{LiN}^i\text{Pr}_2$  in 3:2 THF/Et<sub>2</sub>O (3 mL). 1,3-difluorobenzene (5  $\mu\text{L}$ ) was added as an internal standard. <sup>1</sup>H, <sup>7</sup>Li, <sup>13</sup>C, and <sup>19</sup>F NMR spectra were obtained at -29.6 °C. Following the general RI-NMR procedure 0.3 mL of a 0.125 M solution of **2-Li** in 3:2 THF/Et<sub>2</sub>O was injected and <sup>19</sup>F spectra were obtained every 2 seconds for 7 minutes after which <sup>19</sup>F spectra were obtained every 10 seconds for 40 minutes. Post kinetic analysis was then performed. A concentration versus time graph is shown in Figure S-9. Figure 1 in the main paper shows an Eyring plot of the data.

**<sup>19</sup>F RINMR Formation of Heterotetramers**

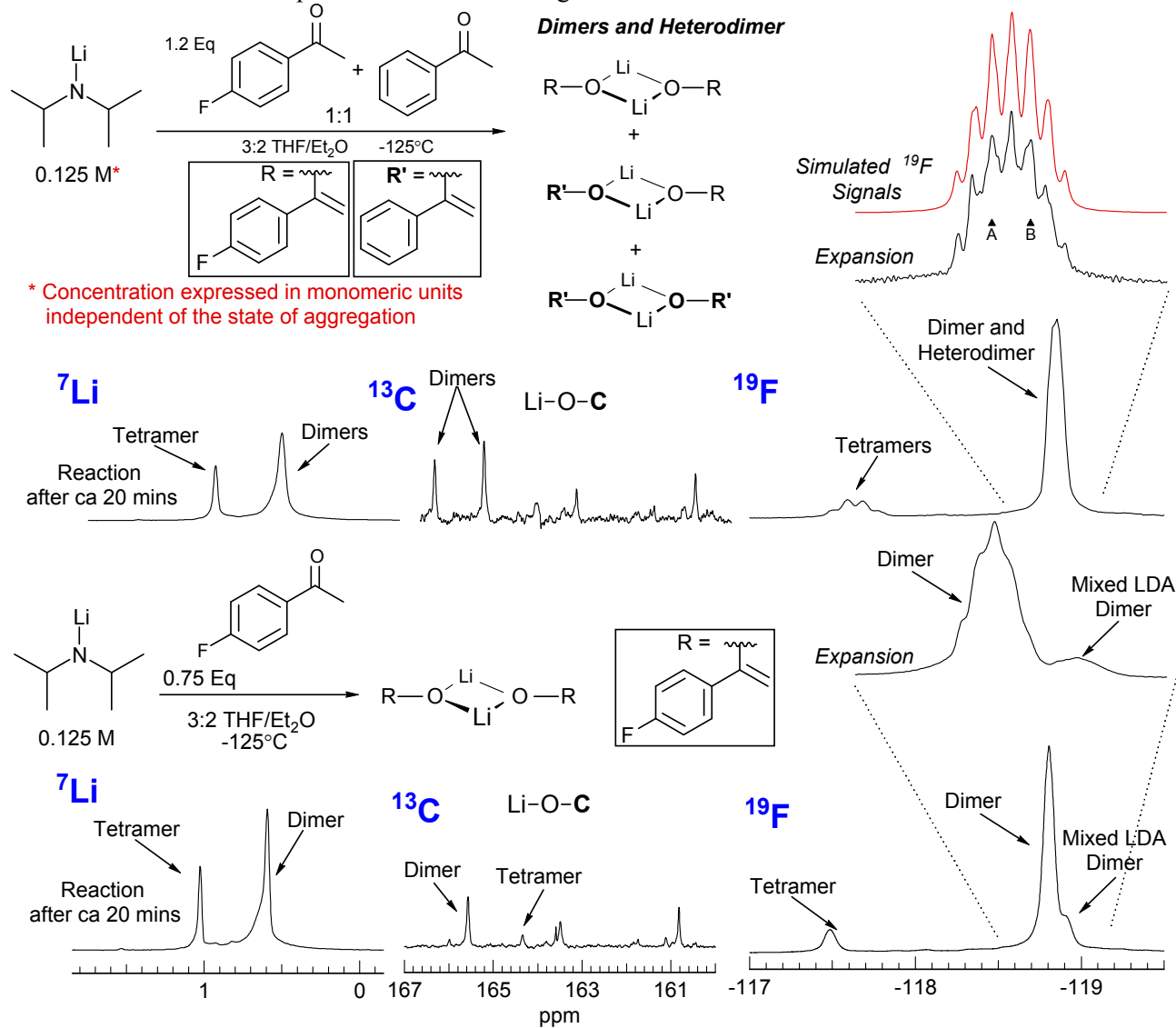
**Figure S-9.** A concentration versus time graph for the injection of **2-Li** into a solution of **1-Li** at -29.6 °C under reduced concentration of both enolates. The dashed line corresponds to a first order fit for the first 10% dissociation of **(1-Li)<sub>4</sub>** with the rate constant indicated on the graph. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M Tetrameric Enolate **(1-Li)<sub>4</sub>**.)

**Formation of Dimeric 4-Fluoroacetophenone Enolate ( $1\text{-Li}$ )<sub>2</sub> at  $-125\text{ }^{\circ}\text{C}$ .** 1,3-Dimethyl-2-fluorobenzene ( $5\text{ }\mu\text{L}$ ) was added to  $3\text{ mL}$  of a freshly prepared  $3:2\text{ THF/Et}_2\text{O}$  solution of  $0.1\text{ M LiN}^i\text{Pr}_2$  in a dried thin-walled  $10\text{ mm}$  NMR tube.  $^{13}\text{C}$ ,  $^{19}\text{F}$  and  $^7\text{Li}$  spectra were acquired at  $-125\text{ }^{\circ}\text{C}$  to check concentration and sample integrity. Following the general RI-NMR procedure, 4-fluoroacetophenone ( $0.15\text{ mL}$  of a  $2.0\text{ M}$  solution) was added and  $^{19}\text{F}$  NMR spectra were obtained for the first 15 minutes of reaction.  $^{13}\text{C}$ ,  $^{19}\text{F}$  and  $^7\text{Li}$  spectra were acquired at ca 20 minutes and ca 150 minutes after the initial ketone addition. Spectra are shown in Figure S-10.



**Figure S-10.**  $^7\text{Li}$ ,  $^{13}\text{C}$ , and  $^{19}\text{F}$  NMR of the reaction of LDA with 4-fluoroacetophenone (**1-H**) in  $3:2\text{ THF/Et}_2\text{O}$  at  $-125\text{ }^{\circ}\text{C}$  at ca 20 minutes (B) and ca 150 minutes (C). Spectra for LDA (A) and tetrameric **4-Li** (D) are shown for comparison. (Note from written procedure to figure:  $0.125\text{ M}$  LDA expressed in monomeric units.)

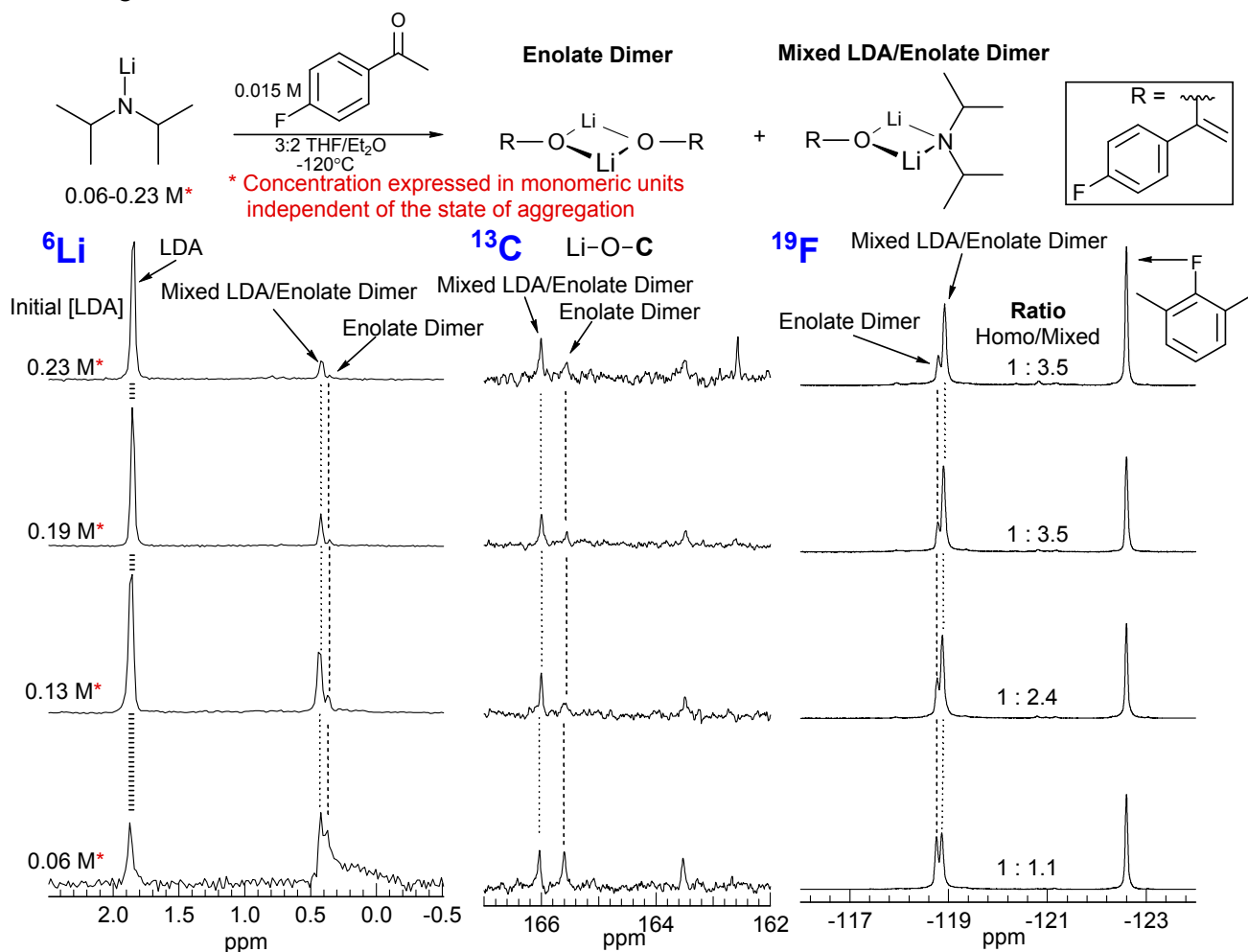
**LDA Enolization of 4-Fluoroacetophenone and Acetophenone Mixture.** 1,3-Dimethyl-2-fluorobenzene (5  $\mu$ L) was added to 3 mL of a freshly prepared 3:2 THF/Et<sub>2</sub>O solution of 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> in a dried thin-walled 10 mm NMR tube. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -125 °C to check concentration and sample integrity. Following the general RI-NMR procedure, 4-Fluoroacetophenone and acetophenone (0.15 mL of a 2.2 M solution of 1:1 ketones) were added and <sup>19</sup>F NMR spectra were obtained for the first 15 minutes of reaction. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired 20 minutes after the initial ketone addition. The <sup>19</sup>F NMR spectrum of the mixed and homo dimers of two superimposed multiplets was simulated using WINDMR<sup>[S3]</sup> using the dddd DNMR two spin simulation ( $J = 8.8, 8.8, 6.6, 6.6$  Hz,  $k_{ab} + k_{ba} = 0$ ,  $A\% = B\% = 50\%$ ). Spectra along with the simulated <sup>19</sup>F NMR spectrum are shown in Figure S-11.



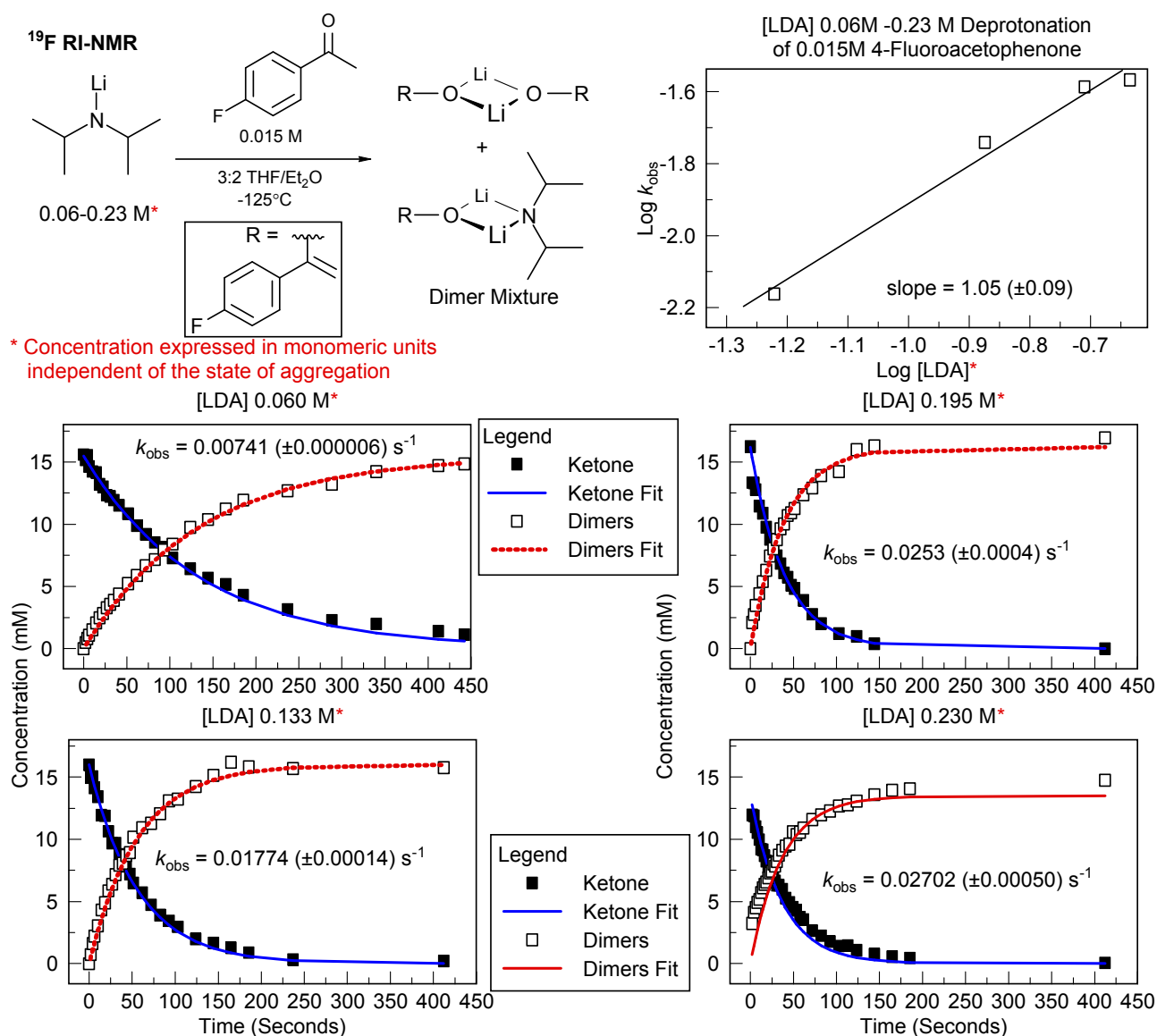
**Figure S-11.** Ketone mixing experiment for the formation of kinetic dimers of 4-fluoroacetophenone and acetophenone. Top Spectra: <sup>7</sup>Li, <sup>13</sup>C, and <sup>19</sup>F NMR of the reaction of LDA with a 1:1 mixture of 4-fluoroacetophenone (**1-H**) and acetophenone (**2-H**) in 3:2 THF/Et<sub>2</sub>O at -125 °C at ca 20 minutes. Bottom Spectra: The reaction of LDA with 4-fluoroacetophenone (**1-H**) in 3:2 THF/Et<sub>2</sub>O at -125 °C at ca 20 minutes shown for comparison. (Note from written procedure to figure: 0.125 M LDA expressed in monomeric units.)



**Reaction Order in LDA for the LDA Mediated Enolization of 1-H.** Samples were prepared in the following manner. Solvent was added, 1.8 mL of THF and 1.2 mL of Et<sub>2</sub>O, including 1-2  $\mu$ L of <sup>13</sup>C enriched (10%) (Me<sub>3</sub>Si)<sub>3</sub>CH as a shift thermometer<sup>[S2]</sup> to a dried thin-walled 10 mm NMR tube that had been stored under vacuum, fitted with septa, and flushed with N<sub>2</sub> or Ar. The NMR tube was cooled to -78 °C under positive N<sub>2</sub> or Ar pressure and the appropriate amounts of diisopropylamine and *n*-butyllithium were added to the solution. The solution was warmed to 0 °C in an ice bath for 5 minutes and the solution was cooled to -78 °C under positive N<sub>2</sub> or Ar pressure. 1,3-Dimethyl-2-fluorobenzene (5  $\mu$ L) was added. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -125 °C to check concentration and sample integrity. LDA concentration was determined based on <sup>13</sup>C NMR integration data relative to 1,3-dimethyl-2-fluorobenzene. Following the general RI-NMR procedure, 4-fluoroacetophenone (0.15 mL of a 0.5 M solution) was added and <sup>19</sup>F NMR spectra were obtained. The <sup>19</sup>F NMR spectrum of the mixed and homo dimer was simulated using WINDMR<sup>[S3]</sup> using the dddd DNMR simulation ( $J = 8.8, 8.8, 6.6, 6.6$  Hz,  $k_{ab} + k_{ba} = 0$ ) to determine the relative ratios at the end of the reaction. Spectra are shown in Figure S-12. The kinetic pathway of these reactions were simulated with COPASI<sup>[S5]</sup> using a parameter estimation routine and the Nelder-Mead or Levenberg-Marquardt methods, and fitting ketone and enolate concentration to the first order reaction Ketone  $\rightarrow$  Enolate ( $d[\text{Enolate}]/dt = k[\text{Ketone}]$  and  $d[\text{Ketone}]/dt = -k[\text{Ketone}]$ ). Concentration versus time plots with the fit simulation values and a log plot of  $k_{\text{obs}}$  versus LDA concentration are shown in Figure S-13.

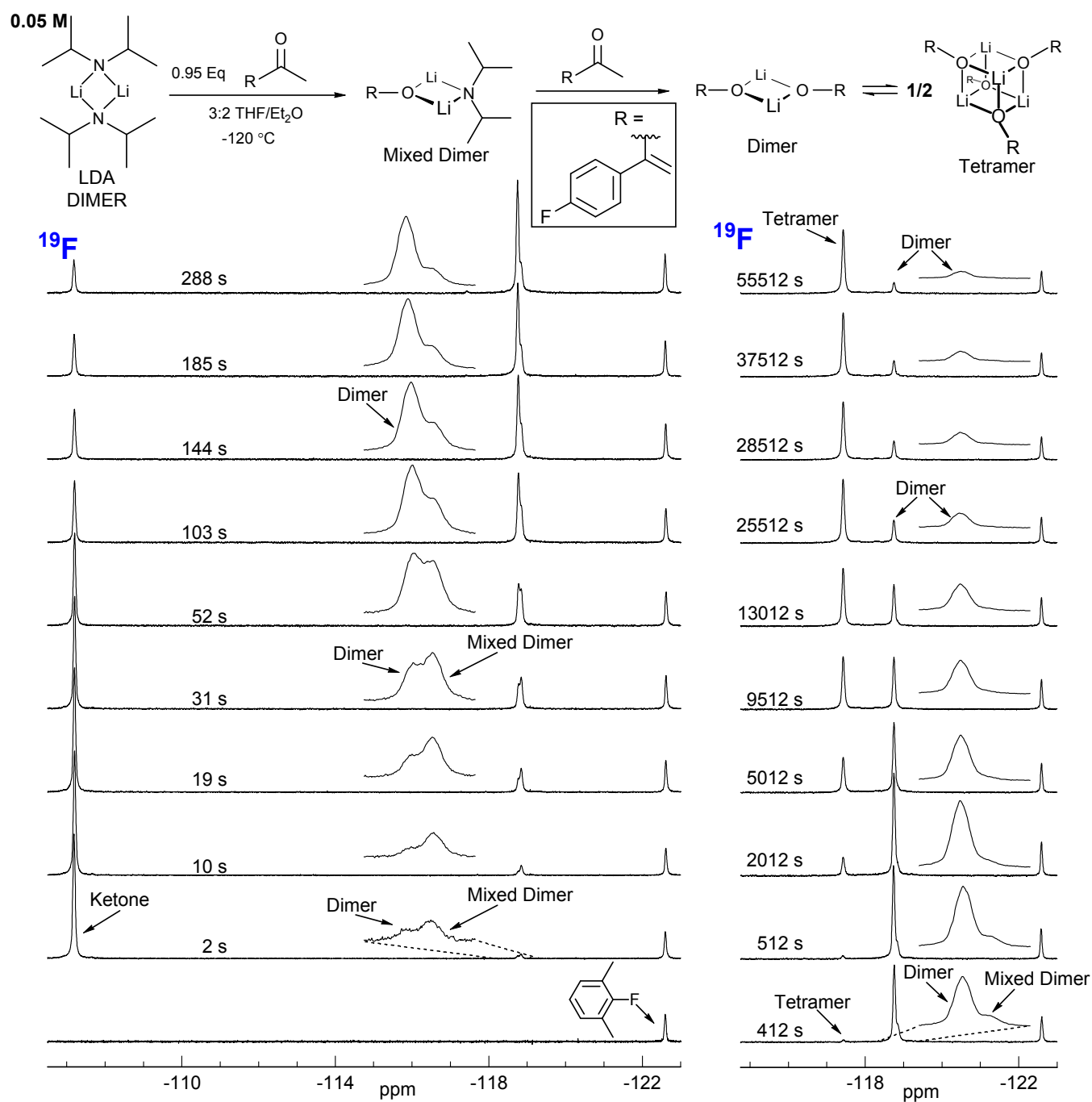


**Figure S-12.** <sup>6</sup>Li, <sup>13</sup>C and <sup>19</sup>F NMR spectra of the resulting solutions from the reaction of 0.015M 4-fluoroacetophenone with various concentrations of LDA (0.06-0.23 M) in 3:2 THF/Et<sub>2</sub>O at -125 °C at >95% reaction. These spectra demonstrate that as the concentration of LDA was increased, the ratio of mixed LDA dimer to homo enolate dimer increased. (Note from written procedure to figure: [LDA] expressed in monomeric units.)

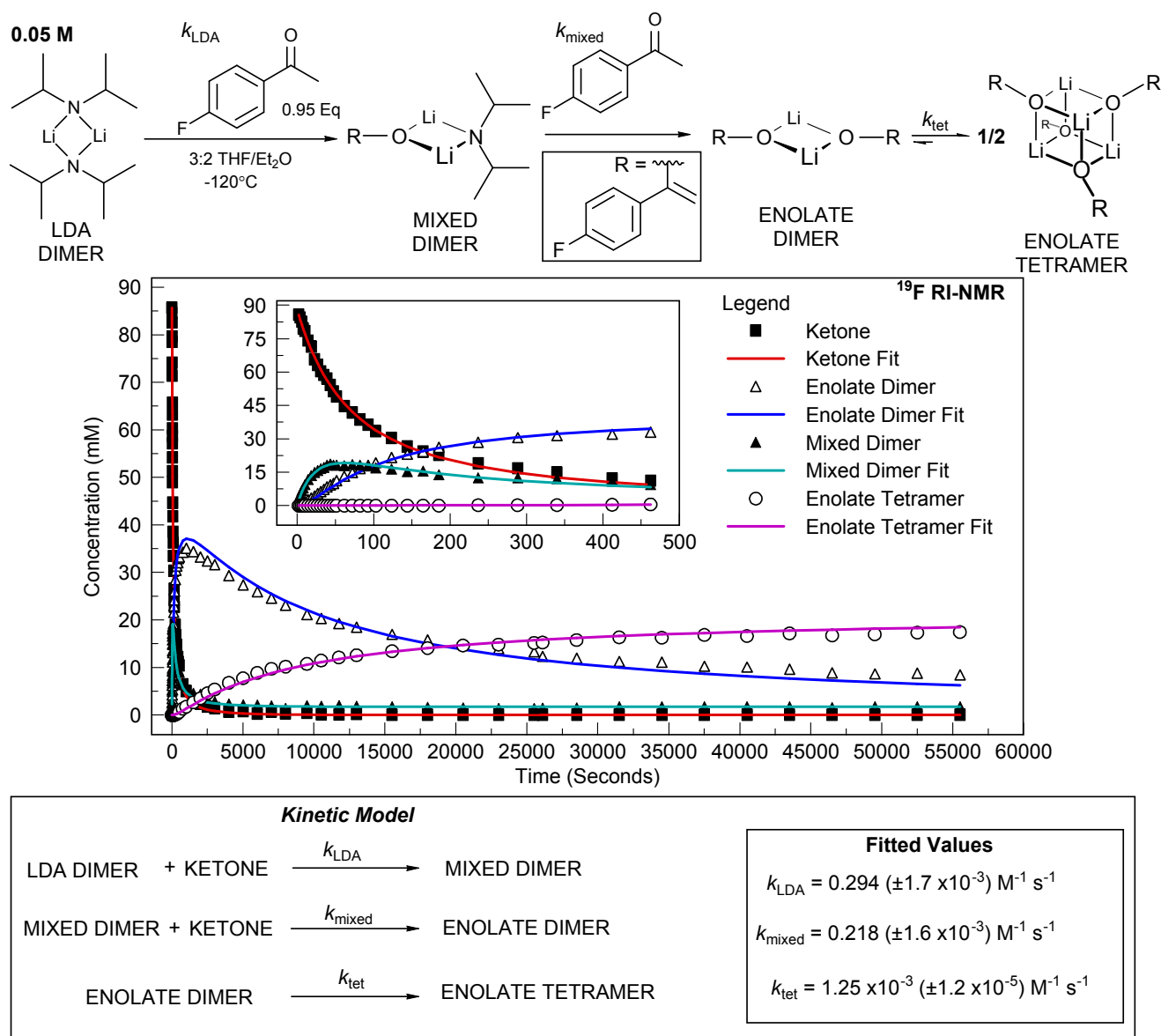


**Figure S-13.** Reaction order in LDA for the enolization of 4-fluoroacetophenone with LDA in 3:2 THF/Et<sub>2</sub>O at -125 °C. A first order dependence on LDA concentration was found indicating direct reaction with the LDA dimer. (Note from written procedure to figure: [LDA] expressed in monomeric units.)

**<sup>19</sup>F RI-NMR of LDA Enolization of 1 Equivalent of 4-Fluoroacetophenone at -120 °C.** 1,3-Dimethyl-2-fluorobenzene (5 μL) was added to 3 mL of a freshly prepared 3:2 THF/Et<sub>2</sub>O solution of 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> in a dried thin-walled 10 mm NMR tube. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C to check concentration and sample integrity. Following the general RI-NMR procedure, 4-Fluoroacetophenone (0.15 mL of a 2.0 M solution) was added and <sup>19</sup>F NMR spectra were obtained for several hours. Spectra are shown in Figure S-14. The <sup>19</sup>F NMR spectrum of the mixed and homo dimer was simulated using the NUTS automated line fitting routine.<sup>[S6]</sup> All other concentrations were determined by integration techniques relative to 1,3-dimethyl-2-fluorobenzene. The kinetic pathway of this reaction was simulated with COPASI<sup>[S5]</sup> using the parameter estimation routine and the Nelder-Mead or Levenberg-Marquardt methods, and was fit to the reaction scheme shown in Figure S-15. Concentration versus time plot along with the fit simulation values are shown in Figure S-15. Data from this experiment is presented in Figure 2 of the main paper.



**Figure S-14.** <sup>19</sup>F RI-NMR experiment of LDA mediated enolization of 4-fluoroacetophenone (**1-H**) in 3:2 THF/Et<sub>2</sub>O at -120 °C. Insets are included to show the mixed LDA/enolate dimer and enolate dimer signals more clearly. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)

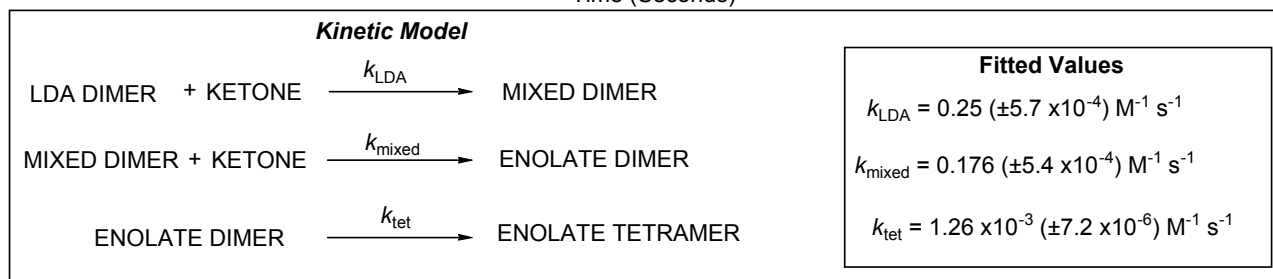
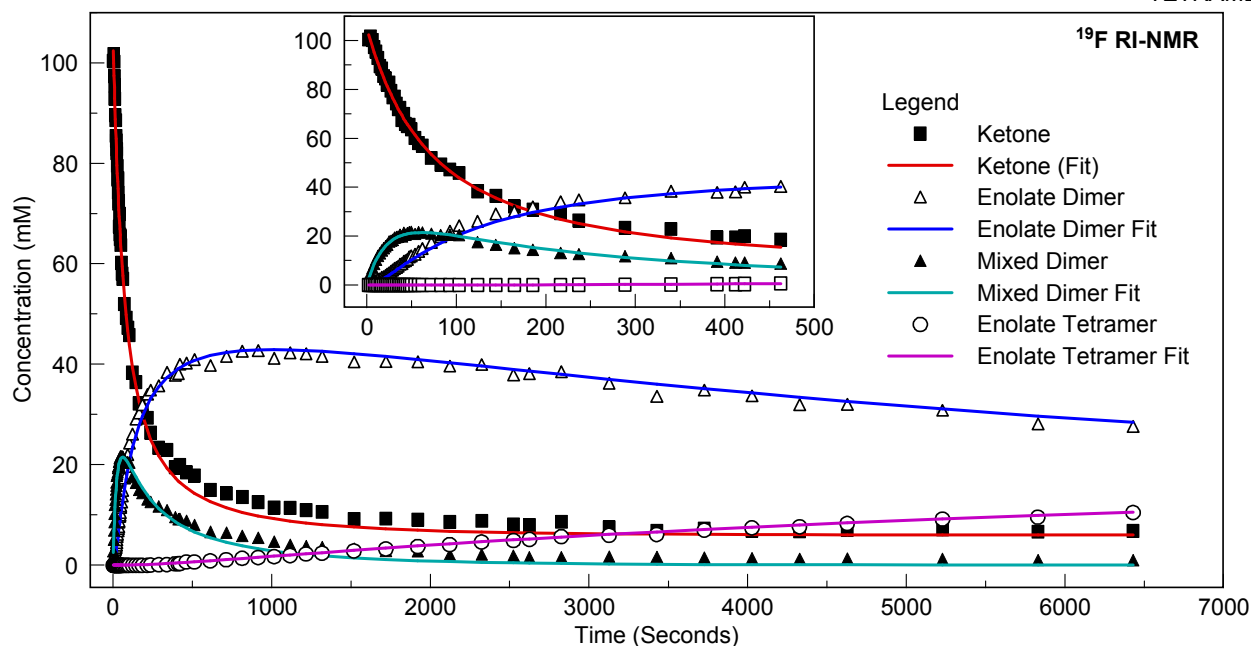
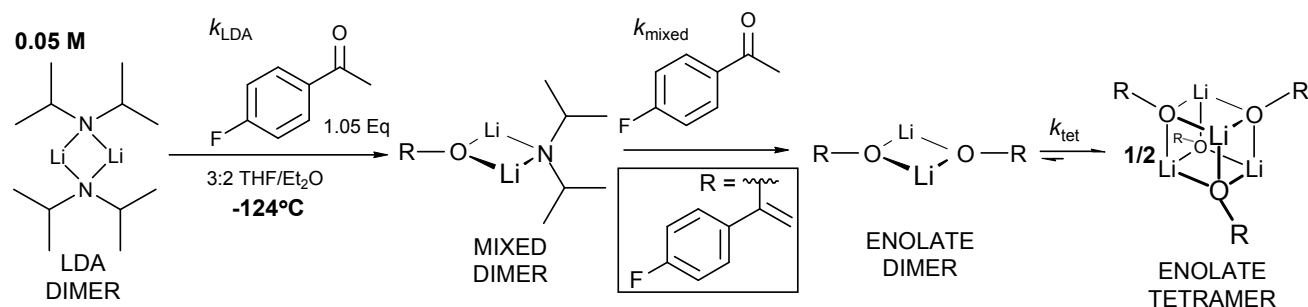


**Figure S-15.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -120 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M Li<sup>n</sup>iPr<sub>2</sub> = 0.05 M LDA dimer (Li<sup>n</sup>iPr<sub>2</sub>)<sub>2</sub>)

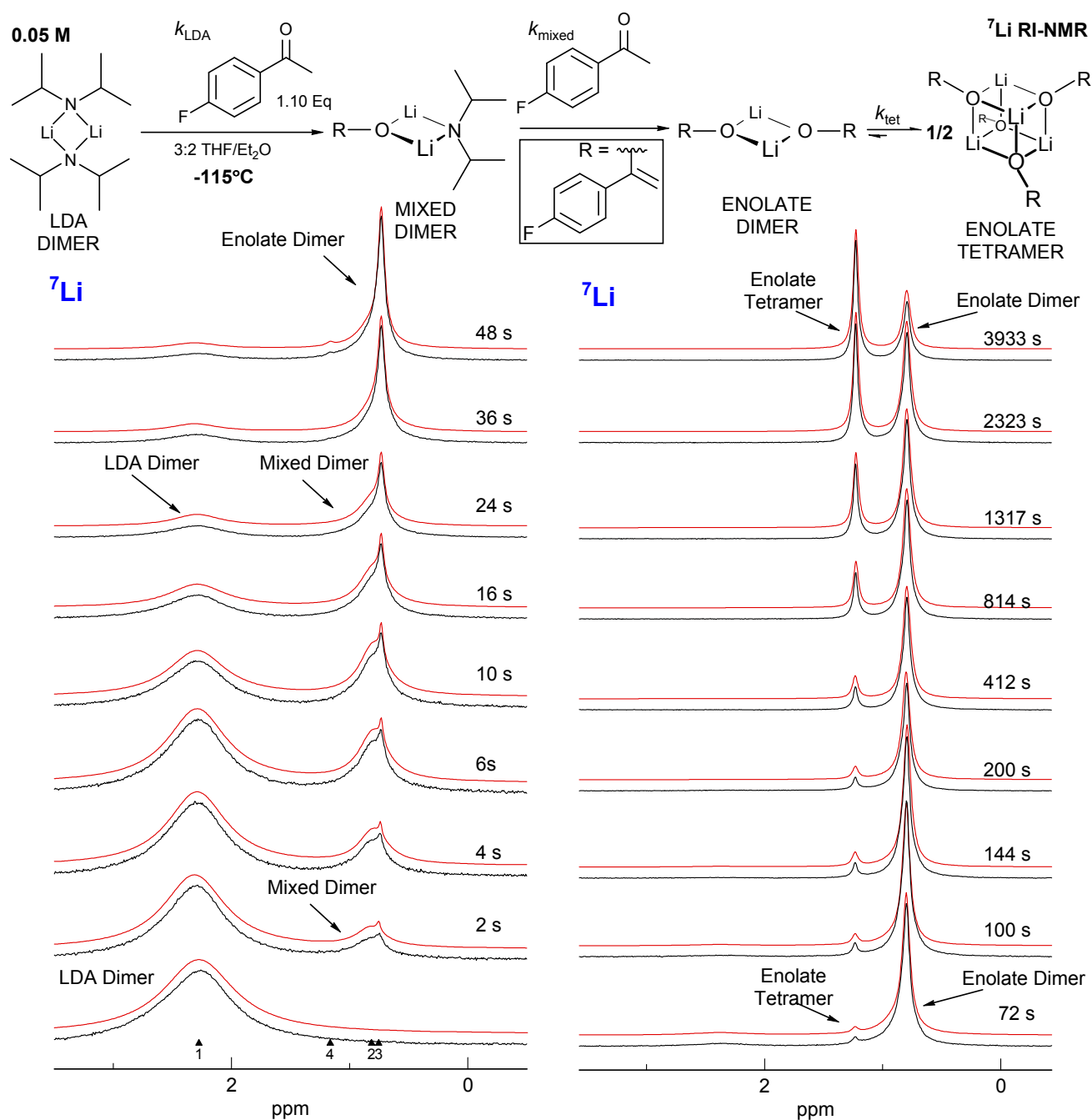
**General Procedure for the RI-NMR of LDA Enolization of 4-Fluoroacetophenone.** 1,3-Dimethyl-2-fluorobenzene (5  $\mu$ L) was added to 3 mL of a freshly prepared 3:2 THF/Et<sub>2</sub>O solution of LiN<sup>i</sup>Pr<sub>2</sub> in a dried thin-walled 10 mm NMR tube. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at the temperature specified to check concentration and sample integrity. Following the general RI-NMR procedure, 4-Fluoroacetophenone (0.15 mL of a 2.0 M solution) was added and <sup>19</sup>F or <sup>7</sup>Li NMR spectra were obtained for several hours. The <sup>19</sup>F NMR spectrum of the mixed and homo dimer was simulated using the NUTS automated line fitting routine.<sup>[S6]</sup> All other concentrations were determined by integration techniques relative to 1,3-dimethyl-2-fluorobenzene. <sup>7</sup>Li NMR spectra were simulated using the four spin singlet simulation in WINDNMR<sup>[S3]</sup> from which the relative area of each peak was measured and the concentration of ketone and enolate were determined based on <sup>19</sup>F NMR measurements post reaction. The kinetic pathway of these reactions were simulated with COPASI<sup>[S5]</sup> using the parameter estimation routine and the Nelder-Mead or Levenberg-Marquardt methods, and was fit to the reaction scheme shown in Figure S-15. A summary of the kinetic data obtained from these experiments is presented in Table S-2. Concentration versus time plot along with the fit simulation values for these experiments are shown in Figures S-16 to S-28.

**Table S-2.** Summary of Kinetic Data from the RI-NMR studies of the LDA Enolization of 4-Fluoroacetophenone at various temperatures in 3:2 THF/Et<sub>2</sub>O.

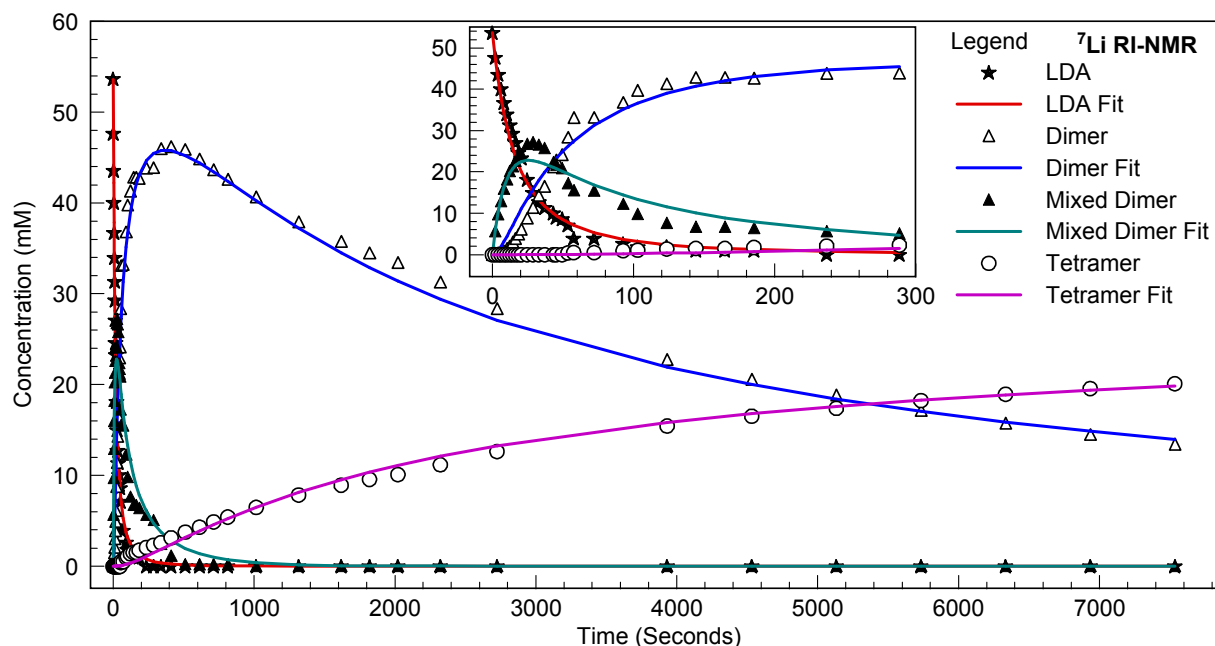
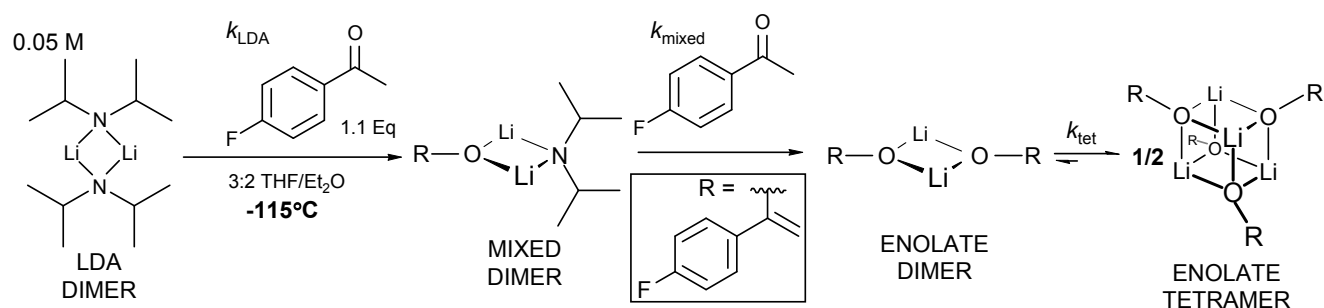
RI-NMR Nucleus	[LDA] <sub>2</sub> (M)	[1-H] (M)	Temperature (°C)	$k_{\text{LDA}}$ (M <sup>-1</sup> s <sup>-1</sup> )	$k_{\text{mixed}}$ (M <sup>-1</sup> s <sup>-1</sup> )	$k_{\text{tet}}$ (M <sup>-1</sup> s <sup>-1</sup> )	Figure Number
<sup>19</sup> F	0.05	0.1	-124	0.25	0.176	0.0013	S-16
<sup>19</sup> F	0.05	0.85	-120	0.29	0.218	0.0013	S-15
<sup>7</sup> Li	0.05	0.11	-115	0.53	0.392	0.0036	S-17,S-18
<sup>19</sup> F	0.048	0.1	-103	2.2	1.8	0.1	S-19
<sup>19</sup> F	0.042	0.12	-98	5	4	0.21	S-20
<sup>7</sup> Li	0.4	0.11	-94	4.9	2.2	0.43	S-21,S-22
<sup>19</sup> F	0.048	0.097	-84	19.8	11.4	2.1	S-23
Experiments Varying the Concentration of LDA or 4-Fluoroacetophenone							
<sup>19</sup> F	0.055	0.13	-120	0.43	0.24	0.0015	S-24
<sup>19</sup> F	0.029	0.8	-120	0.34	0.17	0.0013	S-25
<sup>19</sup> F	0.054	0.204	-120	0.42	0.26	0.0024	S-26
Experiments Utilizing <i>d</i> <sub>3</sub> -4-Fluoroacetophenone							
<sup>19</sup> F ( <i>d</i> <sub>3</sub> )	0.042	0.12	-120	0.24	0.04	0.0018	S-27
<sup>19</sup> F ( <i>d</i> <sub>3</sub> )	0.042	0.11	-120	0.28	0.036	0.0017	S-28, S-29



**Figure S-16.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -124 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



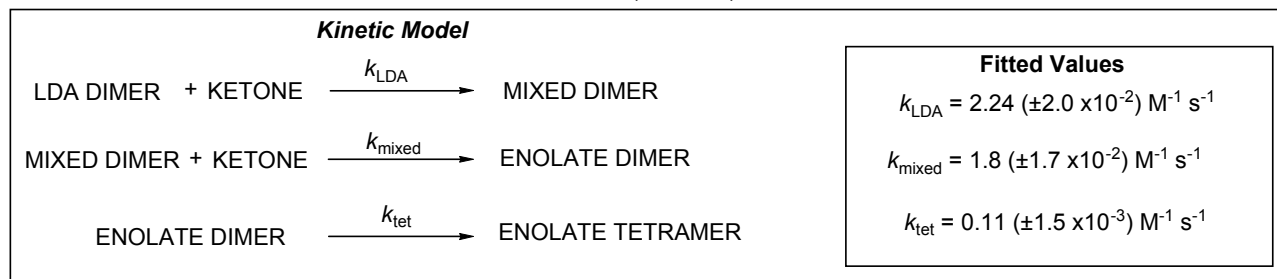
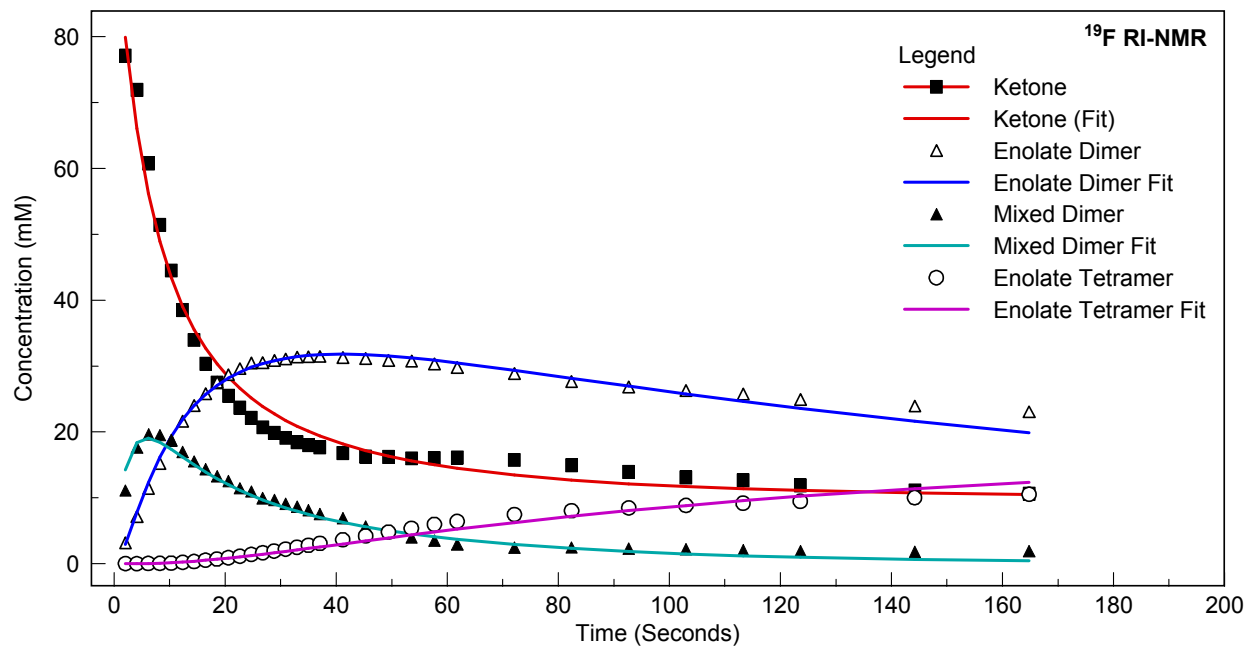
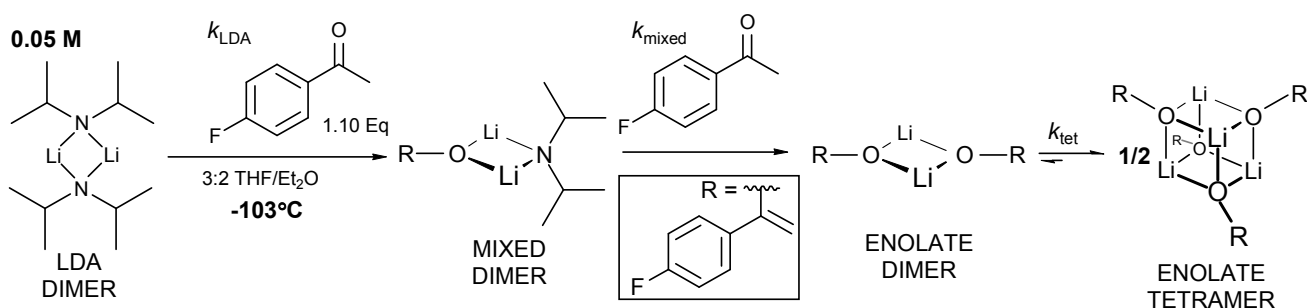
**Figure S-17.**  $^7\text{Li}$  RI-NMR experiment of LDA mediated enolization of 4-fluoroacetophenone (**1-H**) in 3:2 THF/Et<sub>2</sub>O at -115 °C. Red upper lines correspond to lineshape simulations using the four spin singlet simulation in WINDNMR<sup>[S3]</sup> from which the relative area of each peak was determined. The concentration of ketone and enolate were determined based on  $^{19}\text{F}$  NMR measurements post reaction. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



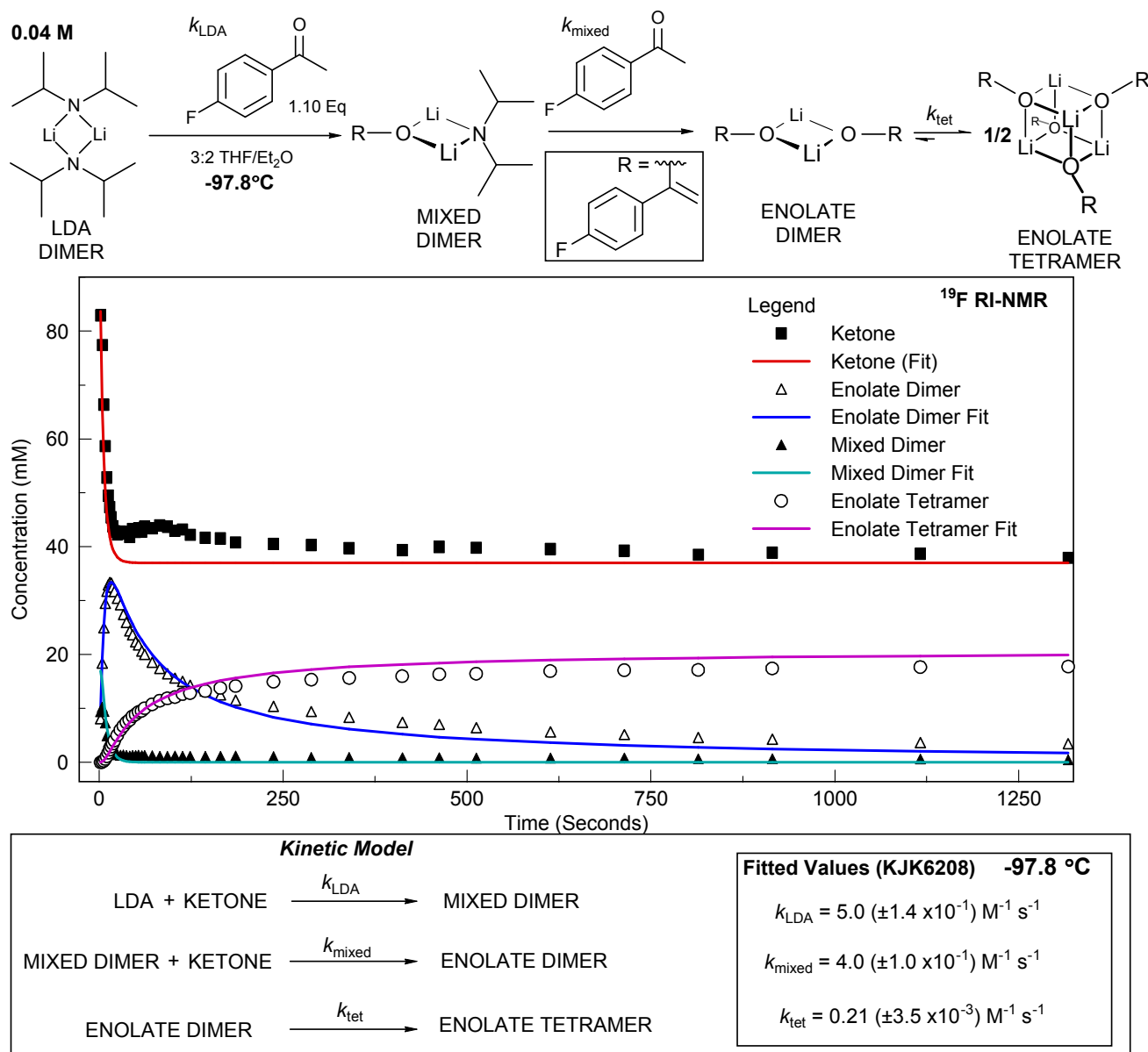
Kinetic Model			Fitted Values
			-115 °C
LDA + KETONE	$\xrightarrow{k_{LDA}}$	MIXED DIMER	$k_{LDA} = 0.533 (\pm 4.0 \times 10^{-3}) \text{ M}^{-1} \text{ s}^{-1}$
MIXED DIMER + KETONE	$\xrightarrow{k_{\text{mixed}}}$	ENOLATE DIMER	$k_{\text{mixed}} = 0.392 (\pm 3.3 \times 10^{-3}) \text{ M}^{-1} \text{ s}^{-1}$
ENOLATE DIMER	$\xrightarrow{k_{\text{tet}}}$	ENOLATE TETRAMER	$k_{\text{tet}} = 0.0036 (\pm 5.1 \times 10^{-5}) \text{ M}^{-1} \text{ s}^{-1}$

**Figure S-18.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 1 equivalent of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -115 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)

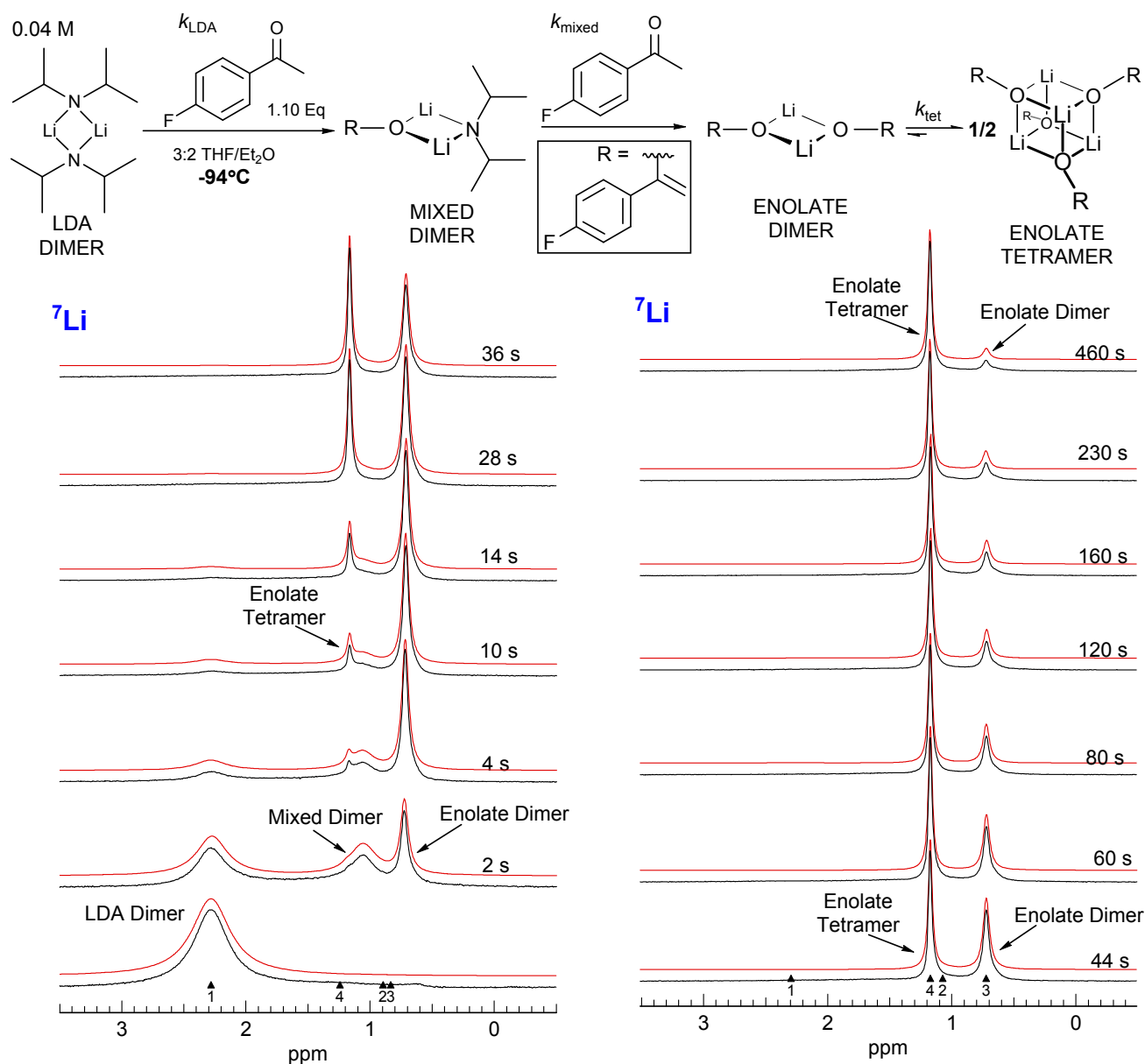




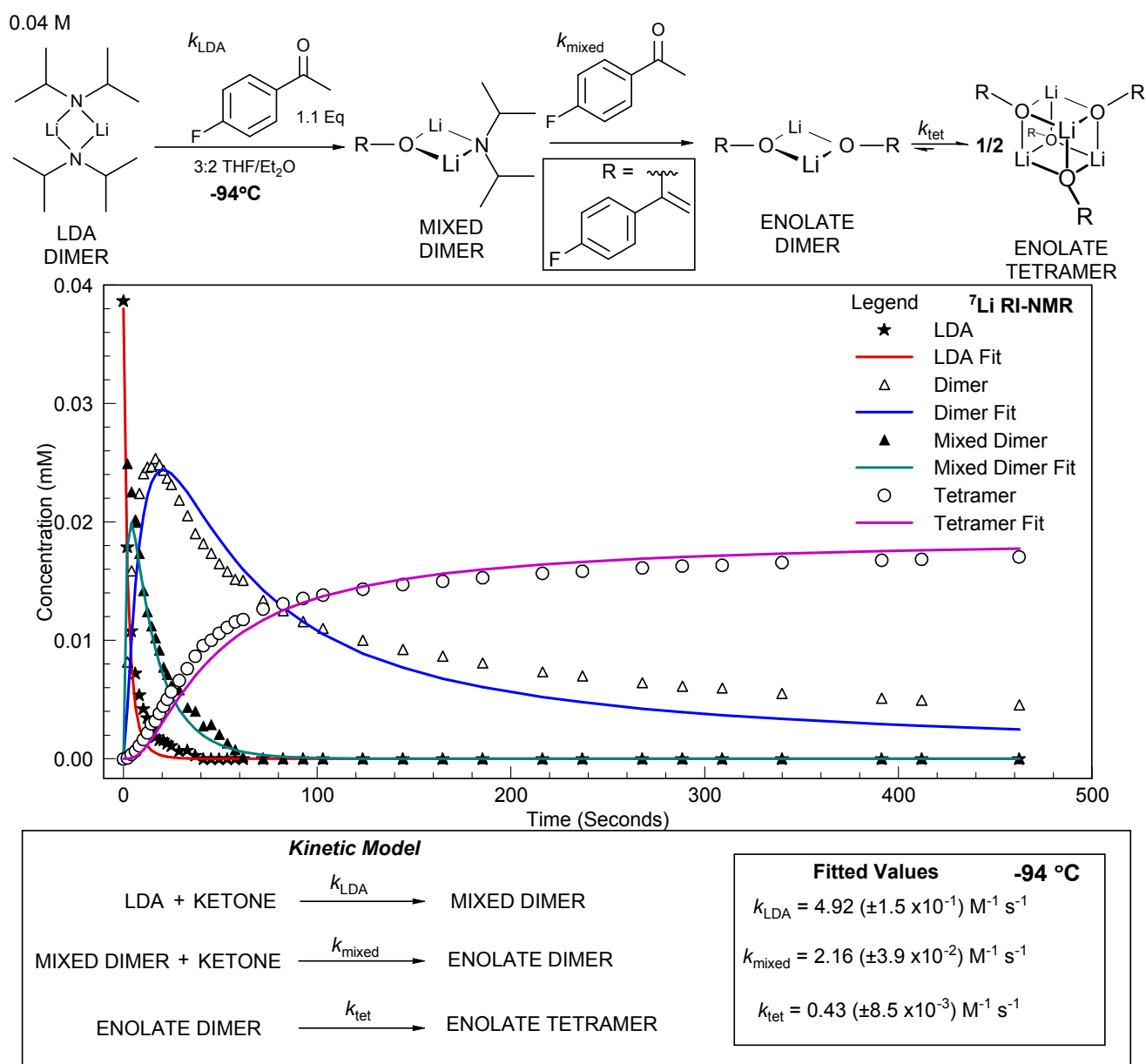
**Figure S-19.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -103 °C. Lines correspond to COPASI<sup>[55]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M Li<sup>n</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (Li<sup>n</sup>Pr<sub>2</sub>)<sub>2</sub>)



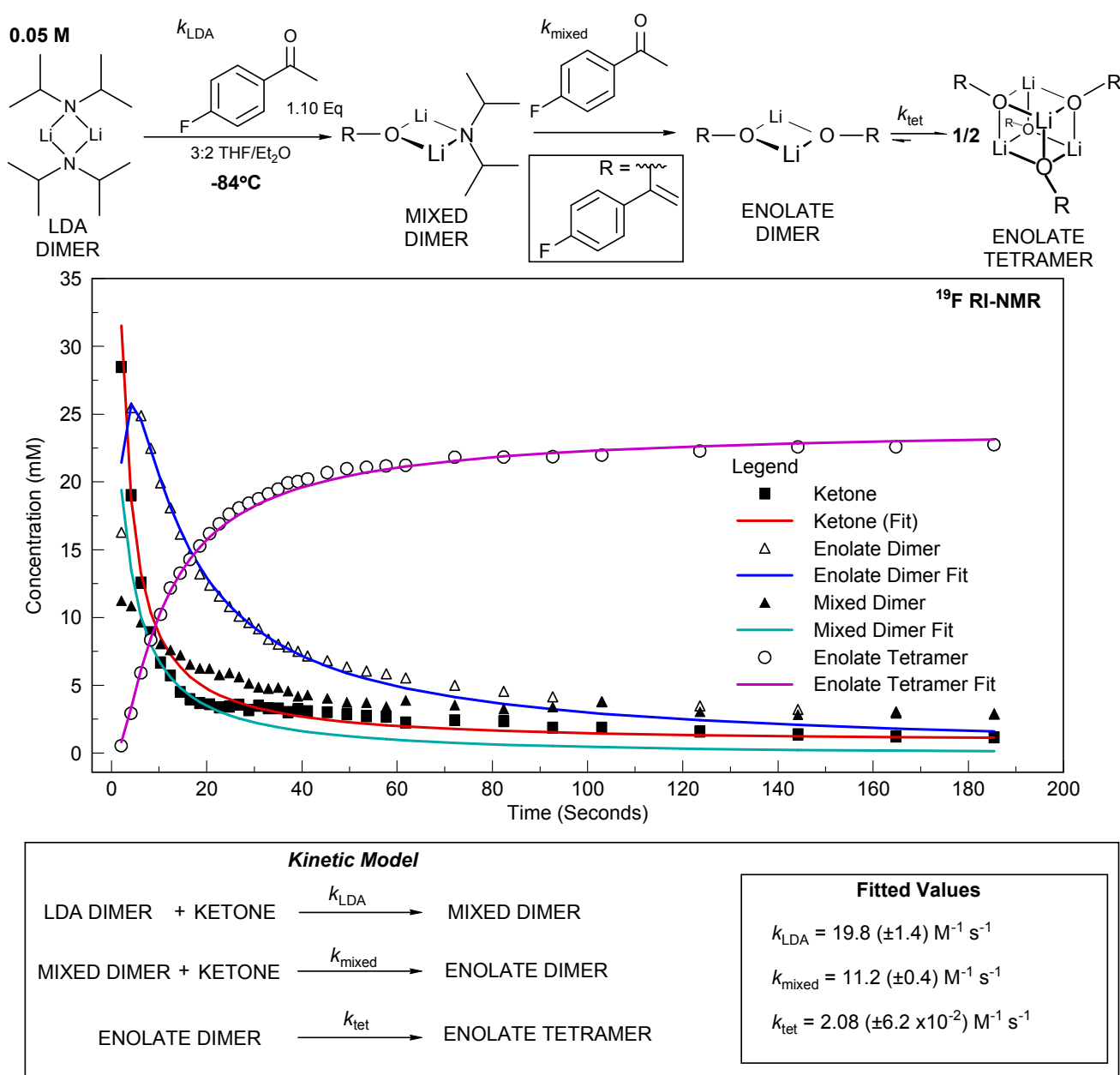
**Figure S-20.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at  $-98^\circ\text{C}$ . Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



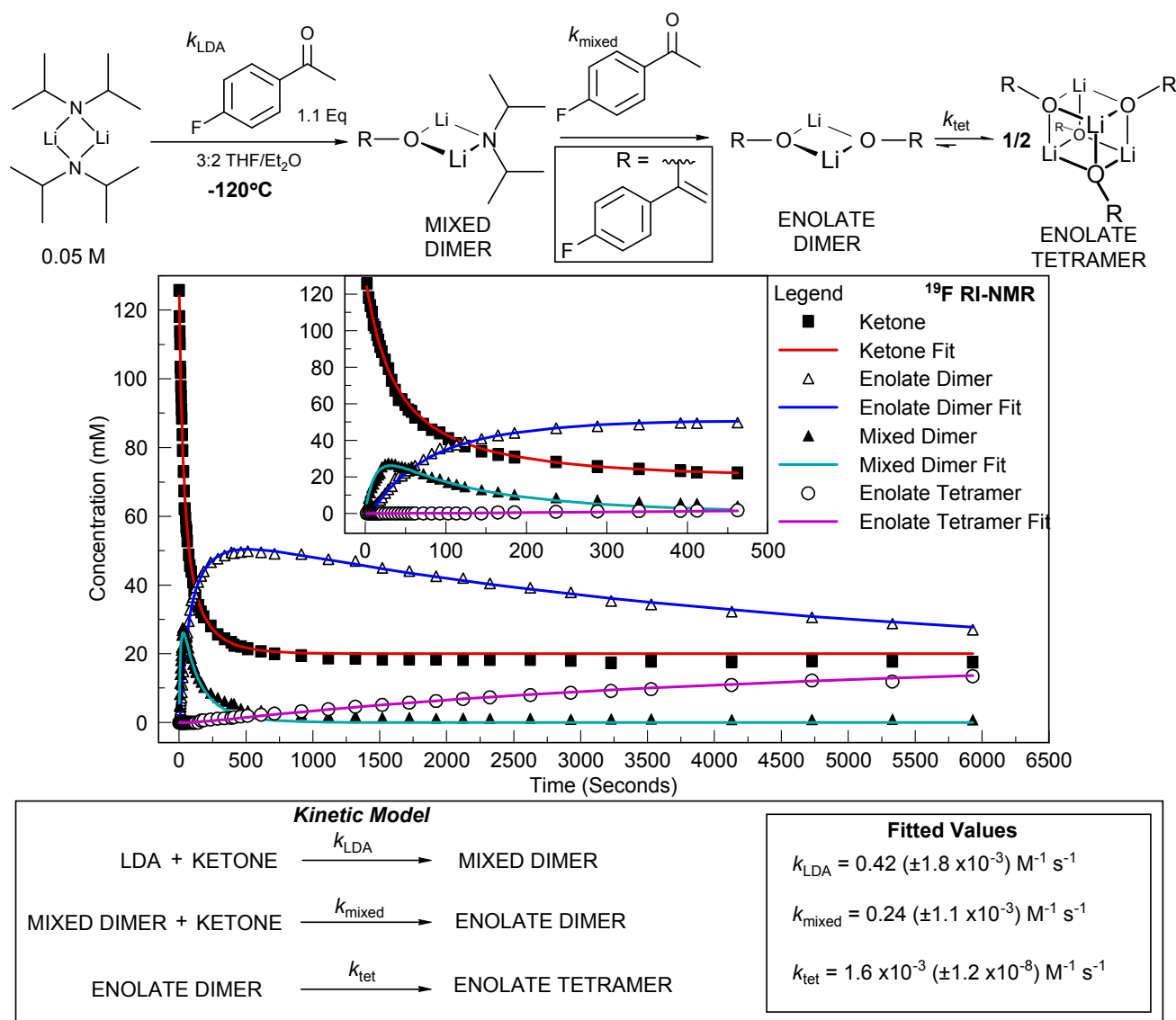
**Figure S-21.**  $^7\text{Li}$  RI-NMR experiment of LDA mediated enolization of 4-fluoroacetophenone (**1-H**) in 3:2 THF/Et<sub>2</sub>O at -94 °C. Red upper lines correspond to lineshape simulations using the four spin singlet simulation in WINDNMR<sup>[S3]</sup> from which the relative area of each peak was determined. The concentration of ketone and enolate were determined based on  $^{19}\text{F}$  NMR measurements post reaction. (Note from written procedure to figure: 0.1 M  $\text{LiN}^i\text{Pr}_2$  = 0.05 M LDA dimer ( $\text{LiN}^i\text{Pr}_2$ )<sub>2</sub>)



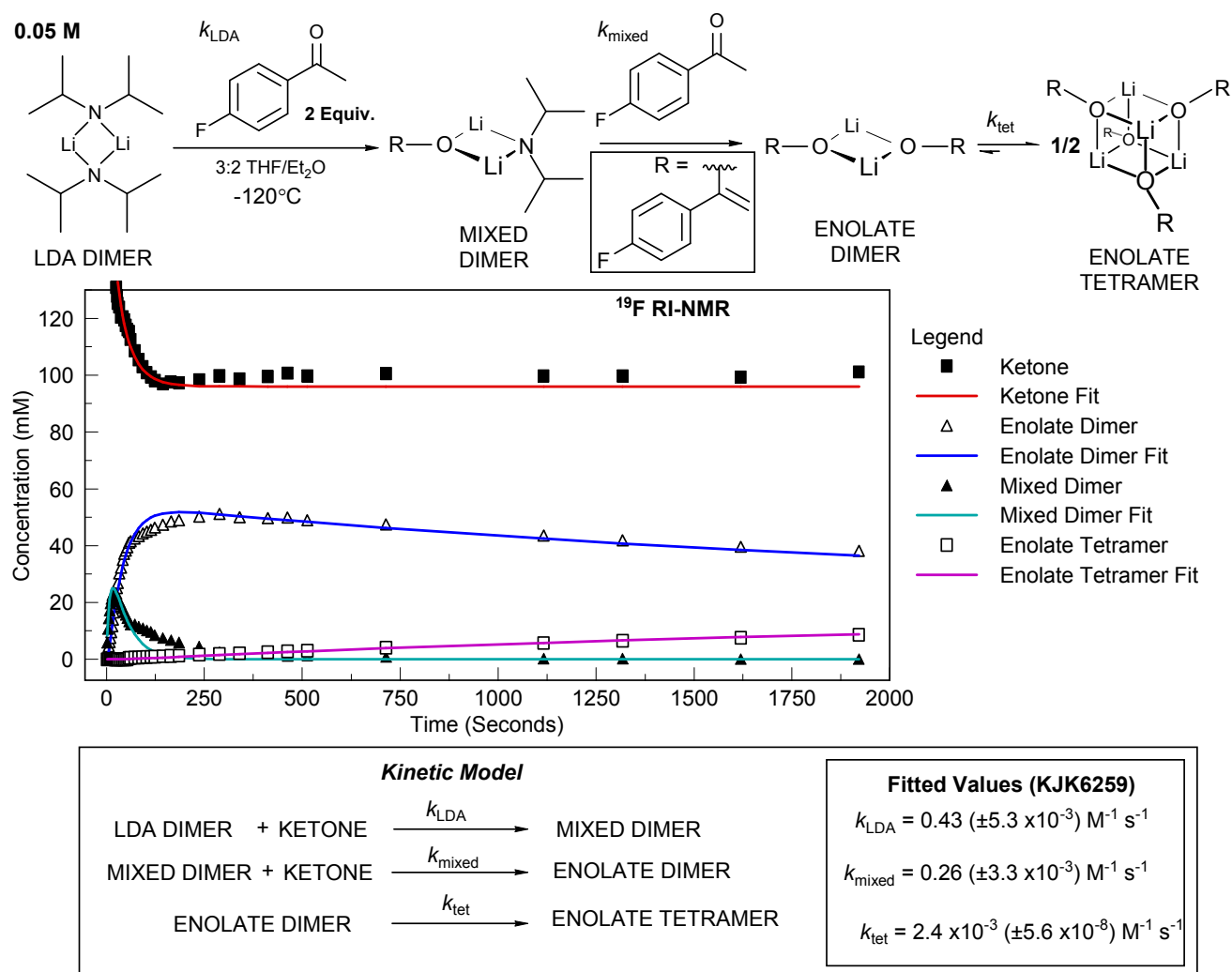
**Figure S-22.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -94 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



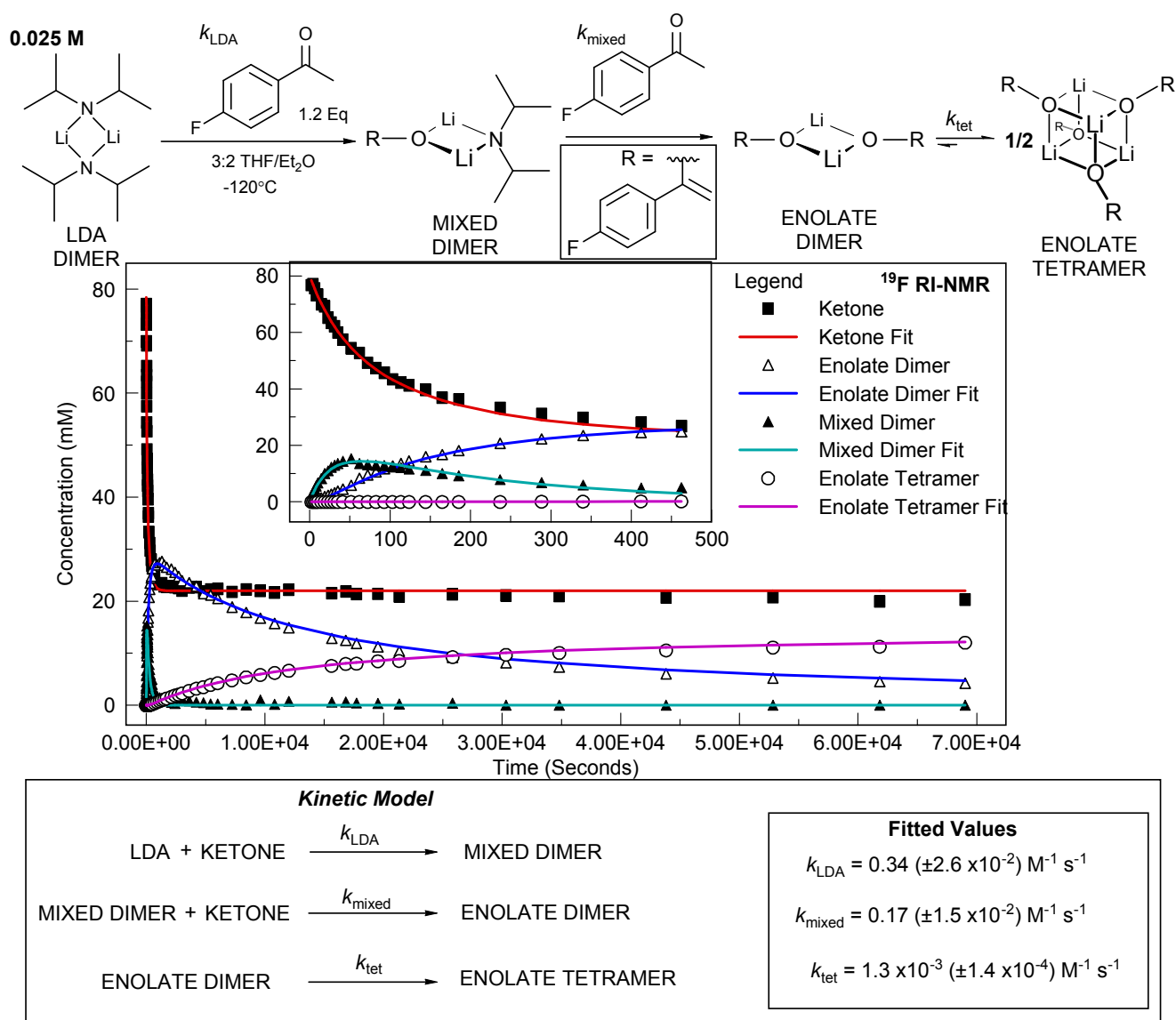
**Figure S-23.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -84 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



**Figure S-24.** Concentration versus time plot and modeling result for the kinetic path of 0.05 M LDA dimer mediated enolization of 1.1 equivalents 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -120 °C. Lines correspond to COPASI<sup>[SS]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M Li<sup>n</sup>iPr<sub>2</sub> = 0.05 M LDA dimer (Li<sup>n</sup>iPr<sub>2</sub>)<sub>2</sub>)

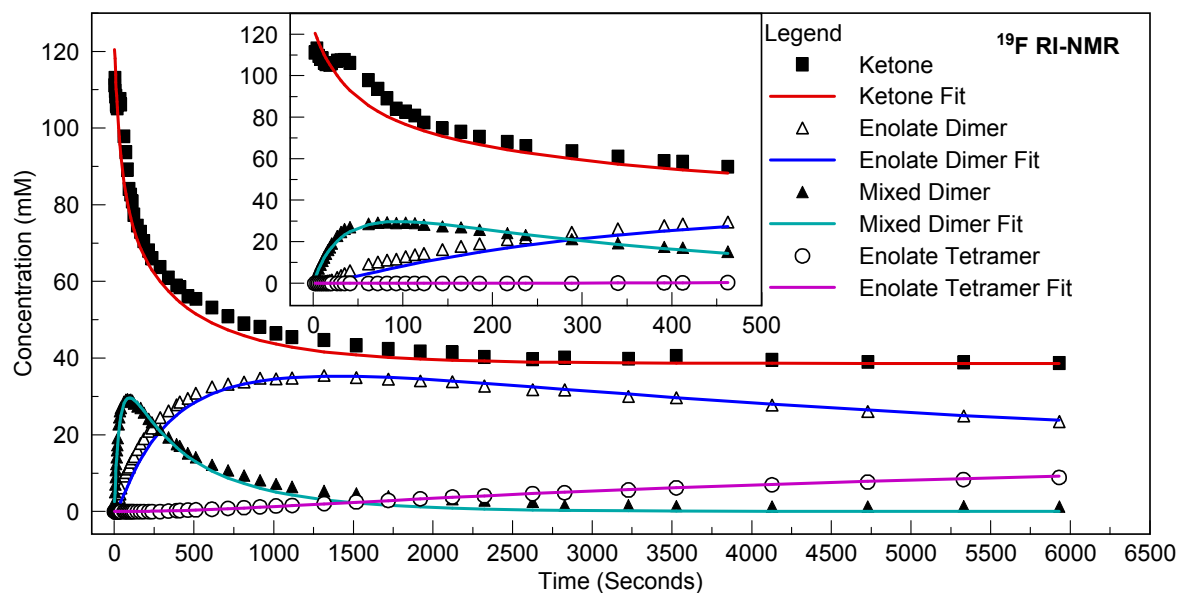
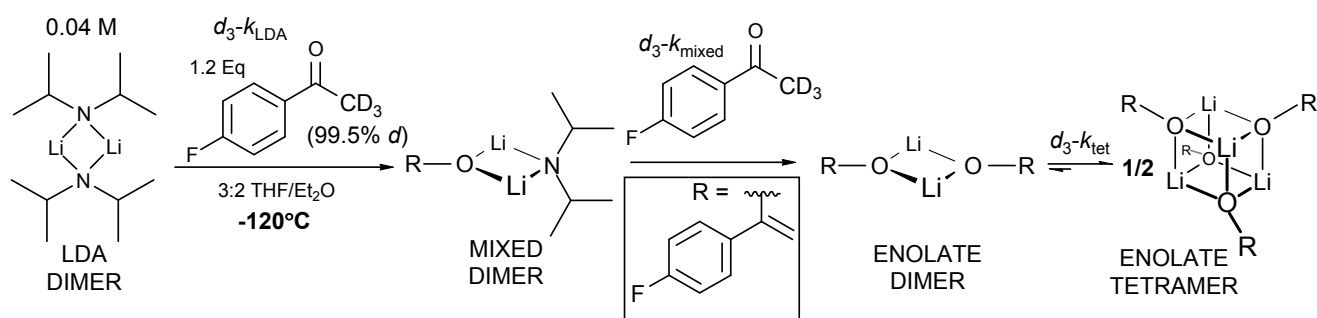


**Figure S-25.** Concentration versus time plot and modeling result for the kinetic path of 0.5 M LDA dimer mediated enolization of 2 equivalents of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -120 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



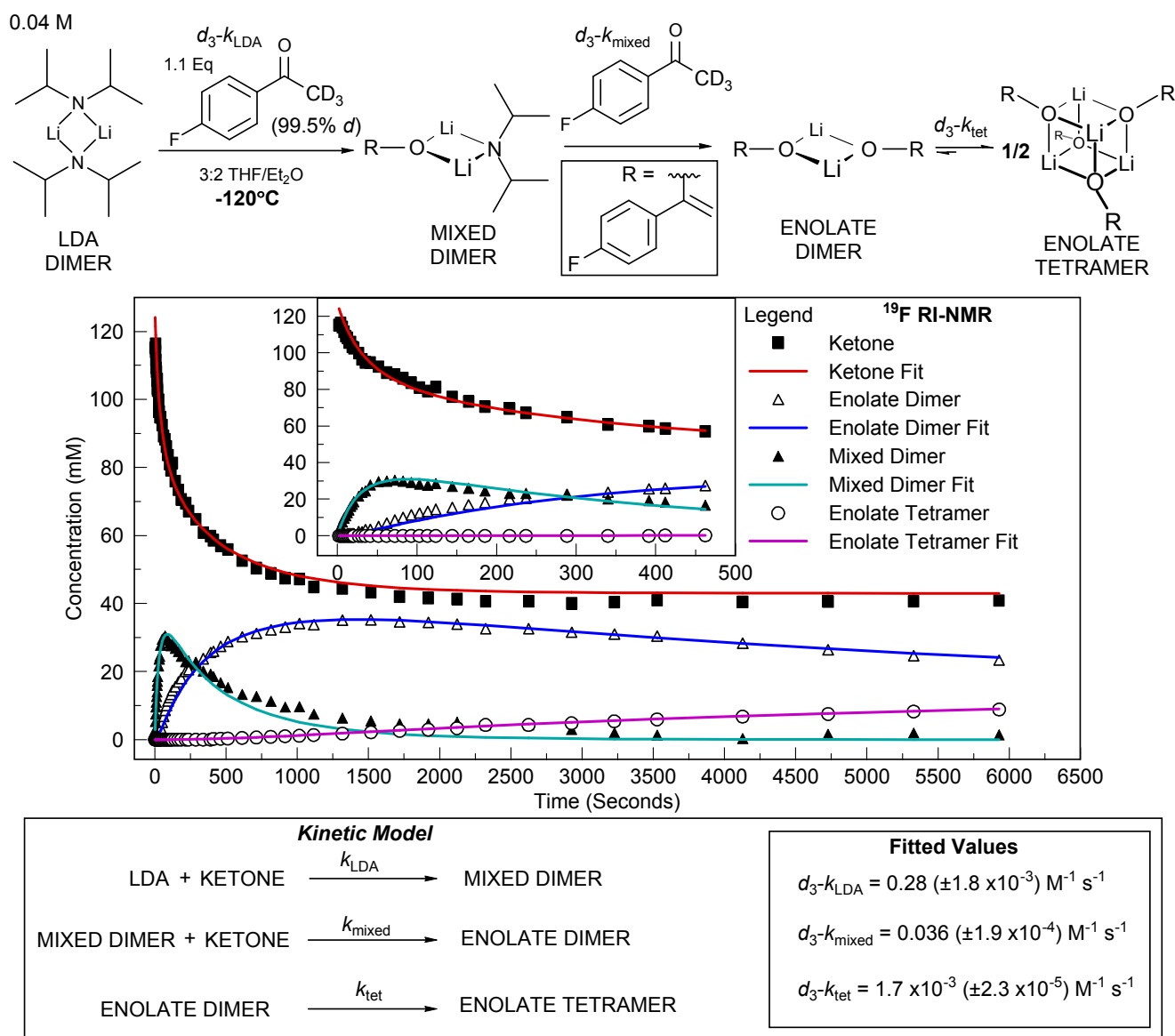
**Figure S-26.** Concentration versus time plot and modeling result for the kinetic path of 0.025 M LDA dimer mediated enolization of 1 equivalent of 4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -120 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M Li<sup>n</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (Li<sup>n</sup>Pr<sub>2</sub>)<sub>2</sub>)



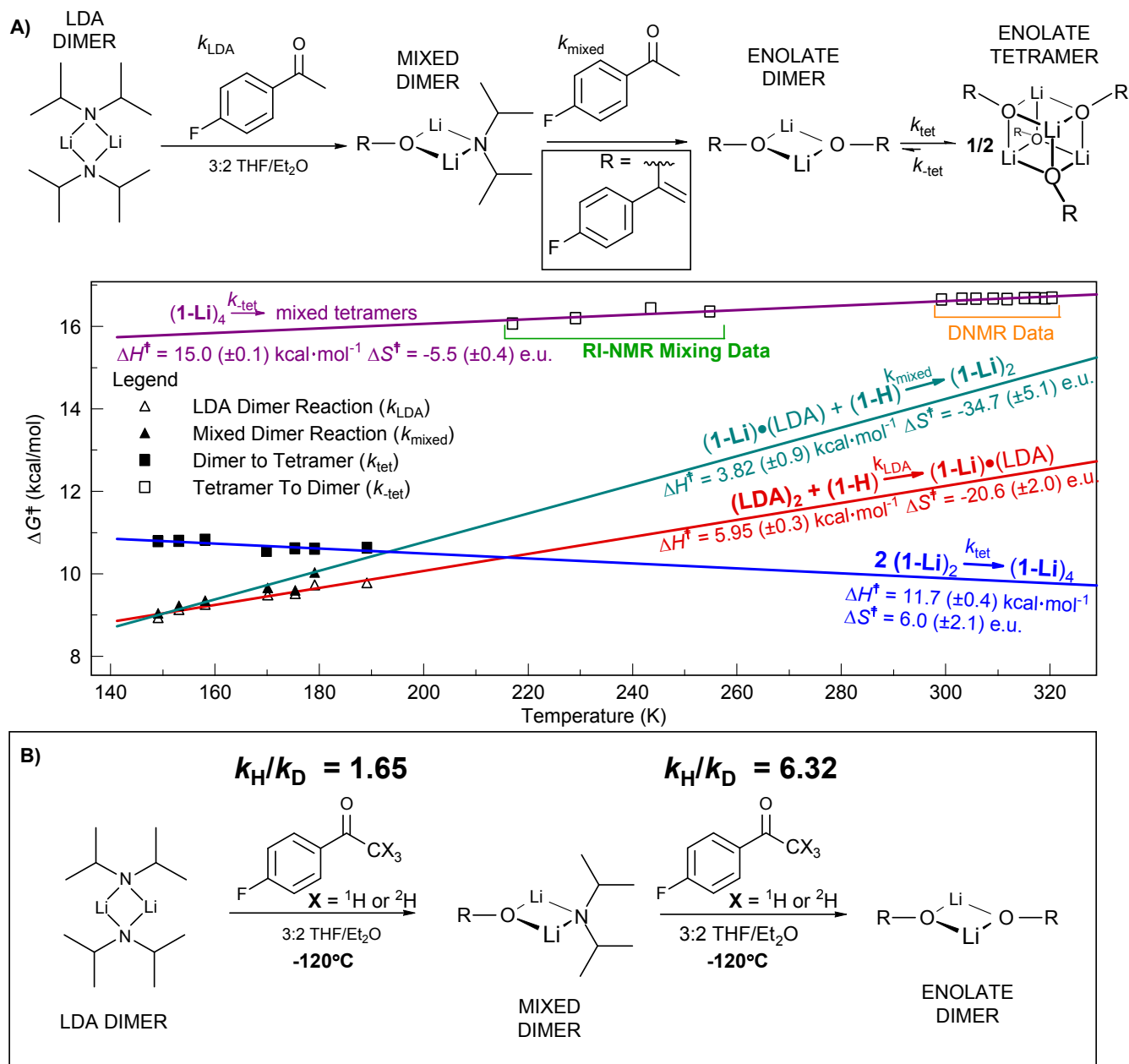


Kinetic Model			Fitted Values
LDA + KETONE	$\xrightarrow{k_{LDA}}$	MIXED DIMER	
MIXED DIMER + KETONE	$\xrightarrow{k_{mixed}}$	ENOLATE DIMER	
ENOLATE DIMER	$\xrightarrow{k_{tet}}$	ENOLATE TETRAMER	
			$d_3-k_{LDA} = 0.24 (\pm 1.9 \times 10^{-3}) \text{ M}^{-1} \text{ s}^{-1}$ $d_3-k_{mixed} = 0.04 (\pm 2.6 \times 10^{-4}) \text{ M}^{-1} \text{ s}^{-1}$ $d_3-k_{tet} = 1.8 \times 10^{-3} (\pm 2.8 \times 10^{-5}) \text{ M}^{-1} \text{ s}^{-1}$

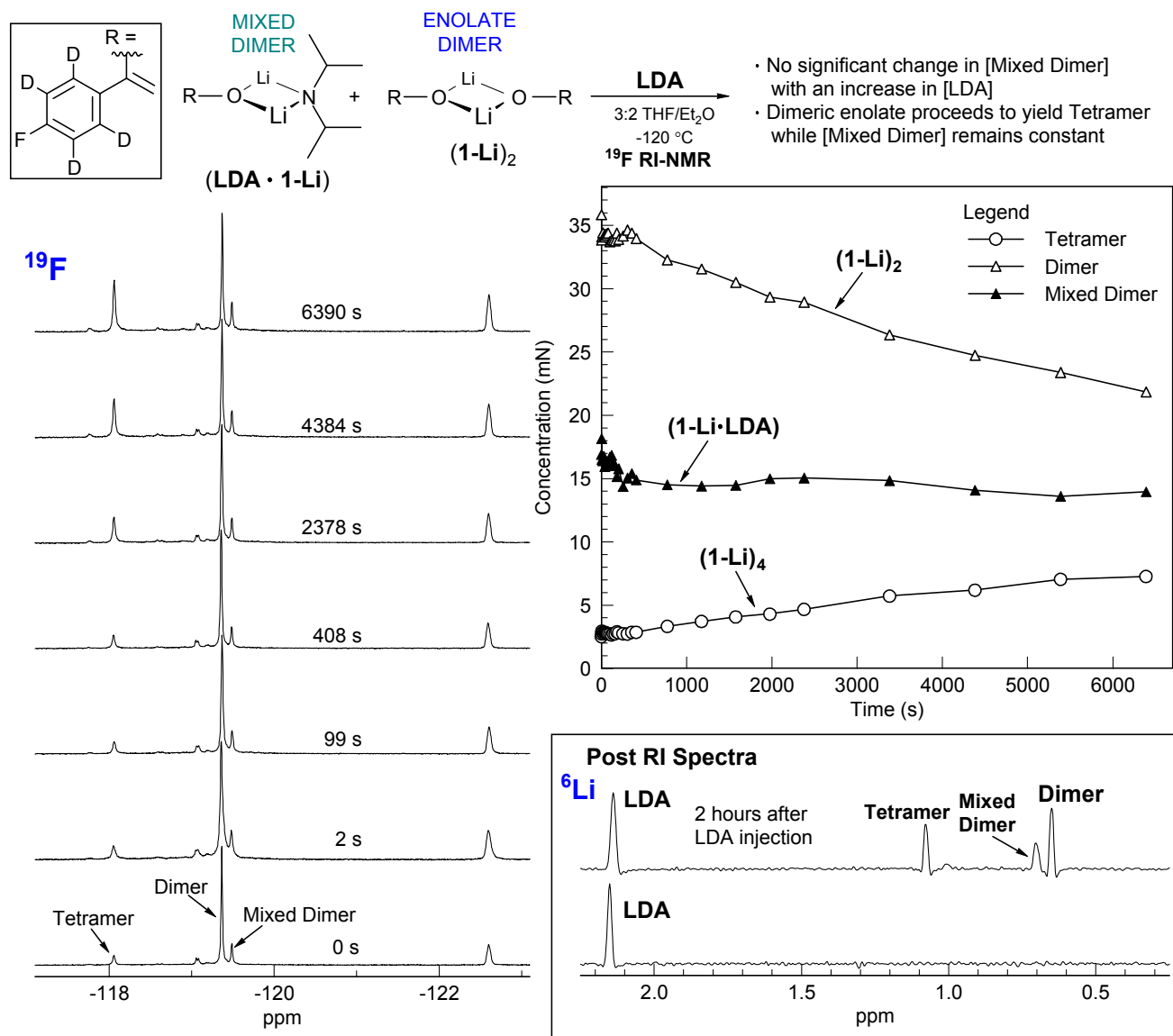
**Figure S-27.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of  $d_3$ -4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -120 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)



**Figure S-28.** Concentration versus time plot and modeling result for the kinetic path of LDA mediated enolization of 1.1 equivalents of  $d_3$ -4-fluoroacetophenone in 3:2 THF/Et<sub>2</sub>O at -120 °C. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> = 0.05 M LDA dimer (LiN<sup>i</sup>Pr<sub>2</sub>)<sub>2</sub>)

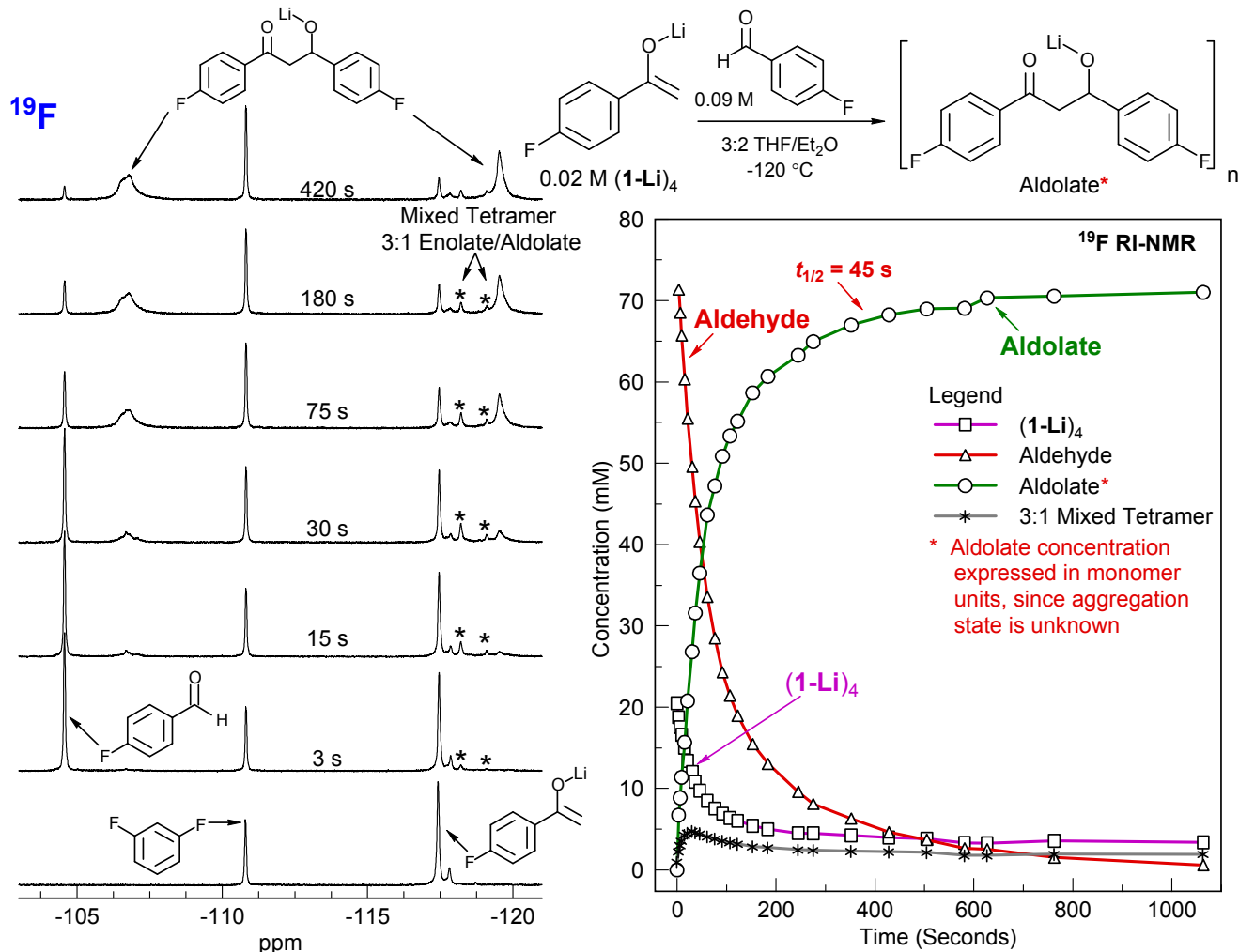


**Addition of LDA to Dimeric 4-Fluoroacetophenone Enolate ( $(1\text{-Li})_2$ ) at  $-120^\circ\text{C}$ .** 1,3-Dimethyl-2-fluorobenzene (5  $\mu\text{L}$ ) was added to 3 mL of a freshly prepared 3:2 THF/ $\text{Et}_2\text{O}$  solution of 0.1 M  $\text{LiN}^i\text{Pr}_2$  in a dried thin-walled 10 mm NMR tube.  $^{13}\text{C}$ ,  $^{19}\text{F}$  and  $^6\text{Li}$  spectra were acquired at  $-120^\circ\text{C}$  to check concentration and sample integrity. Following the general RI-NMR procedure, 2,3,5,6-tetradeutero-4-fluoroacetophenone (36  $\mu\text{L}$ , 0.3 mmol, in 0.15 mL THF) was added and  $^{19}\text{F}$  NMR spectra were obtained until all ketone was consumed. Then again following the general RI-NMR procedure, LDA (0.15 mL of a 2 M solution, 0.3 mmol) was added and  $^{19}\text{F}$  NMR spectra were obtained for 1.5 h. After this time a  $^6\text{Li}$  spectrum was acquired to confirm that LDA remained in the sample. Spectra and a concentration versus time plot are shown in Figure S-30.

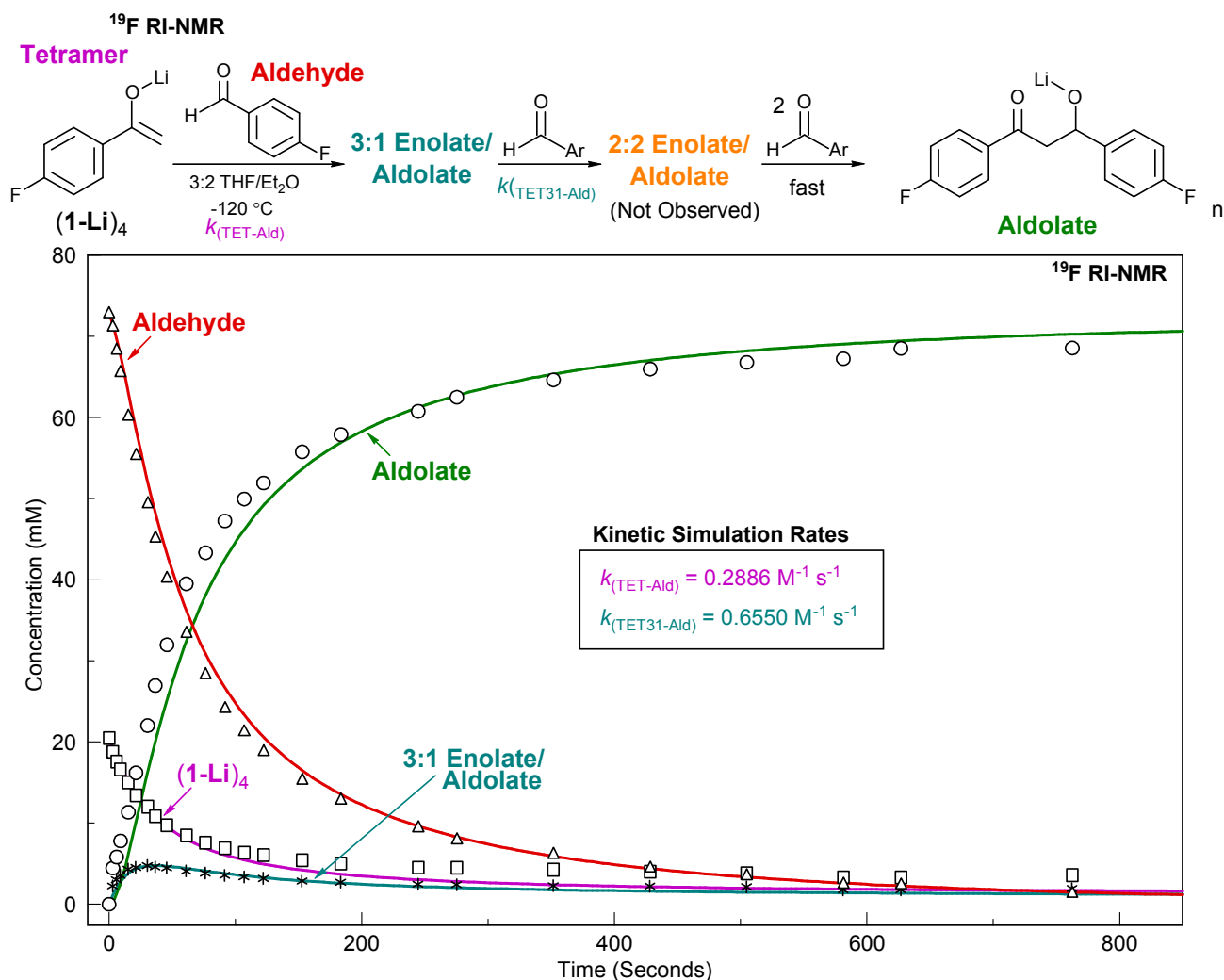


**Figure S-30.** Addition of lithium diisopropylamide (LDA) to solution of lithium enolate dimer of 4-fluoroacetophenone ( $(1\text{-Li})_2$ ) at  $-120^\circ\text{C}$  monitored by  $^{19}\text{F}$  RI-NMR. Increasing LDA concentration in a solution of enolate dimer ( $(1\text{-Li})_2$ ) and mixed dimer ( $(1\text{-Li} \cdot \text{LDA})$ ) resulted in no significant change in the concentration of either species. This indicated that under these conditions equilibration of the form  $(\text{LDA})_2 + (1\text{-Li})_2 \rightleftharpoons 2 (1\text{-Li} \cdot \text{LDA})$  does not occur to an appreciable extent. Warming the sample to  $-78^\circ\text{C}$  produced a solution composed of enolate tetramer  $(1\text{-Li})_4$  and LDA.

**Aldol Reaction of (1-Li)<sub>4</sub> with 4-Fluorobenzaldehyde at -120 °C.** 4-Fluoroacetophenone (33  $\mu$ L, 0.3 mmol) was added to a 0.1 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) was added and <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C. 4-Fluorobenzaldehyde (0.15 mL of a 1.7 M solution, 0.26 mmol) was added using our RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Spectra and a concentration versus time plot are shown in Figure S-31. Kinetic simulation of the tetramer reaction was carried out and shown in Figure S-32. Data from this experiment is presented in Figure 4 of the main paper.

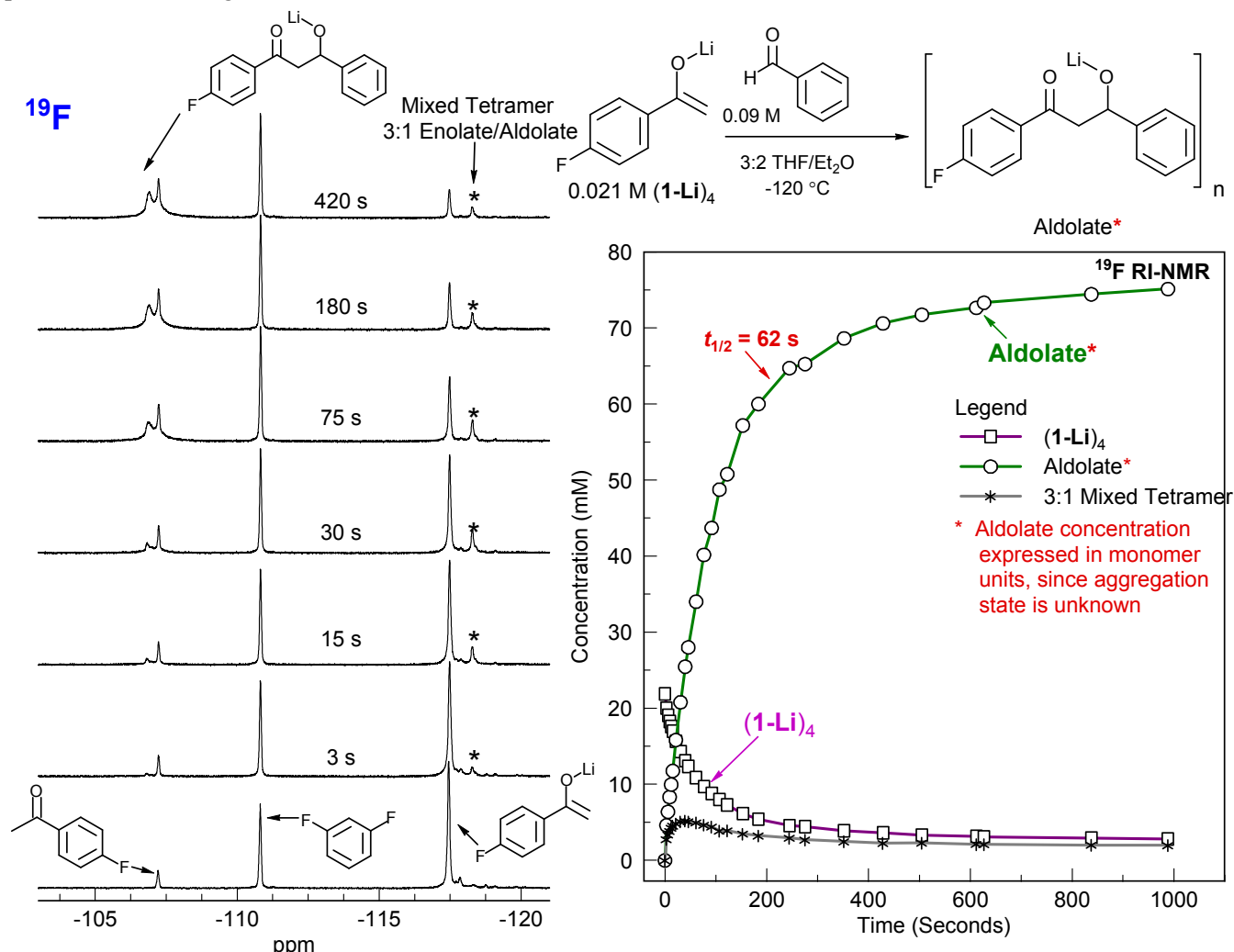


**Figure S-31.** The aldol reaction of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with 4-fluorobenzaldehyde in 3:2 THF/Et<sub>2</sub>O at -120 °C monitored by <sup>19</sup>F RI-NMR. The lines correspond to connection of the individual concentration points over time. Assignment of the <sup>19</sup>F NMR signals originating from the enolate and aldehyde was confirmed by comparison of the reaction of **1-Li** with 4-fluorobenzaldehyde to the reaction of **1-Li** with benzaldehyde at -125 °C. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)



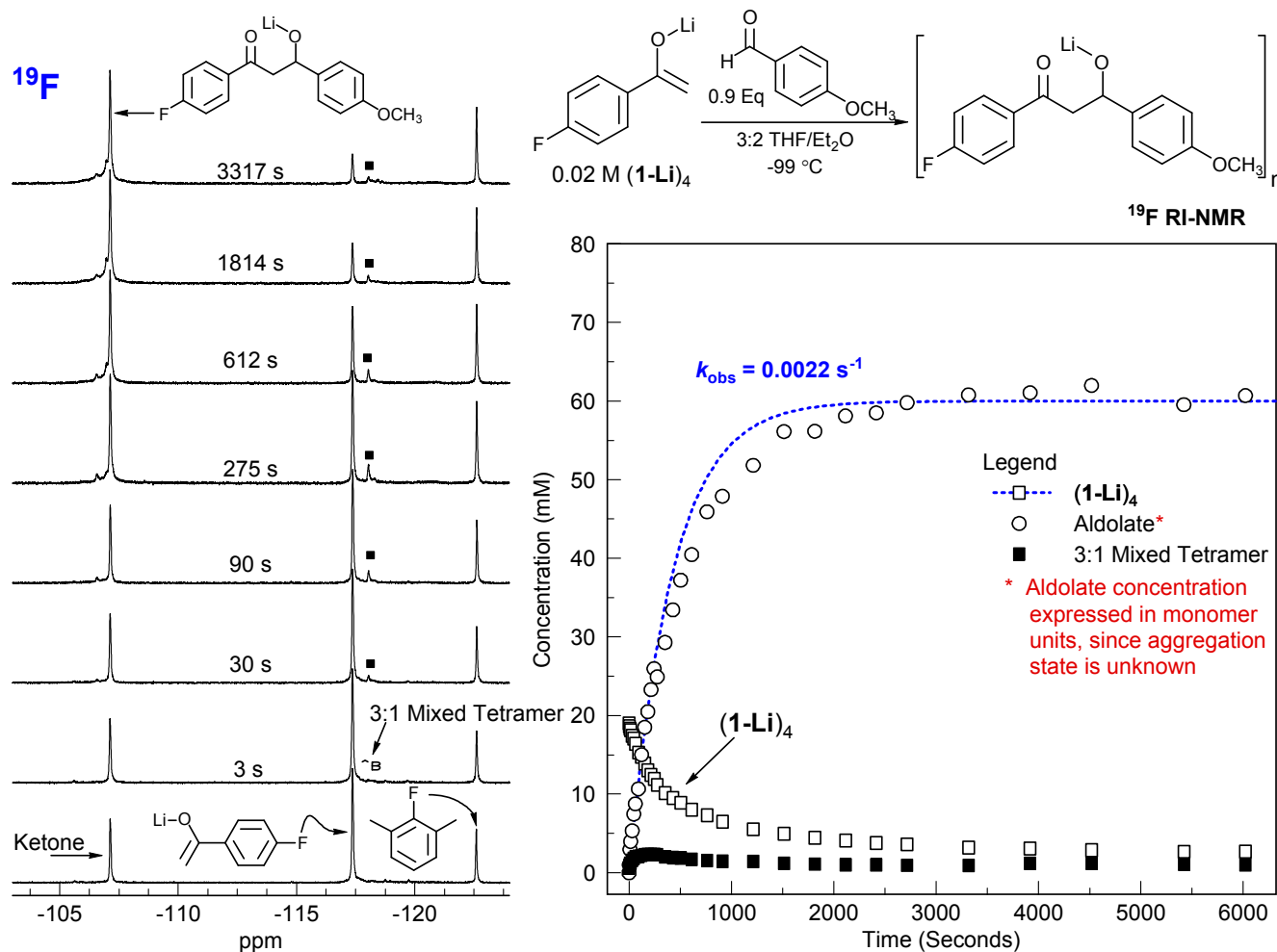
**Figure S-32.** The aldol reaction of the tetrameric form of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with 4-fluorobenzaldehyde in 3:2 THF/Et<sub>2</sub>O at -125 °C monitored by <sup>19</sup>F RI-NMR. The lines correspond simulations based on the kinetic scheme shown above with the rate constants indicated on the graph. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

**Aldol Reaction of (1-Li)<sub>4</sub> with Benzaldehyde at -120 °C.** 4-Fluoroacetophenone (33  $\mu$ L, 0.3 mmol) was added to a 0.1 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) was added and <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C. Benzaldehyde (0.15 mL of a 1.7 M solution, 0.26 mmol) was added using our RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Spectra and a concentration versus time plot are shown in Figure S-33.



**Figure S-33.** The aldol reaction of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with benzaldehyde in 3:2 THF/Et<sub>2</sub>O at -125 °C monitored by <sup>19</sup>F RI-NMR. The lines correspond to connection of the experimental concentration points over time. Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

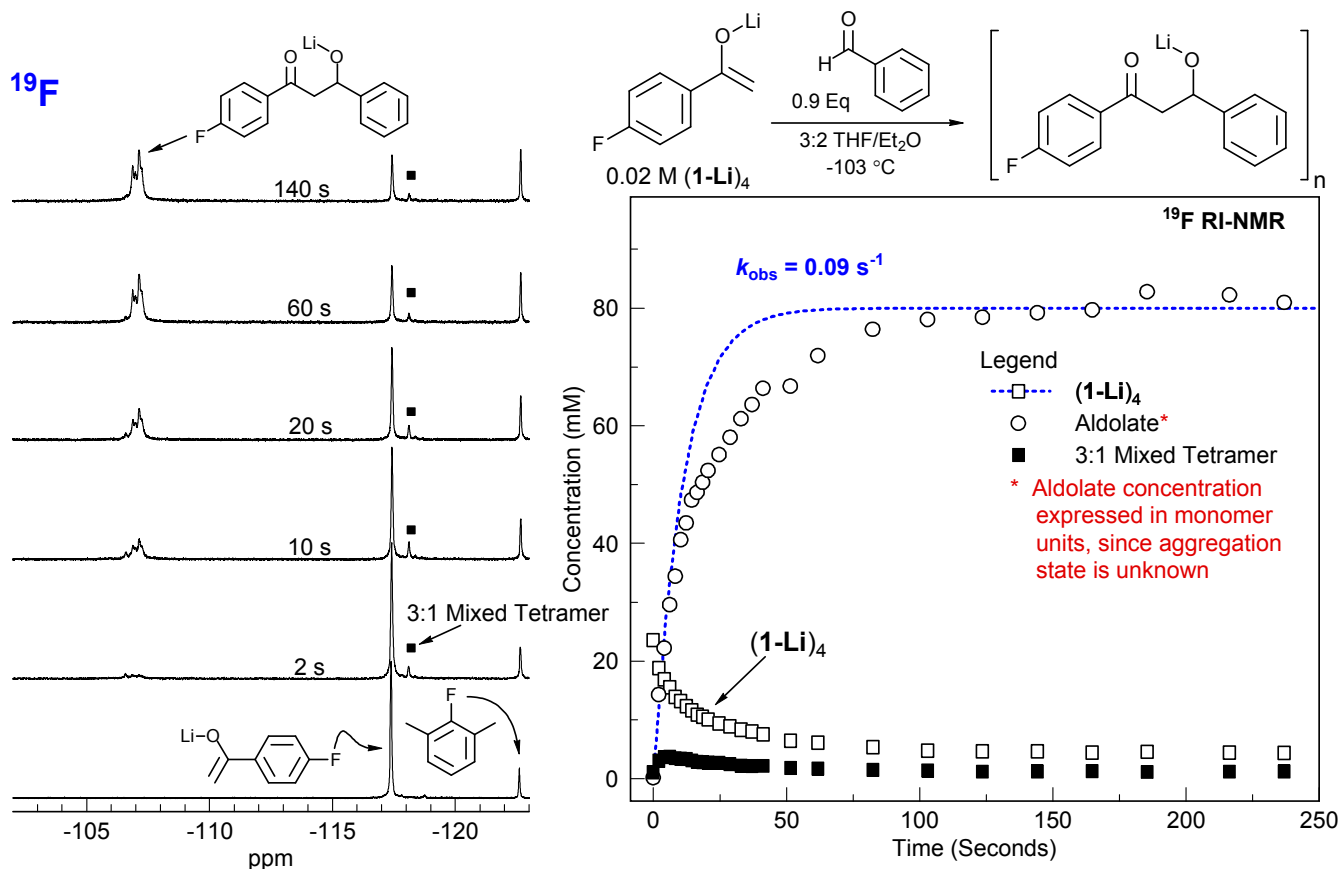
**Aldol Reaction of (1-Li)<sub>4</sub> with 4-Methoxybenzaldehyde at -100 °C.** 4-Fluoroacetophenone (33  $\mu$ L, 0.3 mmol) was added to a 0.1 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) was added and <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -100 °C. 4-Methoxybenzaldehyde (0.15 mL of a 1.7 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Spectra and a concentration versus time plot are shown in Figure S-34. A Hammett plot for the reaction of lithium enolate of 4-fluoroacetophenone (**1-Li**) with several substituted benzaldehydes is shown in Figure S-38.



**Figure S-34.** The aldol reaction of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with 4-methoxybenzaldehyde in 3:2 THF/Et<sub>2</sub>O at -100 °C monitored by <sup>19</sup>F RI-NMR. The dashed line corresponds to a first order fit for the first 10% formation of the aldolate with the rate constant indicated on the graph. Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

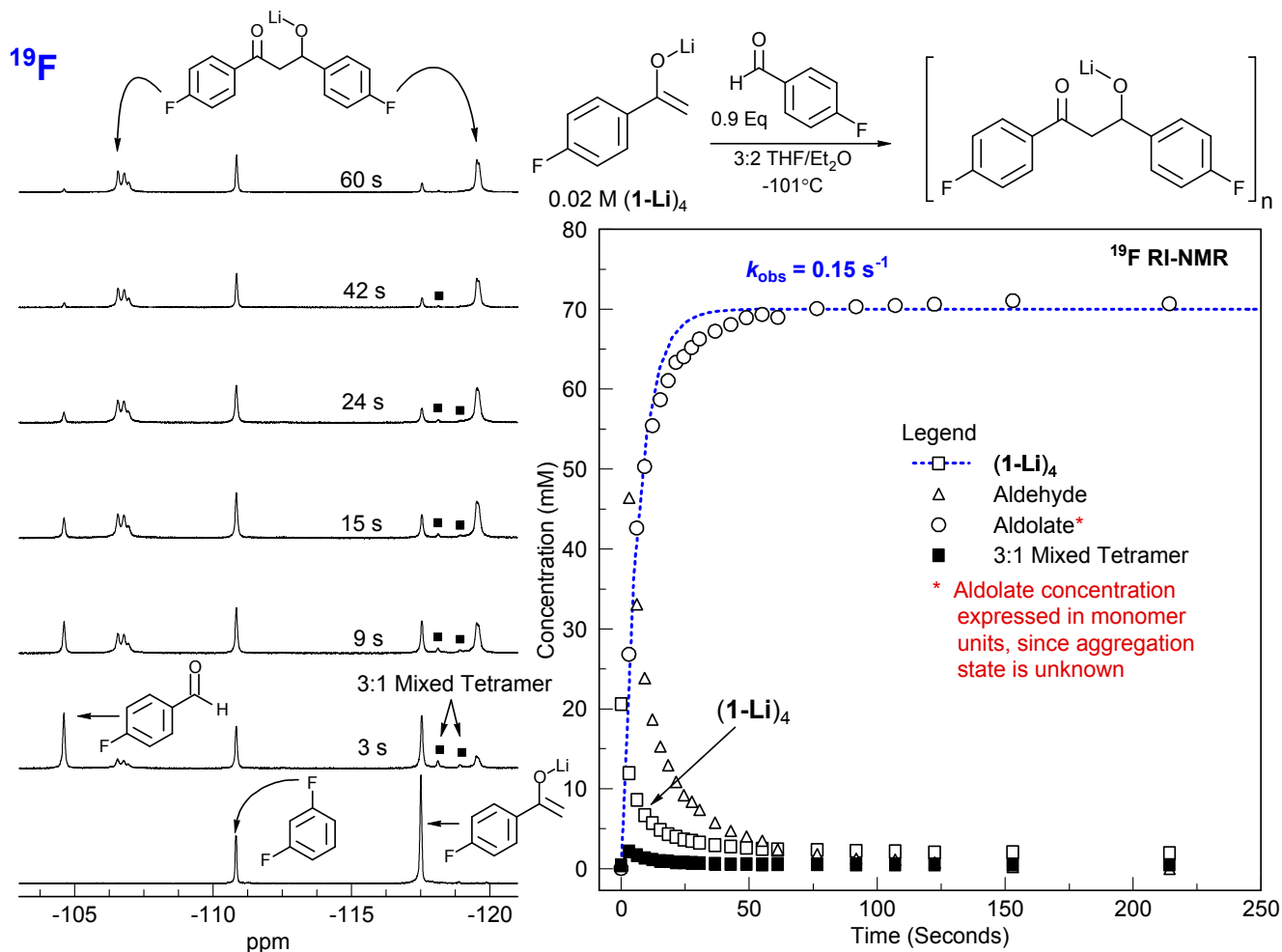


**Aldol Reaction of (1-Li)<sub>4</sub> with Benzaldehyde at -100 °C.** 4-Fluoroacetophenone (33  $\mu$ L, 0.3 mmol) was added to a 0.1 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) was added and <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -100 °C. Benzaldehyde (0.15 mL of a 1.7 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Spectra and a concentration versus time plot are shown in Figure S-35. A Hammett plot for the reaction of lithium enolate of 4-fluoroacetophenone (**1-Li**) with several substituted benzaldehydes is shown in Figure S-38.



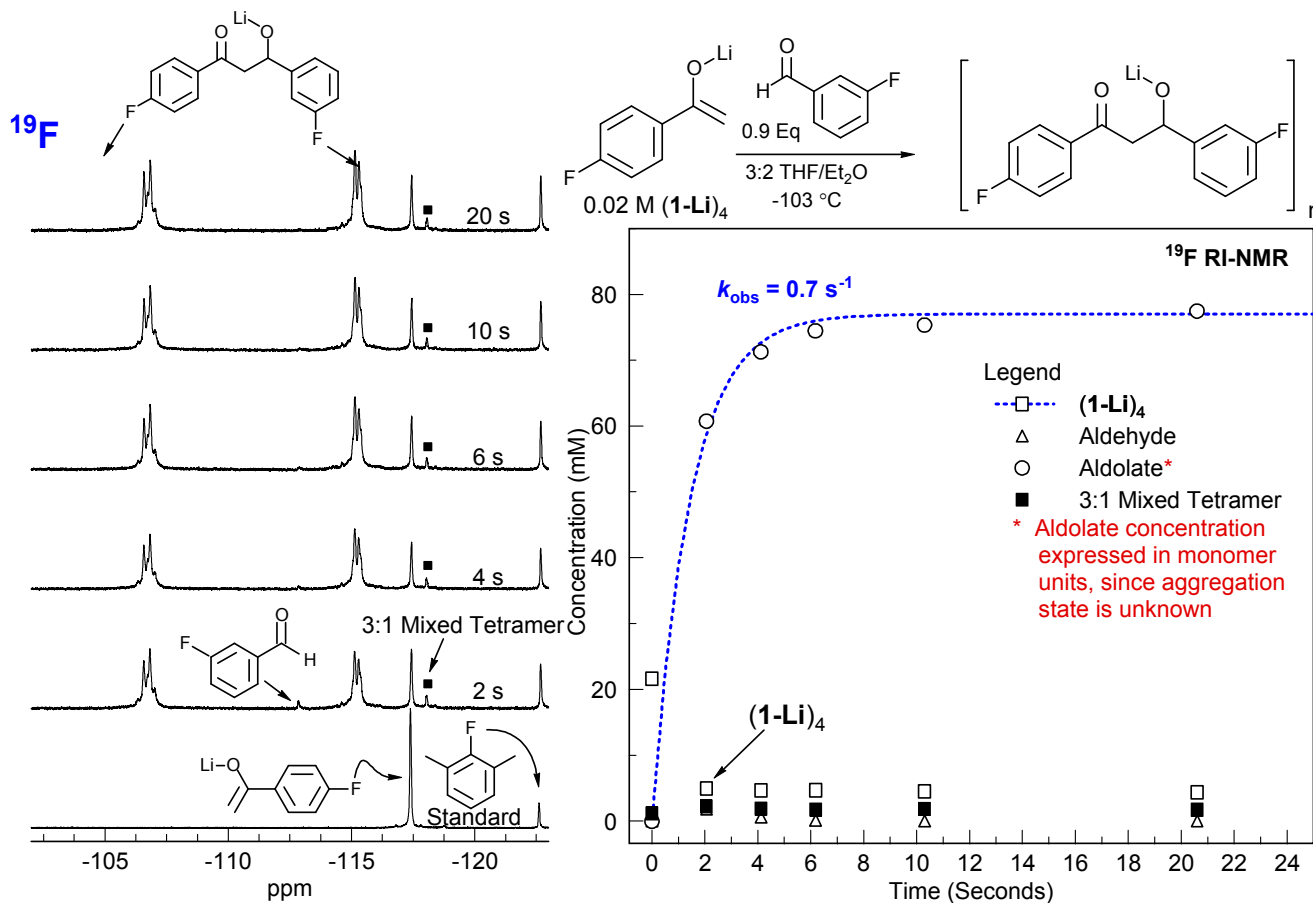
**Figure S-35.** The aldol reaction of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with benzaldehyde in 3:2 THF/Et<sub>2</sub>O at -100 °C monitored by <sup>19</sup>F RI-NMR. The dashed line corresponds to a first order fit for the first 20% formation of the aldolate with the rate constant indicated on the graph. Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

**Aldol Reaction of (1-Li)<sub>4</sub> with 4-Fluorobenzaldehyde at -100 °C.** 4-Fluoroacetophenone (33  $\mu$ L, 0.3 mmol) was added to a 0.1 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) was added and <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -100 °C. 4-Fluorobenzaldehyde (0.15 mL of a 1.7 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Spectra and a concentration versus time plot are shown in Figure S-36. A Hammett plot for the reaction of lithium enolate of 4-fluoroacetophenone (**1-Li**) with several substituted benzaldehydes is shown in Figure S-38.

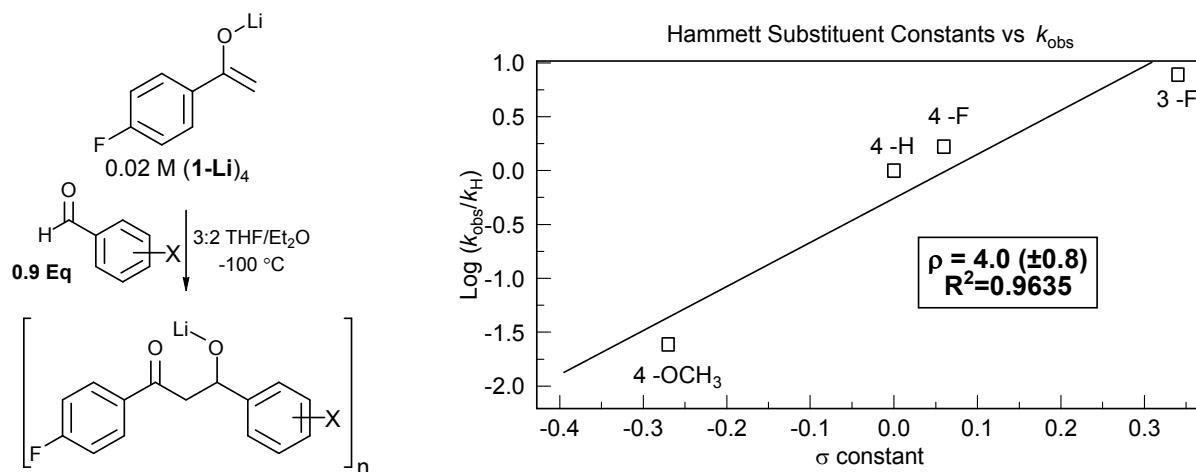


**Figure S-36.** The aldol reaction of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with 4-fluorobenzaldehyde in 3:2 THF/Et<sub>2</sub>O at -100 °C monitored by <sup>19</sup>F RI-NMR. The dashed line corresponds to a first order fit for the first 50% formation of the aldolate with the rate constant indicated on the graph. Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

**Aldol Reaction of (1-Li)<sub>4</sub> with 3-Fluorobenzaldehyde at -100 °C.** 4-Fluoroacetophenone (33  $\mu$ L, 0.3 mmol) was added to a 0.1 M solution (3:2 THF/Et<sub>2</sub>O) of freshly prepared LDA. 1,3-Difluorobenzene (5  $\mu$ L) was added and <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -100 °C. 3-Fluorobenzaldehyde (0.15 mL of a 1.7 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Spectra and a concentration versus time plot are shown in Figure S-37. A Hammett plot for the reaction of lithium enolate of 4-fluoroacetophenone (**1-Li**) with several substituted benzaldehydes is shown in Figure S-38.



**Figure S-37.** The aldol reaction of the lithium enolate of 4-fluoroacetophenone (**1-Li**) with 3-fluorobenzaldehyde in 3:2 THF/Et<sub>2</sub>O at -100 °C monitored by <sup>19</sup>F RI-NMR. The dashed line corresponds to a first order fit for the first 50% formation of the aldolate with the rate constant indicated on the graph. Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

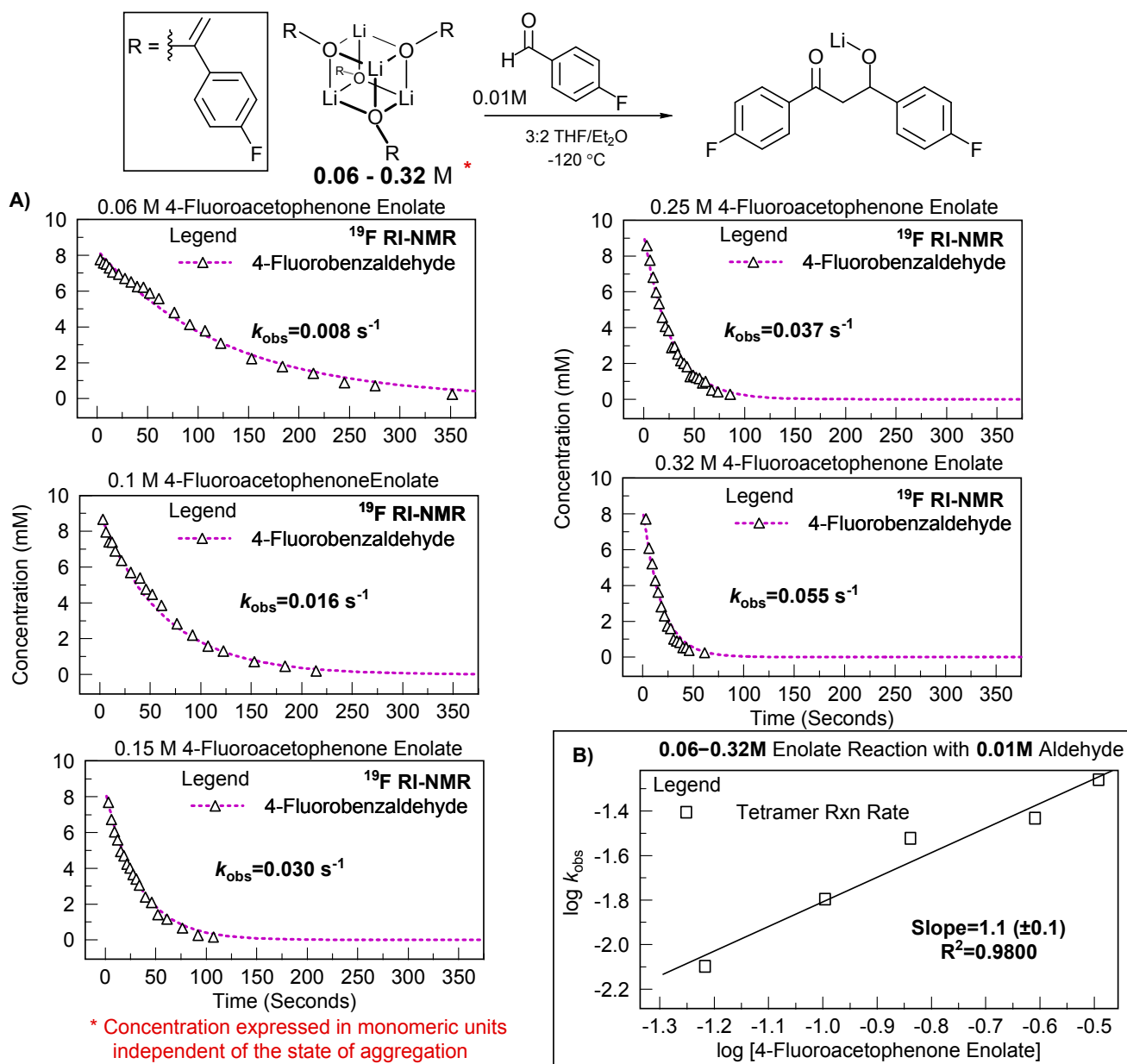


**Figure S-38.** The Hammett plot for the reaction of lithium enolate of 4-fluoroacetophenone (**1-Li**) with several substituted benzaldehydes in 3:2 THF/Et<sub>2</sub>O at -100 °C monitored by <sup>19</sup>F RI-NMR. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.025 M (**1-Li**)<sub>4</sub>; actual concentrations determined based on integration relative to the internal standard.)

#### Purification and Preparation of a Stock Solution of Lithium Enolate of 4-Fluoroacetophenone:

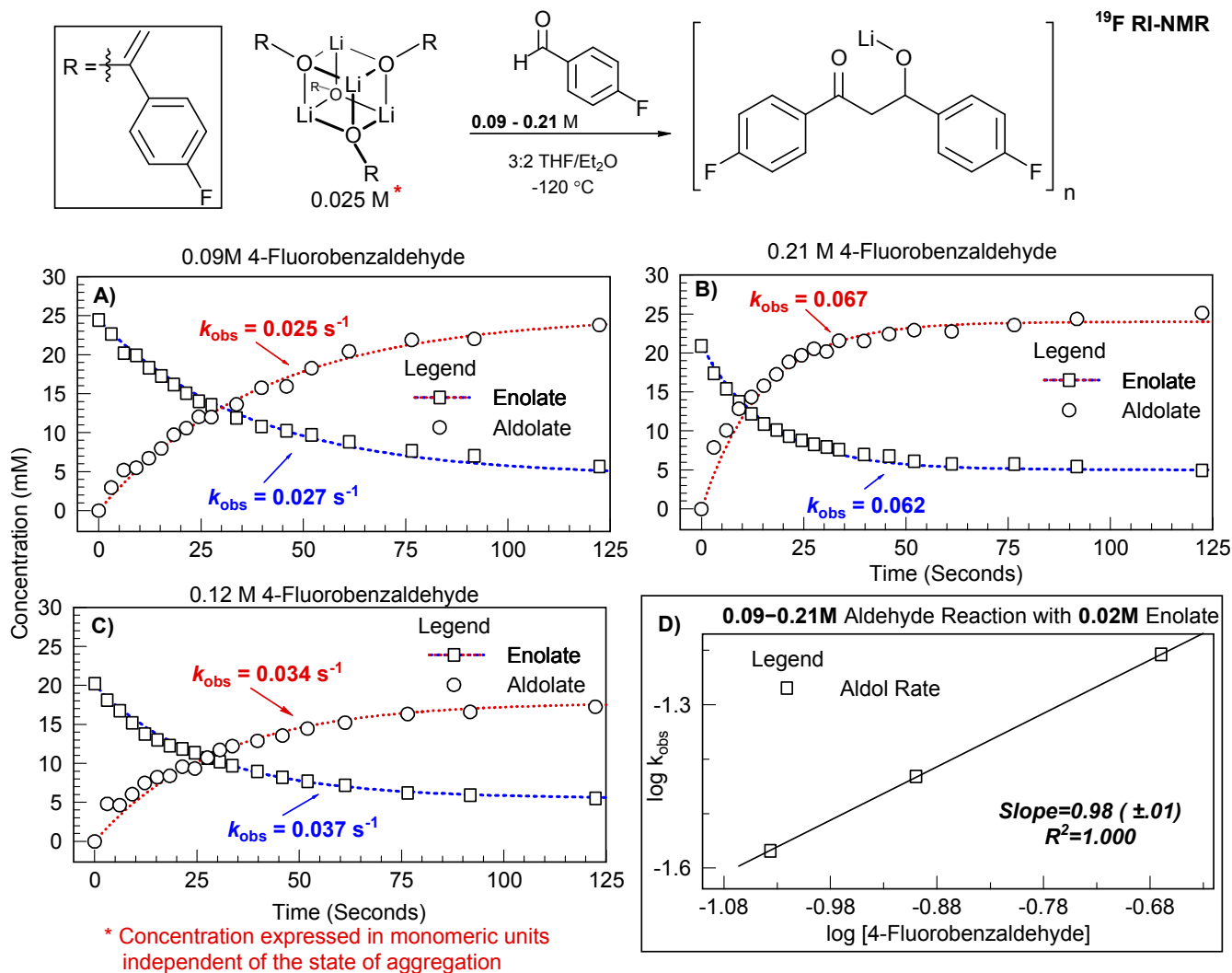
Stock solutions of the lithium enolate of 4-fluoroacetophenone were prepared according to the following procedure. A conical flask was flame dried, purged with Ar, and sealed with a septum. The enol silyl ether of 4-fluoroacetophenone (2.354 g, 11.2 mmol) was added via syringe. The flask was cooled to -78 °C back filling with Ar after which 3 mL of dry Me<sub>2</sub>O distilled from n-BuLi was added via cannula. *n*-Butyllithium (4.5 mL, 11.2 mmol) was added via syringe over several minutes after which the flask was shaken to mix the reactants. Upon standing overnight in a -78 °C freezer white crystals formed. The solvent was removed via cannula, and the crystals were placed under vacuum for 30 minutes. The flask was purged with Ar for 30 minutes. THF (9 mL) was added to produce 10 mL of a solution which based upon NMR integration versus an internal standard was found to be 0.58 M concentration (51 % yield).

**(1-Li)<sub>4</sub> Aldol Rate Dependence on Concentration of Enolate.** Using the stock solution of enolate **1-Li** samples with a total volume of 3 mL were prepared in the following manner. Enolate **4-Li** (0.4 mL for 0.06 M; 0.6 mL for 0.1 M; 0.9 mL for 0.15 M; 1.3 mL for 0.25 M; 1.8 mL for 0.32 M) was added to a 10 mm NMR tube sealed with a septa, purged with Ar, and containing 1.2 mL of Et<sub>2</sub>O and 1-2  $\mu$ L of <sup>13</sup>C enriched (10%) (Me<sub>3</sub>Si)<sub>3</sub>CH as a shift thermometer.<sup>[S2]</sup> The sample was diluted to 3 mL total volume with THF and 1,3-Difluorobenzene (5  $\mu$ L) was added. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C to check concentration and sample integrity. 4-Fluorobenzaldehyde (0.15 mL of a 0.25 M solution, 0.03 mmol) was added using our RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Pseudo first order rates ( $k_{obs}$ ) were determined by fitting to a first order line. Concentration versus time plots of the reaction for the samples of various concentrations of enolate are shown in Figure S-39 along with a plot of log  $k_{obs}$  versus log enolate concentration.



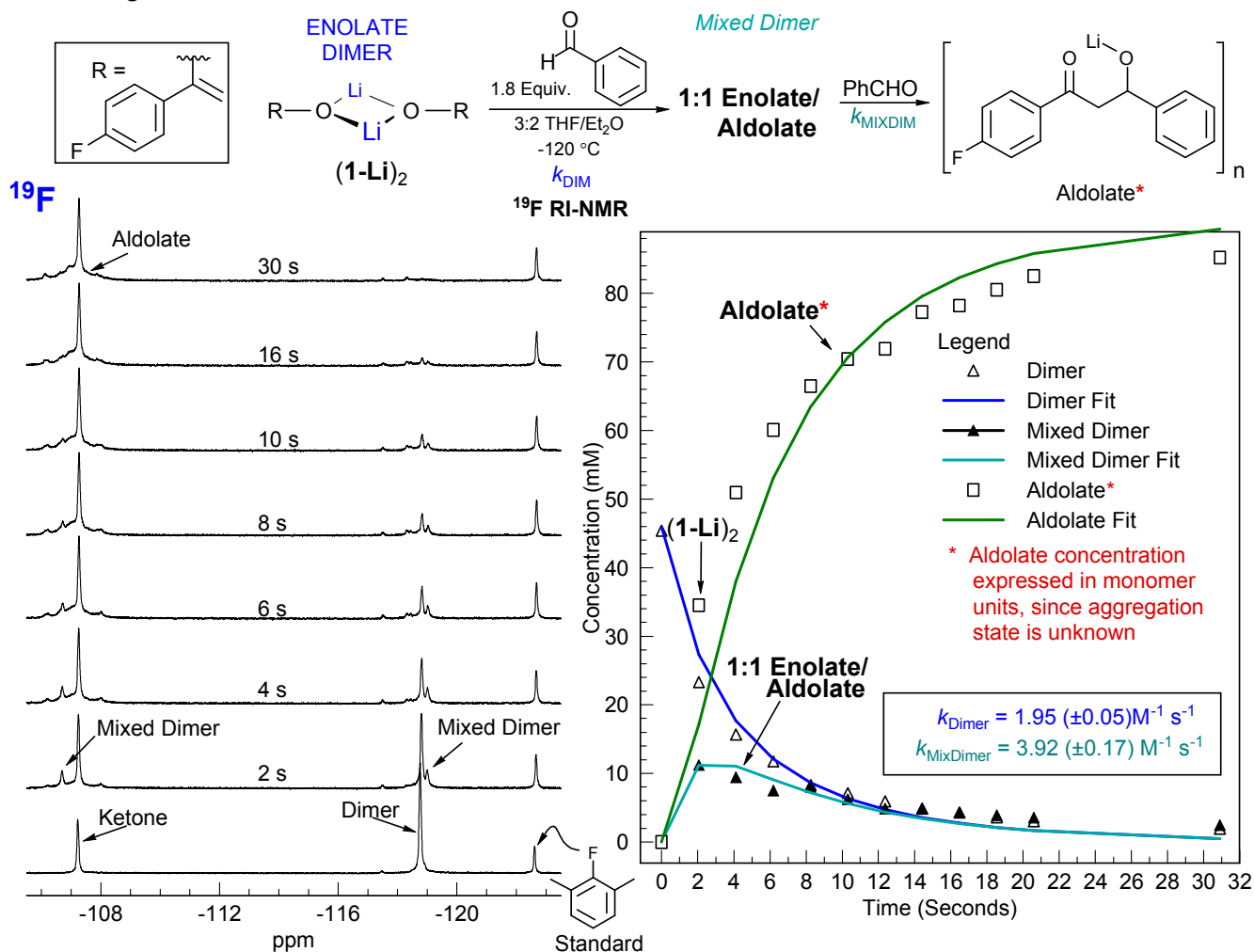
**Figure S-39.** The concentration dependence of enolate **1-Li** on the rate of the aldol reaction with 4-fluorobenzaldehyde at  $-120^\circ\text{C}$ . A) Reactions of **1-Li** (0.06–0.32 M) with 4-fluorobenzaldehyde (0.015 M). Lines correspond to first order decrease of aldehyde with the corresponding rate constants indicated on the graph. B) A plot of  $\log k_{\text{obs}}$  versus  $\log$  concentration of enolate indicates that the reaction is first order in enolate.

**(1-Li)<sub>4</sub> Aldol Rate Dependence on Concentration of Aldehyde.** Using the stock solution of enolate **1-Li** samples with a total volume of 3 mL were prepared in the following manner. Enolate **1-Li** (0.15 mL for 0.025 M) was added to a 10 mm NMR tube sealed with a septa, purged with Ar, and containing 1.2 mL of Et<sub>2</sub>O and 1-2  $\mu$ L of <sup>13</sup>C enriched (10%) (Me<sub>3</sub>Si)<sub>3</sub>CH as a shift thermometer.<sup>[S2]</sup> The sample was diluted to 3 mL total volume with THF (1.65 mL) and 1,3-Difluorobenzene (5  $\mu$ L) was added. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C to check concentration and sample integrity. 4-Fluorobenzaldehyde (0.15 mL of a 1.8 M solution for 0.09 M reaction; 0.15 mL of a 2.4 M solution for 0.12 M reaction; 0.15 mL of a 4.2 M solution for 0.21 M reaction; ) was added using our RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. Pseudo first order rates (*k*<sub>obs</sub>) were determined by fitting to a first order line. Concentration versus time plots of the reaction with various concentrations of aldehyde are shown in Figure S-40 along with a plot of log *k*<sub>obs</sub> versus log aldehyde concentration.



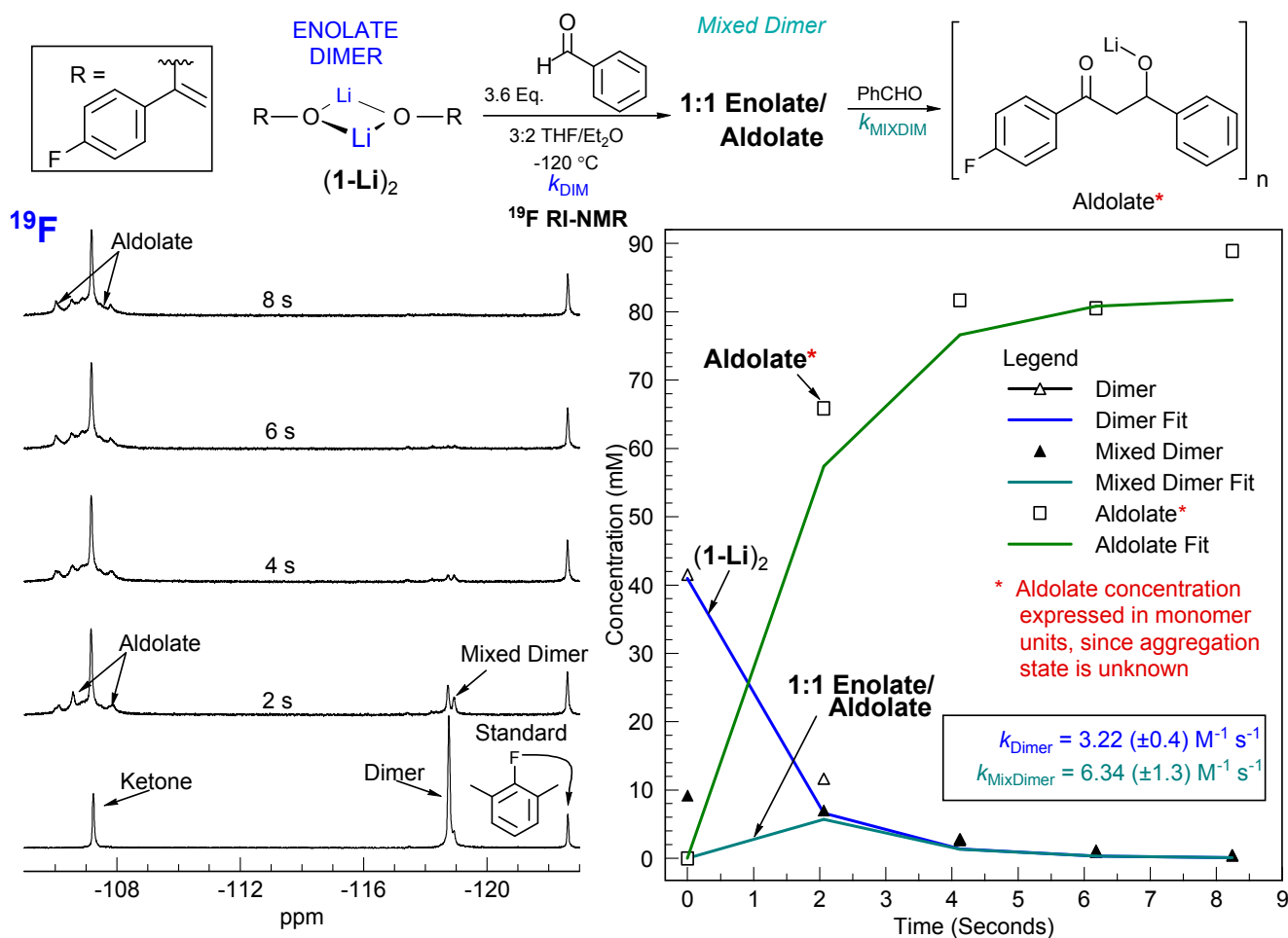
**Figure S-40.** The concentration dependence of 4-fluorobenzaldehyde on the rate of the aldol reaction with 4-fluoroacetophenone enolate at -120 °C. A-C) Reactions of **1-Li** (0.025 M) with 4-fluorobenzaldehyde (0.09-0.21 M). Solid lines correspond to first order decrease of enolate and dashed lines correspond to first order increase of aldolate with the corresponding rate constants indicated on the graph. D) A log plot of *k*<sub>obs</sub> versus aldehyde concentration indicates that the reaction is first order in aldehyde.

**Aldol Reaction of (1-Li)<sub>2</sub> with 1.8 Equivalents of Benzaldehyde at -120 °C.** 1,3-Dimethyl-2-fluorobenzene (5  $\mu$ L) was added a freshly prepared 3:2 THF/Et<sub>2</sub>O solution of 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> in a dried thin-walled 10 mm NMR tube. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C to check concentration and sample integrity. Following the general RI-NMR procedure, 4-fluoroacetophenone (0.15 mL of a 2.0 M solution) was added and <sup>19</sup>F NMR spectra were obtained for a period of 8 minutes to allow for consumption of the LDA and formation of the kinetically stable dimeric lithium enolate of 4-fluoroacetophenone (**1-Li**)<sub>2</sub>. Then following the general RI-NMR procedure, benzaldehyde (0.15 mL of a 2.9 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. The <sup>19</sup>F NMR spectrum of the mixed and homo dimer was simulated using the NUTS automated line fitting routine.<sup>[S6]</sup> All other concentrations were determined by integration techniques relative to 1,3-dimethyl-2-fluorobenzene. Spectra and a concentration versus time plot are shown in Figure S-41.



**Figure S-41.** The aldol reaction of the dimeric form of the lithium enolate of 4-fluoroacetophenone (**1-Li**)<sub>2</sub> with 1.8 equivalents of benzaldehyde in 3:2 THF/Et<sub>2</sub>O at -120 °C monitored by <sup>19</sup>F RI-NMR. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.05 M (**1-Li**)<sub>2</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)

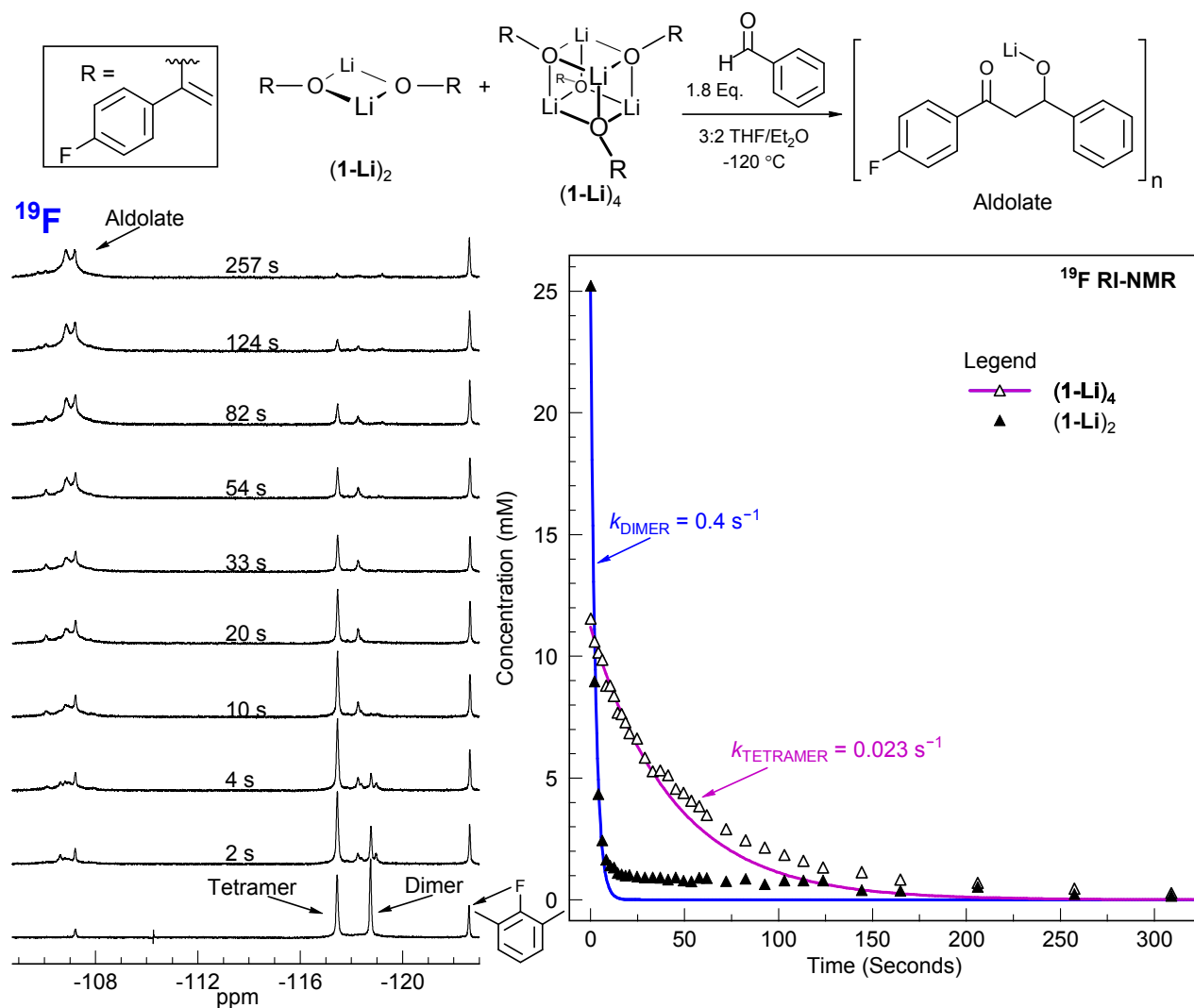
**Aldol Reaction of (1-Li)<sub>2</sub> with 3.6 Equivalents of Benzaldehyde at -120 °C.** 1,3-Dimethyl-2-fluorobenzene (5  $\mu$ L) was added a freshly prepared 3:2 THF/Et<sub>2</sub>O solution of 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> in a dried thin-walled 10 mm NMR tube. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C to check concentration and sample integrity. Following the general RI-NMR procedure, 4-fluoroacetophenone (0.15 mL of a 2.0 M solution) was added and <sup>19</sup>F NMR spectra were obtained for a period of 8 minutes to allow for consumption of LDA and formation of the kinetically stable dimeric lithium enolate of 4-fluoroacetophenone (**1-Li**)<sub>2</sub>. Then following the general RI-NMR procedure, benzaldehyde (0.30 mL of a 2.9 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. The <sup>19</sup>F NMR spectrum of the mixed and homo dimer was simulated using the NUTS automated line fitting routine.<sup>[S6]</sup> All other concentrations were determined by integration techniques relative to 1,3-dimethyl-2-fluorobenzene. Spectra and a concentration versus time plot are shown in Figure S-42.



**Figure S-42.** The aldol reaction of the dimeric form of the lithium enolate of 4-fluoroacetophenone (**1-Li**)<sub>2</sub> with 3.6 equivalents of benzaldehyde in 3:2 THF/Et<sub>2</sub>O at -120 °C monitored by <sup>19</sup>F RI-NMR. Lines correspond to COPASI<sup>[S5]</sup> simulation values determined from the kinetic model shown above. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.05 M (**1-Li**)<sub>2</sub>; Aldolate concentration was plotted as if it were monomer, since the aggregation state is not known. Concentrations were determined based on integration relative to the internal standard.)



**Aldol Reaction of (1-Li)<sub>2</sub> and (1-Li)<sub>4</sub> with 1.8 Equivalents of Benzaldehyde at -120 °C.** 1,3-Dimethyl-2-fluorobenzene (5  $\mu$ L) was added a freshly prepared 3:2 THF/Et<sub>2</sub>O solution of 0.1 M LiN<sup>i</sup>Pr<sub>2</sub> in a dried thin-walled 10 mm NMR tube. <sup>13</sup>C, <sup>19</sup>F and <sup>7</sup>Li spectra were acquired at -120 °C to check concentration and sample integrity. Following the general RI-NMR procedure, 4-fluoroacetophenone (0.15 mL of a 2.0 M solution) was added and <sup>19</sup>F NMR spectra were obtained for a period of 2 hours to allow for consumption of LDA, formation of the kinetically stable dimeric lithium enolate of 4-fluoroacetophenone (**(1-Li)<sub>2</sub>**), and partial equilibration to form (**(1-Li)<sub>4</sub>**). Then following the general RI-NMR procedure, benzaldehyde (0.15 mL of a 2.9 M solution, 0.26 mmol) was added via the RI-NMR apparatus and <sup>19</sup>F NMR spectra were obtained. The <sup>19</sup>F NMR spectrum of the mixed and homo dimer was simulated using the NUTS automated line fitting routine.<sup>[S6]</sup> All other concentrations were determined by integration techniques relative to 1,3-dimethyl-2-fluorobenzene. Spectra and a concentration versus time plot are shown in Figure S-43.



**Figure S-43.** The aldol reaction of the dimeric (**(1-Li)<sub>2</sub>**) and tetrameric (**(1-Li)<sub>4</sub>**) forms of the lithium enolate of 4-fluoroacetophenone with 1.8 equivalents of benzaldehyde in 3:2 THF/Et<sub>2</sub>O at -120 °C monitored by <sup>19</sup>F RI-NMR. The dashed lines correspond to a first order fits for the first 50% reaction with the rate constants indicated on the graph. (Note from written procedure to figure: 0.1 M Lithium Enolate = 0.05 M (**(1-Li)<sub>2</sub>**); actual concentrations determined based on integration relative to the internal standard.)

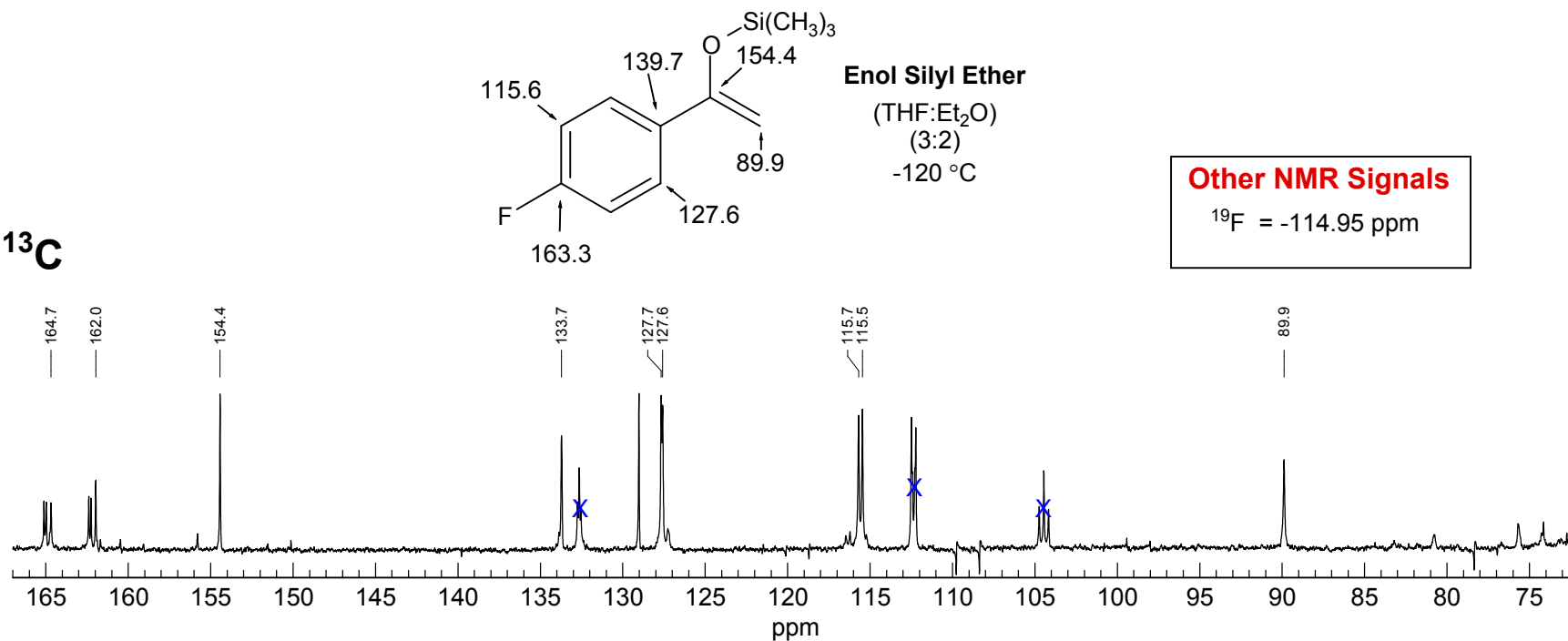
#### S4. NMR Data and Spectra

Species*	C-O	$\Delta \delta^{**}$	O-C=C	$\Delta \delta^{**}$	C-F	$\Delta \delta^{**}$	$^{19}\text{F}$	$\Delta \delta^{**}$
<b>1-TMS</b>	154.46	0	89.9	0	163.3	0	-114.95	0
<b>1-MOM</b> (CDCl <sub>3</sub> , RT)	157.2	2.74	85.8	-4.1	163.2	-0.1	-114.42	+0.53
<b>1-H</b> (Enol) <sup>[S1]</sup>	156.3	1.84	82.6	-7.3	162.8	-0.5	-116.51	-1.56
<b>(1-Li)<sub>4</sub></b>	164.4	9.94	80.4	-9.5	162.6	-0.7	-117.44	-2.49
<b>(1-Li)<sub>2</sub></b>	165.6	11.14	76.0	-13.9	162.2	-1.1	-118.75	-3.80
<b>(1-Li)•LDA</b>	166.0	11.54	74.6	-15.3	162.2	-1.1	-118.86	-3.91
<b>(1-Li)•TMTAN</b> (THF/Me <sub>2</sub> O)	165.45	10.99	71.9	-18.0	161.8	-1.5	-120.14	-5.19
<b>1-P4</b> <sup>[S1]</sup> (Me <sub>2</sub> O)	166.1	11.64	68.1	-21.8	161.5	-1.8	-122.04	-7.09

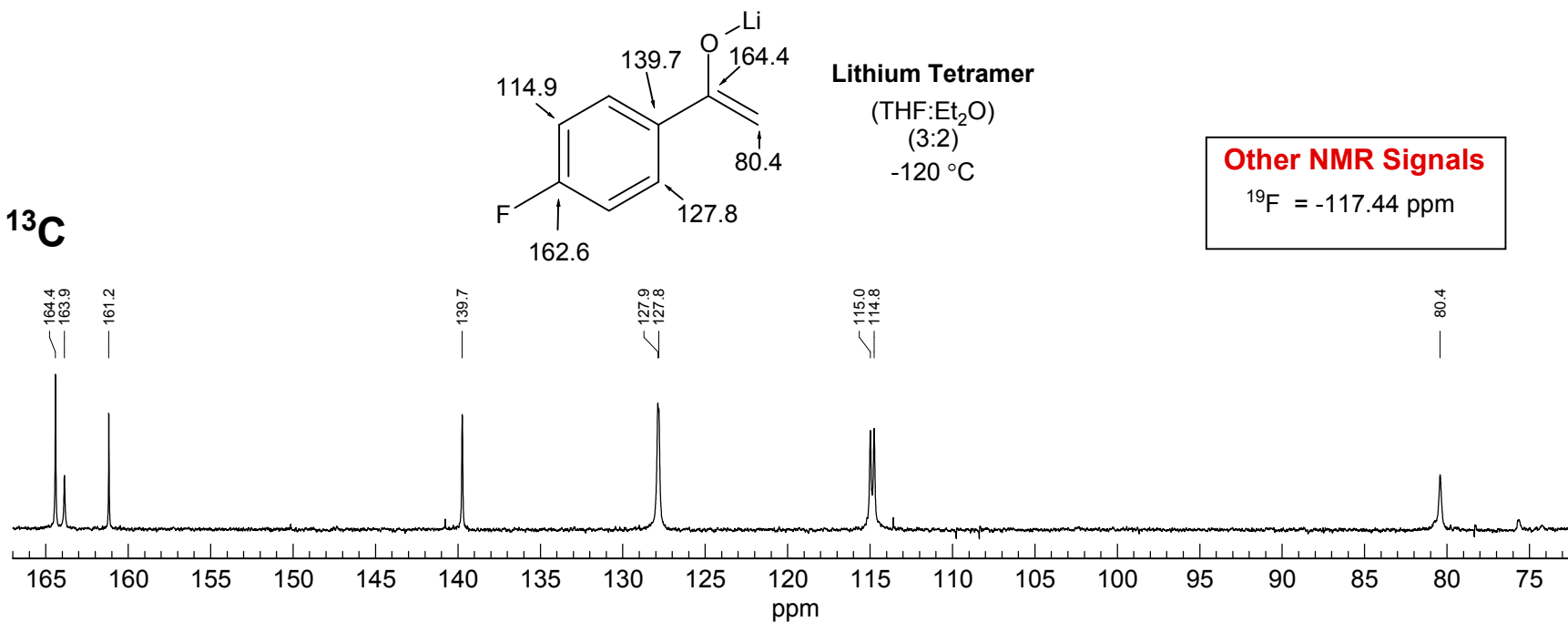
\* Chemical shifts obtained in 3:2 THF/Et<sub>2</sub>O at -120 °C unless noted.

\*\*The difference in chemical shift between the enolate and the enol silyl ether. See reference [S7] for similar enolate NMR data.

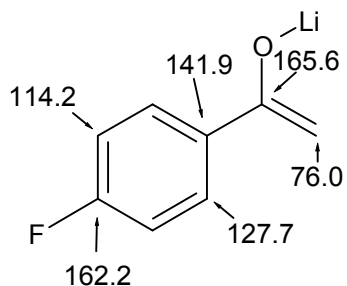
**$^{13}\text{C}$**



**$^{13}\text{C}$**



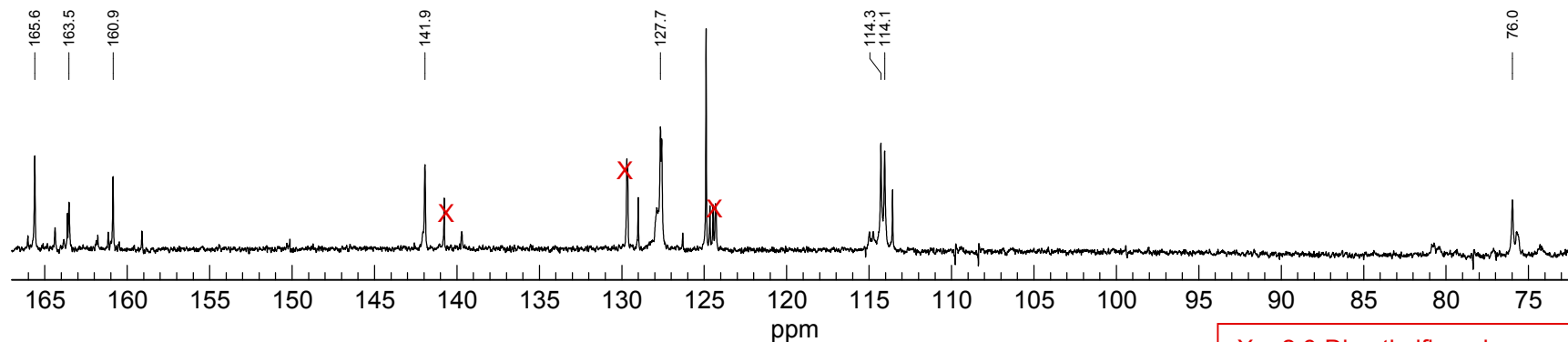
**$^{13}\text{C}$**



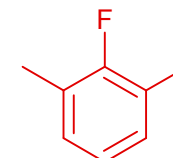
**Lithium Dimer**  
(THF:Et<sub>2</sub>O)  
(3:2)  
-125 °C

**Other NMR Signals**

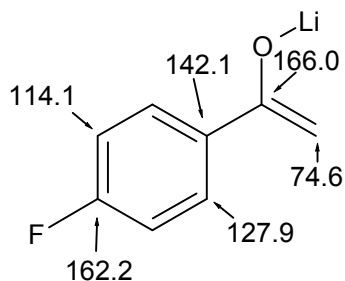
$^{19}\text{F}$  = -118.79 ppm



X = 2,6-Dimethylfluorobenzene



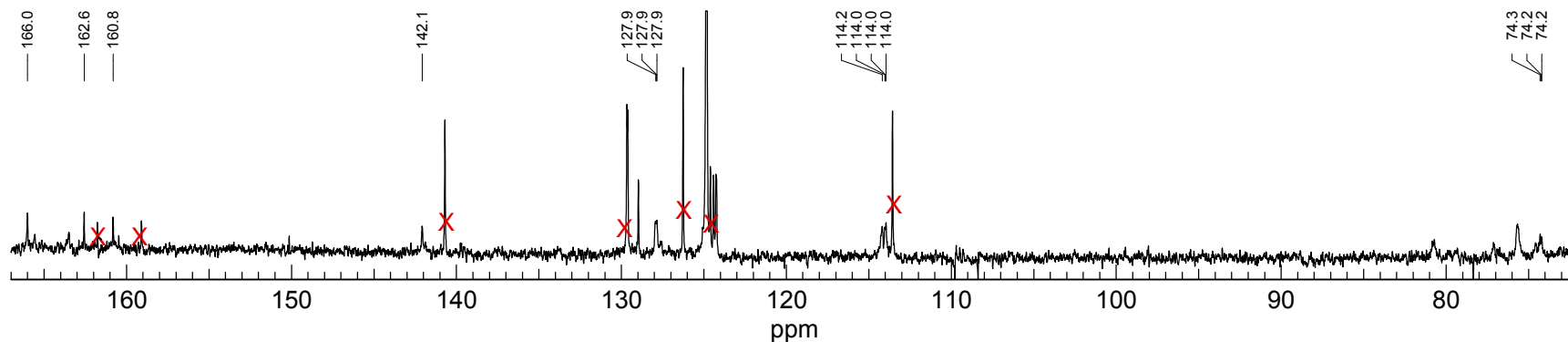
**$^{13}\text{C}$**

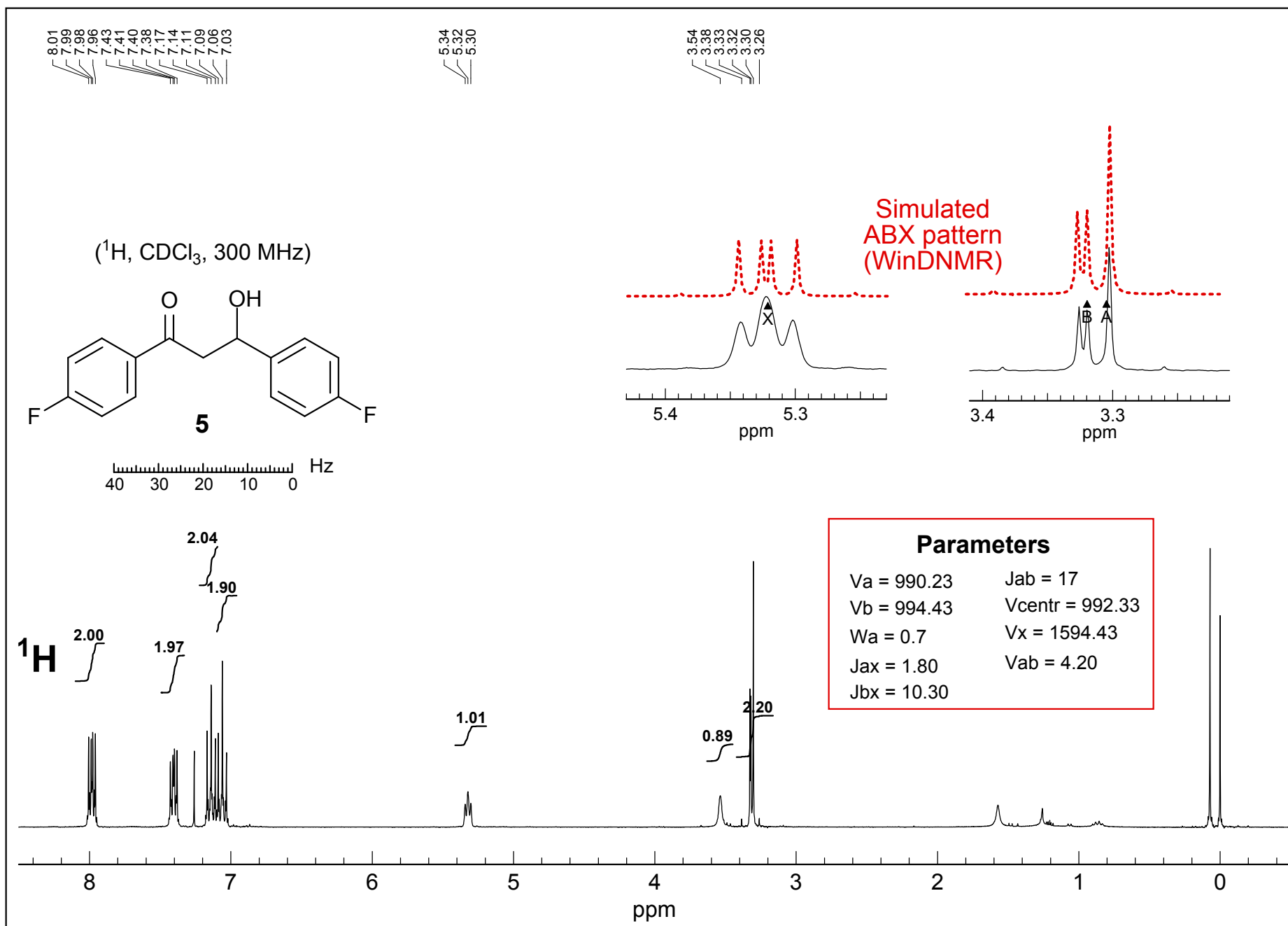


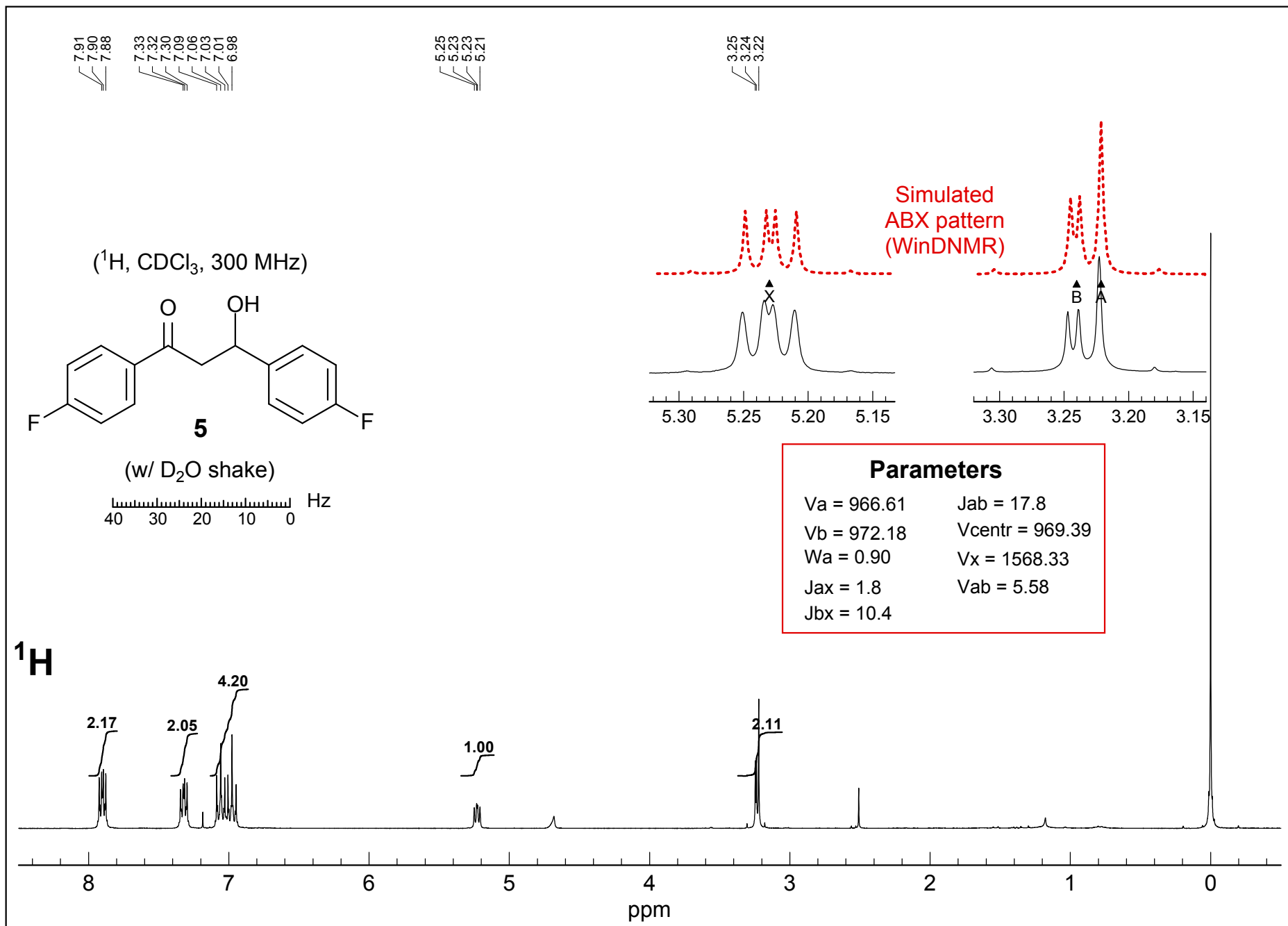
**Mixed LDA Dimer**  
(THF:Et<sub>2</sub>O)  
(3:2)  
-125 °C

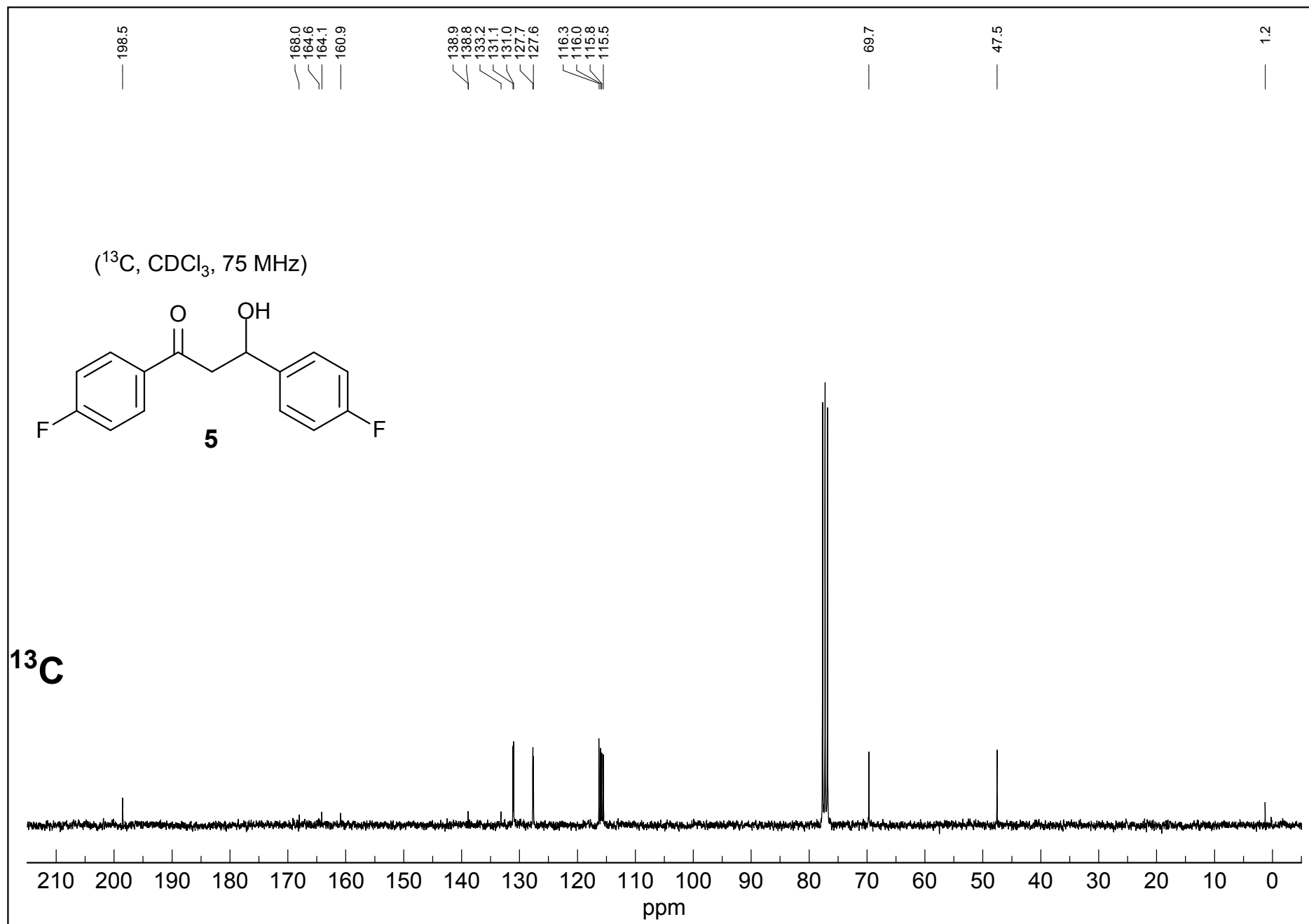
**Other NMR Signals**

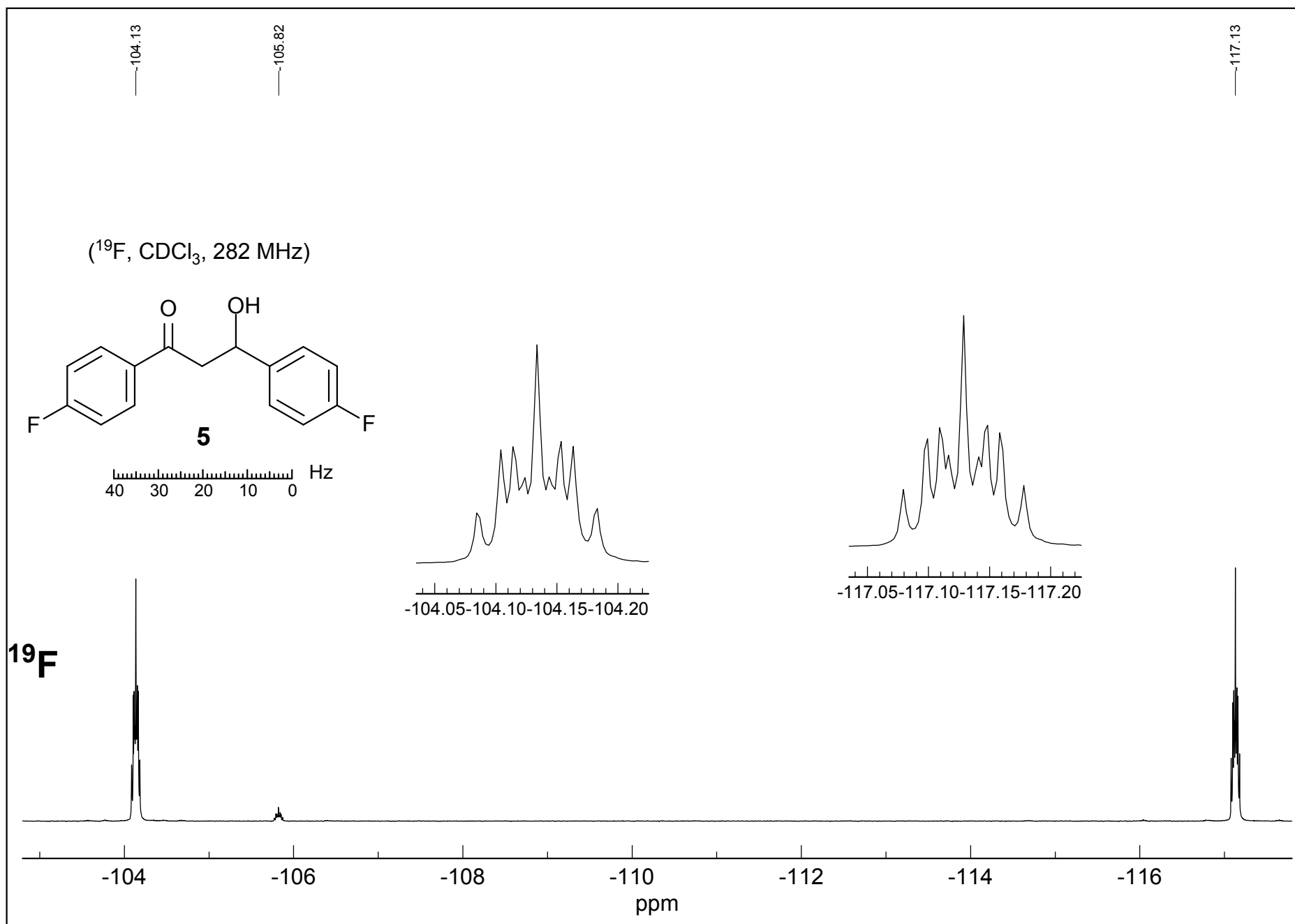
$^{19}\text{F}$  = -118.86 ppm



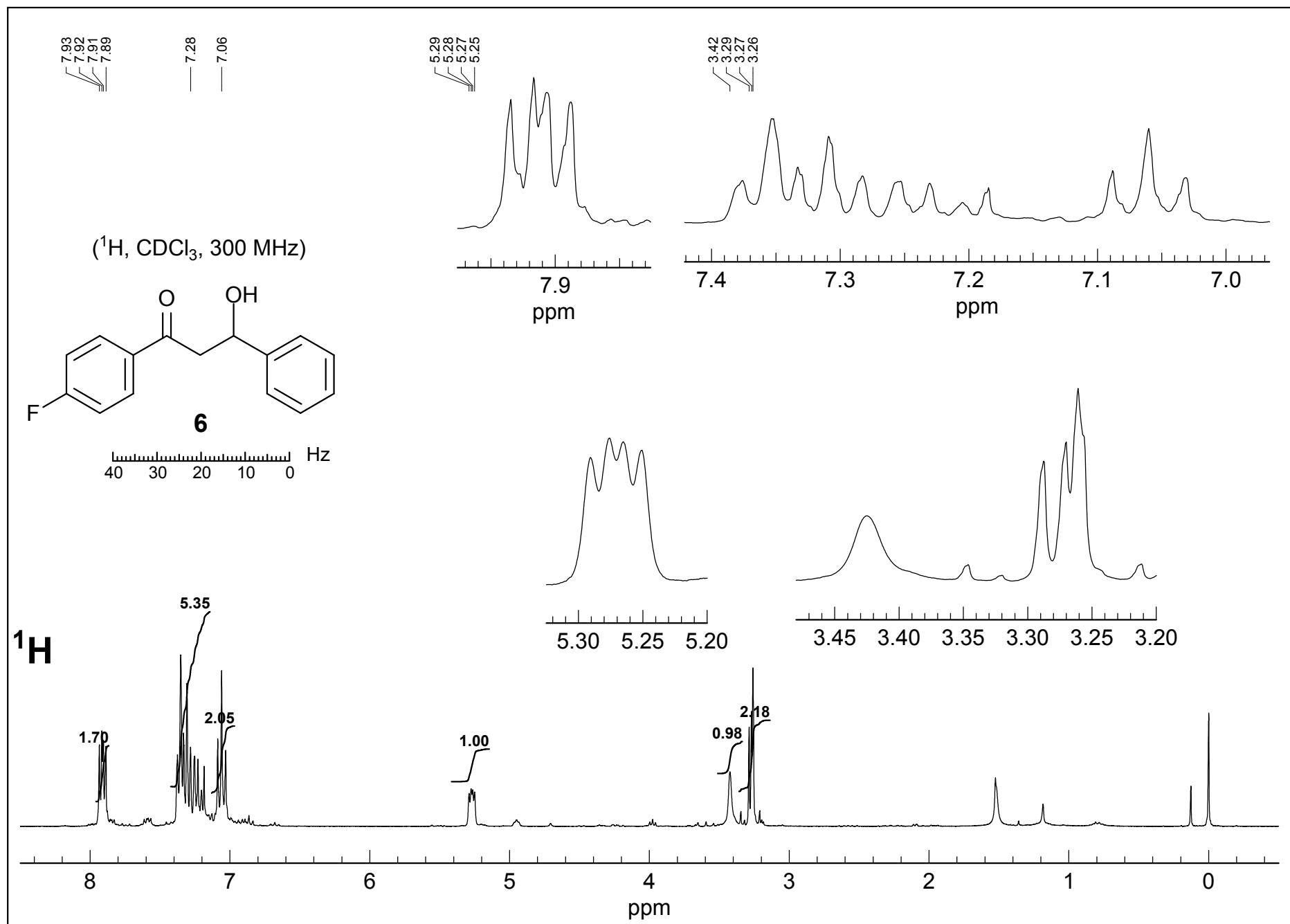


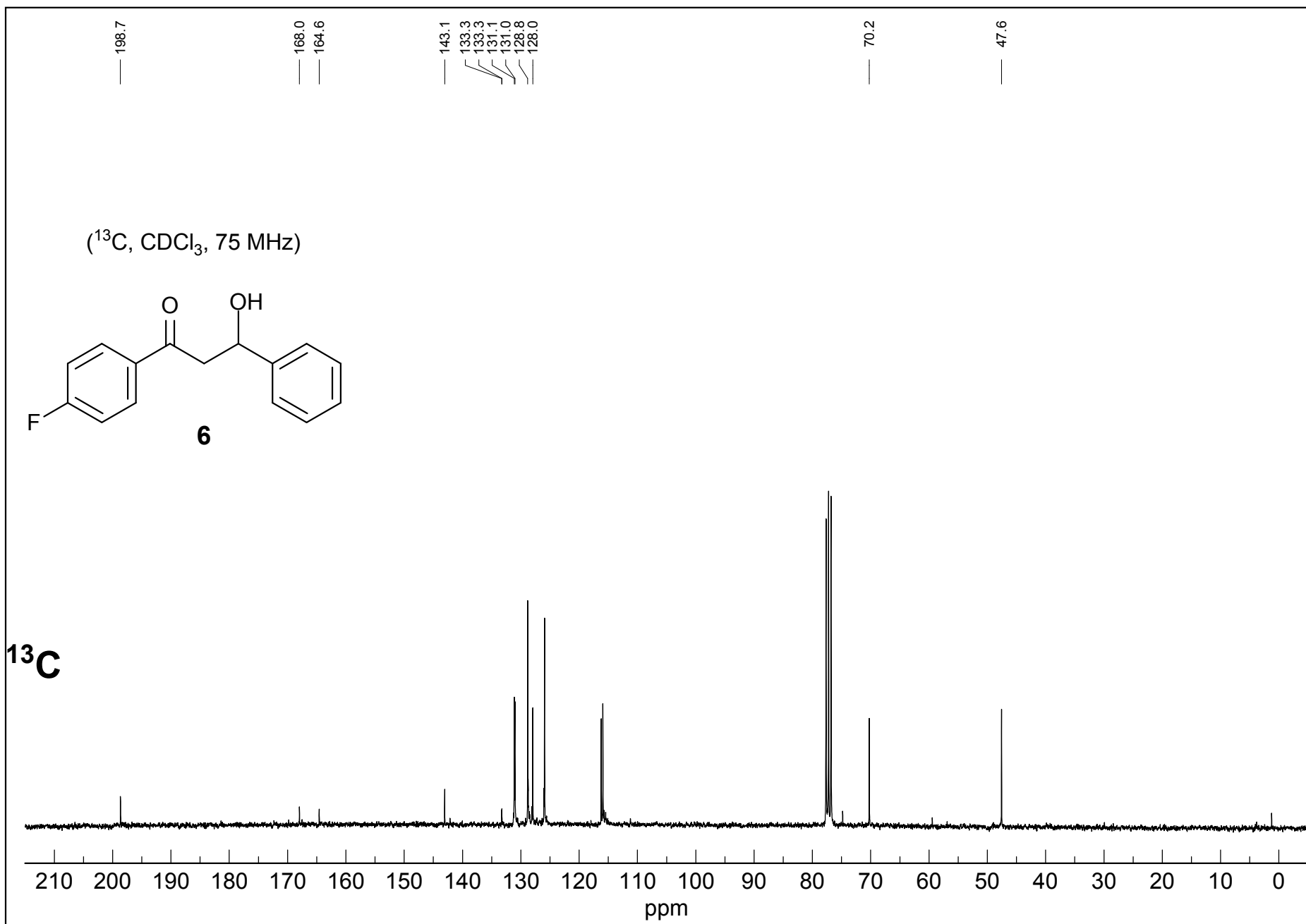


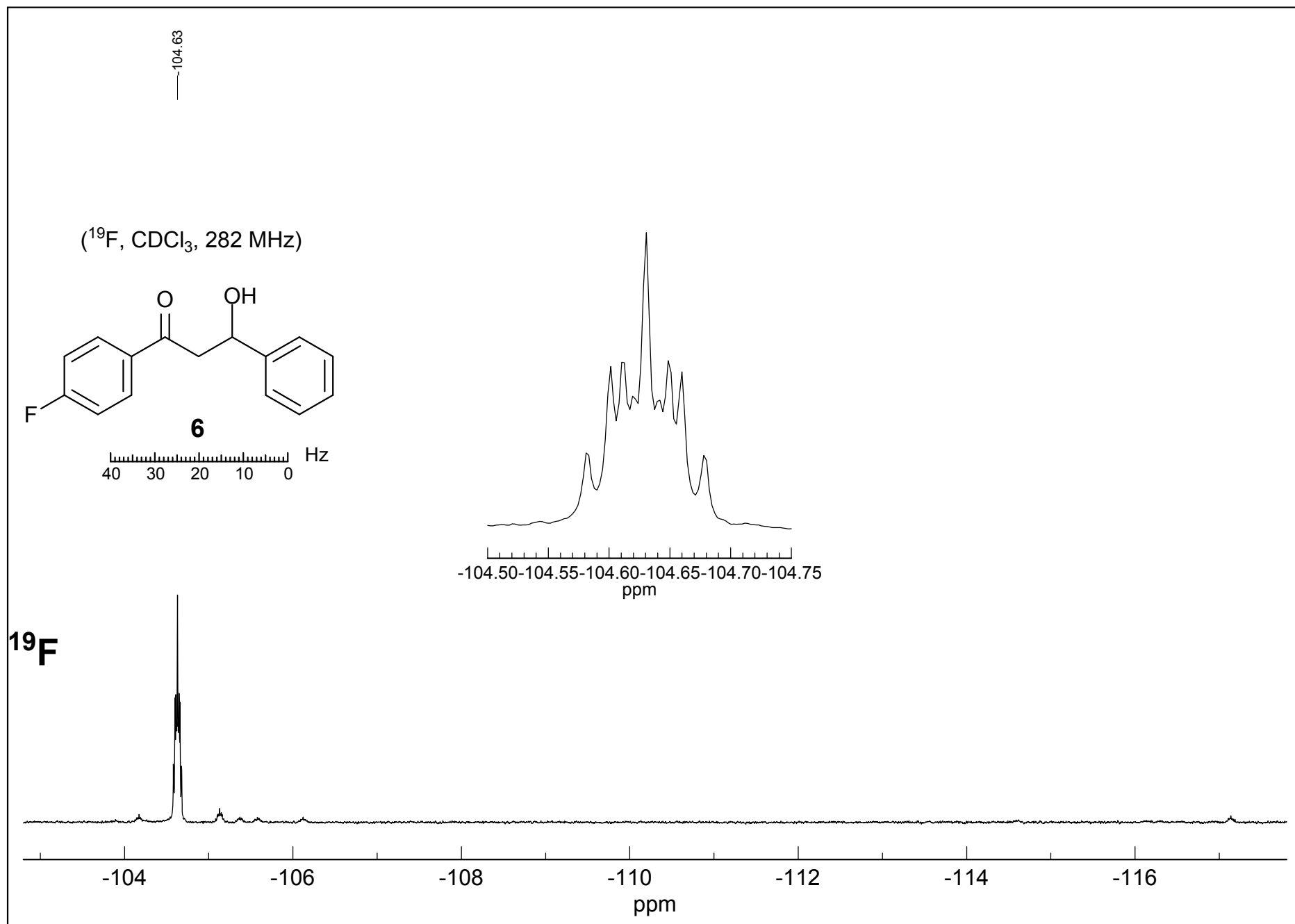


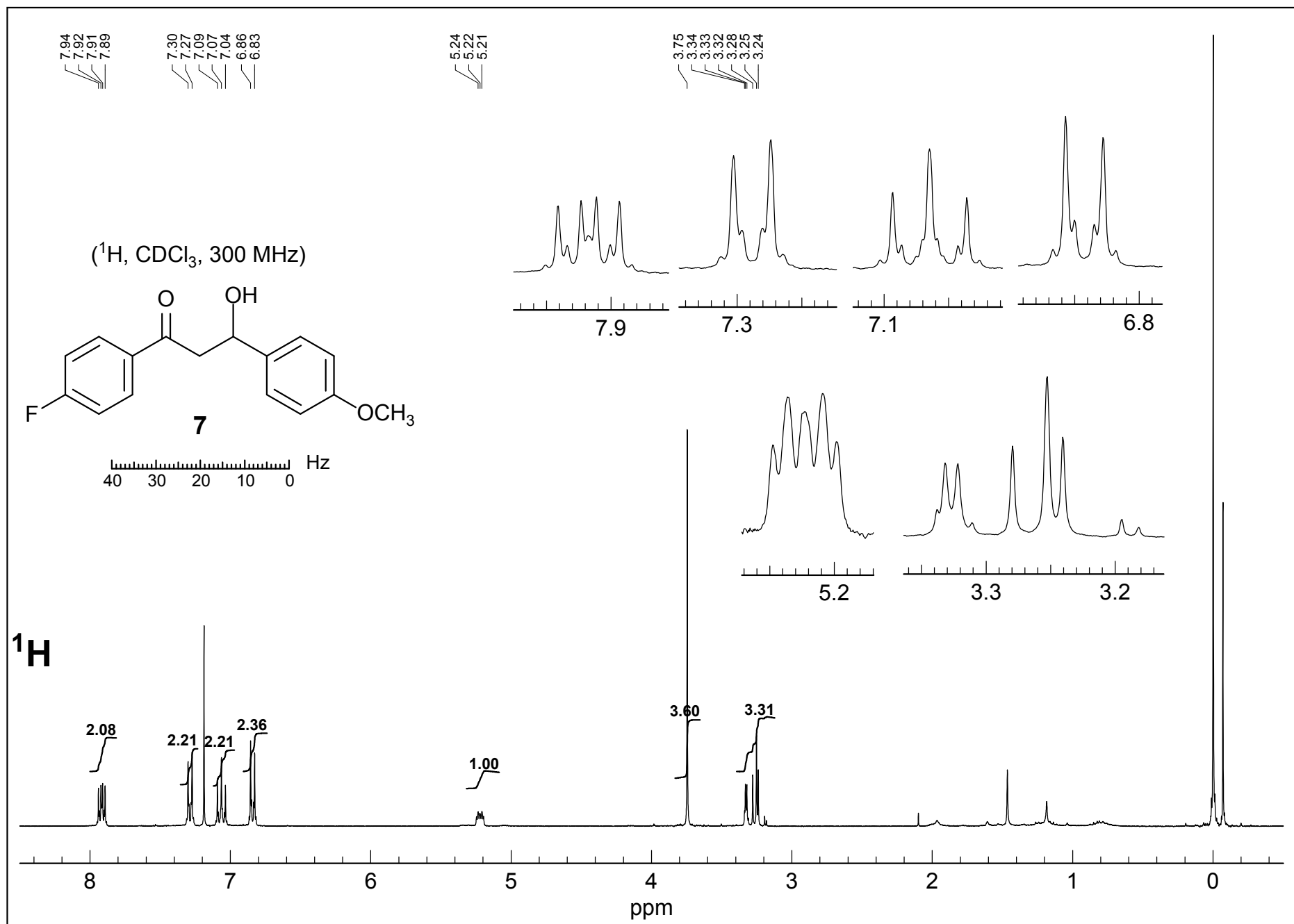


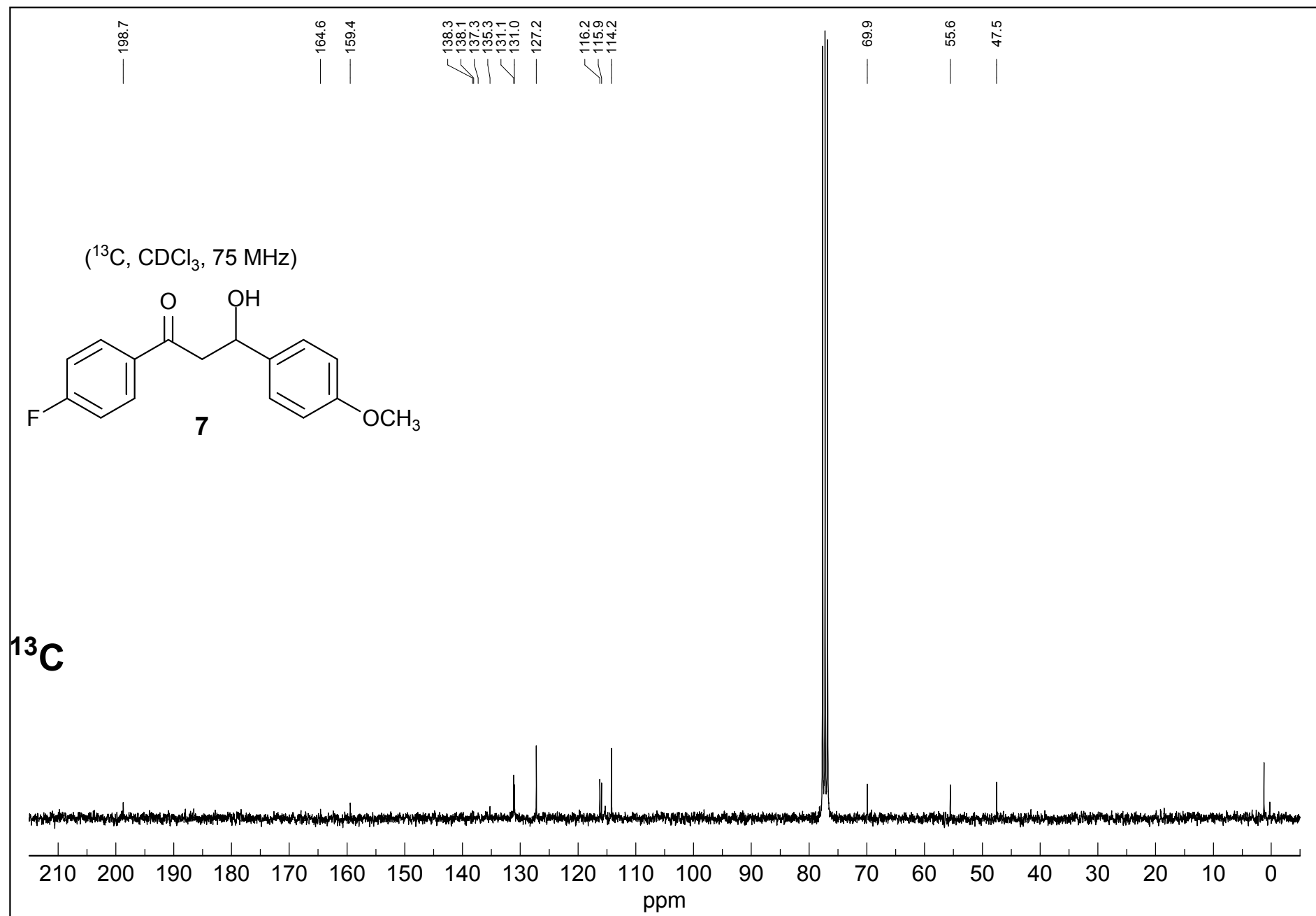


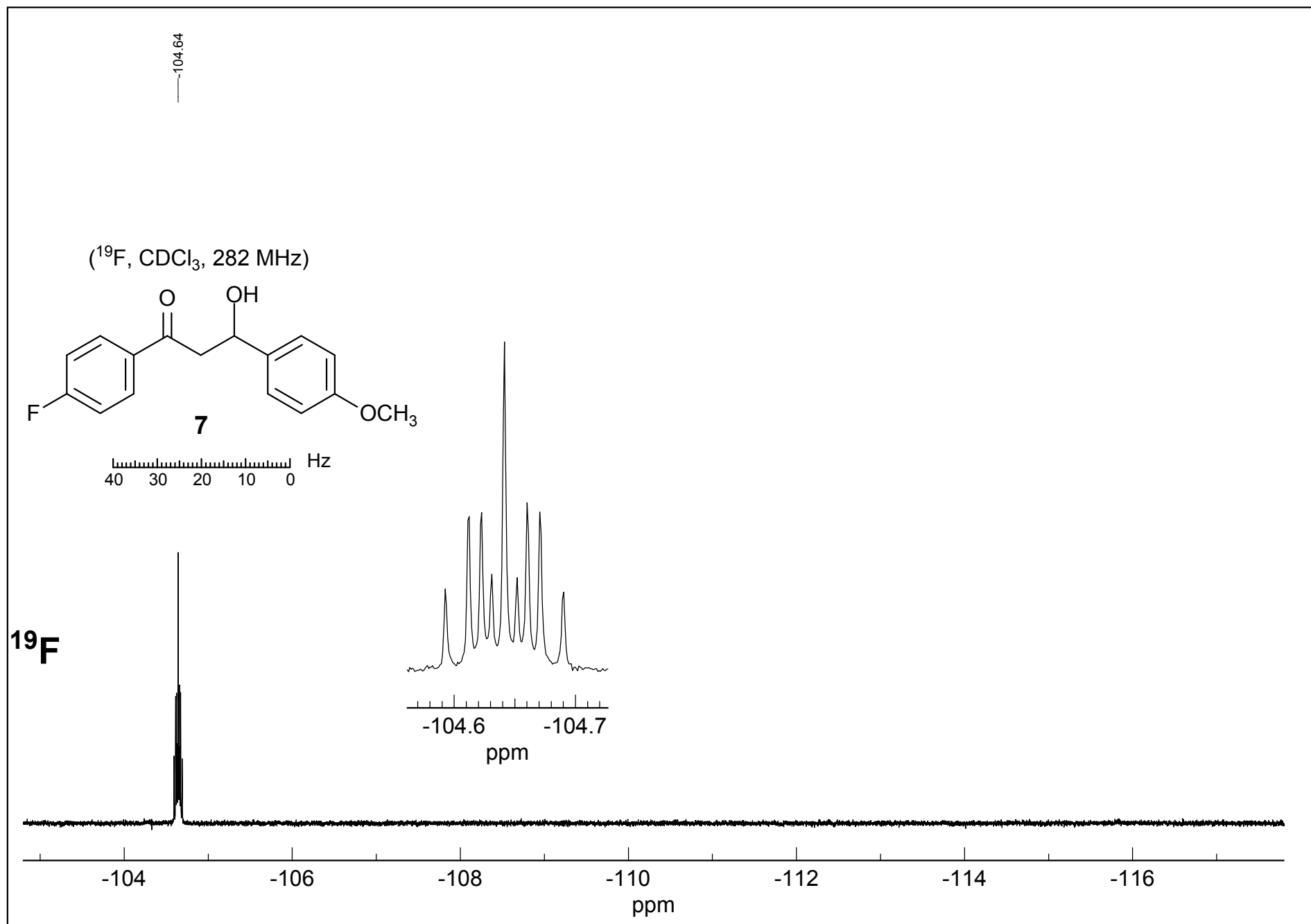


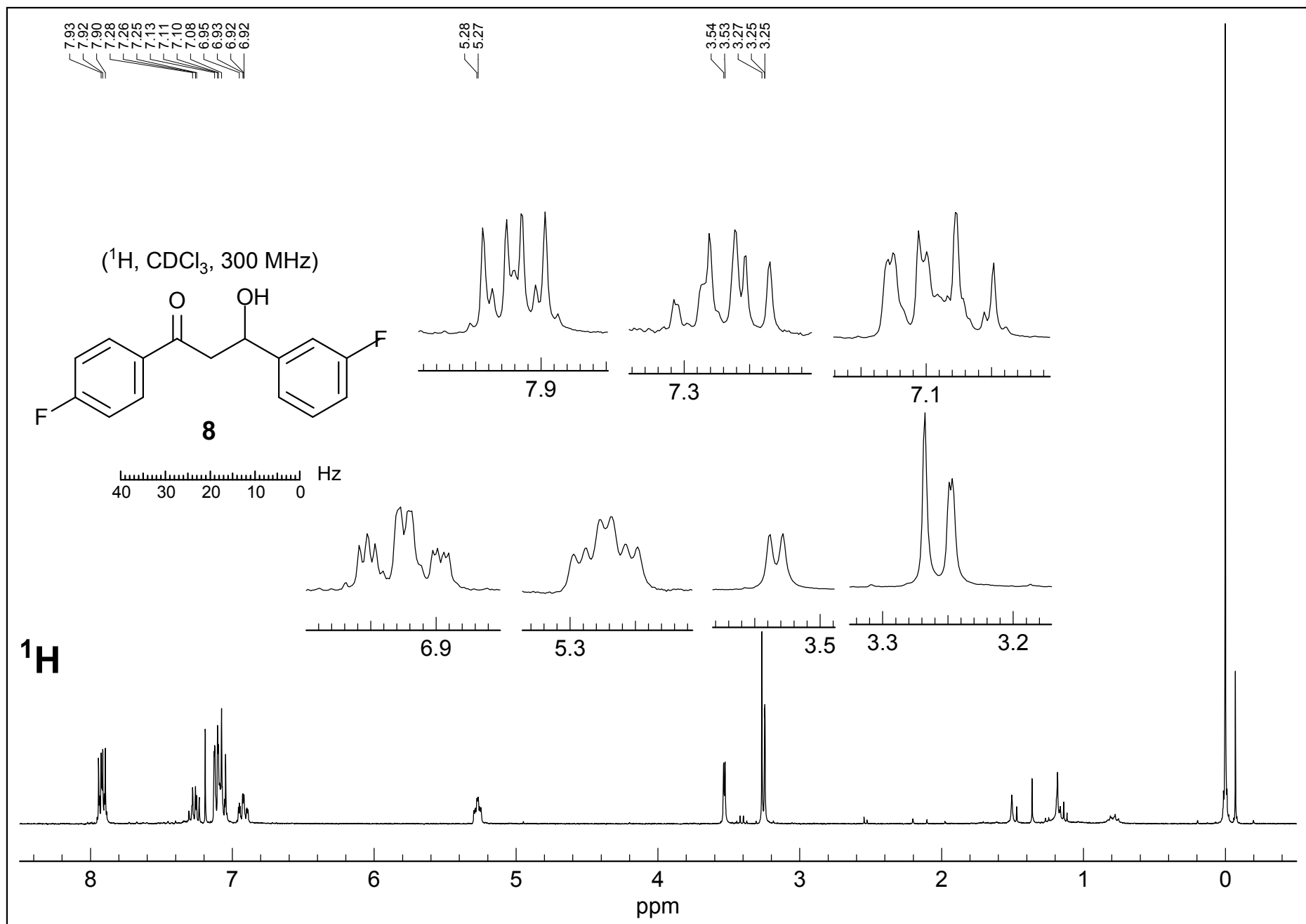


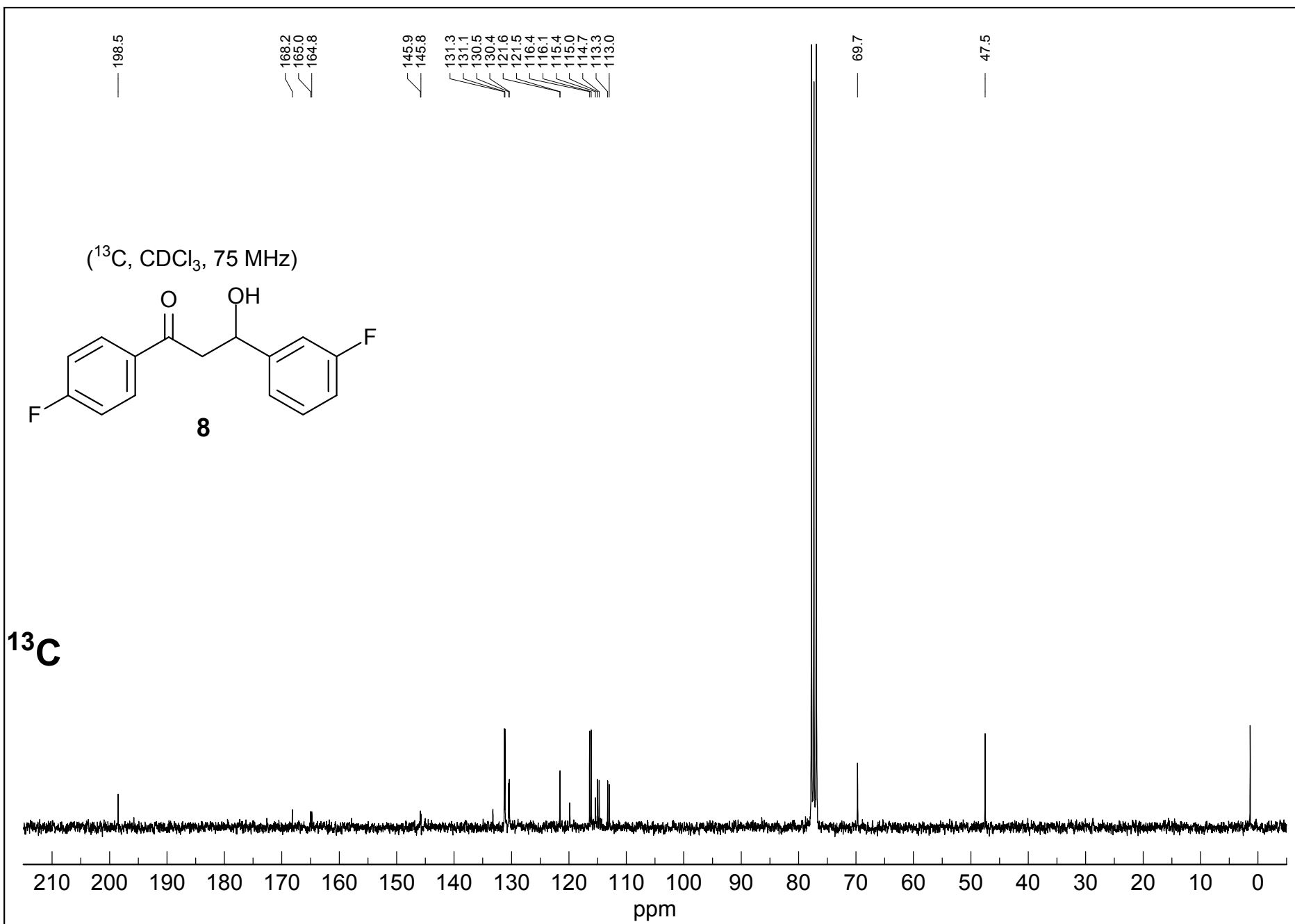




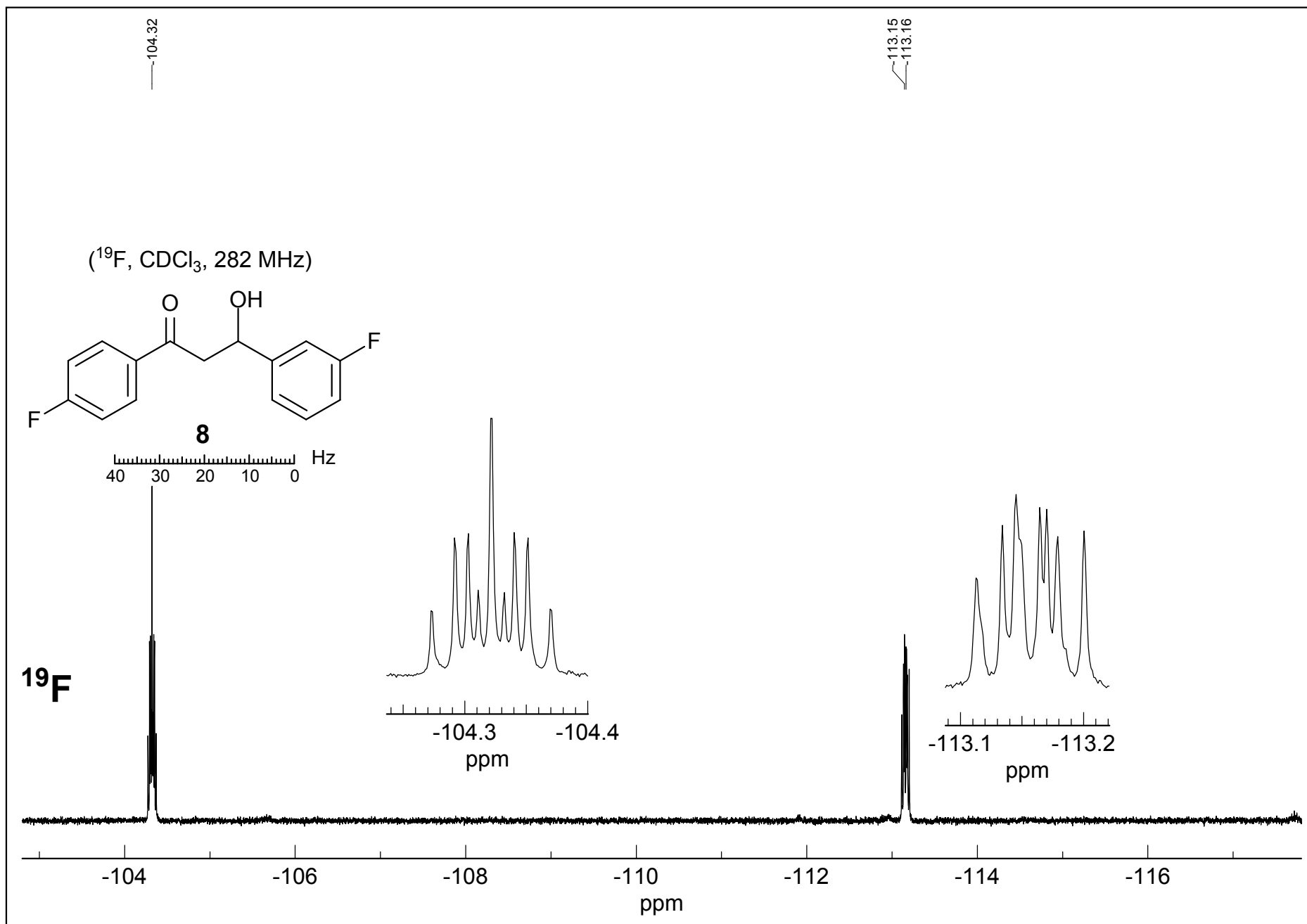


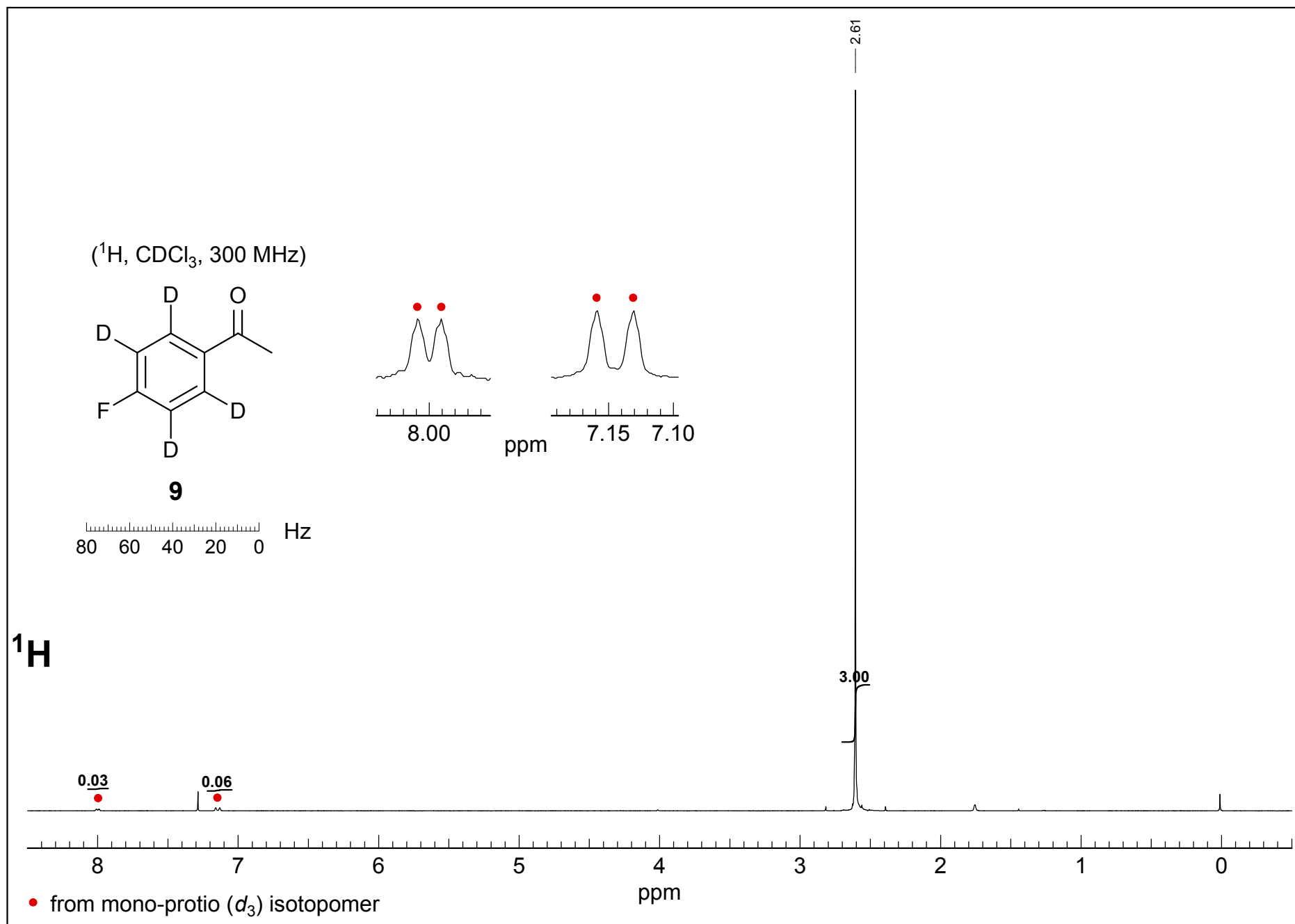


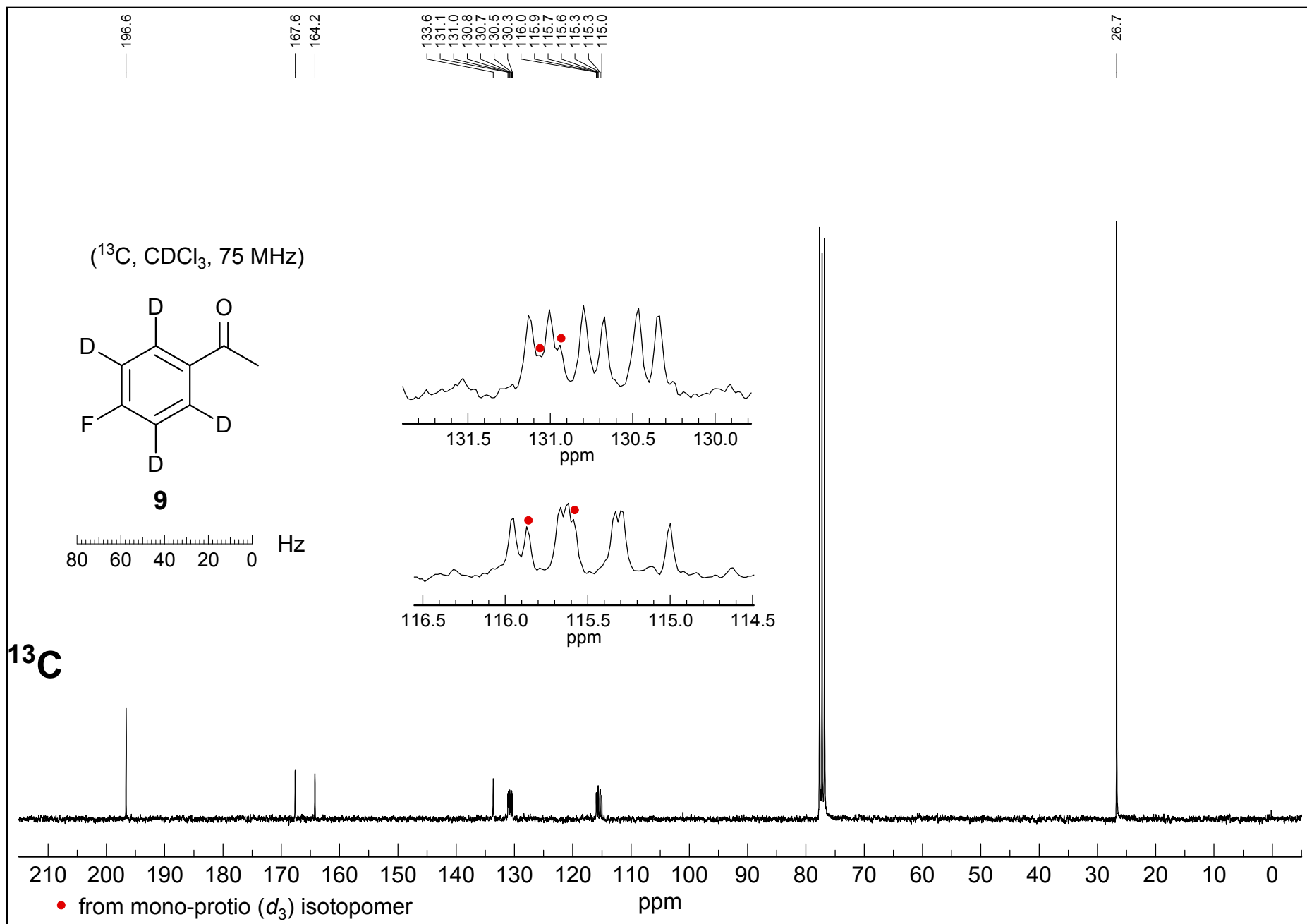


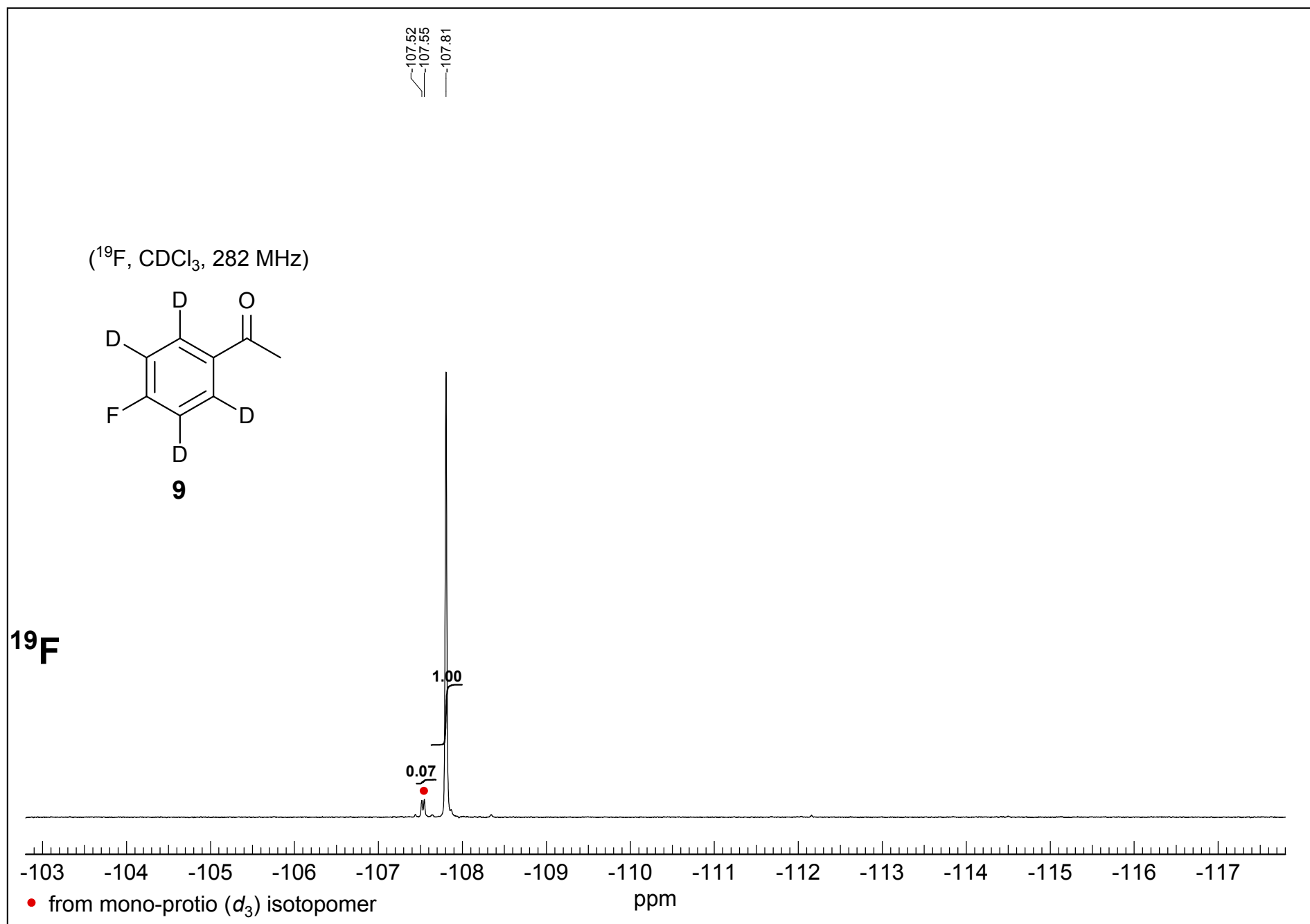








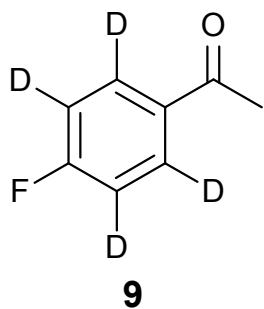




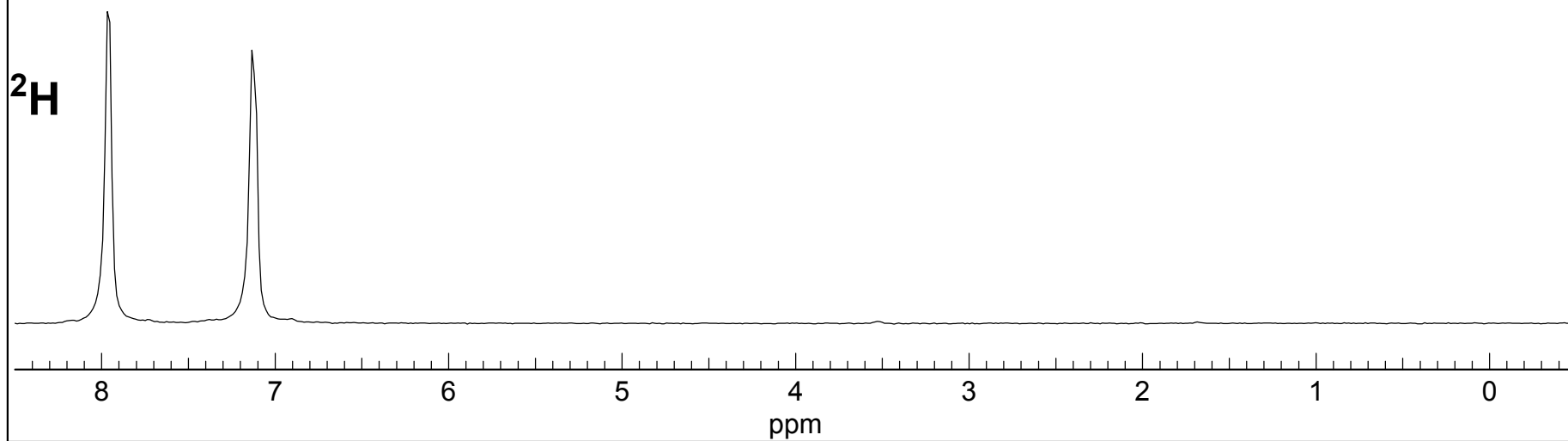
— 7.96

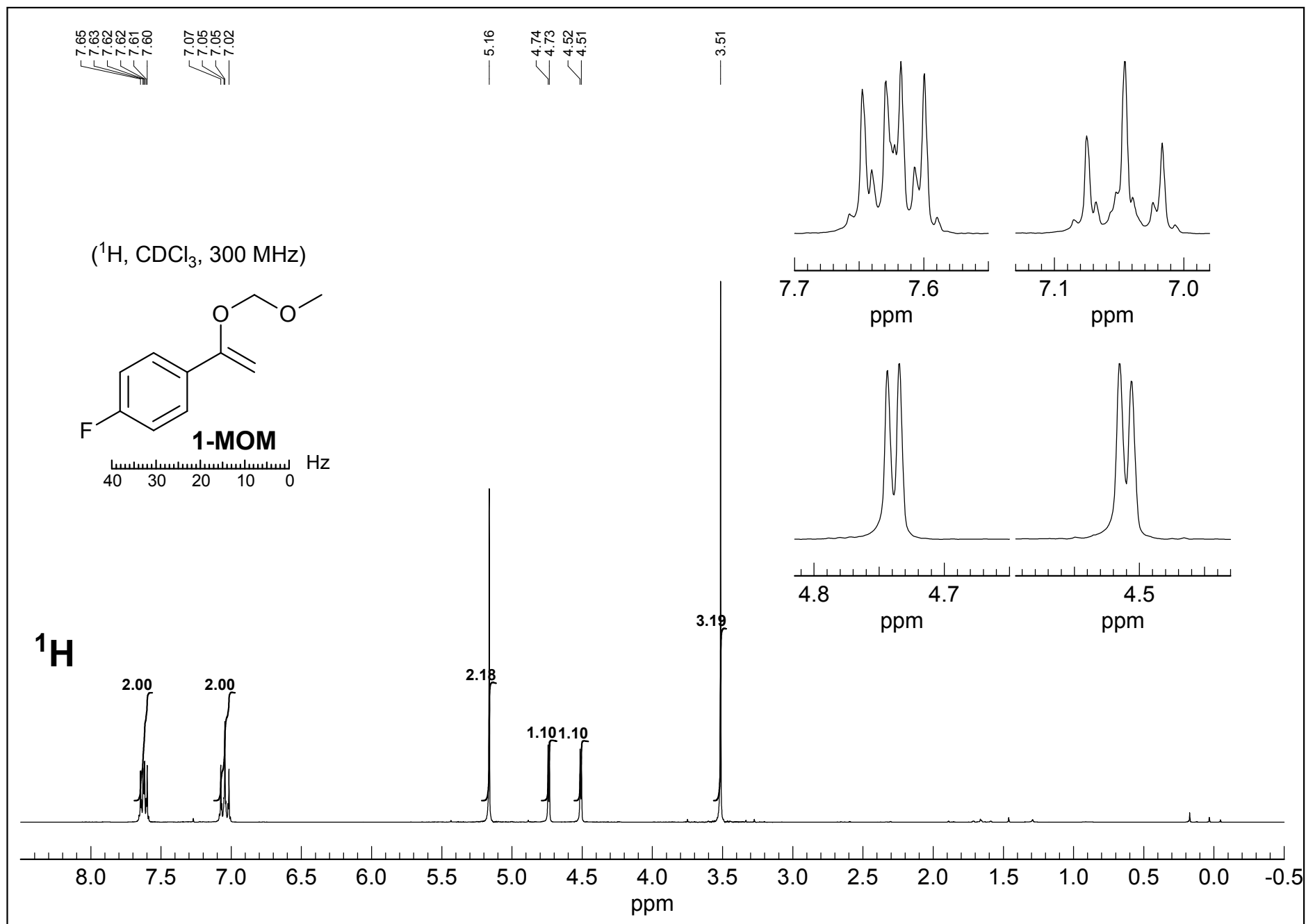
— 7.12

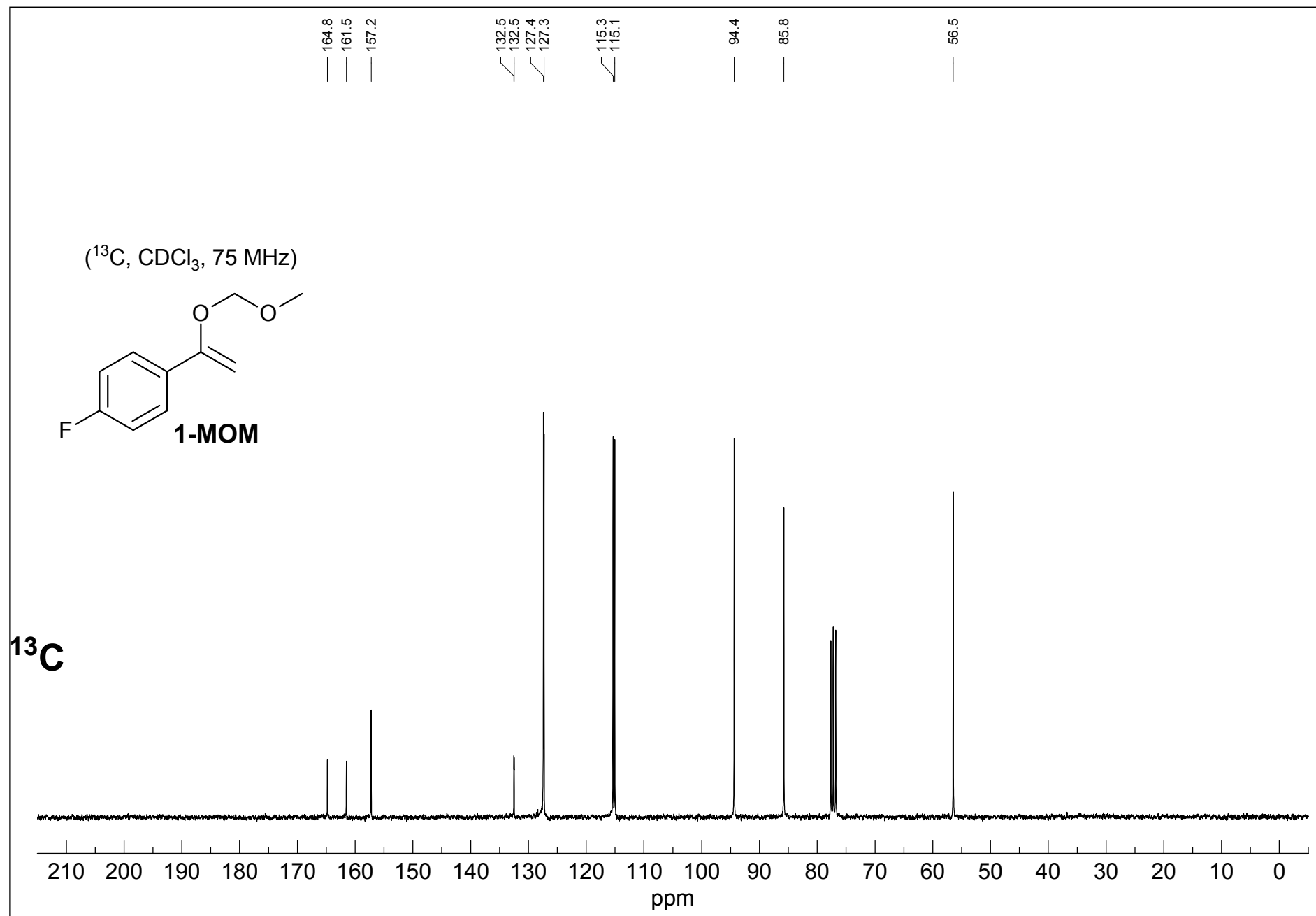
( $^2\text{H}$ , 3:2 THF:Et<sub>2</sub>O, 55.3 MHz)

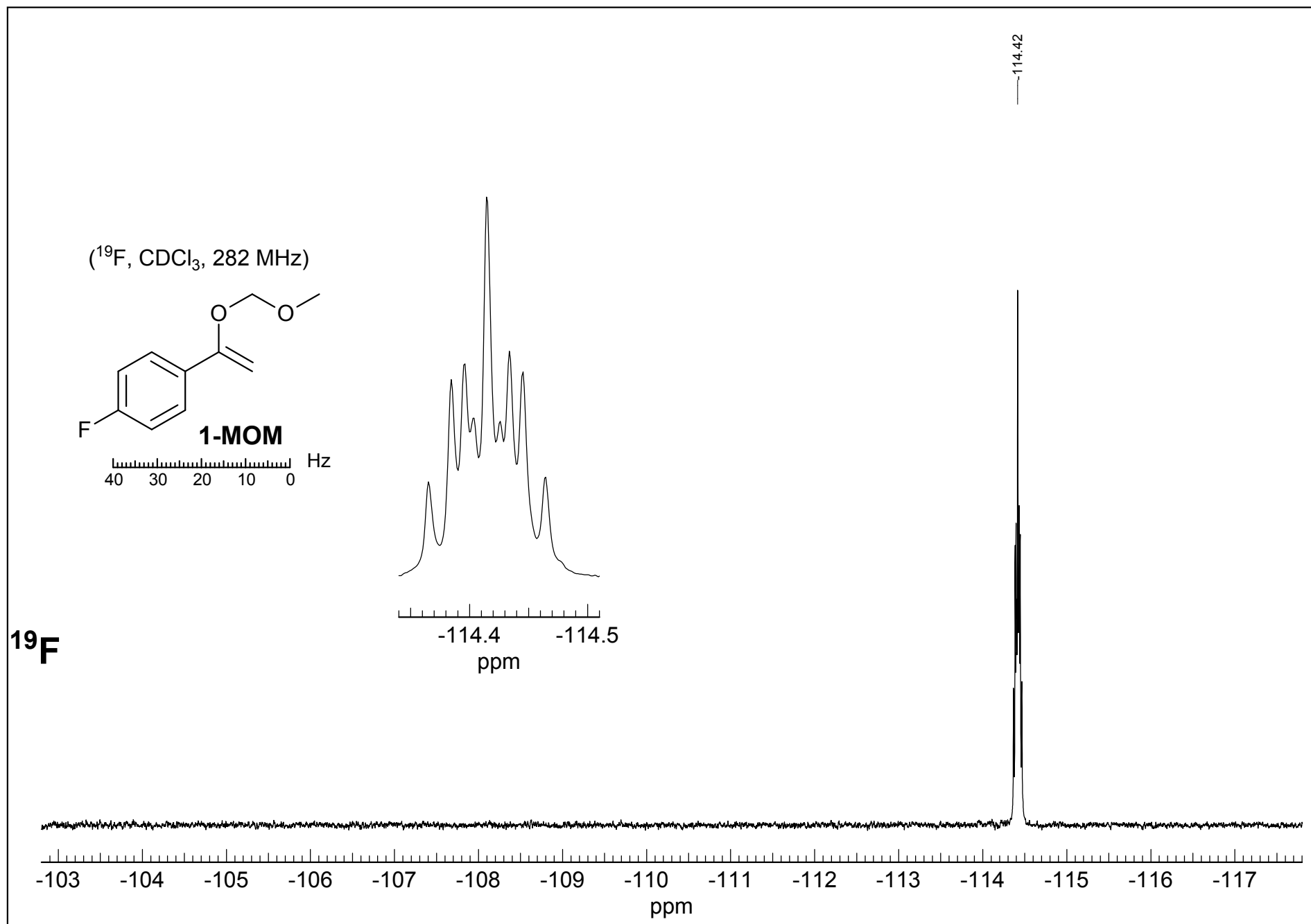


$^2\text{H}$











## S5. References

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<http://www.copasi.org>
- [S6] NUTS - NMR Utility Transform Software, 1D Version, Acorn NMR, <http://www.acornnmr.com>
- [S7] “Structure and Dynamics of  $\alpha$ -Aryl Amide and Ketone Enolates: THF, PMDTA, TMTAN, HMPA, and Crypt-Solvated Lithium Enolates, and Comparison with Phosphazanium Analogues” Kolonko, K. J.; Guzei, I. A.; Reich, H. J. *J. Org. Chem.* **2010**, *75*, 6163–6172.