

Supporting Information

Stabilization of Ketone and Aldehyde Enols by Formation of Hydrogen Bonds to Phosphazene Enolates and Their Aldol Products

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S1. General Experimental.

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 Et₂O were freshly distilled from sodium benzophenone ketyl under N₂. Commercially available starting materials and reagents were obtained from Aldrich Chemical Company and included: Phosphazene base P4-*t*Bu (1-*tert*-Butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylideneamino]-2,4,5-catenadi(phosphazene)) 1 M solution in hexanes, 1,3-diphenyl-2-propanone, 4-fluorophenylacetic acid, 4-fluoroacetophenone (**2**), 4-fluorobenzaldehyde, benzaldehyde and *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl).

Low-temperature NMR spectra were acquired on a Bruker AVANCE spectrometer using a 10 mm broadband probe at the following frequencies: 360.131 MHz (¹H), 90.556 MHz (¹³C), 338.827 MHz (¹⁹F) and 145.785 MHz (³¹P). 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. ³¹P NMR spectra were referenced externally to 1.0 M PPh₃ in THF (δ -6.00) or internally to free HMPA (δ 26.40). ¹⁹F NMR spectra were acquired without proton decoupling and were referenced internally to CFCl₃ (δ 0.0), 1,3-difluorobenzene (δ -110.8), or 1,2-difluorobenzene (δ -140). Probe temperatures were measured internally with the ¹³C chemical shift thermometer: 10% ¹³C enriched (Me₃Si)₃CH.^[S1]

S2. NMR Characterization of Phosphazene Enolate Structures

General Preparation of Samples for Multinuclear NMR Spectroscopy. Samples of ketone, aldehyde or ester (0.3-0.1 mmol) in 3 mL of solvent (1.8 mL of THF and 1.2 mL of Et₂O unless noted), including 1-2 μL of ¹³C enriched (10%) Me₃Si)₃CH as a shift thermometer,^[S1] and 5 μL of 1,3-difluorobenzene or 1,2-difluorobenzene as an internal ¹⁹F standard were prepared in thin-walled 10 mm NMR tubes that had been stored under vacuum, fitted with septa, and flushed with N₂ 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. 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 ¹³C FID of the THF peak. Spectra of NMR active nuclei which usually included ¹³C, ³¹P, ¹⁹F, and ¹H were then acquired. At this point, a phosphazene 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 desired NMR spectra were measured, including a ¹³C NMR spectrum to determine the sample temperature.

The ¹³C and ¹⁹F NMR shifts are summarized in Table S-3.

P4-*t*Bu Titration of 1,3-Diphenyl-2-propanone. A solution of dibenzyl ketone (62.7 mg, 0.3 mmol) was prepared using the general procedure for sample preparation. ^{13}C and ^1H NMR spectra were obtained at $-130\text{ }^\circ\text{C}$. P4-*t*Bu was added as a 1M solution in hexanes and ^{13}C , ^1H , and ^{31}P NMR spectra were obtained at $-130\text{ }^\circ\text{C}$ with 0.5, 1.0, and 1.25 equiv. of P4-*t*Bu. ^{13}C NMR spectra are shown in Figure S-1. Additional ^{13}C NMR spectra of the lithium dimer (Z,Z) produced by deprotonation of dibenzyl ketone and of the lithium bis-HMPA monomer are shown for comparison.

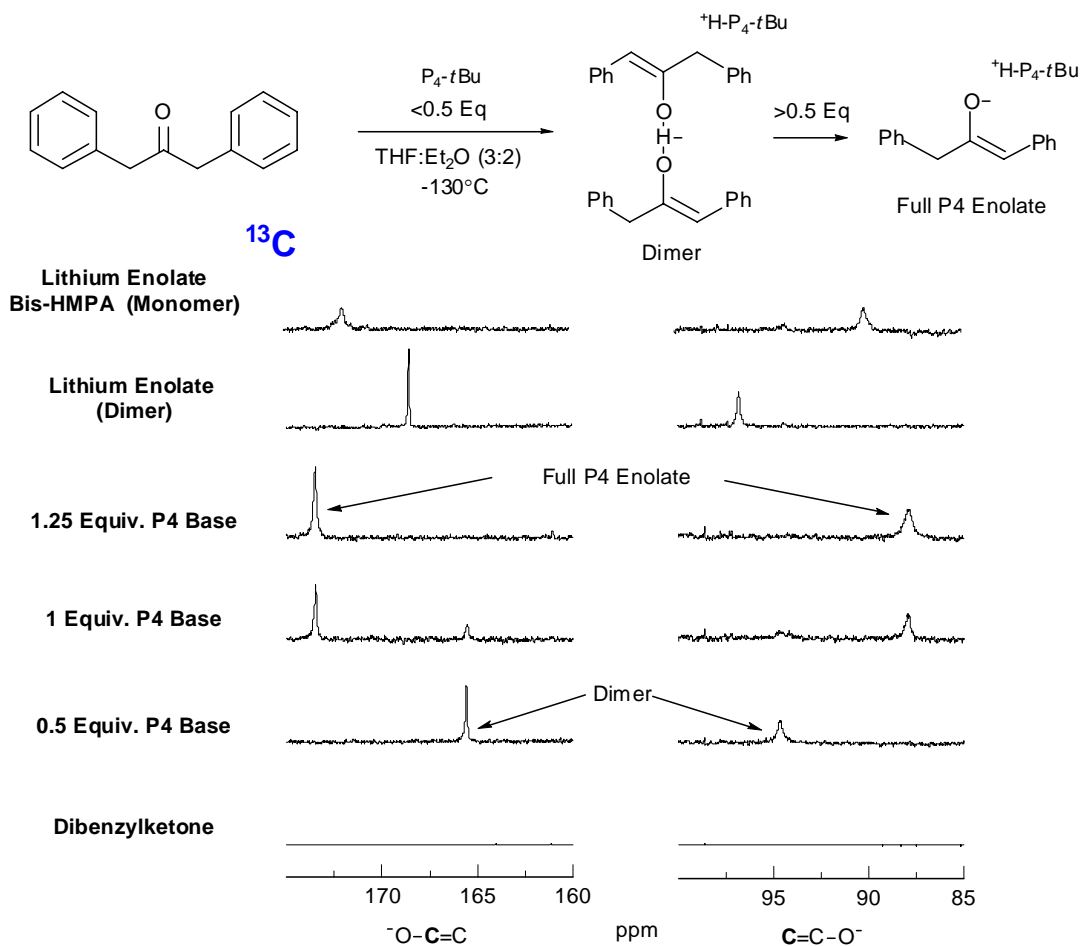


Figure S1. P4-*t*Bu titration of 0.1 M dibenzyl ketone in 3:2 THF/Et₂O at $-130\text{ }^\circ\text{C}$ with the selected lithium enolate spectra shown for comparison.

P₄-*t*Bu Titration of 1,3-Bis-(4-fluorophenyl)-2-propanone (1a). A solution of 1,3-bis-(4-fluorophenyl)-2-propanone (**1a**) (74.8 mg, 0.3 mmol) was prepared using the general procedure for sample preparation. ¹³C, ¹H and ¹⁹F NMR spectra were obtained at -130 °C. P₄-*t*Bu was added as a 1M solution in hexanes and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -130 °C with 0.1, 0.25, 0.4, 0.5, 0.75, and 1.0 equiv. of P₄-*t*Bu. Spectra are shown in Figure S-2.

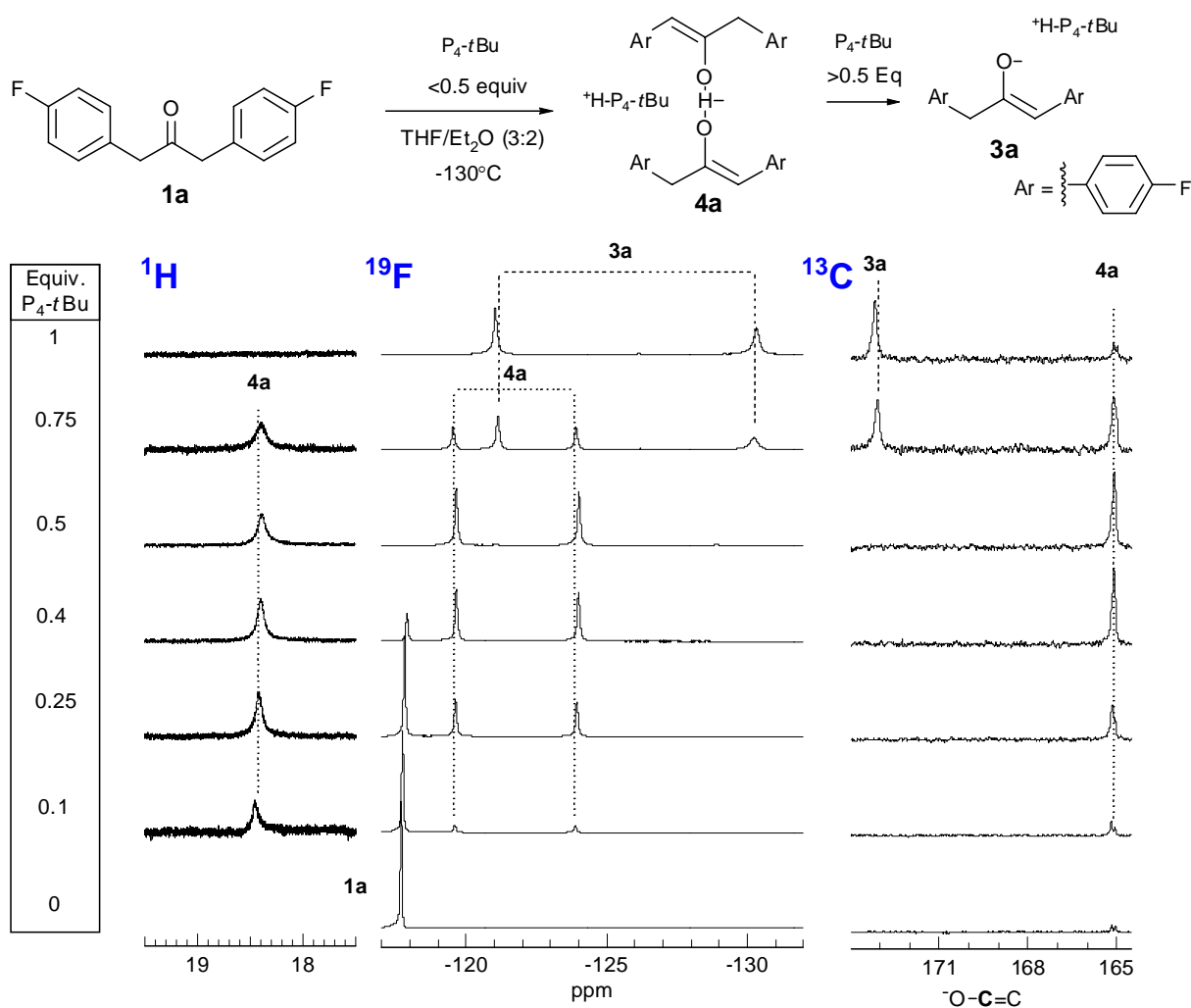


Figure S-2. P₄-*t*Bu Titration of 1,3-Bis-(4-fluorophenyl)-2-propanone 0.1 M in 3:2 THF/Et₂O at -130 °C.

Variable Temperature NMR Experiment of 4a and 3a. A 10 mm NMR sample was prepared according to standard procedure from 73 mg (0.29 mmol) of 1,3-bis-(4-fluorophenyl)-2- propanone , followed by 0.23 mL of P4-*t*Bu (1 M) to give a red solution of approximately equal concentration of **4a** and **3a**. ^{13}C and ^{19}F spectra were obtained at -128 °C, -103 °C , -82 °C , -60 °C , -37 °C , -26 °C , and -14 °C until coalescence of the fluorine signals were observed. Rates were determined by simulation.^[S3] (The exchange of **4a** and **3a** was further investigated in the following experiment presented in Figure S-4.) The coalescence temperature of -14 °C for **4a** and **3a** for ^{19}F NMR signals corresponds to a $\Delta G^\ddagger = 11.4$ kcal/mol. Spectra for the variable temperature experiment are shown in Figure S-3.

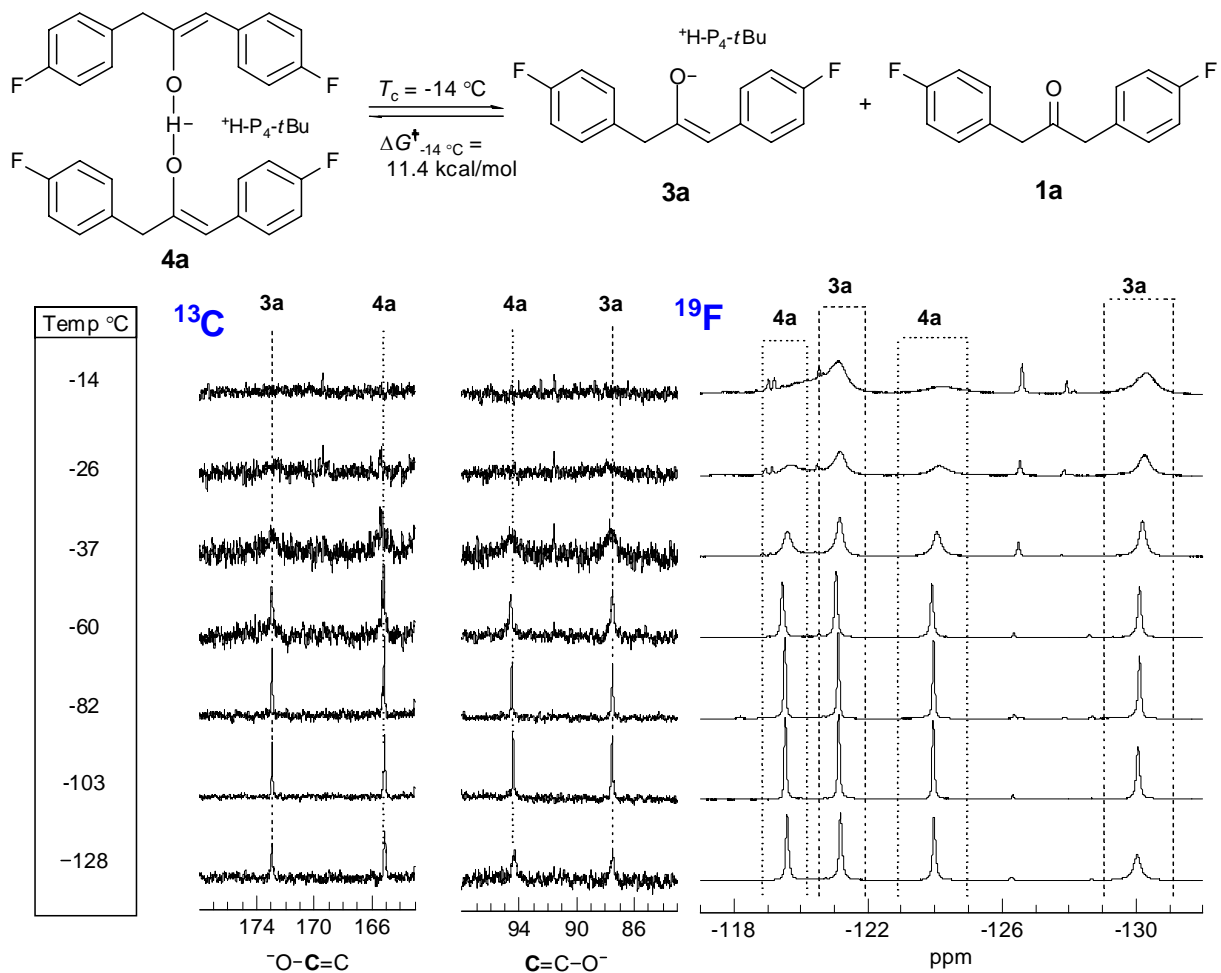


Figure S-3. Variable temperature NMR experiment of 0.1 M 1,3-bis-(4-fluorophenyl)-2-propanone with 0.75 equiv. P4-*t*Bu enolate in 3:2 THF/Et₂O.

Exchange Rate of 4a \rightleftharpoons 3a + 1a Dependence on the Concentration of 3a. A 10 mm NMR sample was prepared according to the standard procedure from 41 mg (0.16 mmol) of 1,3-bis-(4-fluorophenyl)-2-propanone and 0.10 mL of P4-*t*Bu (1 M) to give a red solution of approximately equal concentrations of 4a and 3a. ^{13}C and ^{19}F spectra were obtained at -35 °C, -25 °C, and -15 °C. P4-*t*Bu (0.015 mL of 1 M hexane solution) was added and ^{13}C and ^{19}F spectra were obtained at -35 °C, -25 °C, and -15 °C. P4-*t*Bu (0.03 mL of 1 M solution) was added and ^{13}C and ^{19}F spectra were obtained at -35 °C, -25 °C, and -15 °C. Rates were determined by simulation of the NMR spectra,^[S3] two tt ($J = 9, 5.5$ Hz) due to the ^1H coupling of the ^{19}F signals, using the mutual exchange of two dddd ($J = 9, 9, 5.5, 5.5$ Hz) simulation in WINDNMR.^[S3] Spectra with simulated fits are shown in Figure S-4 and the simulation data is presented in Table S-1. A negligible change in k_{4a3a} was observed at different concentrations of 3a indicating this to be a simple unimolecular dissociation.

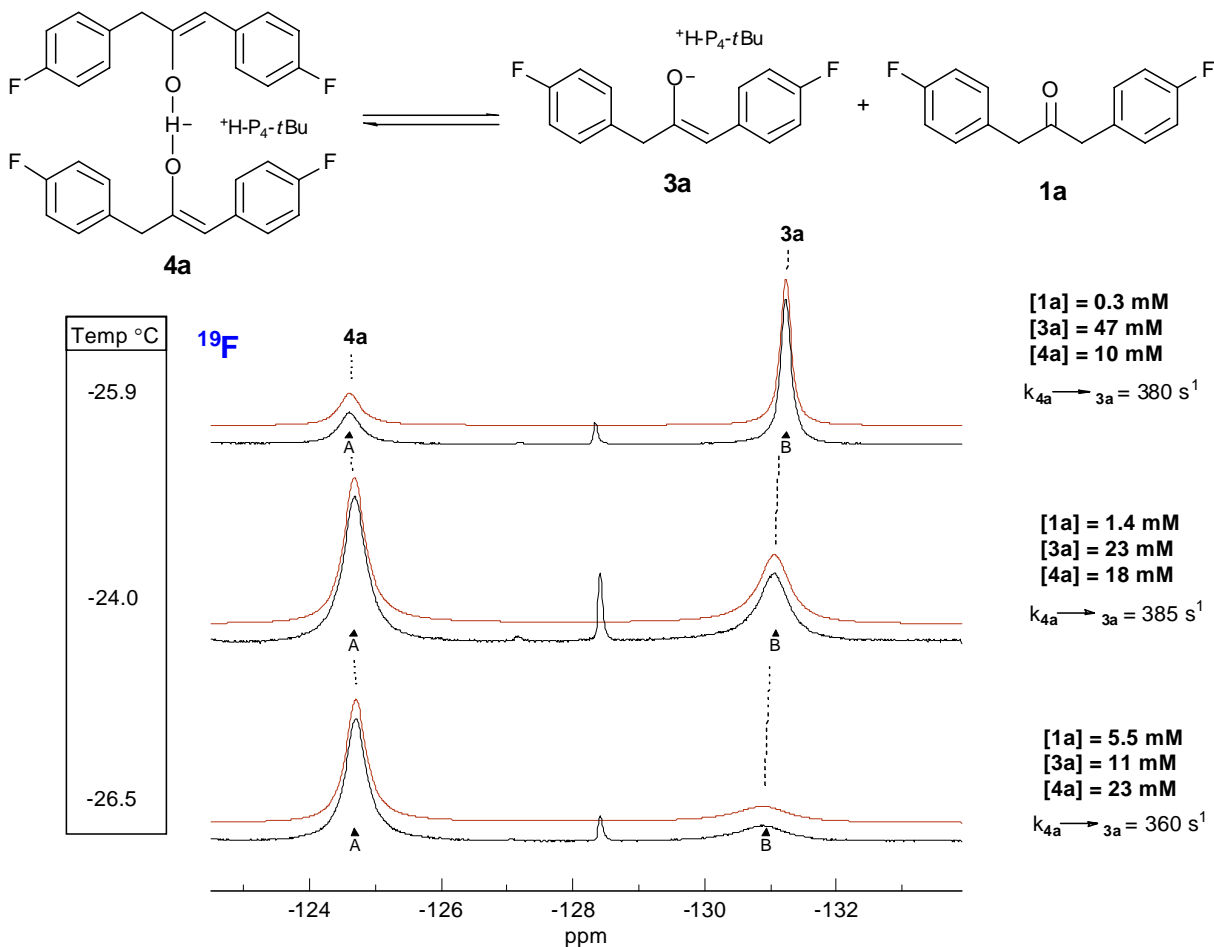


Figure S-4. Variable concentration of 3a DNMR experiment on interconversion of 3a with 4a in 3:2 THF/Et₂O at -25 °C. The red upper lines are simulations.^[S3]

Table S-1. Data for Simulation of the ^{19}F Spectra of the Interconversion of **3a** and **4a** (Fig.S-4).

Temperature $^{\circ}\text{C}$	-26.5	-24.0	-25.9
ν_{4a} /Hz	4881	4878	4880
ν_{3a} /Hz	2766	2707	2633
$k_{4a3a} + k_{3a4a}$ / sec^{-1}	1371	953	549
% 4a	73.7	59.5	30.9
W_{4a}^* /Hz	5	5	5
W_{3a}^* /Hz	5	5	5
k_{4a3a} / sec^{-1}	360	385	379
ΔG^{\ddagger} / kcal/mol	11.45	11.54	11.46
k_{3a4a} / sec^{-1}	1010	567	169
ΔG^{\ddagger} / kcal/mol	10.95	11.35	11.85

*Line width in the absence of exchange.

K_{eq} of $3a + 1a \rightleftharpoons 4a$ at Various Temperatures by ^{19}F NMR. A 10 mm NMR sample was prepared according to standard procedure from 41 mg (0.16 mmol) of 1,3-bis-(4-fluorophenyl)-2-propanone and 0.10 mL of P4-*t*Bu (1 M) to give a red solution of approximately equal concentration of **4a** and **3a**. ^{13}C and ^{19}F spectra were obtained at -35 °C, -25 °C, and -15 °C. P4-*t*Bu (0.015 mL of 1 M hexane solution) was added and ^{13}C and ^{19}F NMR spectra were obtained at -35 °C, -25 °C, and -15 °C. 0.03 mL of P4-*t*Bu (1 M) was added and ^{13}C and ^{19}F NMR spectra were obtained at -35 °C. ^{19}F NMR spectra and a plot of ΔG vs temperature are shown in Figure S-5.

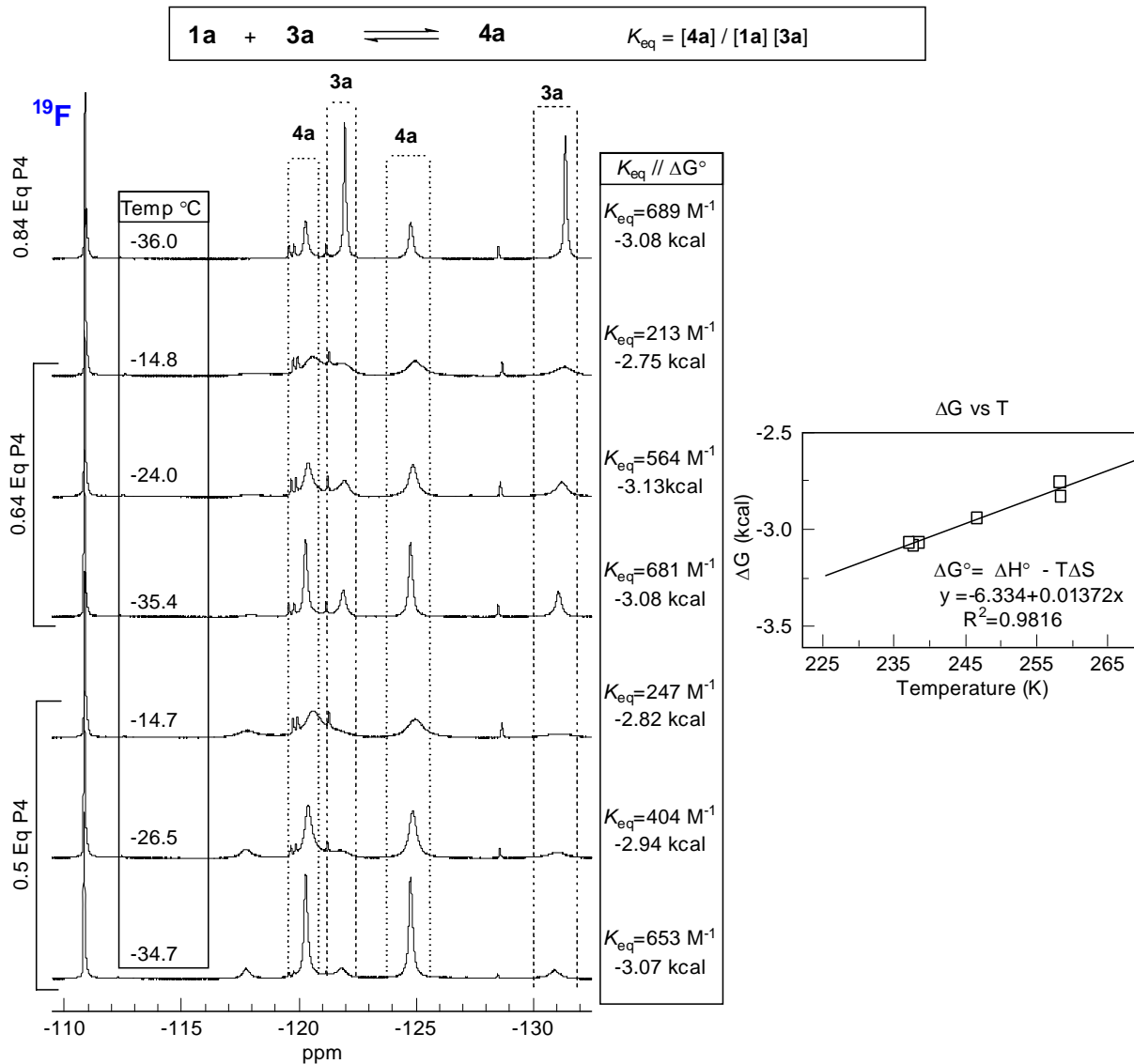


Figure S-5. Determination of K_{eq} by ^{19}F NMR spectroscopy of $3a + 1a \rightleftharpoons 4a$ in 3:2 THF/ Et_2O at various temperatures and equivalents of P4-*t*Bu.

Deuterium shift of 4a. A solution of 1,3-bis-(4-fluorophenyl)-2-propanone (**1a**)-*d*₄ (61 mg, 0.25 mmol) was prepared according to the standard procedure. ¹³C, ¹H and ¹⁹F NMR spectra were obtained at -130 °C. P4-*t*Bu was added as a 1M solution in hexane and ¹³C, ¹H, ¹⁹F, ²H and ³¹P NMR spectra were obtained at -130 °C with 0.5 equiv. of P4-*t*Bu. ²H signals were too broad due to efficient relaxation at this temperature. The sample was warmed to -103 °C which allowed for the observation of ²H signals of **4a** and ¹³C, ¹H, ¹⁹F, ²H and ³¹P NMR spectra were obtained. $\Delta[\delta(^1\text{H})-\delta(^2\text{H})]$ was determined by comparison of the ²H spectra of (**4a**)-*d*₄ to the ¹H NMR spectra of (**4a**) at 103 °C obtained in the Variable Temperature NMR Experiment of **4a** and **3a** (Figure S-5).^[S4] ¹H, ¹⁹F, and ²H spectra are shown in Figure S-6.

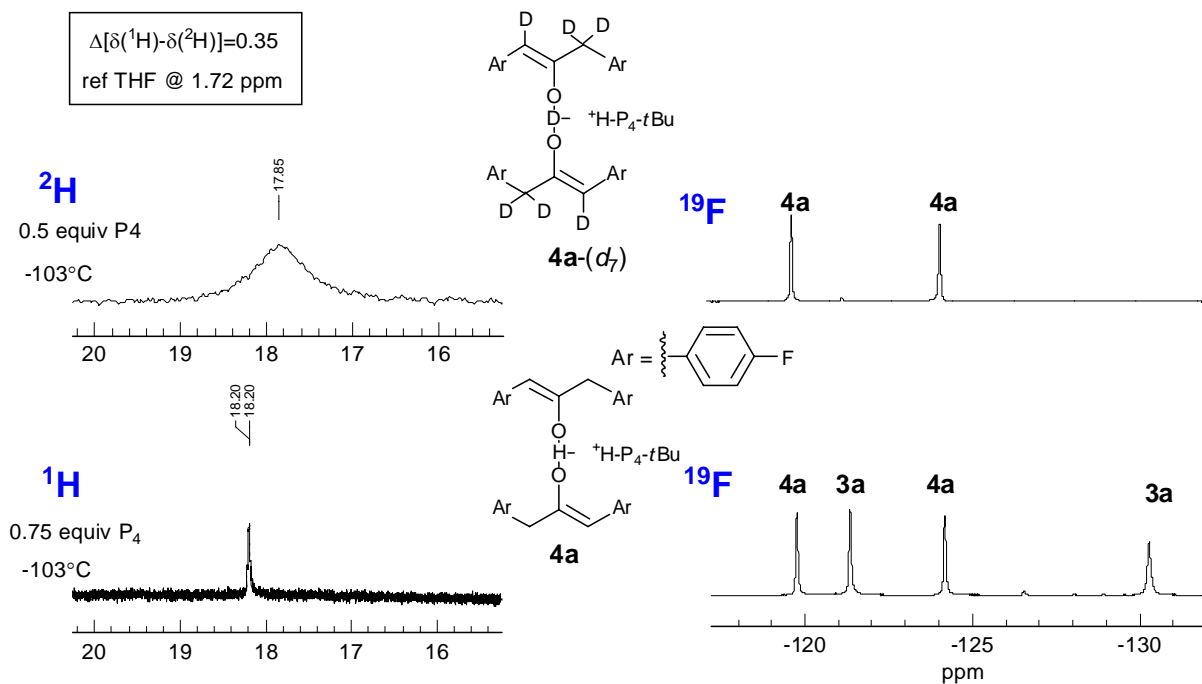


Figure S-6. Comparison of the ¹H to ²H NMR shift of the low barrier hydrogen bond signal of **4a** in 3:2 THF/Et₂O at -103 °C.

P4-*t*Bu Titration of 1-Phenyl-2-(4-fluorophenyl)ethanone (1b). A solution of 1-phenyl-2-(4-fluorophenyl)ethanone (**1b**) (82 mg, 0.38 mmol) was prepared according to the standard procedure. ^{13}C , ^1H and ^{19}F NMR spectra were obtained at $-130\text{ }^\circ\text{C}$. P4-*t*Bu was added as a 1M solution in hexane and ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra were obtained at $-130\text{ }^\circ\text{C}$ with 0.3, 0.6, 0.9, and 1.2 equiv. of P4-*t*Bu. Spectra are shown in Figure S-7. K_{eq} ($4\text{b} \rightleftharpoons 3\text{b} + 1\text{b}$) was determined by ^{19}F NMR integration for the individual species versus an internal standard (1,2-difluorobenzene).

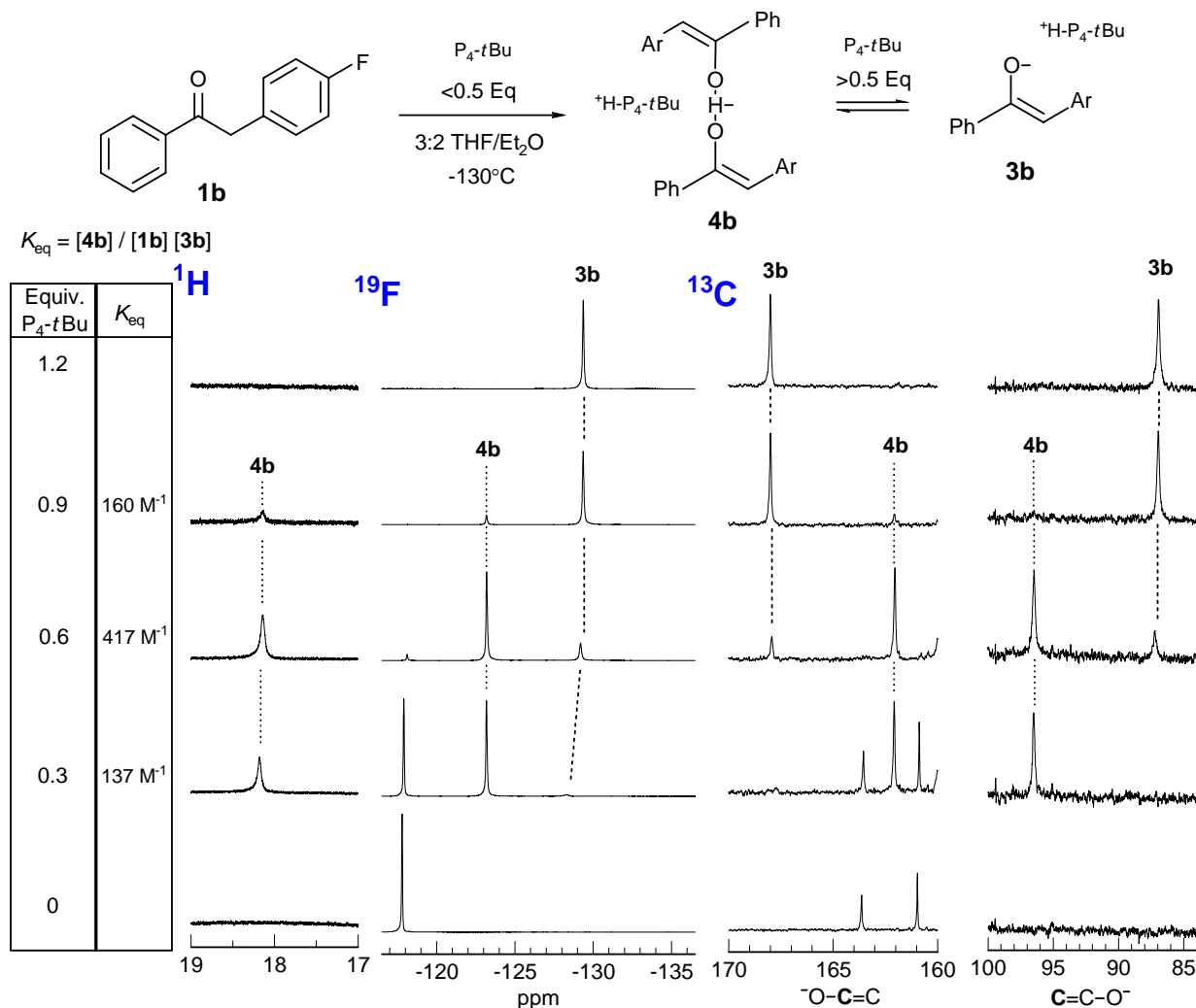


Figure S-7. P4-*t*Bu Titration of 1-phenyl-2-(4-fluorophenyl)ethanone (**1b**) 0.1M in 3:2 THF/Et₂O at $-130\text{ }^\circ\text{C}$.

K_{eq} and Exchange Rate of $4b \rightleftharpoons 3b + 1b$ at -37 °C. A 10 mm NMR sample was prepared according to standard procedure from 36 mg (0.17 mmol) of 1-phenyl-2-(4-fluorophenyl)ethanone and 0.10 mL of P4-*t*Bu (1 M) to give a solution of approximately equal concentration of **4b** and **3b**. ^{13}C and ^{19}F spectra were obtained at -37 °C, and -125 °C. Rates were determined by simulation of the NMR spectra,^[S3] two tt ($J = 9, 5.5$ Hz) due to the ^1H coupling of the ^{19}F signals, using mutual exchange of two dddd ($J = 9, 9, 5.5, 5.5$ Hz) simulation. Spectra with simulated fits are shown in Figure S-8 and the simulation data is presented in Table S-2.

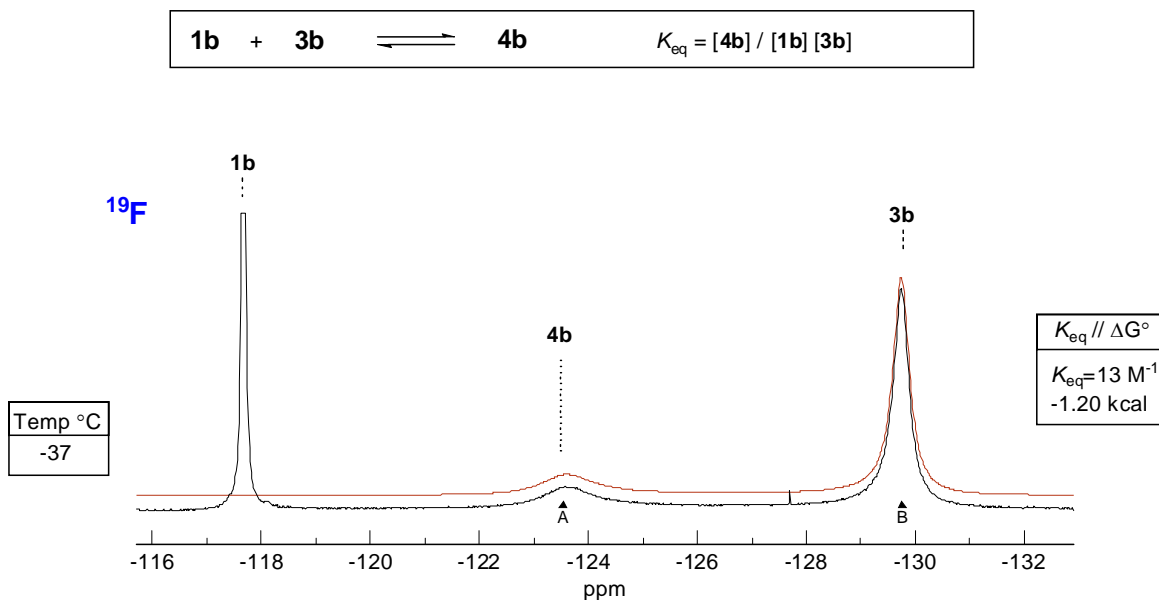


Figure S-8 Simulation of the exchange rate of $4b \rightleftharpoons 3b + 1b$ in 3:2 THF/Et₂O at -37 °C. The red upper line is the simulated spectra.^[S3]

Table S-2. Data for Simulation of the ^{19}F Spectra of the Interconversion of **3b** and **4b** (Fig.S-8).

Temperature °C	-37
ν_{4b} /Hz	10030.1
ν_{3b} /Hz	7920.5
$k_{4b3b} + k_{3b4b}$ / sec ⁻¹	1528
% 4b	23.2
W_{4b}^* /Hz	5
W_{3b}^* /Hz	5
k_{4a3a} / sec ⁻¹	1173.50
ΔG^\ddagger / kcal/mol	10.39
k_{3b4b} / sec ⁻¹	354.49
ΔG^\ddagger / kcal/mol	10.95

*Line width in the absence of exchange.

P4-*t*Bu Titration of a Mixture of 1a and 1b. A solution of 1,3-bis-(4-fluorophenyl)-2-propanone (**1a**) (28.8 mg , 0.12 mmol) and 1-phenyl-2-(4-fluorophenyl)ethanone (**1b**) (33.8 mg , 0.16 mmol) was prepared according to the standard procedure. ^{13}C , ^1H and ^{19}F NMR spectra were obtained at $-130\text{ }^\circ\text{C}$. P4-*t*Bu was added as a 1M solution in hexane and ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra were obtained at $-130\text{ }^\circ\text{C}$ with 0.25, 0.5, 0.75, and 1.0 equiv. of P4-*t*Bu in relation to total ketone. Spectra with interpretation are shown in Figure S-9. The association constant for the formation of the mixed dimer (**4a** + **4b** \rightleftharpoons **2 6**) was determined to be 6.5, slightly larger than the statistical value of 4, which assumes that the mixed dimer has the same stability as the homo dimers .

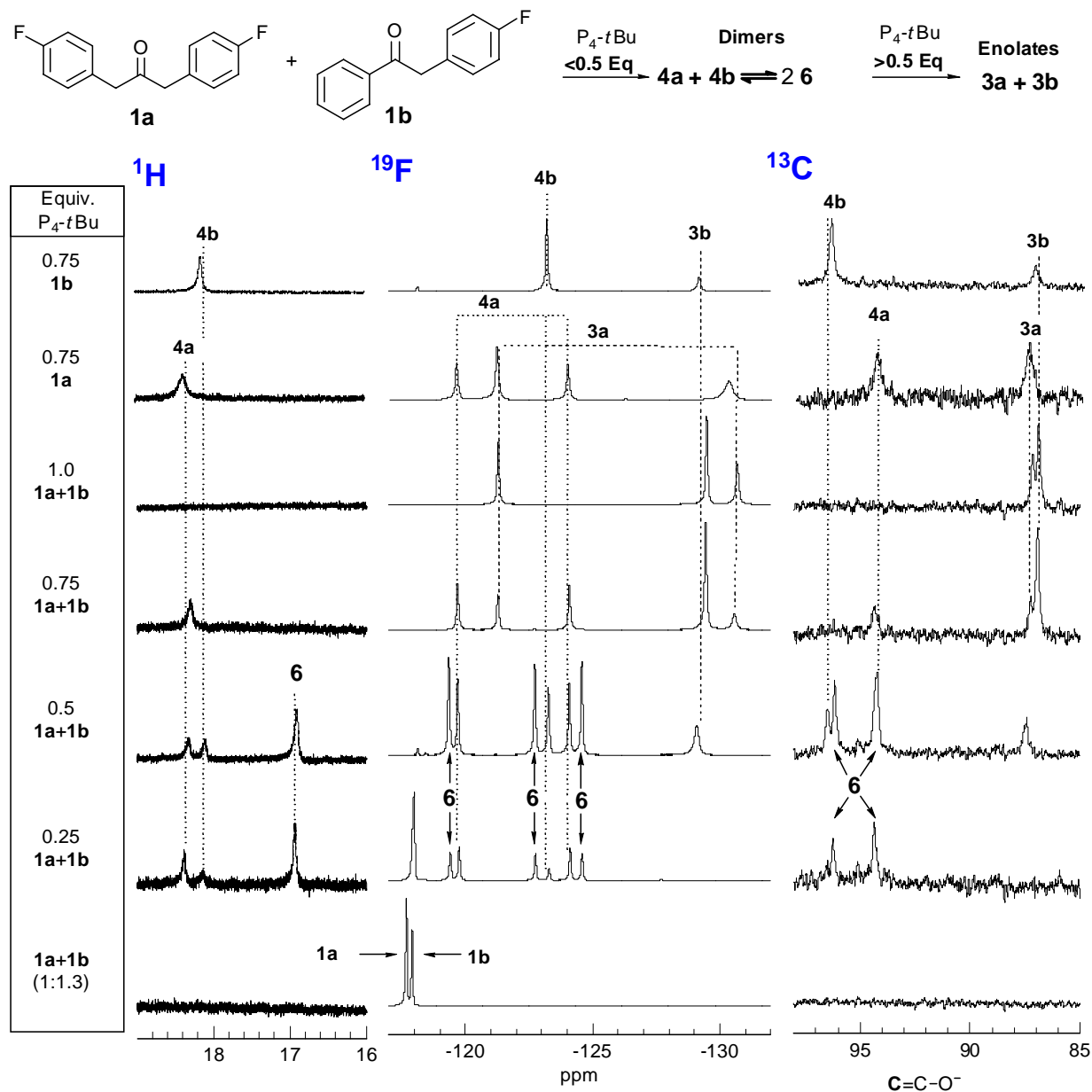


Figure S-9. Titration of 1-phenyl-2-(4-fluorophenyl)ethanone (**1b**) and 1,3-bis-(4-fluorophenyl)-2-propanone (**1a**) 0.1M in 3:2 THF/Et₂O with P4-*t*Bu at $-130\text{ }^\circ\text{C}$.

P4-*t*Bu Titration of (4-Fluorophenyl)ethanal (1c). A solution of 2-(4-fluorophenyl)ethanal (**1c**) (33.6 mg , 0.24 mmol) was prepared according to the standard procedure. ^{13}C , ^1H and ^{19}F NMR spectra were obtained at $-125\text{ }^\circ\text{C}$. Special care was taken with this sample to avoid warming as P4-*t*Bu was added as a 1 M solution in hexane and ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra were obtained at $-125\text{ }^\circ\text{C}$ with 0.15, 0.3,

0.5, 0.9, and 1.15 equiv. of P₄-*t*Bu. Spectra are shown in Figure S-10. The sample was quenched with Me₃SiCl (0.06 ml, 0.47 mmol) and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -100 °C. From this the major product (>10:1) was determined to be the Z isomer of the enol silyl ether based on the following NMR data. ¹H NMR (360 MHz, THF:Et₂O (3:2)), δ 5.30 (d, *J* = 6.5, 1H), 6.68 (d, *J* = 6.7, 1H), 7.16 (t, *J* = 8.0 Hz, 4H), 7.63 (dd, *J* = 7.9, 5.8 Hz, 2H). ¹³C NMR (90.56 MHz, 3:2 THF/Et₂O), δ 107.59 (s), 115.3 (d, *J*_{CF} = 21.5Hz), 130.4 (d, *J*_{CF} = 8.1Hz), 133.8 (d, *J*_{CF} = 3.3Hz), 141.1 (s), 161.1 (d, *J*_{CF} = 242.7Hz). ¹⁹F NMR (282 MHz, CDCl₃) δ -117.3 (tt, *J*_{FH} = 5.5, 8.8 Hz).

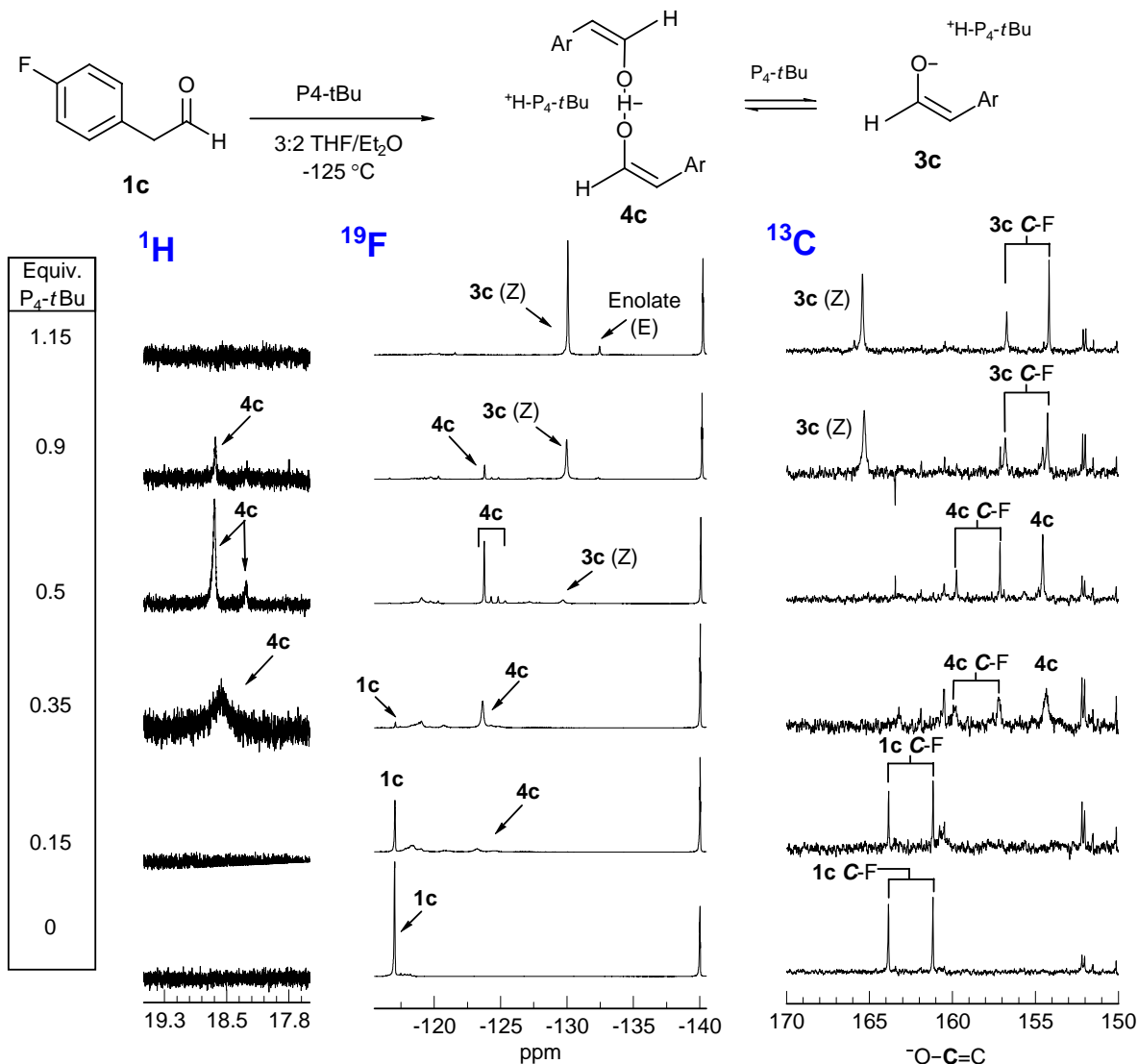


Figure S-10. Titration of 2-(4-fluorophenyl)ethanal (**1c**) 0.1M in 3:2 THF/Et₂O with P₄-*t*Bu at -125 °C.

P₄-*t*Bu Titration of Methyl 2-(4-Fluorophenyl)acetate (1d**).** A solution of methyl 2-(4-fluorophenyl)acetate (**1d**) (58.5 mg, 0.35 mmol) was prepared according to the standard procedure. ¹³C, ¹H and ¹⁹F NMR spectra were obtained at -125 °C. P₄-*t*Bu was added as a 1 M solution in hexane and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -125 °C with 0.5 and 1.0 equiv. of P₄-*t*Bu. Spectra are shown in Figure S-11.

No trace of the H-bonded dimer **4d** or self-condensation products were detected.

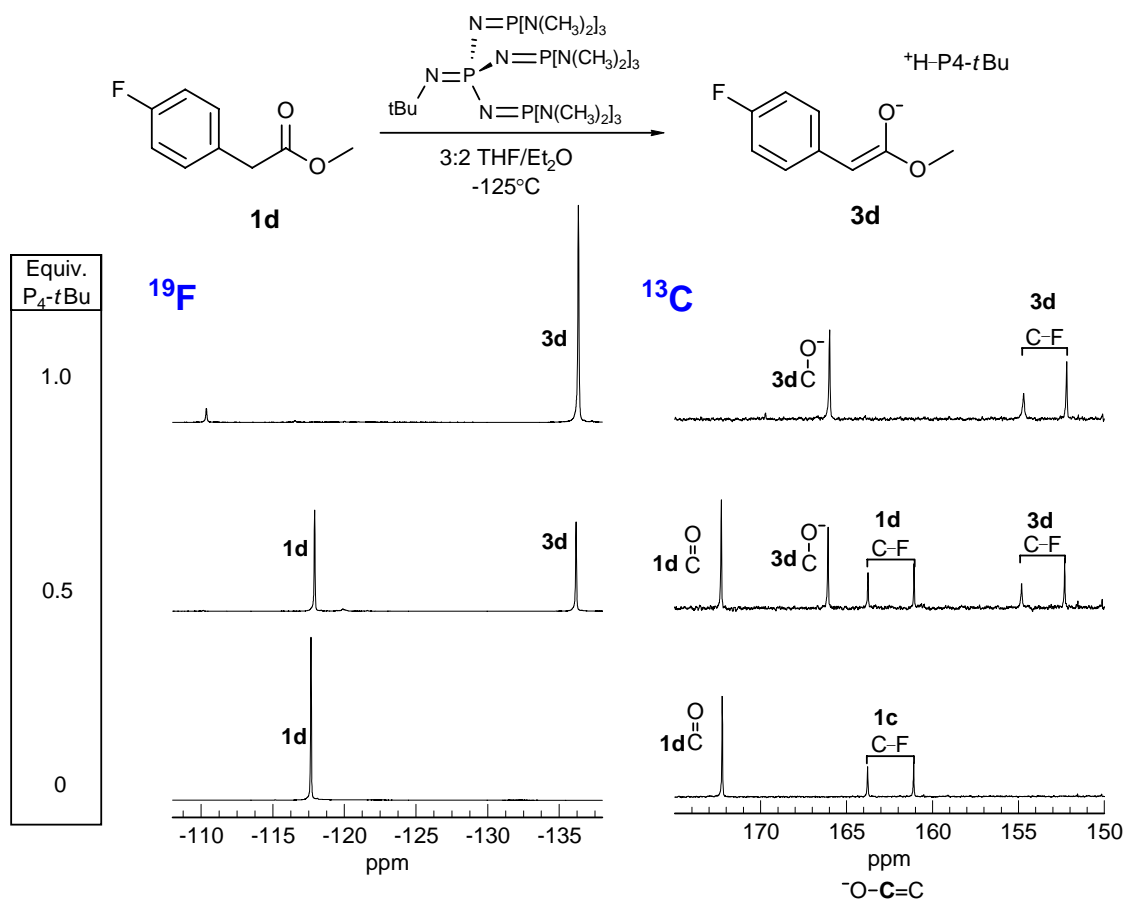


Figure S-11. Titration of methyl 2-(4-fluorophenyl)acetate (**1d**) 0.08 M in 3:2 THF/Et₂O with P₄-*t*Bu at -125 °C.

Characterization of Enol **5a and Effect of Acid Counterion.** A solution of 1,3-bis-(4-fluorophenyl)-2-propanone (**1a**) (38.2 mg, 0.15 mmol) was prepared according to the standard procedure. P4-*t*Bu (0.15 mL, 0.15 mmol) was added and ^{13}C , ^1H and ^{19}F NMR spectra were obtained at $-120\text{ }^\circ\text{C}$. HCl etherate (0.15 mL of a 1.1 M solution, 0.15 mmol) was added using our RINMR apparatus and ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra (Figure S-12a) were obtained at $-120\text{ }^\circ\text{C}$. A solution of BF_3 etherate was added using our RINMR apparatus and ^{13}C , ^1H , ^{19}F and ^{31}P spectra were obtained at $-120\text{ }^\circ\text{C}$ at 1 equiv (Figure S-12b) and 10 equiv (Figure S-12c) of BF_3 . Additionally, enol **5a** was generated using an identical procedure but substituting HBF_4 for HCl as the acid used to quench enolate **3a** (Figure S-12d). Spectra are shown in Figure S-12.

Attempts were made to measure the enol content of a 0.13M (3:2, THF/ Et_2O) solution of **1a** using 470.63 MHz ^{19}F $\{^1\text{H}\}$ NMR spectroscopy. Determination of the K_E (**1a** \rightleftharpoons **5a**) in combination with the previously measured equilibrium K_{eq}^a (**1a** + **3a** \rightleftharpoons **4a**) would allow for the association of $K_{\text{H-bond}}$ (**5a** + **3a** \rightleftharpoons **4a**), to be measured. Low intensity ^{19}F NMR signals ($<0.02\%$ compared to **1a** at $-35\text{ }^\circ\text{C}$) at the appropriate chemical shift were identified as possible signals of the enol **5a** but could not be unambiguously assigned due to their low intensity and the sensitivity of their chemical shift to environment as demonstrated in this experiment. If these signals were actually those of **5a** in equilibrium with **1a**, then at $-35\text{ }^\circ\text{C}$, $K_E = 0.0002$, and $K_{\text{H-bond}} = 3.4 \times 10^6\text{ M}^{-1}$ ($\Delta G_{-35} = -7.1\text{ kcal/mol}$).^[S5]

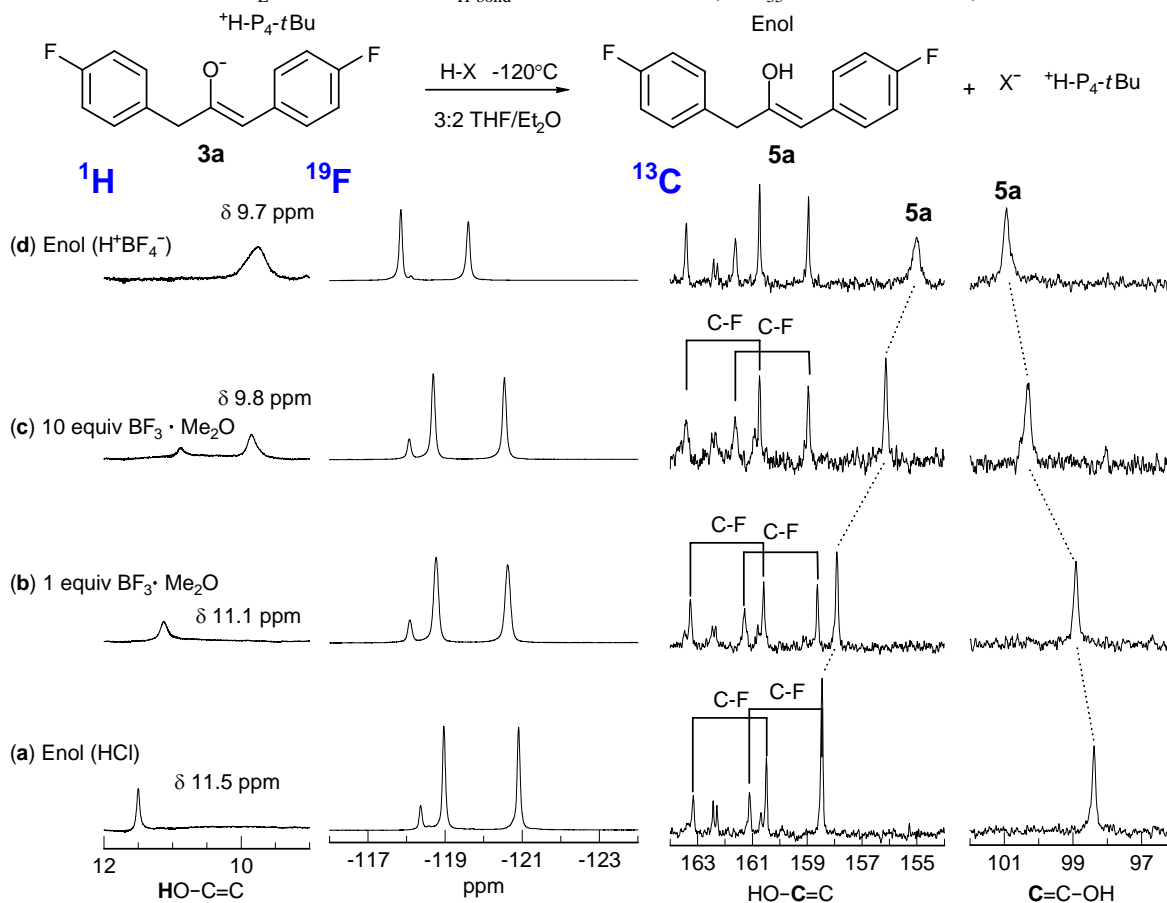


Figure S-12. Selected NMR signals demonstrating the effect of the acid counterion on the NMR shifts of **5a** in 3:2 THF/ Et_2O at $-120\text{ }^\circ\text{C}$. The enol ^{13}C shifts are quite sensitive to the anions present, presumably the result of hydrogen-bonding interactions.^[S6]

Reaction of Enol 5a with Me₃SiCl. A sample 1,3-bis-(4-fluorophenyl)-2-propanone (**1a**) (46 mg, 0.18 mmol) was prepared according to the standard procedure. P4-*t*Bu (0.19 mL, 0.19 mmol) was added and ¹³C, ¹H and ¹⁹F NMR spectra were obtained at -120 °C. HCl etherate (0.15 mL, 1.3 M solution) was added using our RINMR apparatus and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -120 °C. Solutions of Me₃SiCl (0.15 mL, 1.9 M solution) and Et₃N (0.15 mL, 1.9M solution) were then added using the Rapid-Injection NMR apparatus and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -120 °C immediately and at 90 min and 150 min following injection. Spectra are shown in Figure S-13.

Remarkably, solutions of the transient enol **5a** can be silylated without significant competing ketonization, i.e., the rate of O-silylation of the enolate **3b** is higher than the rate of C-protonation.

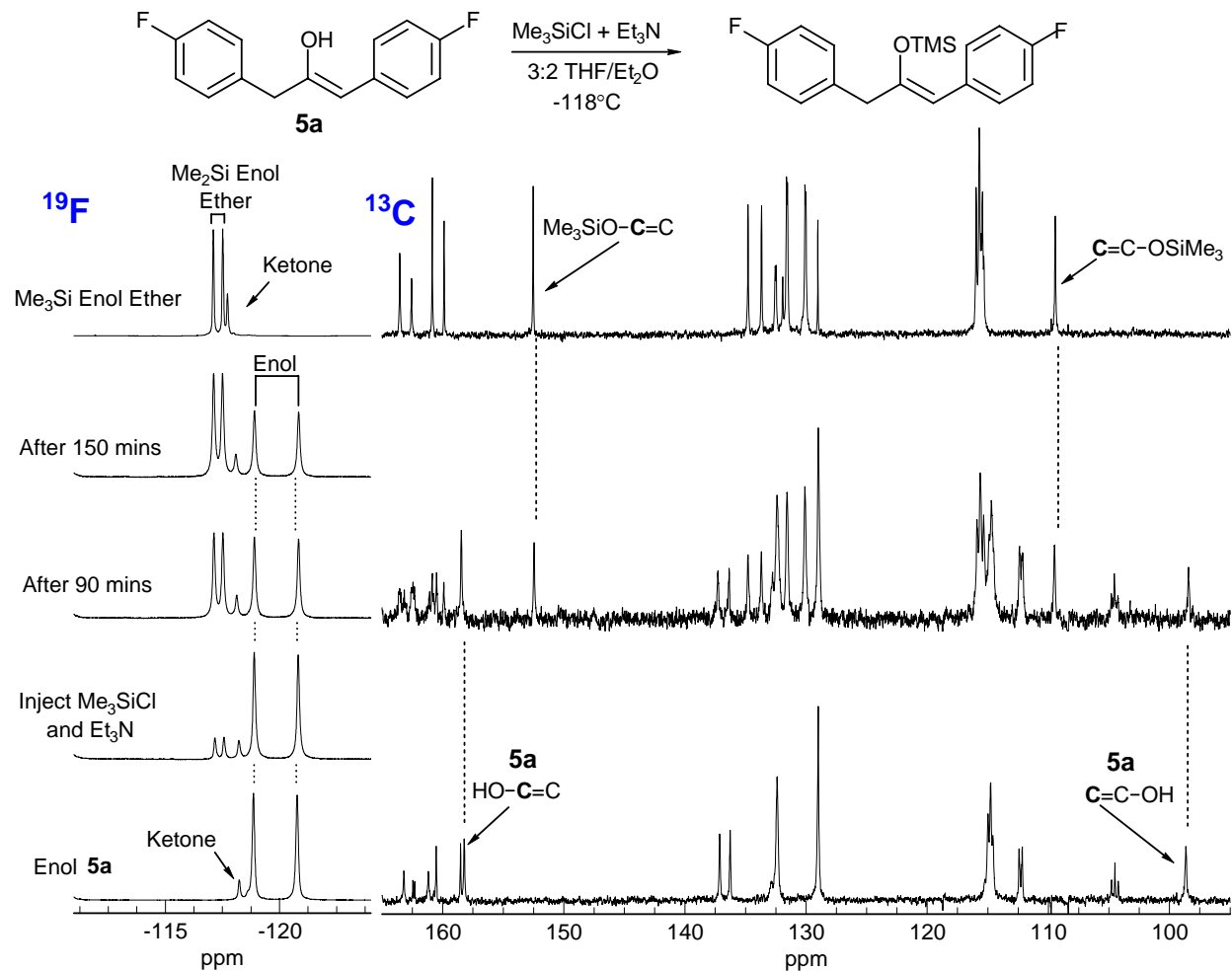


Figure S-13. Reaction of Enol **5a** with Me₃SiCl in 3:2 THF/Et₂O at -118 °C.

P4-*t*Bu Titration of 4-Fluoroacetophenone (2). A solution of 4-fluoroacetophenone (2) (41.4 mg , 0.35 mmol) was prepared according to the standard procedure. ^{13}C , ^1H and ^{19}F NMR spectra were obtained at $-130\text{ }^\circ\text{C}$. P4-*t*Bu was added as a 1 M solution in hexanes and ^{13}C , ^1H , ^{19}F and ^{31}P spectra were obtained at $-130\text{ }^\circ\text{C}$ with 0.25, 0.5 and 0.65 equiv. of P4-*t*Bu. Spectra are shown in Figure S-14 with additional characterization presented in Figure S-14.

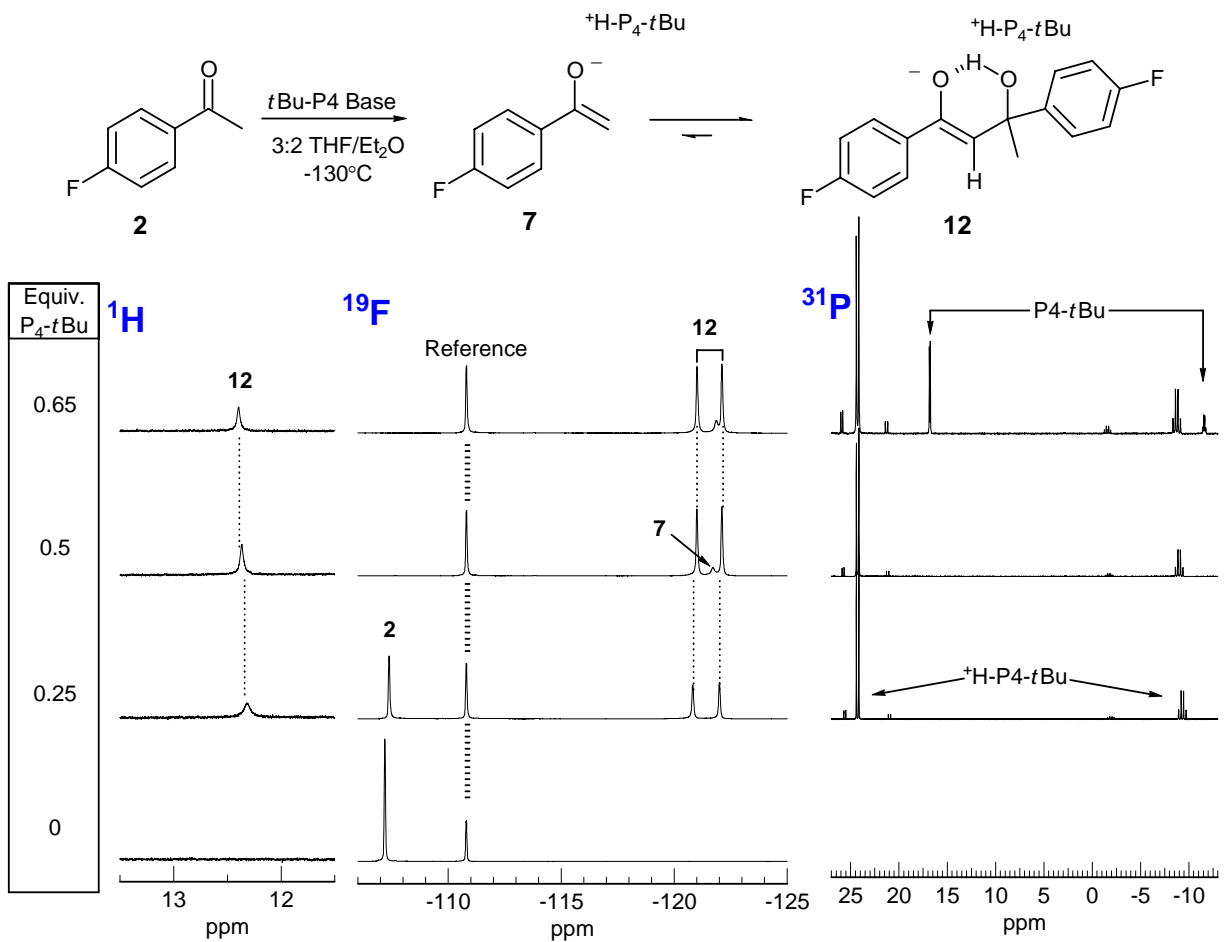


Figure S-14. P4-*t*Bu titration of 0.1M 4-fluoroacetophenone (2) in 3:2 THF/Et₂O at $-130\text{ }^\circ\text{C}$.

Characterization of Reactants and Intermediates in the Self Aldol Reaction of 2.

Characterization data for the intermediates observed in the self aldol reaction of **2** is presented in Figure S-15. ^1H , ^{13}C and ^{19}F NMR spectra for **2** were obtained after the completion of experiment shown in Figure S-17. ^1H , ^{13}C and ^{19}F spectra for **11** were obtained during the first hour of a self aldol reaction under conditions identical to the saturation transfer experiment shown in Figure S-16. ^1H , ^{13}C and ^{19}F spectra for **12** were obtained after the completion of the P4-*t*Bu titration of **2** experiment shown in Figure S-14.

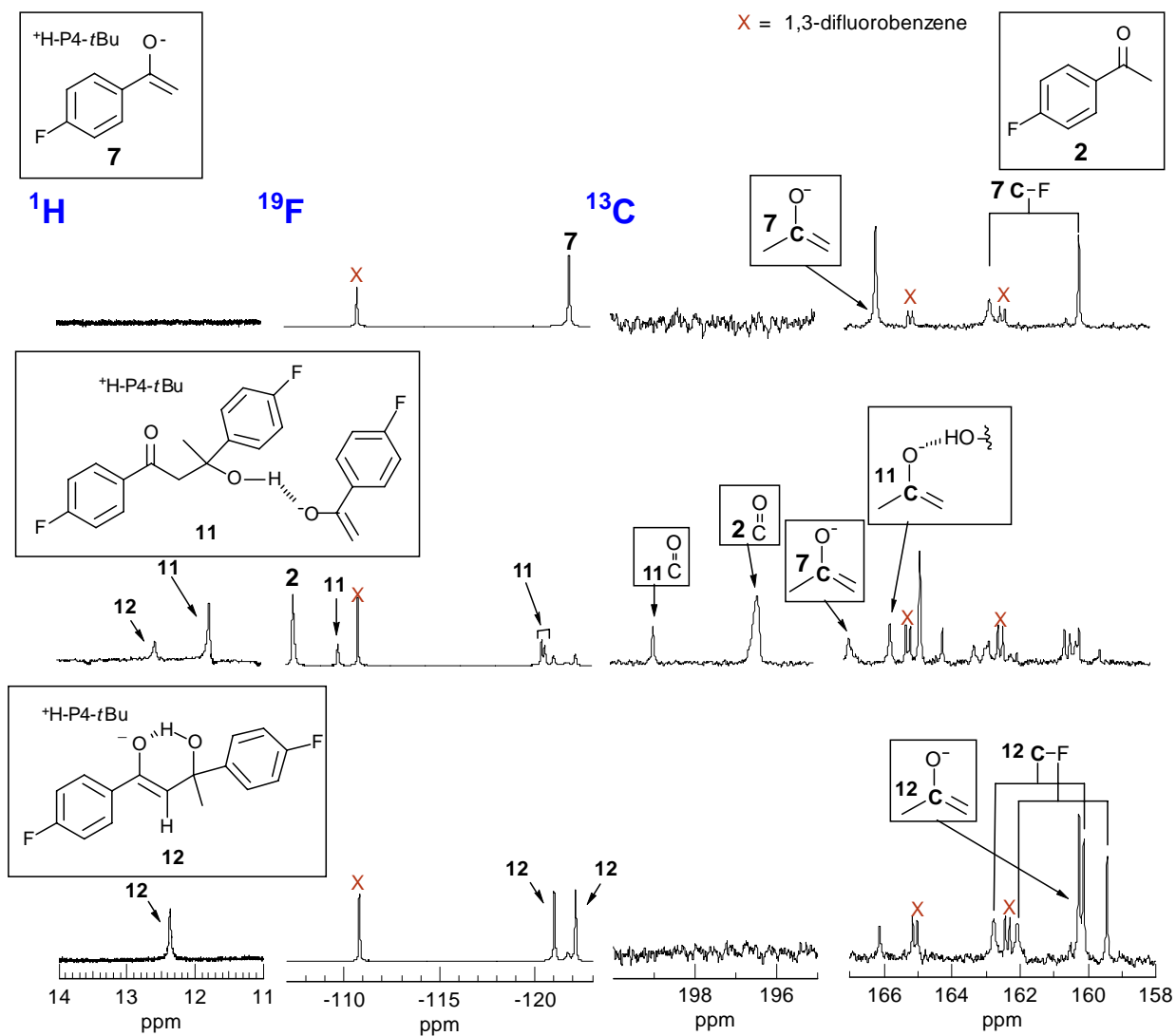


Figure S-15. Characterization data for the reactants and intermediates of the self aldol reaction of 4-fluoroacetophenone (**2**) in 3:2 THF/Et₂O at -120 °C. The peaks marked x are of the ^{19}F internal standard, 1,3-difluorobenzene.

Saturation Transfer Experiment of 11 with 7. A solution of P4-*t*Bu (0.1 mL, 0.1 mmol) sample was prepared according to the standard procedure. The NMR tube was cooled to -78 °C under positive N₂ pressure and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol) was added. ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -120 °C. A solution of **2** (0.15 mL of a 2.6 M solution, 0.39 mmol) was added using our RINMR apparatus and ¹⁹F NMR spectra were obtained between 20 to 60 minutes after injection using a standard Bruker Avance 1D sequence with f1 presaturation (zgpr) at -120 °C. Spectra are shown in Figure S-16. Saturation of the ¹⁹F signal of the enolate **7** (*d*) caused saturation transfer to the ¹⁹F signal for the H-bonded enolate of **11** (*c*).

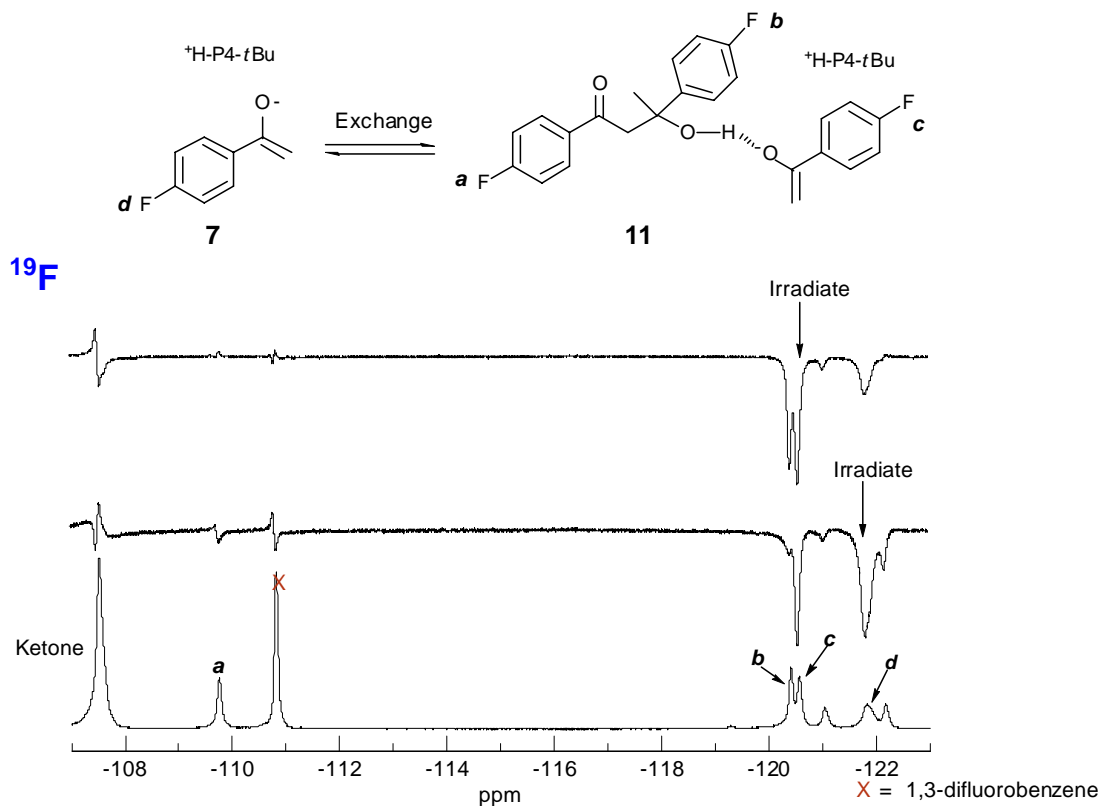


Figure S-16. ¹⁹F NMR saturation transfer experiment demonstrating the exchange of the hydrogen bonded enolate portion of **11** with free enolate **7** in 3:2 THF/Et₂O at -118 °C.

S3. Rapid-Injection NMR (RINMR) 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. The ^{13}C chemical shift thermometer (10% ^{13}C labeled *tris*(trimethylsilyl)methane, 0.004 mL),^[S1] and substrate were measured out, followed by 1.8 mL of freshly distilled THF and 1.2 mL of freshly distilled Et_2O . 1,3-Difluorobenzene (0.005 mL) was added as a ^{19}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_2O 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 ^{13}C NMR.^[S1] The sample was then raised, the septum removed, and the open NMR tube was lowered into the spectrometer and the apparatus was assembled.

^{19}F RINMR experiments were performed as follows (a more detailed description of the sequence and apparatus has been given^[S2]). 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 3 °C (for a 0.15 mL injection into a 3.0 mL sample). 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 (30 s) was selected for the remainder of the experiment (up to 3 h depending). At the completion of the experiment, the temperature of the sample was again checked, and post-kinetics analyses of the sample were performed.

Deprotonation of 4-Fluoroacetophenone (2) with P4-*t*Bu. A solution of 4-*t*Bu (0.35 mL, 0.35 mmol) was prepared according to the standard procedure. ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra were obtained at $-125\text{ }^\circ\text{C}$. 4-Fluoroacetophenone (2) (0.15 mL of 2.0 M solution, 0.30 mmol) was added using the RINMR apparatus and ^{19}F NMR spectra were obtained using a 2 s repetition rate. Spectra and a time vs concentration plot are shown in Figure S-17.

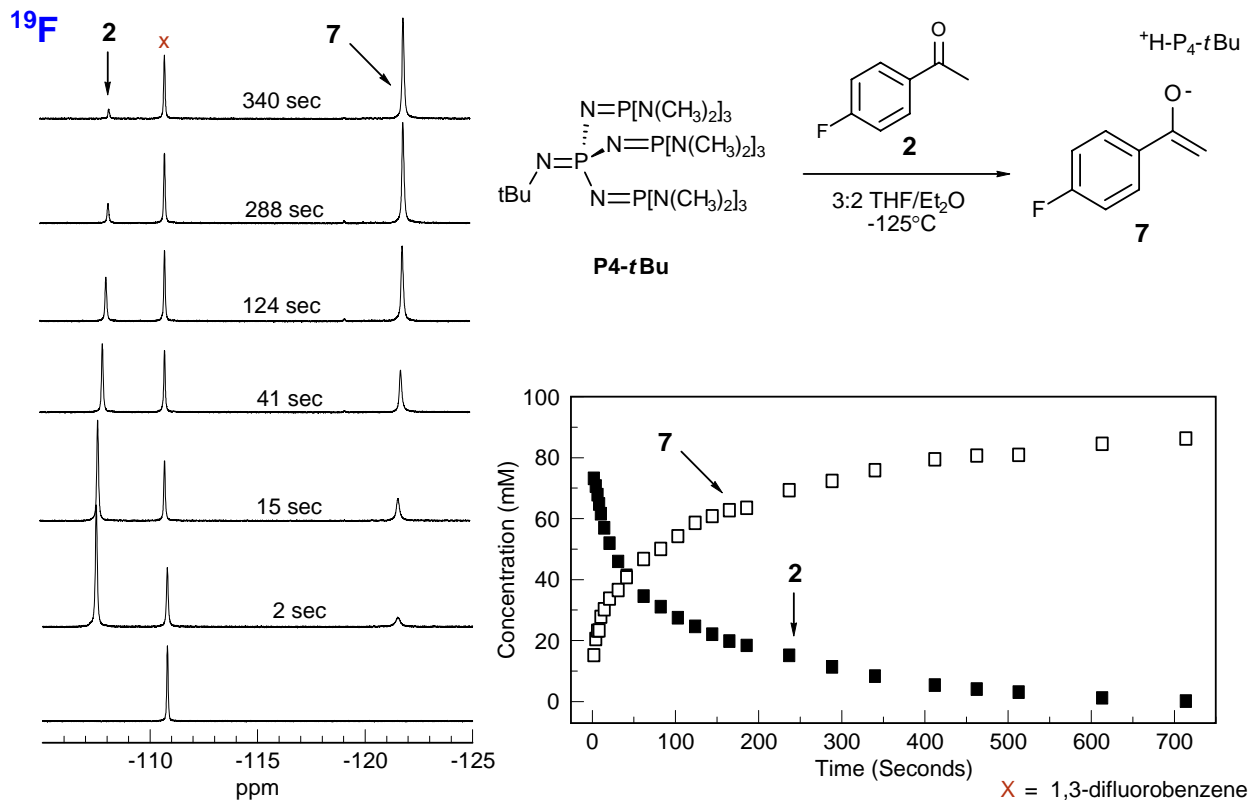


Figure S-17. The deprotonation of 4-fluoroacetophenone (2) by P4-*t*Bu in 3:2 THF/Et₂O at $-125\text{ }^\circ\text{C}$ as monitored by ^{19}F NMR spectroscopy. Reaction $t_{1/2} = 62\text{ s}$ at $-125\text{ }^\circ\text{C}$.

Self-Aldol Reaction of 4-Fluoroacetophenone (2) with 7. A solution of P4-*t*Bu (0.1 mL, 0.1 mmol) was prepared according to the standard procedure. ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra were obtained at -118°C . 4-Fluoroacetophenone (2) (0.15 mL of a 1.0 M solution, 0.15 mmol) was added using our RINMR apparatus and ^{19}F NMR spectra were obtained. A concentration versus time plot and proposed intermediates are shown in Figure S-18.

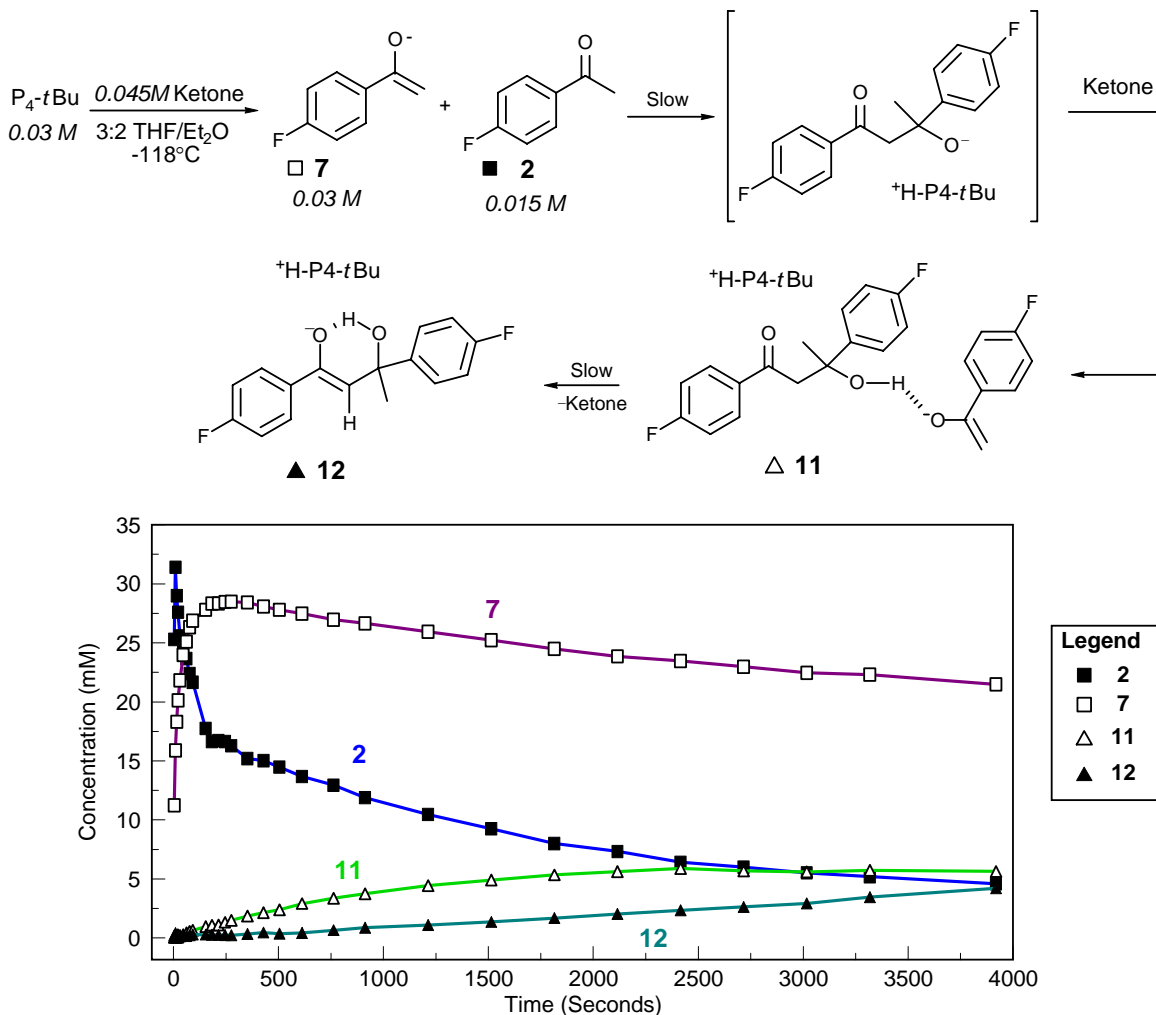


Figure S-18. Concentration time plot for the deprotonation with P4-*t*Bu and self-aldol reaction of 4-fluoroacetophenone in 3:2 THF/Et₂O at -118°C . The increase in 7 during the first 250 s is due to the deprotonation of 2 by P4-*t*-Bu.

Deuterium Isotope Effect Self-Aldol Reaction of 2. Two solutions of P4-*t*Bu (0.1 mL, 0.1 mmol) were prepared according to the standard procedure. ^{13}C , ^1H , ^{19}F and ^{31}P NMR spectra were obtained at -95°C . Protio Rate: 4-Fluoroacetophenone (**2**) (0.15 mL of 1.05 M solution, 0.16 mmol) was added to the first sample using the RINMR apparatus and ^{19}F NMR spectra were obtained. Concentration-Time plot shown in Figure S-19a. Deutero Rate: d_3 -4-Fluoroacetophenone (**2**) (0.15 mL of 1.09 M solution, 0.16 mmol) was added to the second sample using the Rapid-Injection NMR apparatus and ^{19}F NMR spectra were obtained. Concentration-Time plot shown in Figure S-19b. Pseudo first order rates (k_{obs}) were determined by initial rates by fitting to a first order line for 100 seconds of reaction. The initial rate of formation of **11** was identical in the two experiments.

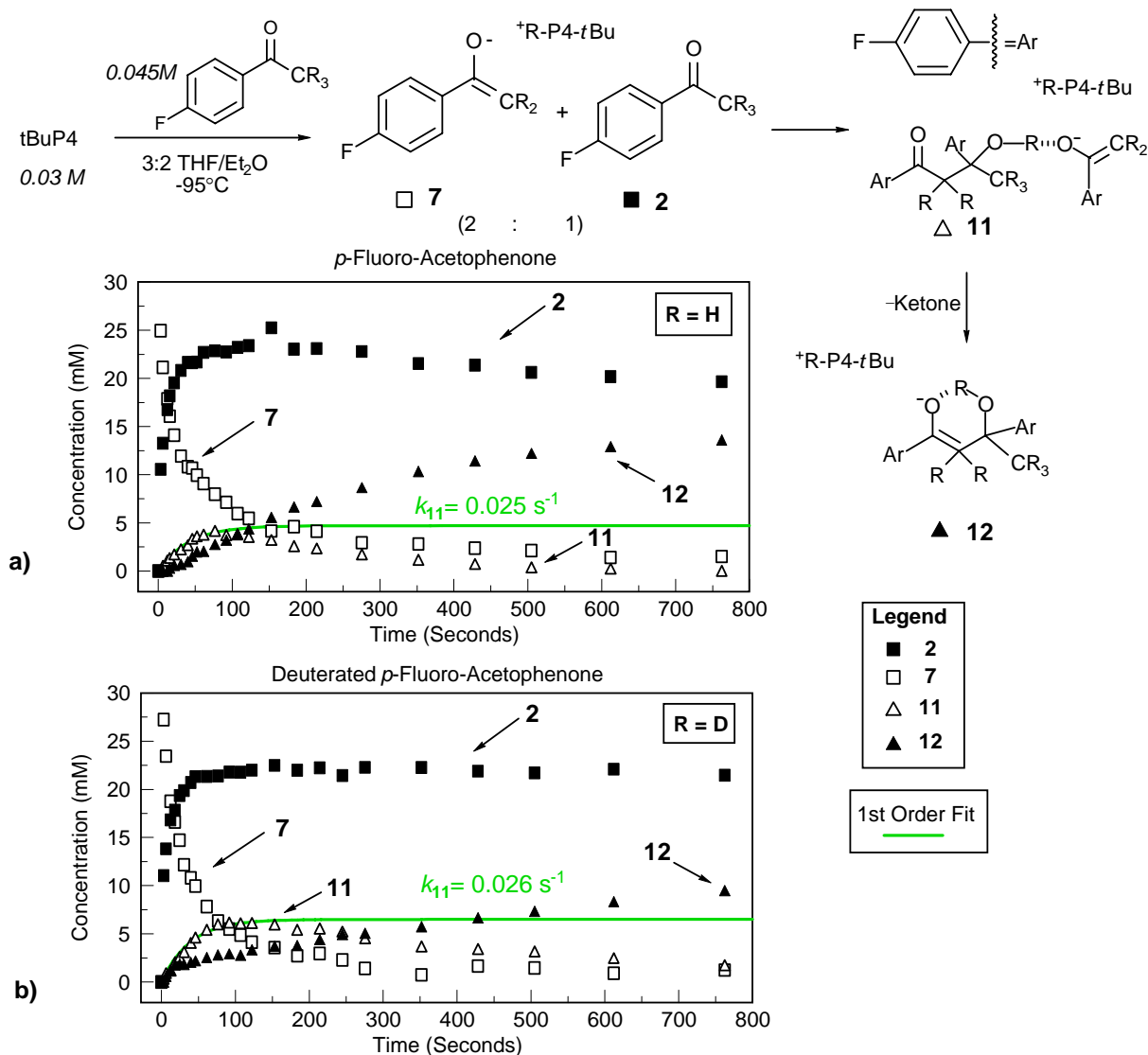


Figure S-19. Deuterium isotope effect on the self-aldol condensation of 4-fluoroacetophenone in 3:2 THF/Et₂O at -95°C . Lines correspond to first order increase of **11** with the corresponding rate constants indicated on the graph.

Self-Aldol Rate Dependence on Concentration of 2. Two samples of P4-*t*Bu (0.025 mL, 0.025 mmol) were prepared according to standard procedure. The NMR tubes were cooled to -78 °C under positive argon pressure after which 4-fluoroacetophenone (**2**) (0.003 mL, 0.025 mmol) was added. ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra of the enolate **7** were obtained at -118 °C. 4-Fluoroacetophenone (**2**) was injected (0.15 mL of 3.0 M solution in 3:2 THF/Et₂O, 0.45 mmol for the 110 mM plot (Figure S-20a) and 0.15 mL of 0.75 M solution in 3:2 THF/Et₂O, 0.11 mmol for the 33 mM plot (Figure S-20b)). The reaction was monitored by ¹⁹F NMR spectroscopy. Concentration time plots are shown in Figure S-20. Pseudo first order rates (*k*_{obs}) were determined for by initial rates for at least the first half-life of reaction (decrease of **7**).

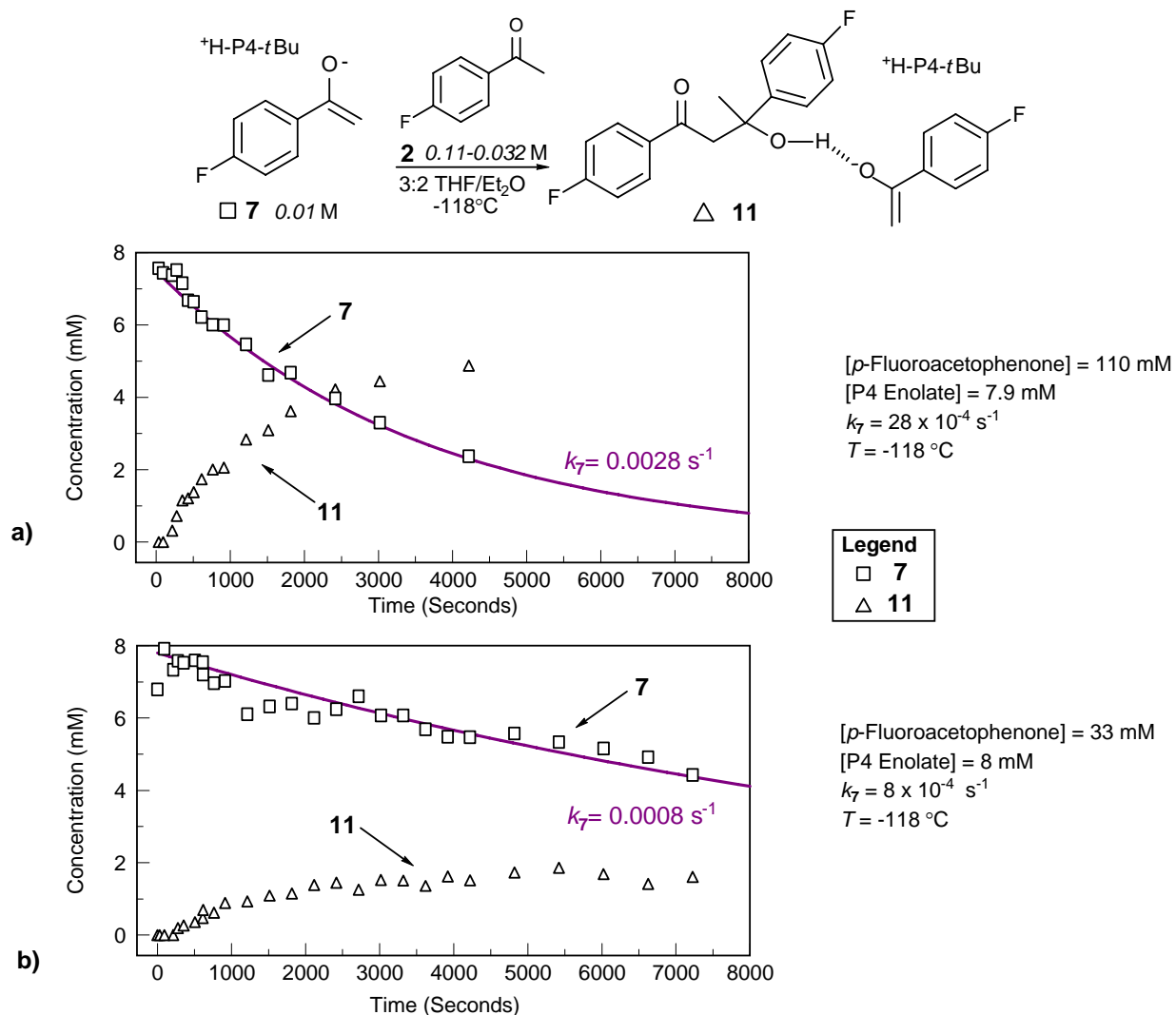


Figure S-20. The effect of varying concentration of **2** on the rate of the self aldol reaction of **2** in 3:2 THF/Et₂O at -118 °C monitored by ¹⁹F NMR spectroscopy. Lines correspond to first order decrease of **7** with the corresponding rate constants indicated on the graph.

Self-Aldol Rate Dependence on Concentration of 7. Sample Prep: A dried 10 mm NMR tube was flushed with argon and 1.8 mL of THF and 1.2 mL of Et₂O were added. The NMR tube was cooled to -78 °C under positive argon pressure. An enolate solution was prepared from P4-*t*Bu (0.3 mL, 0.3 mmol) and 4-fluoroacetophenone (**2**) (0.036 mL, 0.3 mmol) for the top run and P4-*t*Bu (0.15 mL, 0.15 mmol) and 4-fluoroacetophenone (**2**) (0.018 mL, 0.15 mmol) for the bottom run. ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -118 °C. A solution of 4-fluoroacetophenone (**2**) (0.15 mL, 0.33 M in 3:2 THF/Et₂O, 0.05 mmol) was injected for each run, and the reaction was monitored by ¹⁹F NMR spectroscopy. Concentration-time plots are shown in Figure S-21. Pseudo first order rates (*k*_{obs}) were determined from initial rates for the decrease of **2** (first half-life).

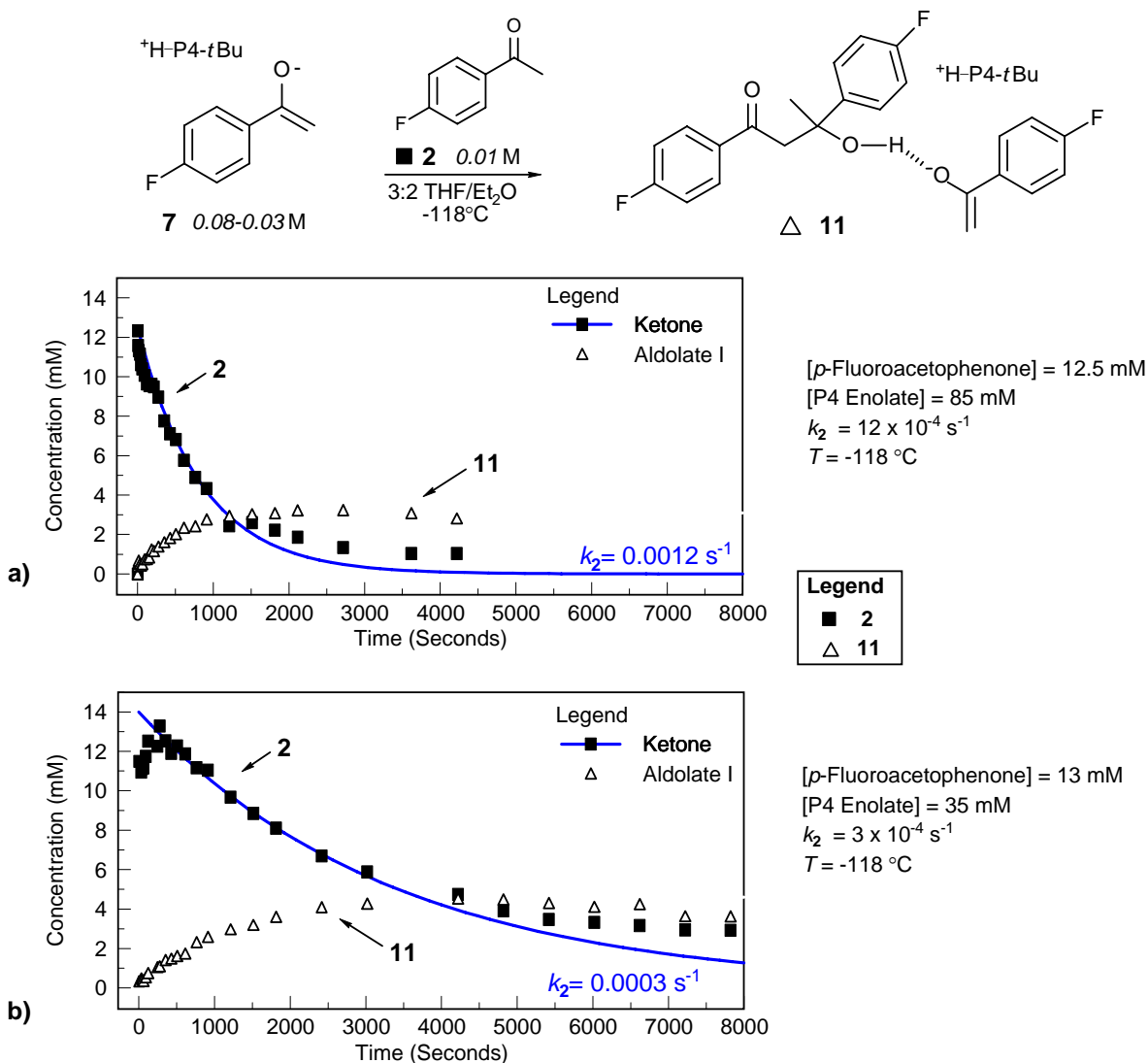


Figure S-21. The effect of varying the enolate **7** concentration on the rate of the self-aldol reaction of **2** in 3:2 THF/Et₂O at -118 °C monitored by ¹⁹F NMR spectroscopy. The blue line corresponds to pseudo first order decrease of **7**.

Self-Aldol Rate Dependence on Temperature. Sample Preparation: A dried 10 mm NMR tube was flushed with argon and 1.8 mL of THF and 1.2 mL of Et₂O were added. The NMR tube was cooled to -78 °C under positive argon pressure and an enolate solution was prepared from P4-*t*Bu (0.1 mL, 0.1 mmol) and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol). ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at 102 °C, -112 °C, or -118 °C depending on the kinetic run. 4-Fluoroacetophenone (**2**) (0.15 mL, 2.7 M in 3:2 THF/Et₂O, 0.4 mmol) was injected for each kinetic run which was monitored by ¹⁹F NMR spectroscopy. Concentration time plots are shown in Figure S-22. Pseudo first order rates (*k*_{obs}) were determined for decrease of **7** by fitting for at least the first half-lives of reaction. Extrapolation of the rate of disappearance of **7** to -130 °C gave a rate constant *k*₇ = 0.00004 s⁻¹ for comparison with the aldehyde aldol rate.

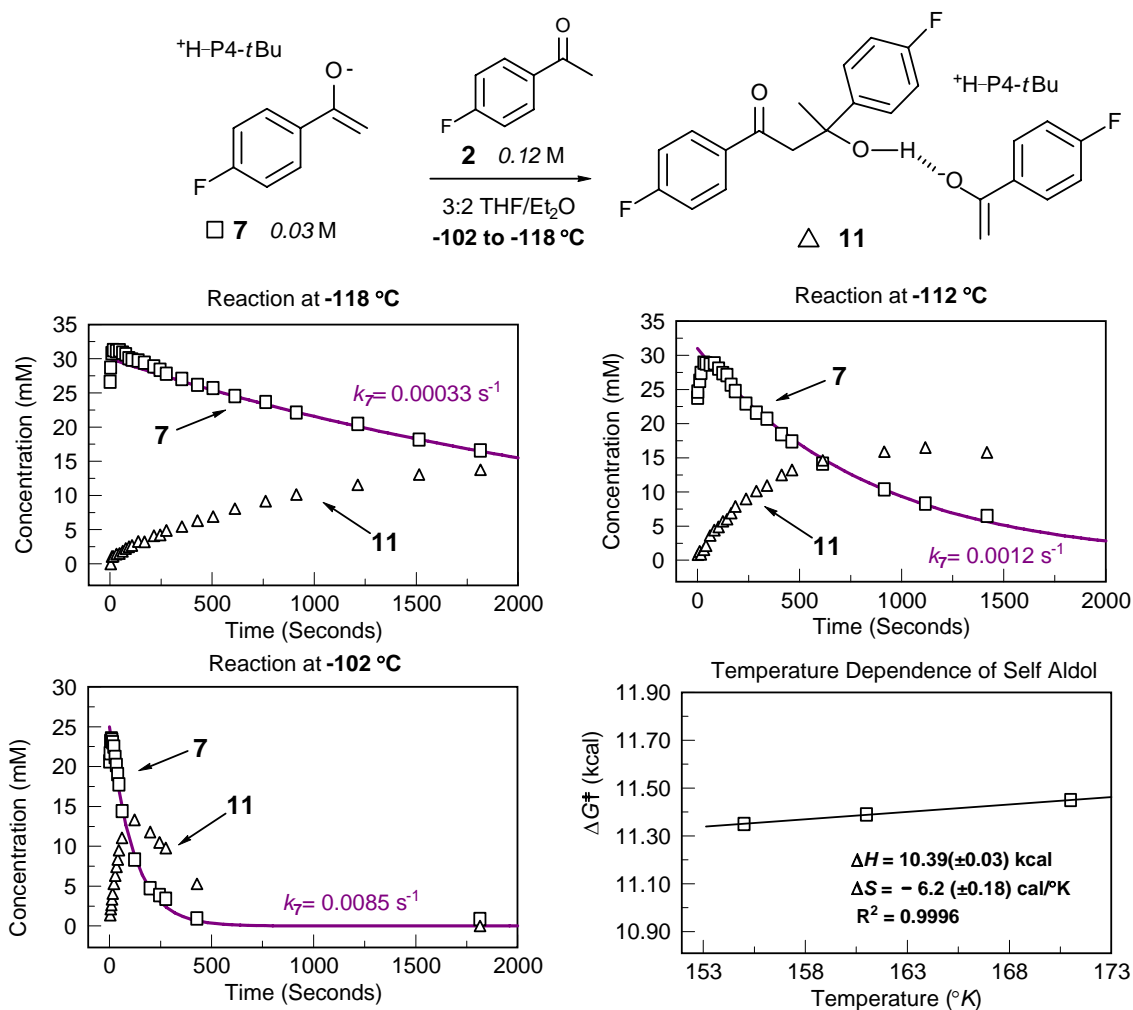


Figure S-22. The effect of temperature on the rate of the self-aldol reaction of **2** in 3:2 THF/Et₂O monitored by ¹⁹F NMR. The lines correspond to first order rates with the corresponding rate constants indicated on the graph.

Formation of 8 by HCl Injection to 7 at -118 °C. A dried 10 mm NMR tube was flushed with argon and 1.8 mL of THF and 1.2 mL of Et₂O were added. The NMR tube was cooled to -78 °C under positive argon pressure and an enolate solution was prepared from P4-*t*Bu (0.1 mL, 0.1 mmol) and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol). ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -118 °C. HCl etherate (0.15 mL, 0.5 M, 0.075 mmol) was injected and ¹⁹F NMR spectra were obtained at -118 °C. Spectra and a concentration time plot are shown in Figure S-23. Rates were determined by fitting the increase of **2** to a first order curve and fitting the decrease of **8** to a first order curve.

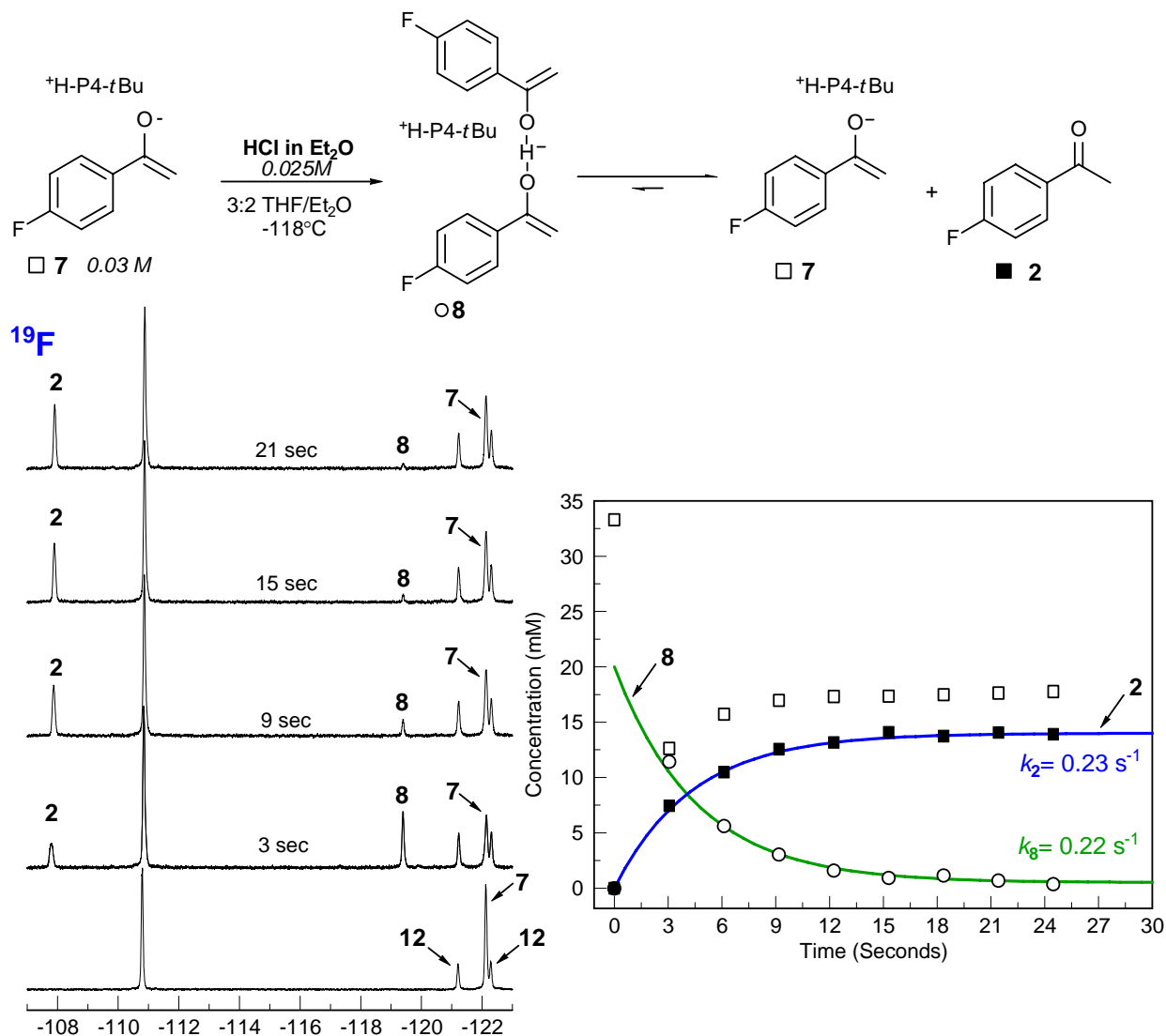


Figure S-23. The formation of **8** and disassociation to **7** and **2** in 3:2 THF/Et₂O at -118 °C monitored by ¹⁹F NMR. The lines correspond to first order rates with the rate constants indicated on the graph. The small amount of **12** in the first spectrum is due to self-aldol during preparation of the solution of **7**.

Characterization of 8 at -138 °C. A dried 10 mm NMR tube was flushed with argon and 3 mL of Me₂O was added via cannula distillation. The NMR tube was cooled to -78 °C under positive argon pressure and an enolate solution was prepared from P4-*t*Bu (0.1 mL, 0.1 mmol) and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol). ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -138 °C. HCl etherate (0.15 mL, 0.5 M, 0.075 mmol) was injected and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -138 °C. The mixed acetophenone sample was prepared in an identical manner from P4-*t*Bu (0.2 mL, 0.2 mmol), 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol), and acetophenone (**2**) (0.012 mL, 0.1 mmol). HCl etherate (0.15 mL, 1.1 M, 0.16 mmol) was injected and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -138 °C. Spectra are shown in Figure S-24.

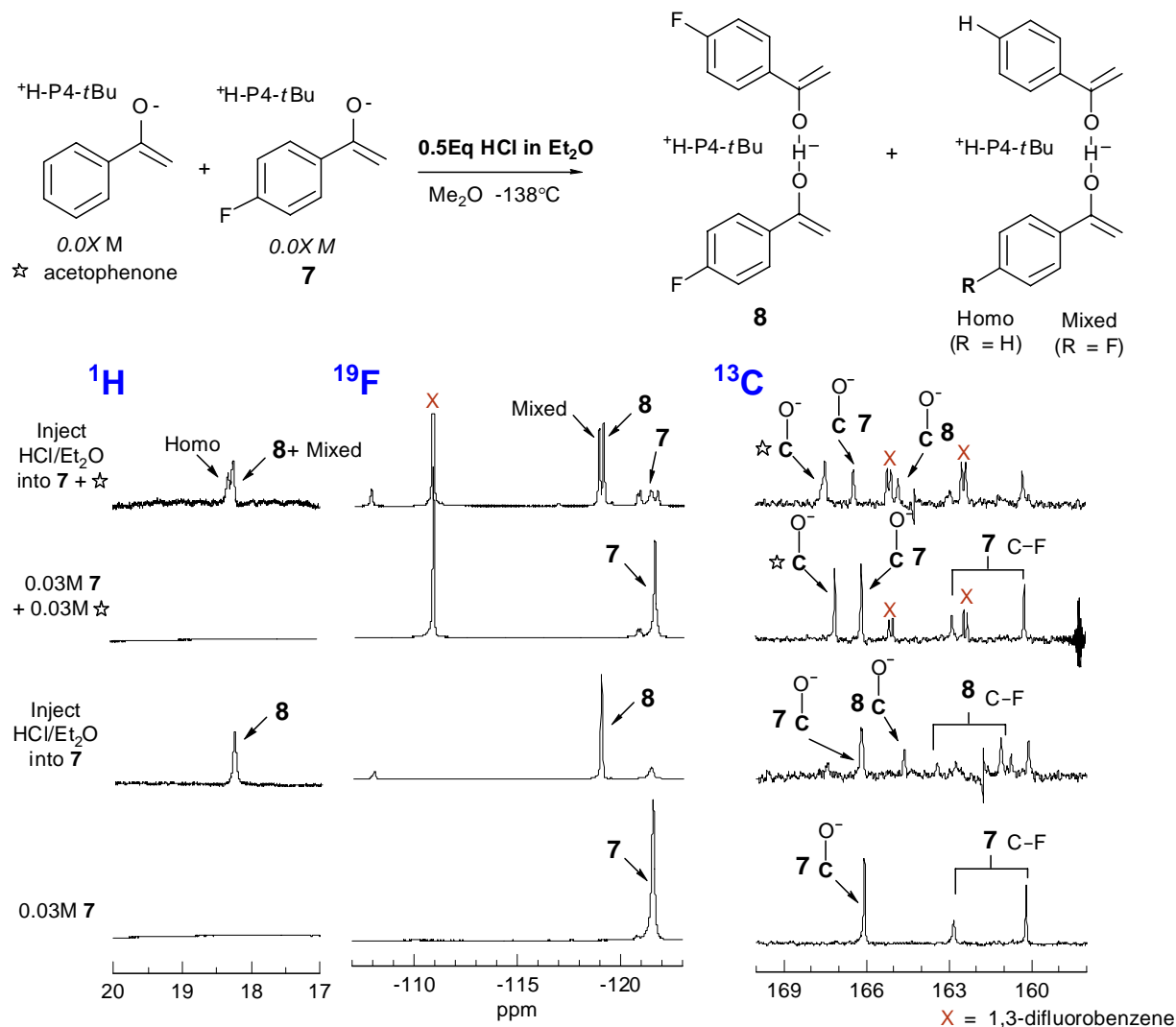


Figure S-24. Characterization of **8** via ¹H, ¹³C and ¹⁹F NMR in Me₂O at -138 °C and by formation of the mixed acetophenone P4 dimer.

Formation of Enol 9 by HCl Injection to 7. A dried 10 mm NMR tube was flushed with argon and 3 mL of Me₂O was added via cannula distillation. The NMR tube was cooled to -78 °C under positive argon pressure and an enolate solution was prepared from P4-*t*Bu (0.1 mL, 0.1 mmol) and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol). ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -138 °C. HCl etherate (0.15 mL, 0.5 M, 0.075 mmol) was injected and ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -138 °C immediately following injection. Spectra are shown in Figure S-25.

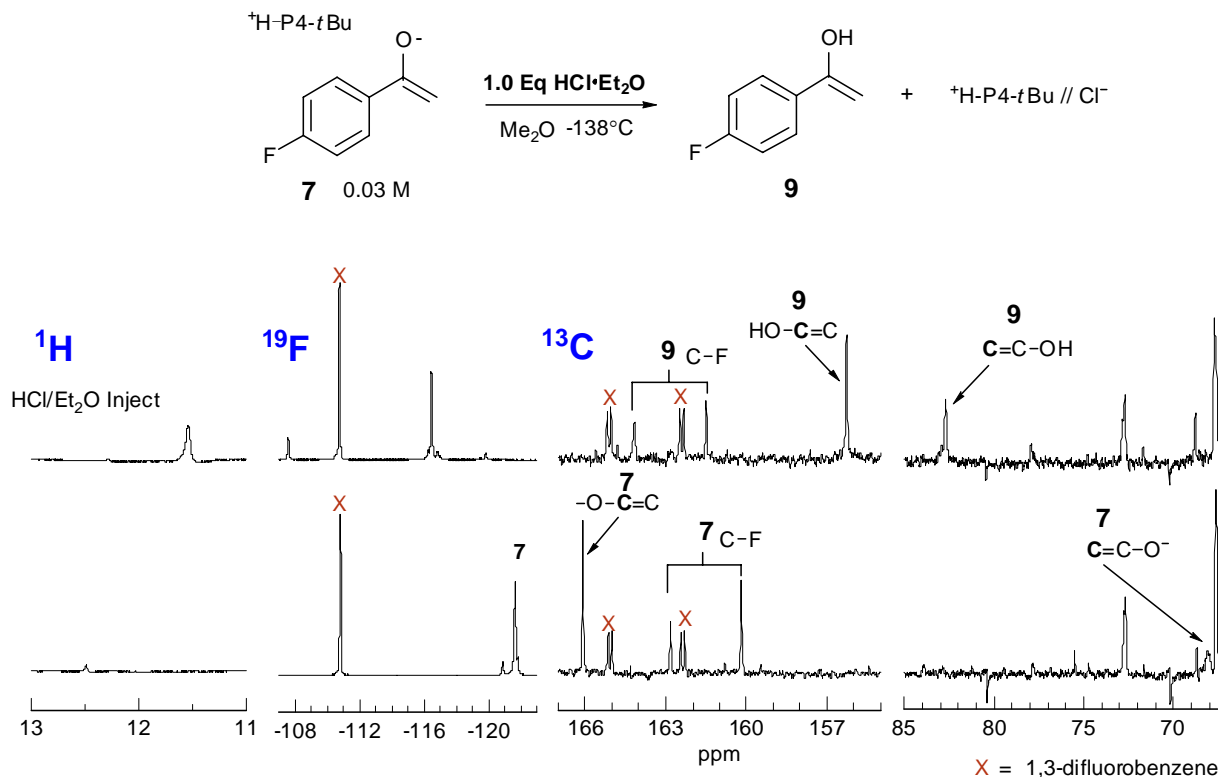


Figure S-25. The formation of enol **9** by HCl injection to **7** and characterization in Me₂O at -138 °C.

Reaction of 7 with 4-Fluorobenzaldehyde and Benzaldehyde. Sample preparation: Dried 10 mm NMR tubes were flushed with argon and 1.8 mL of THF and 1.2 mL of Et₂O were added. The NMR tubes were cooled to -78 °C under positive argon pressure and enolate solutions were prepared from P4-*t*Bu (0.1 mL, 0.1 mmol) and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol). ¹³C, ¹H, ¹⁹F and ³¹P spectra were obtained at -118 °C. 4-Fluorobenzaldehyde 1 equiv: 4-fluorobenzaldehyde (0.15 mL of a 0.6 M solution, 0.09 mmol) was injected and ¹⁹F NMR spectra were obtained at -118 °C. 4-Fluorobenzaldehyde 4 equiv: 4-fluorobenzaldehyde (0.15 mL of a 3.3 M solution, 0.5 mmol) was injected and ¹⁹F and NMR spectra were obtained at -118 °C. Benzaldehyde 4 equiv: Benzaldehyde (0.15 mL of a 3.3 M solution, 0.5 mmol) was injected and spectra were obtained at -118 °C. Spectra are shown in Figure S-26. Comparison of these sets of spectra allow determination of the ratio of consumed aldehyde to enolate (2:1) and help distinguish the fluorine signals which originated from the enolate from those of the aldehyde.

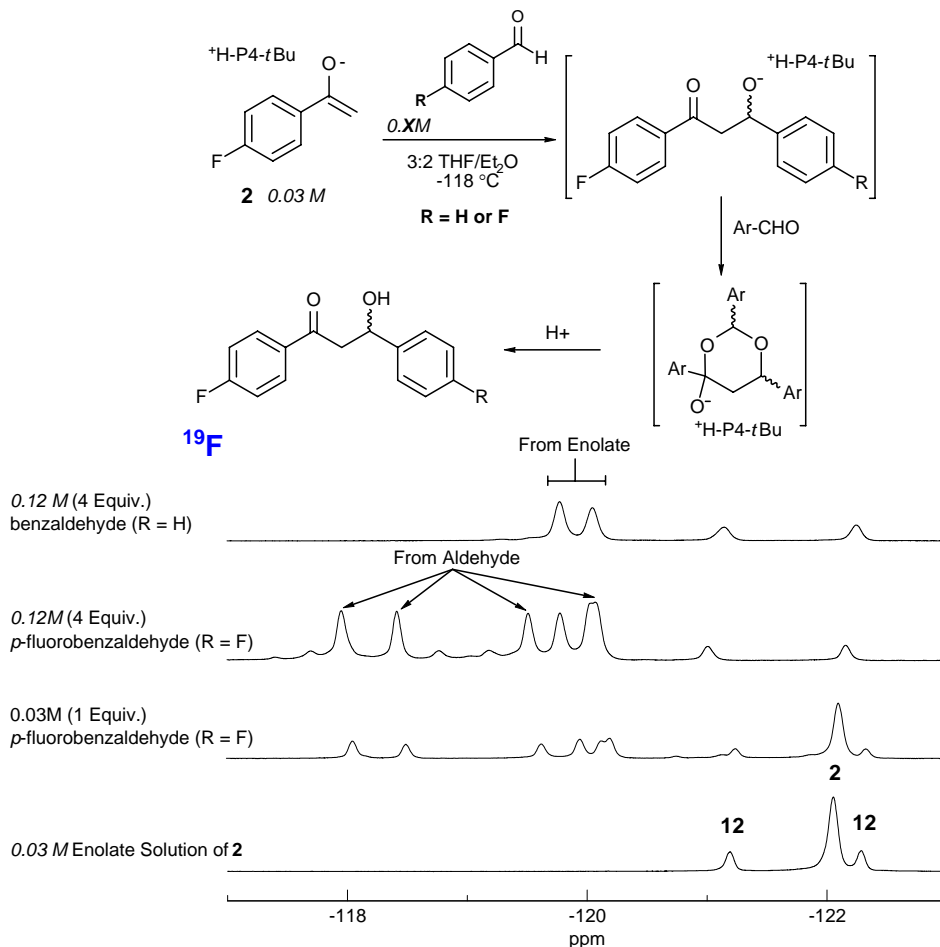


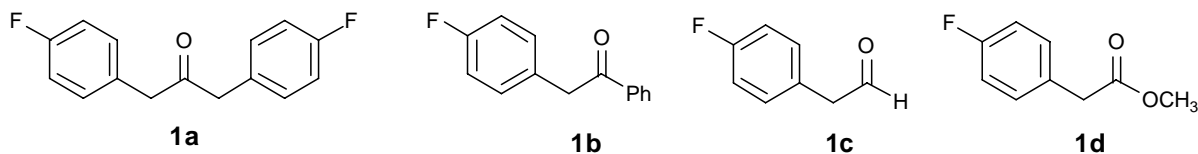
Figure S-26. Reaction of **2** with 4-fluorobenzaldehyde and benzaldehyde followed by ¹⁹F NMR in 3:2 THF/Et₂O at -118 °C. The difference in fluorine signals of the products from these reactions were used to determine the ratio of consumed aldehyde to enolate (2:1) and distinguish the fluorine signals which originated from the enolate from the aldehyde. The small amount of **12** in the first spectrum is due to self-aldol during preparation of the solution of **7**.

Table S-3. Summary of NMR Shifts of Carbonyls, Enolates, Enols, and Dimers

Compound (Shifts obtained in 3:2 THF/Et ₂ O between -120 to -130 °C)	¹³ C O-C=C (ppm)	¹³ C O-C=C (ppm)	¹³ C F-C (ppm)	¹⁹ F (ppm)
Hydrogen Bonded Dimer Dibenzyl ketone	166.3	95.4	NA	NA
Lithium Dimer Enolate of Dibenzyl ketone	168.6	96.8	NA	NA
P4 Dibenzyl ketone Enolate	174.2	88.7	NA	NA
1,3-Bis-(4-fluorophenyl)-2-propanone (1a)	NA	NA	162.3	-117.68
Enol Trimethylsilyl Ether of 1,3-Bis-(4-fluorophenyl)-2-propanone (1a)	152.5	109.4	161.2	-117.61
Methyl Enol Ether of 1,3-Bis-(4-fluorophenyl)-2-propanone (1a)	155.4	106.8	161.0	-117.92
Enol 5a (HBF ₄)	155.02	100.9	160.3	-119.62
Enol 5a (HCl)	158.2	98.7	159.8	-120.76
Hydrogen Bonded Dimer 4a	165.1	94.1	158.4	-123.90
Lithium Enolate Dimer of 1,3-Bis-(4-fluorophenyl)-2-propanone (1a)	168.5	96.1	158.4	-123.89
P4 Enolate 3a	173.1	87.3	155.4	-130.24
1-Phenyl-2-(4-fluorophenyl)ethanone (1b)	NA	NA	162.3	-118.22
Hydrogen Bonded Dimer 4b	162.1	96.5	158.71	-123.06
Lithium Enolate Dimer of 1-Phenyl-2-(4-fluorophenyl)ethanone (1b)	163.9	95.34	158.73	-123.19
P4 Enolate 3b	168.0	87.1	155.8	-128.89
Methyl-2-(4-fluorophenyl)acetate (1d)	NA	NA	162.45	-117.22
P4 Enolate 3d	166.1	65.9	153.6	-135.79
2-(4-fluorophenyl)ethanal (1c)	NA	NA	162.52	-117.13
Enol Trimethylsilyl Ether of 1c	141.1	107.6	161.1	-117.07
Hydrogen Bonded Dimer 4c	154.20	95.50	158.09	-123.78
P4 Enolate 3c	165.07	90.95	155.10	-129.91
4-Fluoroacetophenone (2)	NA	NA	166.22	-107.20
Enol 9 (4-Fluoroacetophenone)*	156.2	82.6	162.8	-116.51
Hydrogen Bonded Dimer 8 (4-Fluoroacetophenone)*	161.1	NA	162.1	-118.86
P4 Enolate 7 (4-Fluoroacetophenone)*	166.4	68.1	161.51	-121.85

*spectra obtained in Me₂O

S4. Syntheses



1,3-Bis-(4-fluorophenyl)-2-propanone (1a): (Prepared using a modified literature procedure.^[S71]) 4-Fluorophenylacetic acid (4.135 g, 26.8 mmol), 4-(dimethylamino)pyridine (3.53 g, 28.8 mmol), *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI.HCl) (5.00 g, 26.0 mmol) and 80 mL of dichloromethane were added to a 250 mL round bottom flask. The solution was stirred for four days at room temperature, and 100 mL of 10% HCl solution was added. The organic layer was separated, washed with 10% HCl twice, saturated NaHCO₃ once, dried over MgSO₄ and the solvent was removed by vacuum. The resulting solid was recrystallized from ethanol to yield 2.35 g (74%) of **1a**. Melting Point 62-64 °C. ¹H NMR (300 MHz, CDCl₃), δ 3.69 (s, 4H), 6.99 (t, *J* = 8 Hz, 4H), 7.09 (dd, *J* = 5.5, 8.8, 4H). ¹³C NMR (75.4 MHz, CDCl₃), δ 48.4 (s), 115.8 (d, *J*_{CF} = 21.5 Hz), 129.7 (d, *J*_{CF} = 3.2Hz), 131.2 (d, *J*_{CF} = 7.8 Hz), 162.2 (d, *J*_{CF} = 246.6 Hz), 205.3 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -116 (tt, *J*_{FH} = 5.5, 8.8 Hz). HRMS (EI) (m/z): calcd. for C₁₅H₁₂F₂O (M+) 246.0856; found 246.0860.

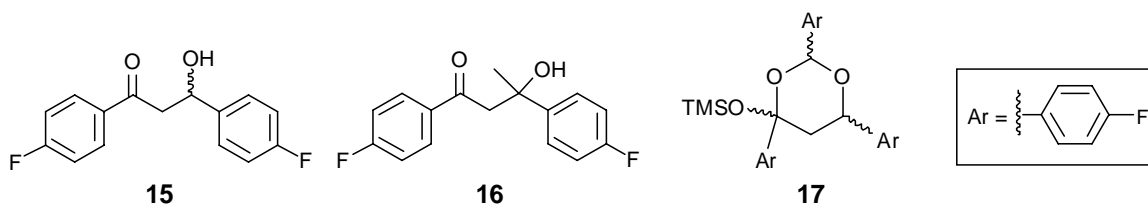
1,3-Bis-(4-fluorophenyl)-2-propanone-*d*₄ (1a)-*d*₄: Deuterium oxide (10 mL, 500 mmol) was placed in a dried 25 mL containing a magnetic stir bar. A pellet of KOH was added and the solution was stirred for 10 min. 1,3-Bis-(4-fluorophenyl)-2-propanone (0.310 g, 12.6 mmol) was added and the solution was vigorously stirred overnight at room temperature. The solution was extracted with Et₂O, dried with MgSO₄, and the solvent was removed under vacuum to yield 0.310 g (98%) of deuterated (97% D by ¹H NMR) 1,3-bis-(4-fluorophenyl)-2-propanone. ¹H NMR (300 MHz, CDCl₃), δ 6.99 (t, *J* = 8.7, 4H), 7.09 (dd, *J* = 5.5, 8.8, 4H). ¹³C NMR (75.4 MHz, CDCl₃), δ 47.7 (pentet, *J*_{CD} = 19), 115.8 (d, *J*_{CF} = 21.5 Hz), 129.6 (d, *J*_{CF} = 3.2Hz), 131.2 (d, *J*_{CF} = 7.8 Hz), 162.2 (d, *J*_{CF} = 248.6 Hz), 205.4 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -115.99 (tt, *J*_{FH} = 5.5, 8.8 Hz). HRMS (EI) (m/z): calcd. for C₁₅H₁₂F₂O (M+) 250.1102; found 250.1099.

1-Phenyl-2-(4-fluorophenyl)ethanone (1b):^[S81] ¹H NMR (300 MHz, CDCl₃), δ 4.262 (s, 2H), 7.02 (t, *J* = 8 Hz, 4H), 7.23 (dd, *J* = 5.5, 8 Hz, 2H), 7.47 (t, *J* = 8 Hz, 2H), 7.57 (t, *J* = 8 Hz, 1H), 8.02 (d, *J* = 8 Hz, 2H). ¹³C NMR (75.4 MHz, CDCl₃), δ 44.7 (s), 115.7 (d, *J*_{CF} = 21.5Hz), 128.7 (s), 128.9 (s), 130.4 (d, *J*_{CF} = 3.3Hz), 131.3 (d, *J*_{CF} = 8.1Hz), 133.5 (s), 136.7 (s), 162.16 (d, *J*_{CF} = 246.6Hz), 197.7 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -116.56 (tt, *J*_{FH} = 5.5, 8.8 Hz). HRMS (EI) (m/z): calcd. for C₁₅H₁₂F₂O (M+) 214.0789; found 214.0795.

2-(4-Fluorophenyl)ethanal (1c): 2-(4-Fluorophenyl)ethanol (0.5044g, 3.6 mmol) and 20 ml of dichloromethane were added to a 50 mL round bottom flask. Dess-Martin periodinane (13 mL, 0.3 M solution) was added and the reaction was stirred for 1 h. The reaction mixture was poured into a 100 ml round bottom flask containing 20 ml of saturated NaHCO₃ :Na₂S₂O₃ (1:1) and stirred for 30 min. The organic layer was separated, washed with a brine solution, dried with MgSO₄ and the solvent was removed under vacuum. The product was purified by distillation 60-62 °C at 0.5 mm Hg yielding 0.455 g (91%) of aldehyde. ¹H NMR (300 MHz, CDCl₃), δ 3.62 (d *J* = 2, 2H), 7.0 (t, *J* = 8 Hz, 4H), 7.12 (dd, *J* = 8, 5.5 Hz, 2H), 9.68 (t, *J* = 2 Hz, 1H). ¹³C NMR (75.4 MHz, CDCl₃), δ 49.8 (s), 116.1 (d, *J*_{CF} = 21.5Hz), 127.7 (d, *J*_{CF} = 3.3Hz), 131.4 (d, *J*_{CF} = 8.1Hz), 162.4 (d, *J*_{CF} = 245.7Hz), 199.2 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -115.5 (tt, *J*_{FH} = 5.5, 8.8 Hz). HRMS (EI) (m/z): calcd. for C₈H₇FO (M+) 138.0476; found 138.0473.

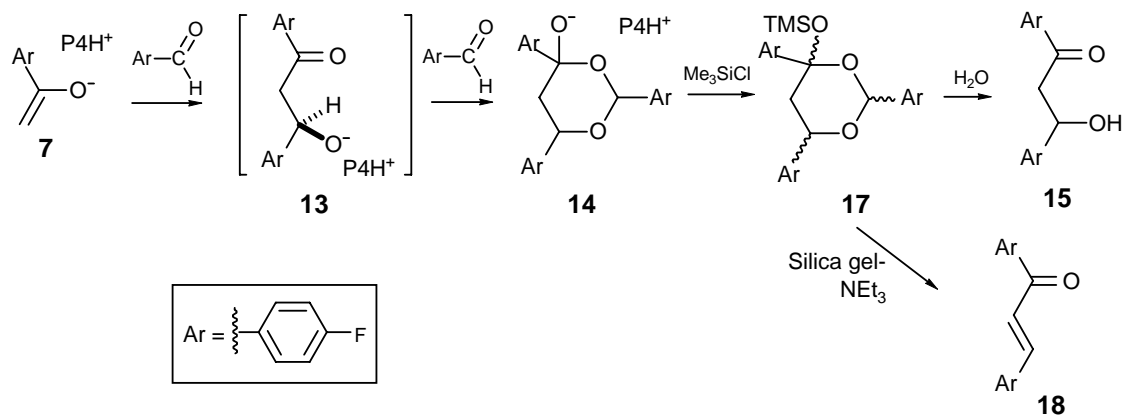
Methyl-2-(4-fluorophenyl)acetate (1d): ^[89] ¹H NMR (300 MHz, CDCl₃), δ 3.60 (s, 2H), 3.69 (s, 3H) 7.0 (t, *J* = 8 Hz, 4H), 7.23 (dd, *J* = 8, 5.5 Hz, 2H). ¹³C NMR (75.4 MHz, CDCl₃), δ 40.4 (s), 52.2 (s), 115.6 (d, *J*_{CF} = 21.5Hz), 129.9 (d, *J*_{CF} = 3.3Hz), 131.0 (d, *J*_{CF} = 8.1Hz), 162.2 (d, *J*_{CF} = 246.6Hz), 172.0 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -116.2 (tt, *J*_{FH} = 5.5, 8.8 Hz). HRMS (EI) (m/z): calcd. for C₁₅H₁₂FO₂ (M⁺) 168.0582; found 168.0578.

4-Fluoroacetophenone-*d*₃: Deuterium oxide (5 mL, 250 mmol) was placed in a dried 25 mL flask containing a magnetic stir bar. A small piece of freshly cut sodium metal (~ 1 x 1 x 1 mm) was added and the solution was stirred for 10 min. 4-Fluoroacetophenone (0.5 mL, 9.6 mmol) was added and the solution was vigorously stirred for 5 days at room temperature. The solution was extracted with Et₂O, dried with MgSO₄, and the solvent was removed under vacuum. The product was purified by distillation (78-80 °C, 11mm Hg) to yield 0.501 g (85%) of deuterated (95% D by NMR) 4-fluoroacetophenone. ¹H NMR (300 MHz, CDCl₃), δ 3.68 (1:2:3:2:1 pentet, *J* = 2.2 Hz 0.18 H), 7.07 (t, *J* = 8.4 Hz, 2H), 7.92 (dd, *J* = 8.9, 5.4, 2H). ¹³C NMR (75.4 MHz, CDCl₃), δ 25.8 (1:2:3:3:2:1 sextet, *J*_{CD} = 19.2 Hz), 115.5 (d, *J*_{CF} = 21.5Hz), 130.8 (d, *J*_{CF} = 9.0 Hz), 133.6 (d, *J*_{CF} = 3.6 Hz), 165.7 (d, *J*_{CF} = 253.6 Hz), 196.4 (s). HRMS (EI) (m/z): calcd. for C₈H₄D₃FO (M⁺) 141.0664; found 141.0666.



1,3-Bis-(4-fluorophenyl)-3-hydroxypropan-1-one (15): Isolated from Rapid-injection NMR experiments identical to **Reaction of 7 with 4-Fluorobenzaldehyde** by workup with propionic acid (1 mL of 3 M solution in Et₂O was added). The sample was then poured into a stirring mixture of 10 mL of saturated NaHCO₃ and 10 mL of Et₂O. The organic layer was separated, washed with saturated NaHCO₃ twice, dried over MgSO₄ and the solvent and remaining starting materials were removed under vacuum. ¹H, ¹⁹F and ¹³C NMR and HRMS were obtained without further purification. Sample could be purified by column chromatography using hexanes/ethyl acetate. ¹H NMR (300 MHz, CDCl₃), δ 3.22 (ABX, *J*_{ab} = 17.7, *J*_{ab} = 1.8, *J*_{ab} = 10.3, *v*_{ab} = 4.2, 2H), 3.56 (bs, 1H), 5.32 (apparent triplet (X of ABX), *J* = 6 Hz, 1H), 7.06 (t, *J* = 8.6 Hz, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 7.40 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.98 (dd, *J* = 8.8, 5.5 Hz, 2H). ¹³C NMR (75.4 MHz, CDCl₃), δ 47.5 (s), 69.7 (s), 115.3 (d, *J*_{CF} = 21 Hz), 116.1 (d, *J*_{CF} = 21 Hz), 127.7 (d, *J*_{CF} = 8 Hz), 131.1 (d, *J*_{CF} = 8 Hz), 133.2 (d, *J*_{CF} = 3 Hz), 138.5 (d, *J*_{CF} = 3 Hz), 162.5 (d, *J*_{CF} = 246 Hz), 166.4 (d, *J*_{CF} = 256 Hz), 198.5 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -104.3 (tt, *J*_{FH} = 8.6, 5.5 Hz), -115.2 (tt, *J*_{FH} = 8.6, 5.5 Hz). HRMS (EI) (m/z): calcd. for C₁₅H₁₂F₂O₂ (M⁺) 262.0805; found 262.0796.

1,3-Bis-(4-fluorophenyl)-3-hydroxy-1-butanone (16): 4-Fluoroacetophenone (**2**) (41.4 mg, 0.35 mmol) was added to a dried 10 mm NMR tube. The tube was flushed with N₂ and 1.8 mL of THF and 1.2 mL of Et₂O were added. The NMR tube was cooled to -78 °C under positive N₂ pressure and P4-*t*Bu (0.16 mL, 0.16 mmol) was added as a 1M solution in hexanes. After five min at -78 °C, propionic acid (1 mL of a 3M solution in Et₂O) was added. The sample was poured into a stirring mixture of 10 mL of saturated NaHCO₃ and 10 mL of Et₂O. The organic layer was separated, washed with saturated NaHCO₃ twice, dried over MgSO₄ and the solvent was removed under vacuum. ¹H, ¹⁹F and ¹³C NMR spectra were obtained without further purification due to the possibility of retro aldol. ¹H NMR (300 MHz, CDCl₃), δ 1.52 (s, 3H), 3.21 (d, *J* = 16.9 Hz, 1H), 3.63 (d, *J* = 16.9 Hz, 1H), 4.62 (bs, 1H), 6.90 (t, *J* = 8.8 Hz, 2H), 7.04 (t, *J* = 8.8 Hz, 2H), 7.35 (dd, *J* = 5.5, 8.8 Hz, 2H), 7.85 (dd, *J* = 5.5, 8.8 Hz, 2H). ¹³C NMR (75.4 MHz, CDCl₃), δ 31.13 (s), 48.7 (s), 73.46 (s), 115.2 (d, *J*_{CF} = 21.5 Hz), 116.1 (d, *J*_{CF} = 21.5 Hz), 126.3 (d, *J*_{CF} = 8.1 Hz), 131.0 (d, *J*_{CF} = 9.6 Hz), 133.5 (d, *J*_{CF} = 3 Hz), 145.5 (d, *J*_{CF} = 3 Hz), 161.8 (d, *J*_{CF} = 246 Hz), 166.3 (d, *J*_{CF} = 256 Hz), 199.7 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -104.1 (tt, *J*_{FH} = 5.5, 8.6 Hz), -117.6 (tt, *J*_{FH} = 5.5, 8.6 Hz).



Hemiacetal aldolate 17.^[S10] A dried 10 mm NMR tube was flushed with argon and 1.8 mL of THF and 1.2 mL of Et₂O were added. 1,3-Difluorobenzene (0.005 mL) and triethylamine (0.1 mL, 7 mmol) were added. The tube was cooled to -78 °C, and an enolate solution was prepared from P4-*t*Bu (0.1 mL, 0.1 mmol) and 4-fluoroacetophenone (**2**) (0.012 mL, 0.1 mmol). ¹³C, ¹H, ¹⁹F and ³¹P NMR spectra were obtained at -118 °C. 4-Fluorobenzaldehyde (0.15 mL, 3.3 M) was injected using the RINMR apparatus at -118 °C, followed by a Me₃SiCl (0.15 mL, 3.3 M, 0.5 mmol) injection. (Similar bench top (non RINMR) experiments at -78 °C produced a mixture of products with the Me₃Si ether of **15** being the major identified product.) NMR spectra were obtained at -118 °C. The sample was poured into a stirring mixture of 10 mL of saturated NaHCO₃ and 10 mL of Et₂O. The organic layer was separated, washed with saturated NaHCO₃, dried over MgSO₄ and the solvent was removed by vacuum. The sample was purified by column chromatography using Et₂O/hexanes (1:9). During the purification some of the hemiacetal aldolate isomers were hydrolyzed to **15**, leaving as major product compound **17**. ¹³C NMR spectra of the reaction mixture and the major isolated product show the loss of some product peaks from the reaction mixture (Figure S-26 a and b). Spectroscopic data for isolated major isomer (all equatorial aryl groups) of **17** with ~20% of a minor isomer: ¹H NMR (300 MHz, CDCl₃), δ -0.13 (s, 9H), 3.02 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.52 (dd *J* = 16.8, 8.5 Hz, 1H), 5.09 (dd, *J* = 8.5, 4.6 Hz, 1H), 5.74 (s, 1H), 6.91 (t, *J* = 8.8 Hz, 2H), 6.97 (t, *J* = 8.8 Hz, 2H), 7.03 (t, *J* = 8.8 Hz, 2H), 7.24 (dd, *J* = 5.5, 8.8 Hz, 2H), 7.31 (dd, *J* = 5.5, 8.8 Hz, 2H), 7.85 (dd, *J* = 5.5, 8.8 Hz, 2H). ¹³C NMR (75.4 MHz, CDCl₃) 47.7 (CH₂), 75.1 (CH), 97.7 (CH), 115.2 (d, *J*_{CF} = 21.5 Hz), 115.3 (d, *J*_{CF} = 21.5 Hz), 115.9 (d, *J*_{CF} = 21.5 Hz), 128.2 (d, *J*_{CF} = 8.1 Hz), 128.3 (d, *J*_{CF} = 8.1 Hz), 131.1 (d, *J*_{CF} = 8.1 Hz), 133.6 (d, *J* = 3 Hz), 137.1 (d, *J* = 3 Hz), 138.6 (d, *J*_{CF} = 3 Hz), 162.4 (d, *J*_{CF} = 255 Hz), 163.0 (d, *J*_{CF} = 245 Hz), 166.0 (d, *J*_{CF} = 246 Hz), 196.1 (s). ¹⁹F NMR (282 MHz, CDCl₃) δ -105.6 (tt, *J*_{FH} = 5.5, 8.6 Hz), -114.1 (tt, *J*_{FH} = 5.5, 8.6 Hz), -115.6 (tt, *J*_{FH} = 5.5, 8.6 Hz). ¹H NOE of the major isolated product data presented in Figure S-28. HSQC data of the major isolated product is presented in Figure S-29. Identifiable minor isomer ¹H NMR (300 MHz, CDCl₃), δ -0.07 (s, 9H), 3.2 (dd, *J* = 16.8, 7.2 Hz, 1H), 5.09 (dd, *J* = 6.7, 4.2 Hz, 1H), 5.37 (s, 1H). ¹⁹F NMR (282 MHz, CDCl₃) δ -104.3 (tt, *J*_{FH} = 5.5, 8.6 Hz), -112.8 (tt, *J*_{FH} = 5.5, 8.6 Hz), -113.3 (tt, *J*_{FH} = 5.5, 8.6 Hz).

Use of 1% Et₃N during column chromatography of a similar reaction mixture did not prevent hydrolysis and resulted in elimination of water to form the α,β unsaturated ketone **18**, recognized by the following ¹H NMR signals: ¹H NMR (300 MHz, CDCl₃), δ 7.03 (t, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 8.8 Hz, 2H), 7.37 (2, *J* = 16.9 Hz, 1H), 7.58 (dd, *J* = 5.5, 8.8 Hz, 2H), 7.72 (2, *J* = 16.9 Hz, 1H), 7.98 (dd, *J* = 5.5, 8.8 Hz, 2H).

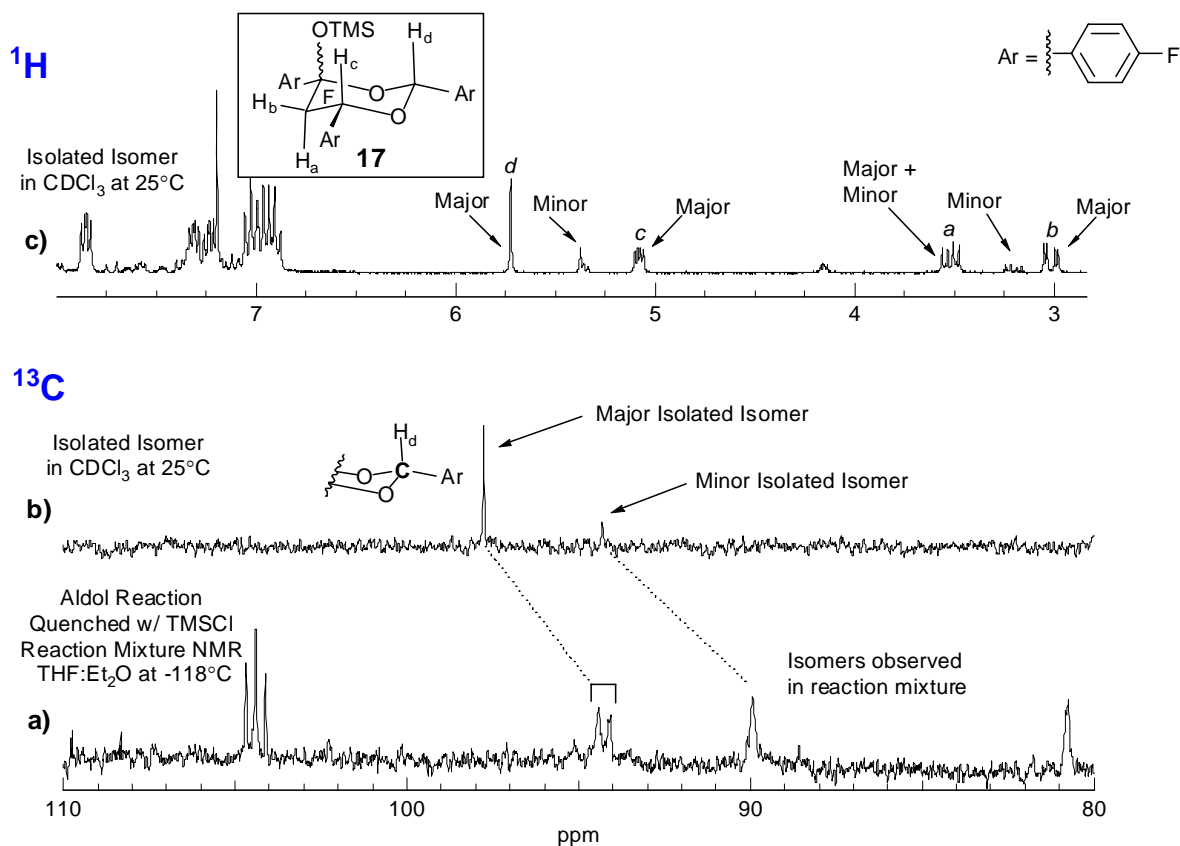


Figure S-27. ¹H (c) and ¹³C (b) spectra of the purified hemiacetal aldolate **17** in CDCl₃ at 25 °C and ¹³C spectrum (a) of crude Me₃SiCl quenched aldol reaction mixture in 3:2 THF/Et₂O at -118 °C. Comparison of the spectra for isolated **17** to the reaction mixture show a loss of carbon signals of the hemiacetal carbon at δ 90-96 (¹³C assignment confirmed by HSQC (Figure S-29)) presumably due to hydrolysis (to **15**) during purification. Shifts of this carbon signal are due to solvent and temperature differences of the samples.

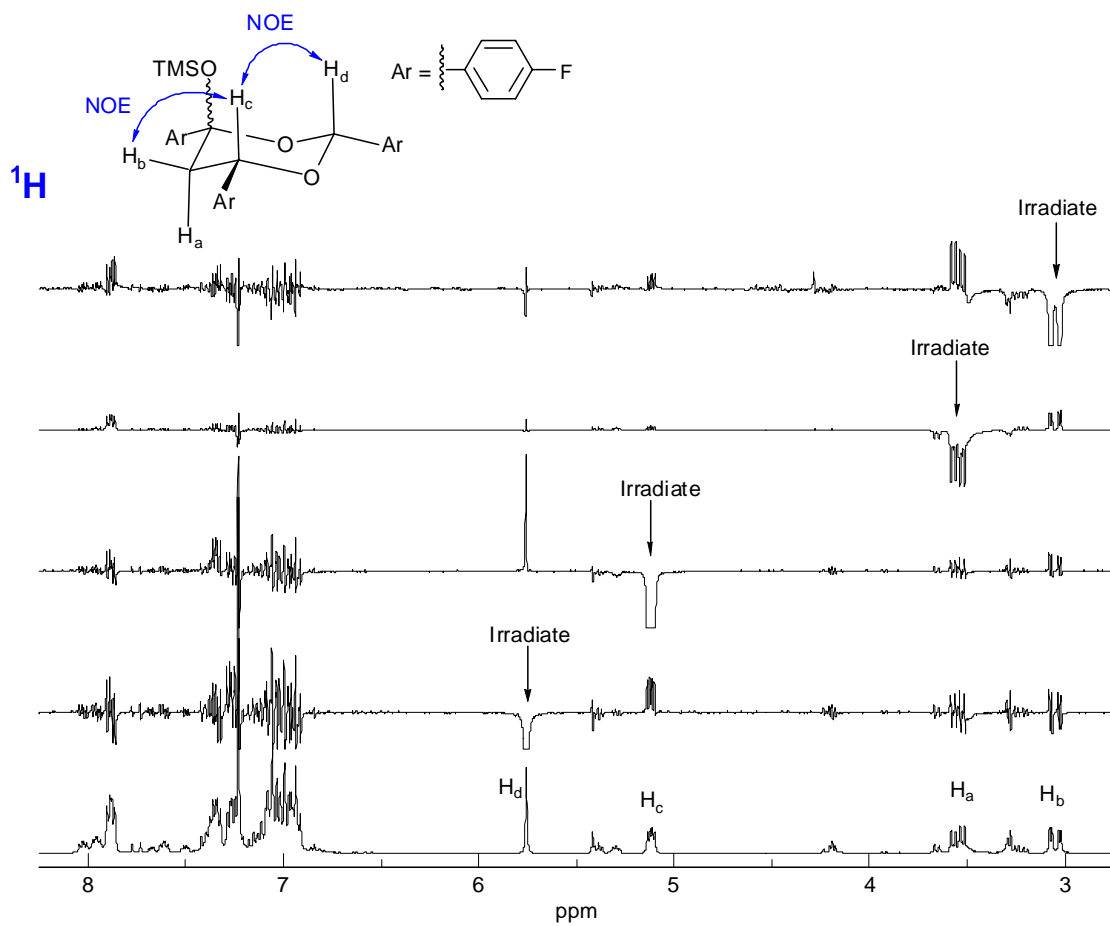


Figure S-28. ^1H NOE data for purified hemiacetal aldolate (**17**, 80:20 mixture of isomers).

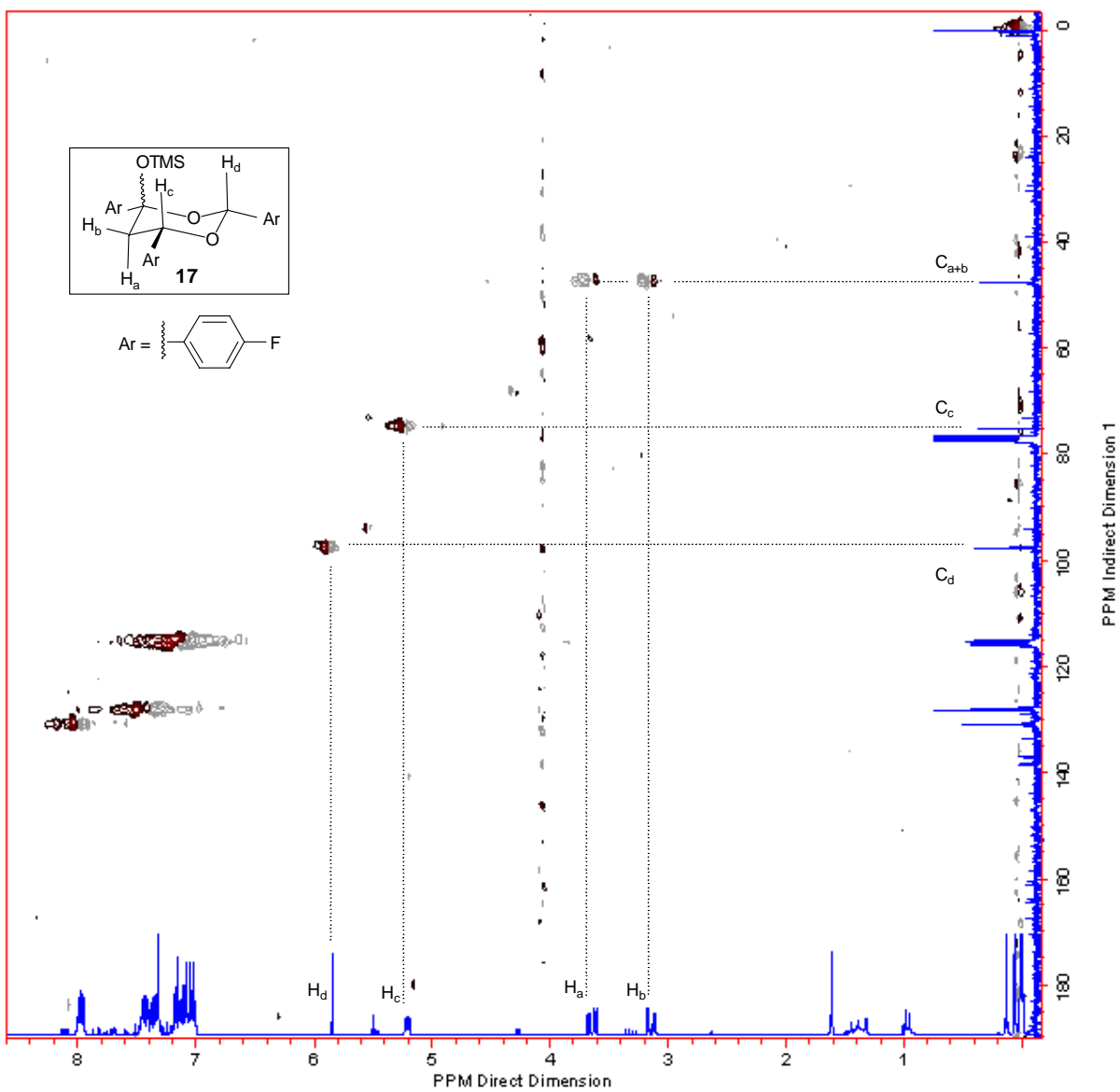
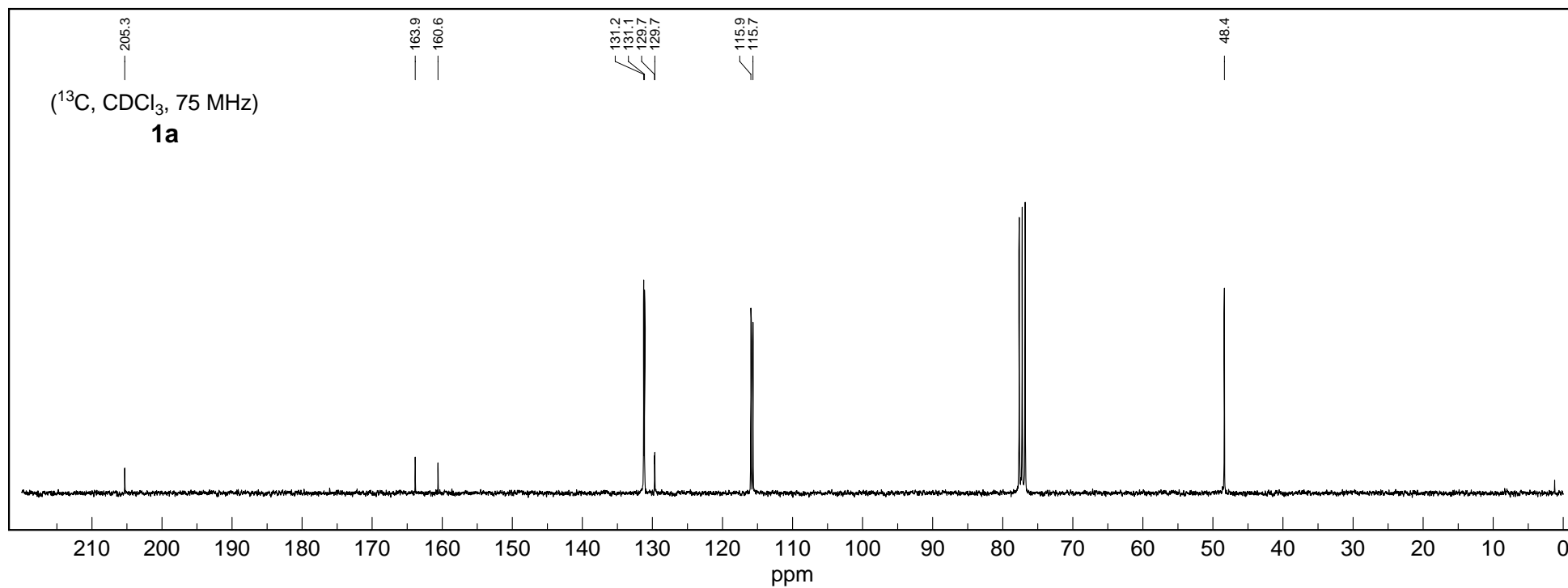
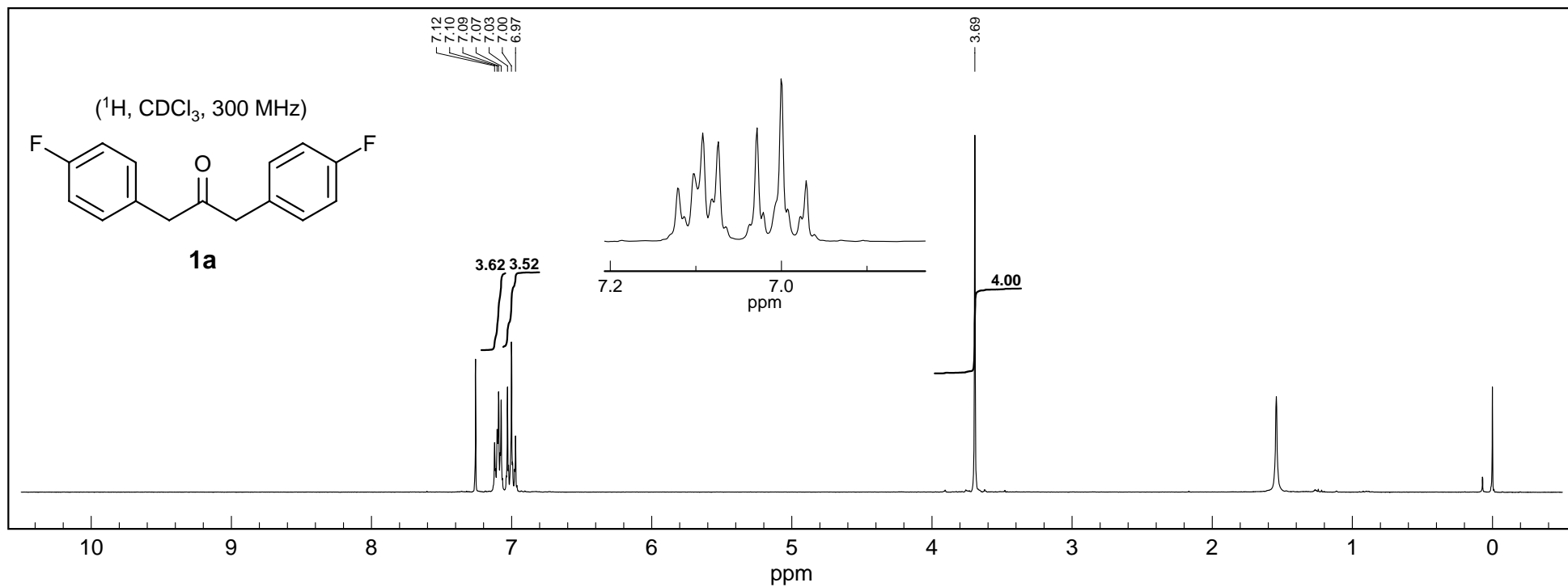
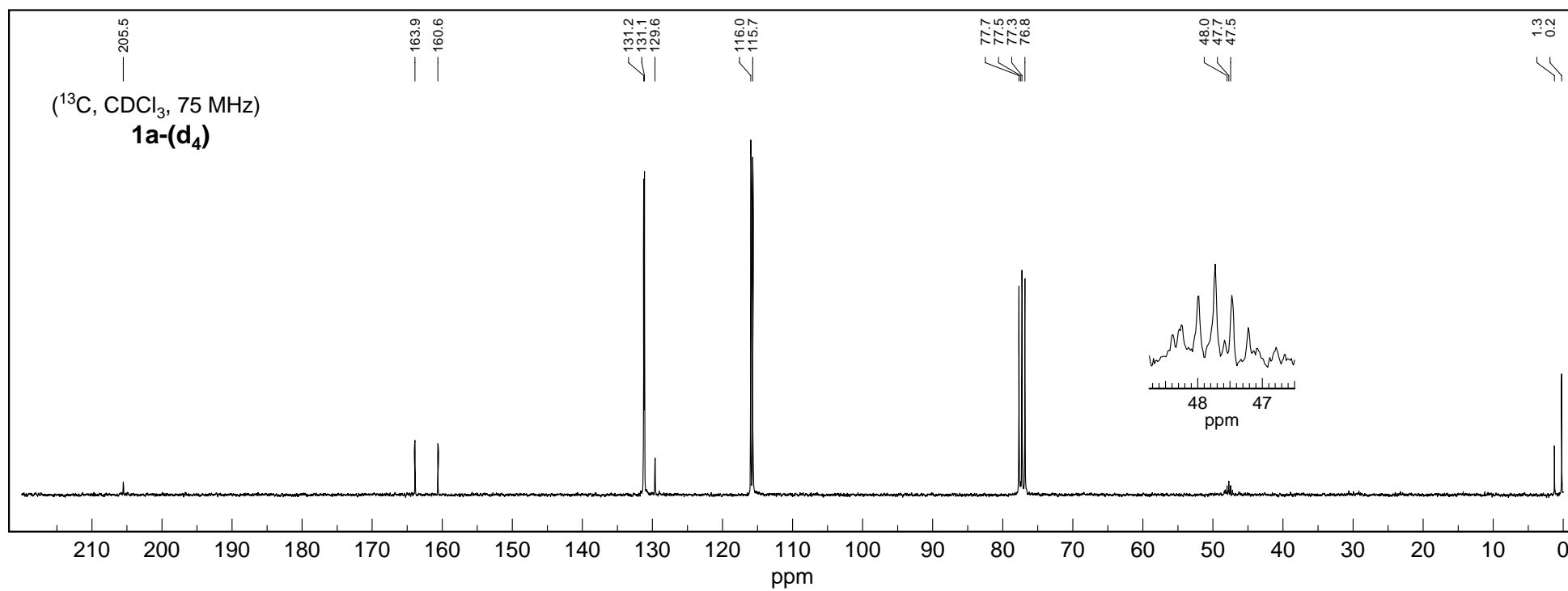
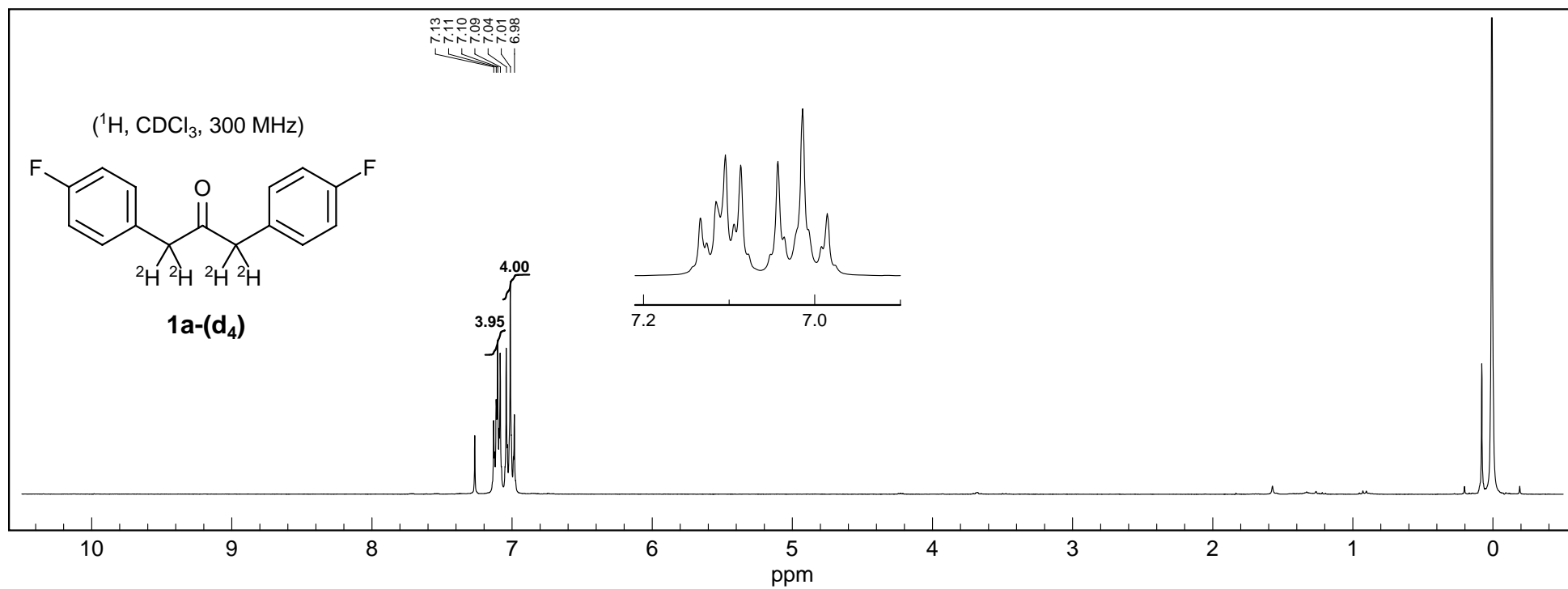
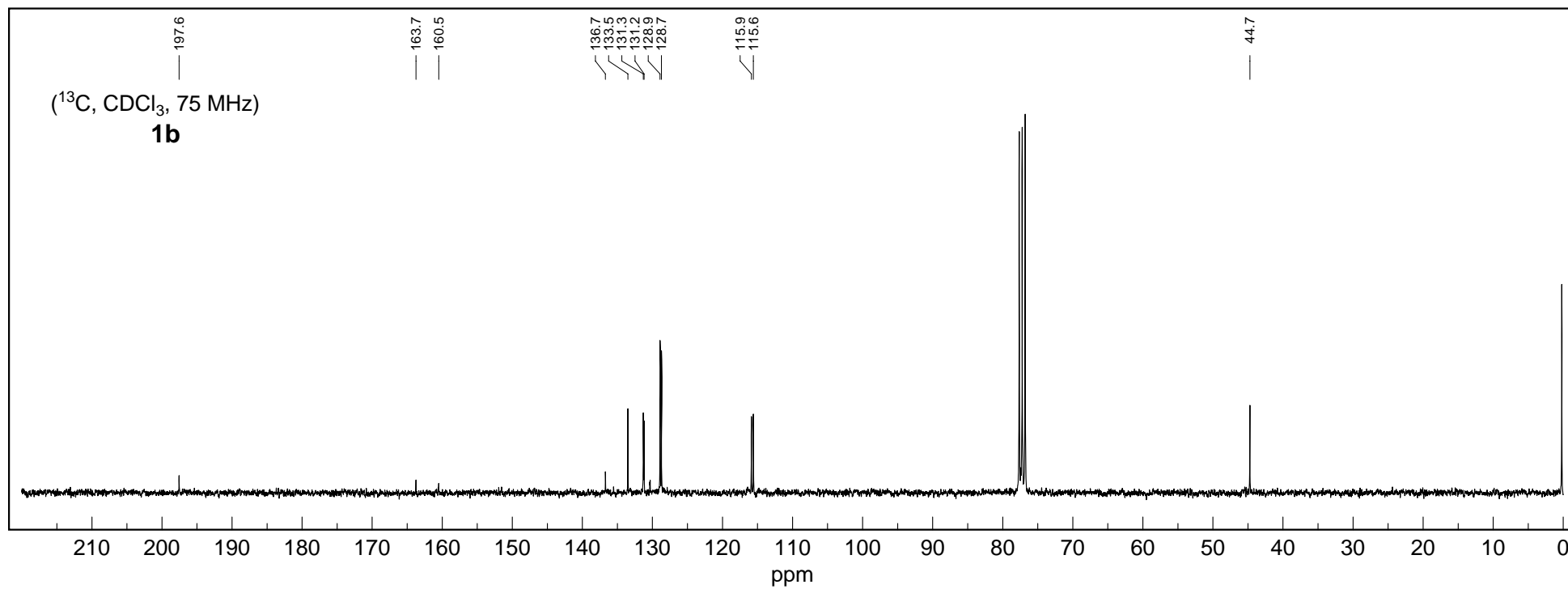
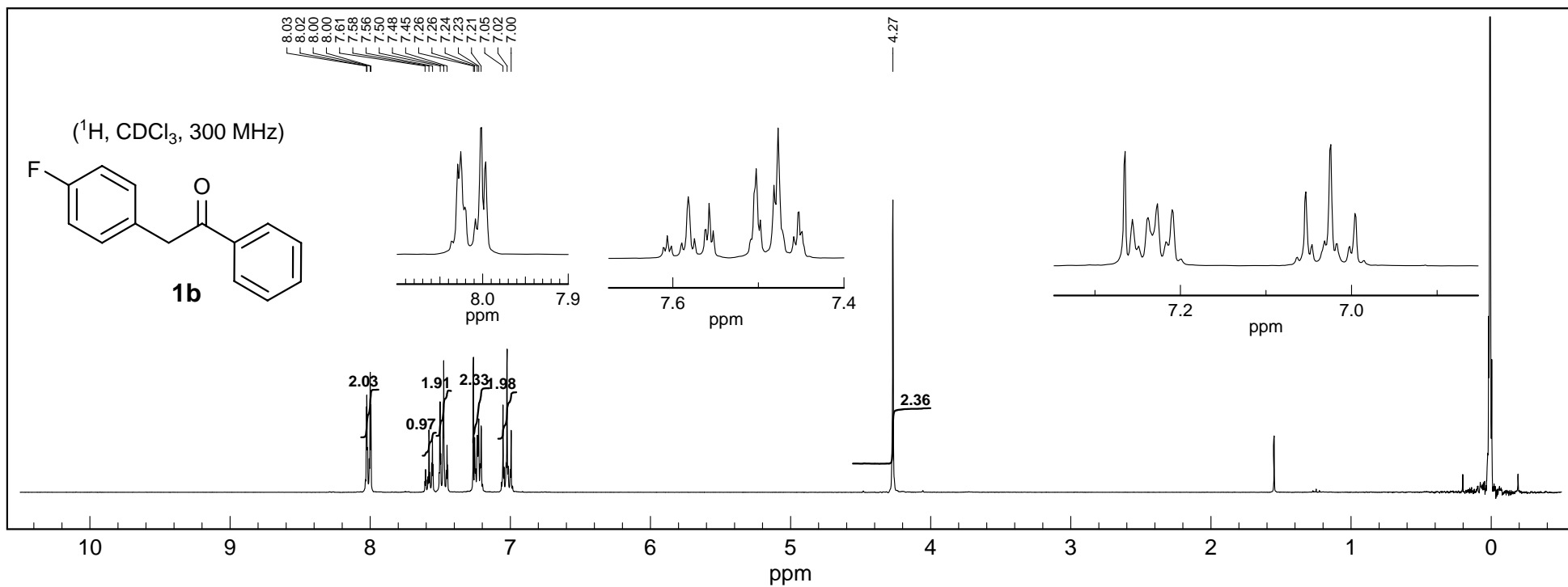
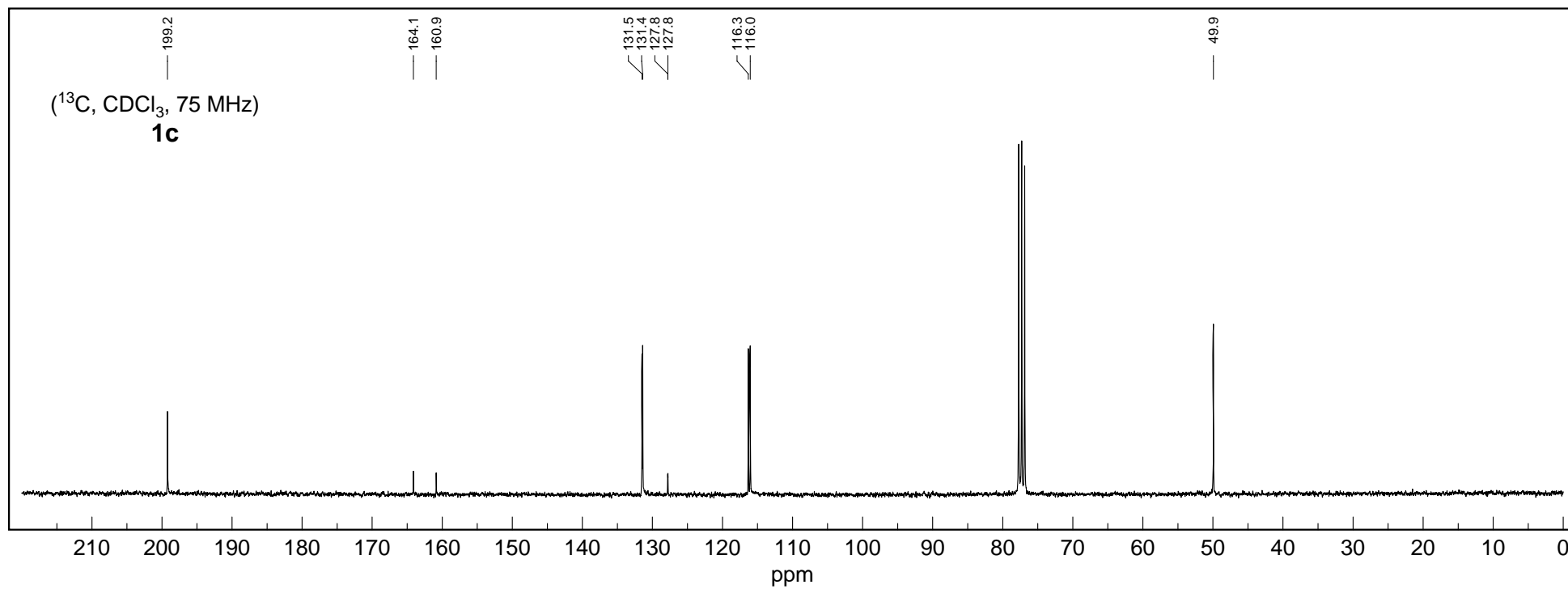
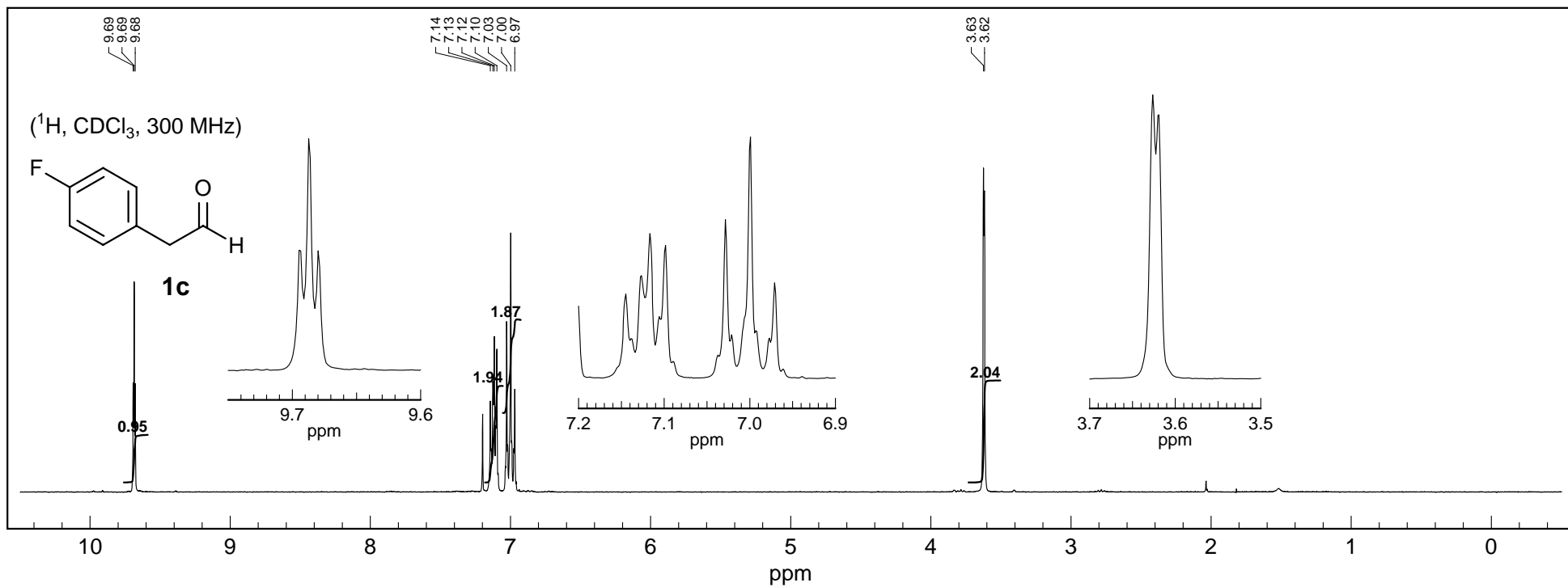


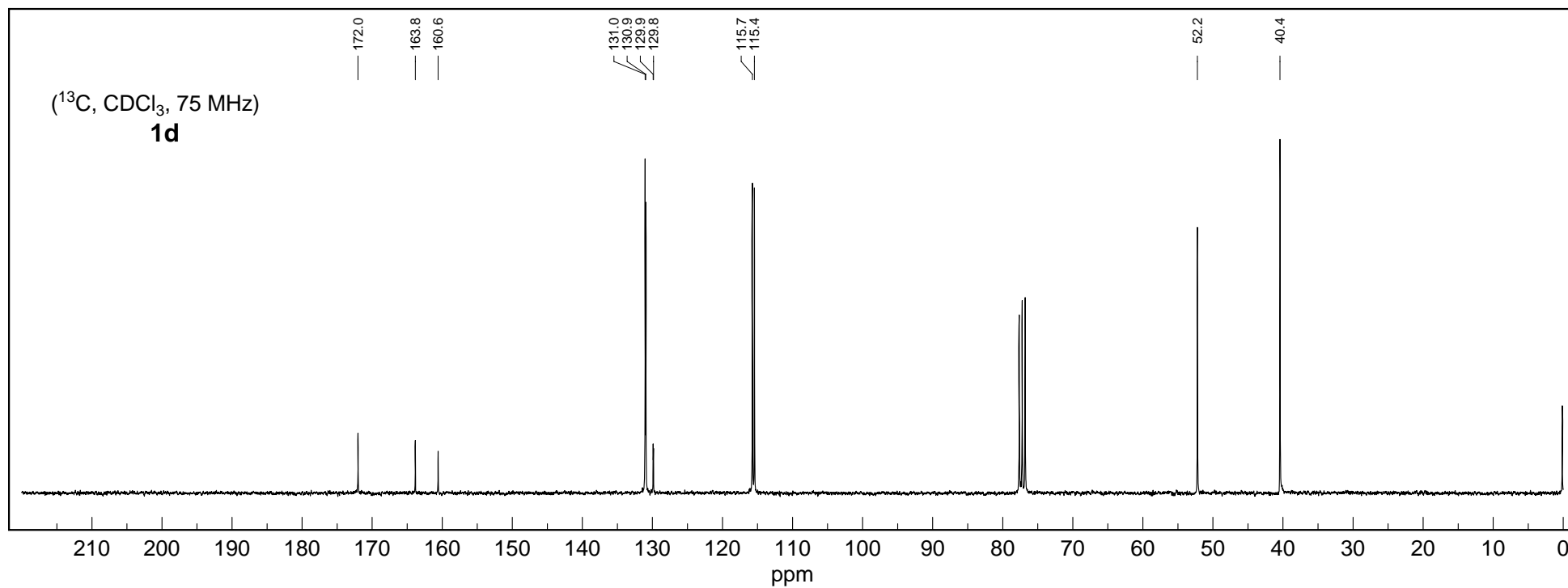
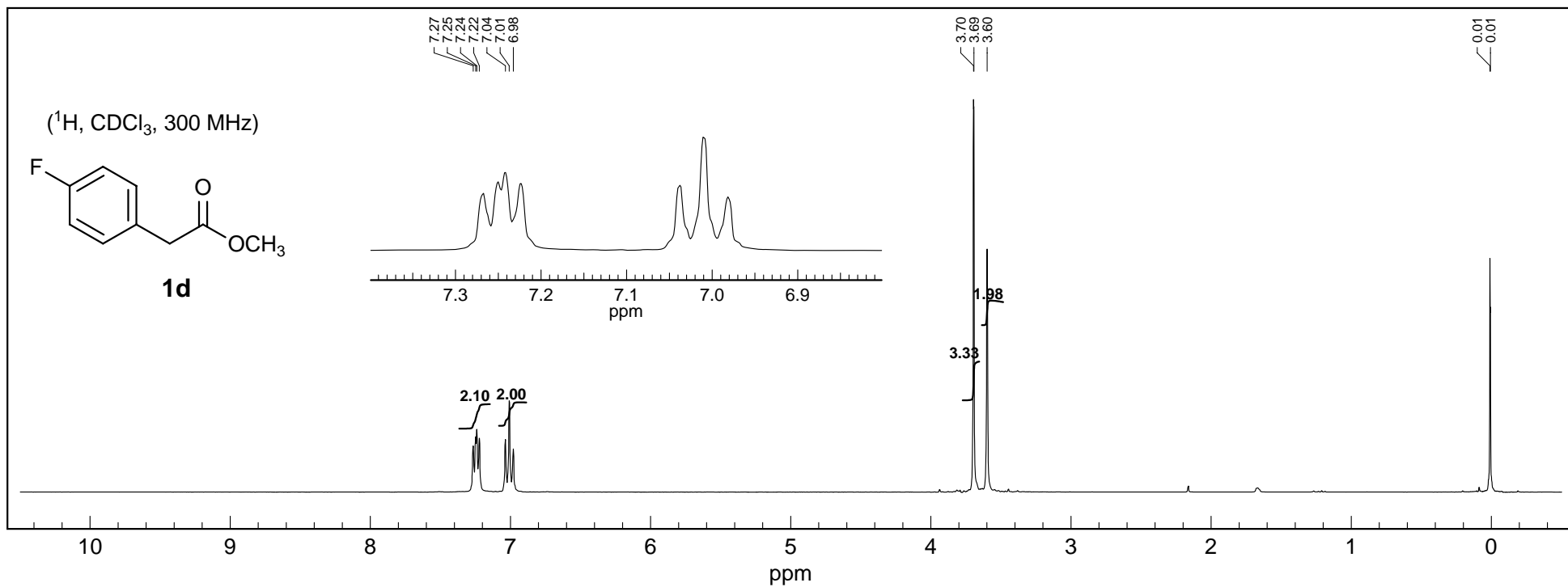
Figure S-29. HSQC of purified hemiacetal aldolate (**17**). Correlations between the carbon and hydrogen signals for the hemiacetal ring are indicated by dotted lines.

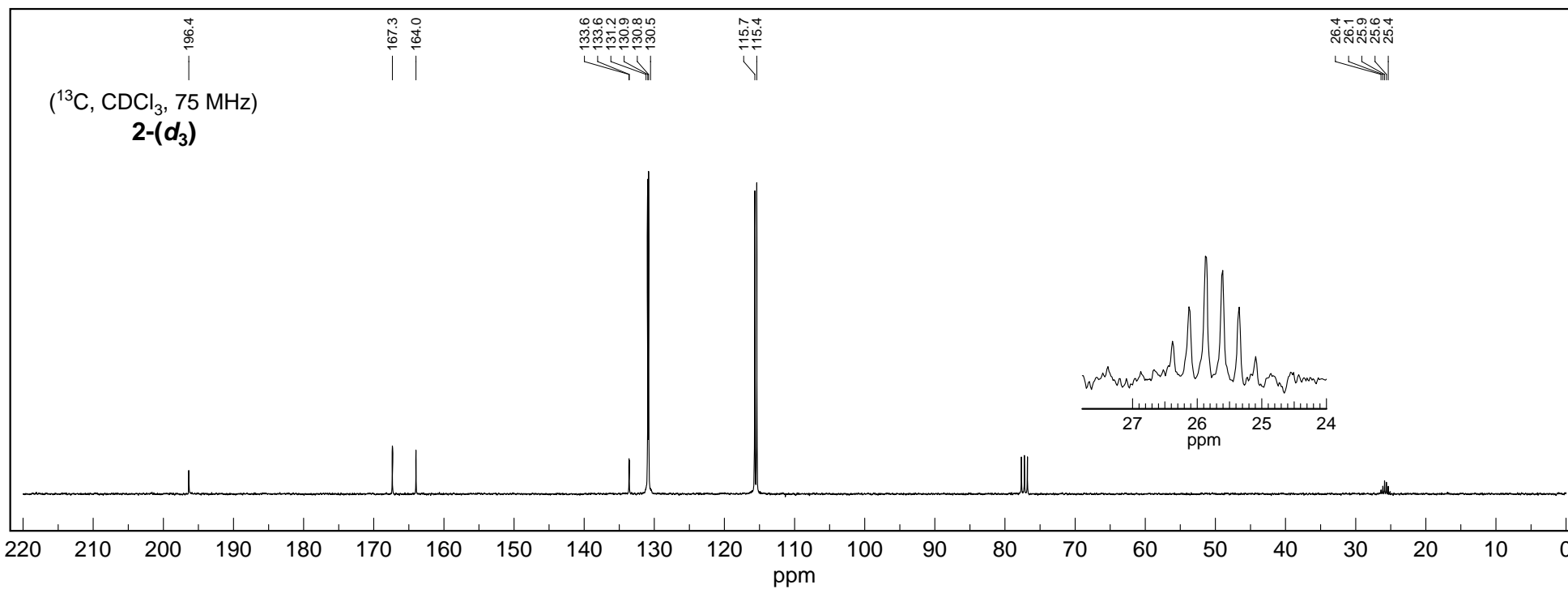
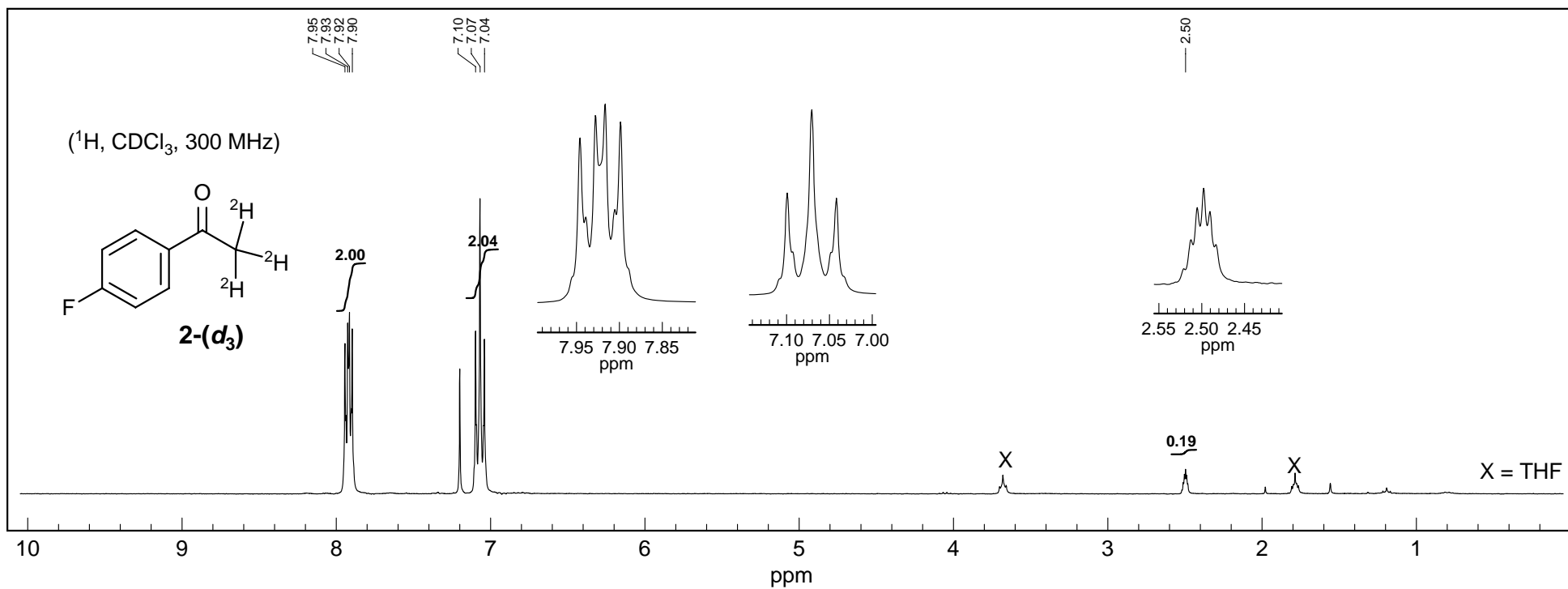


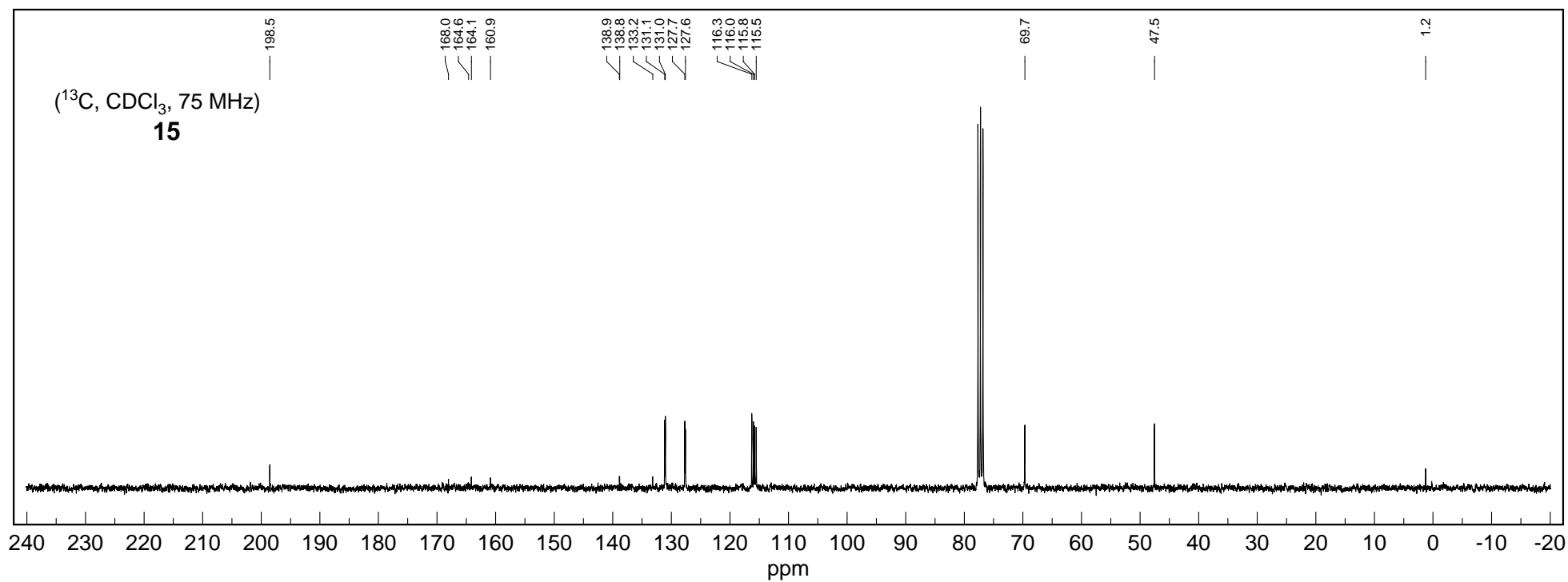
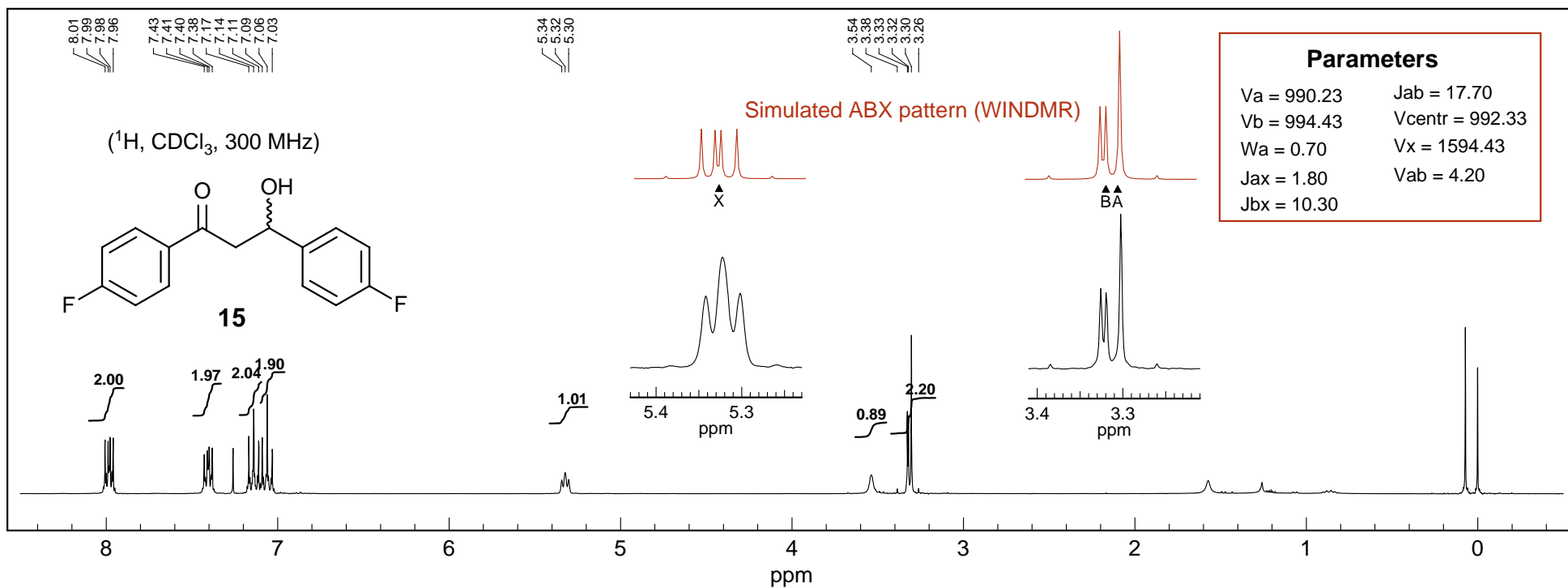


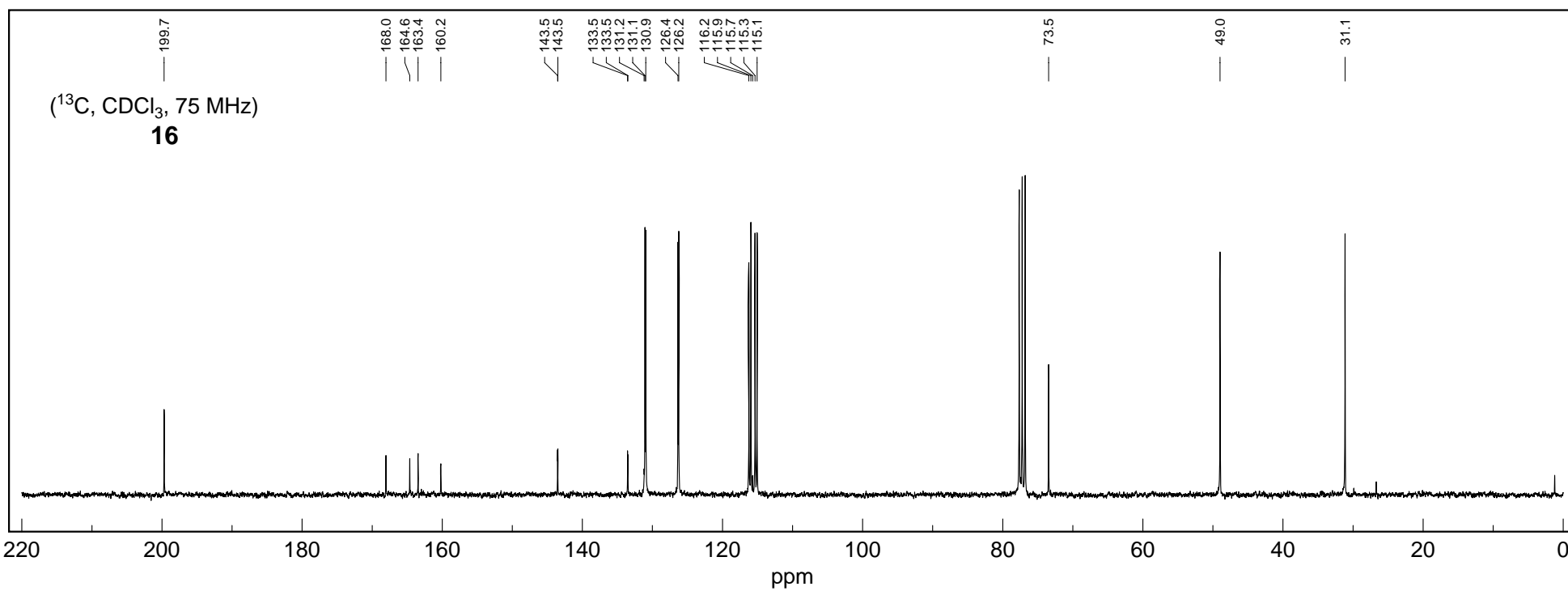
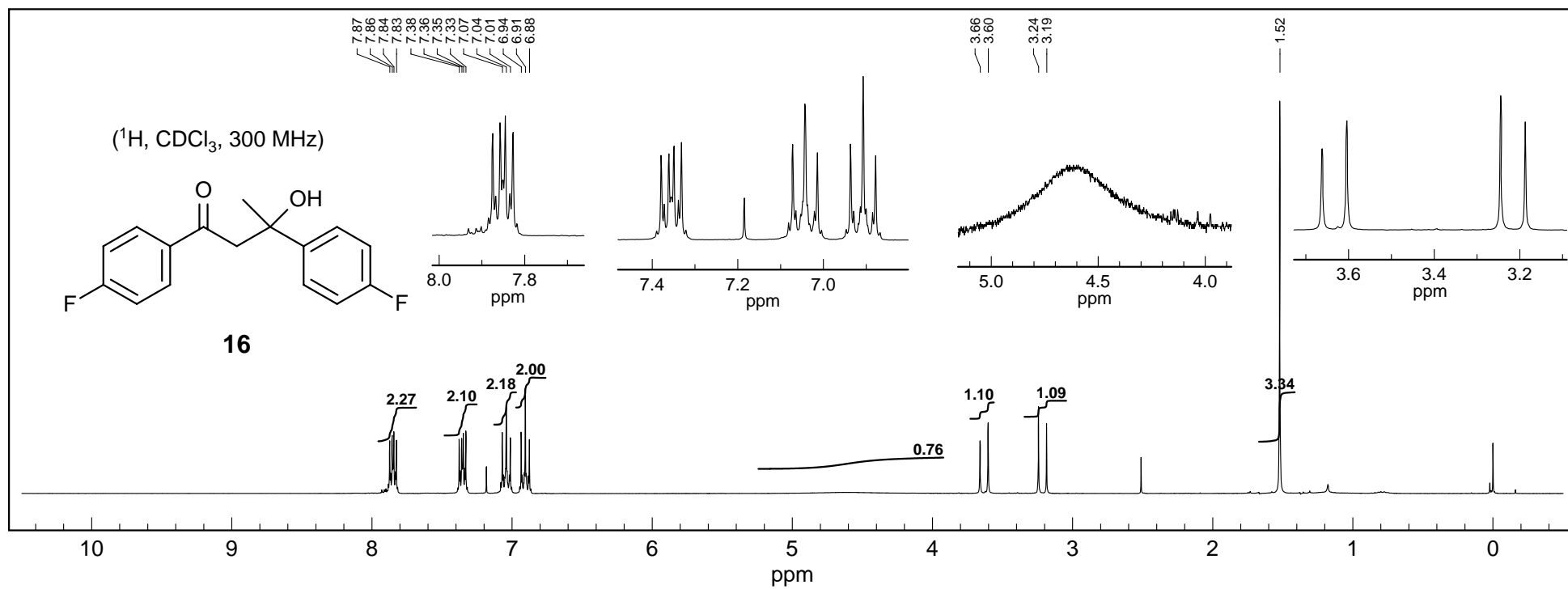


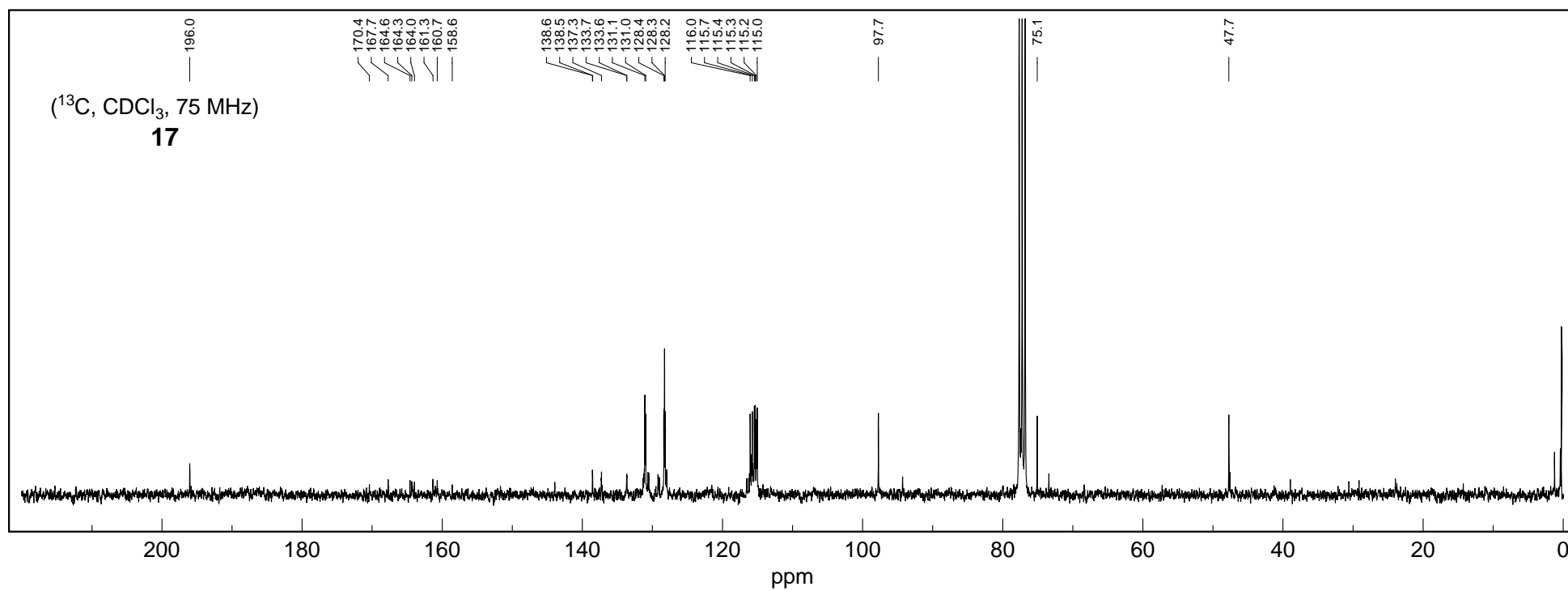
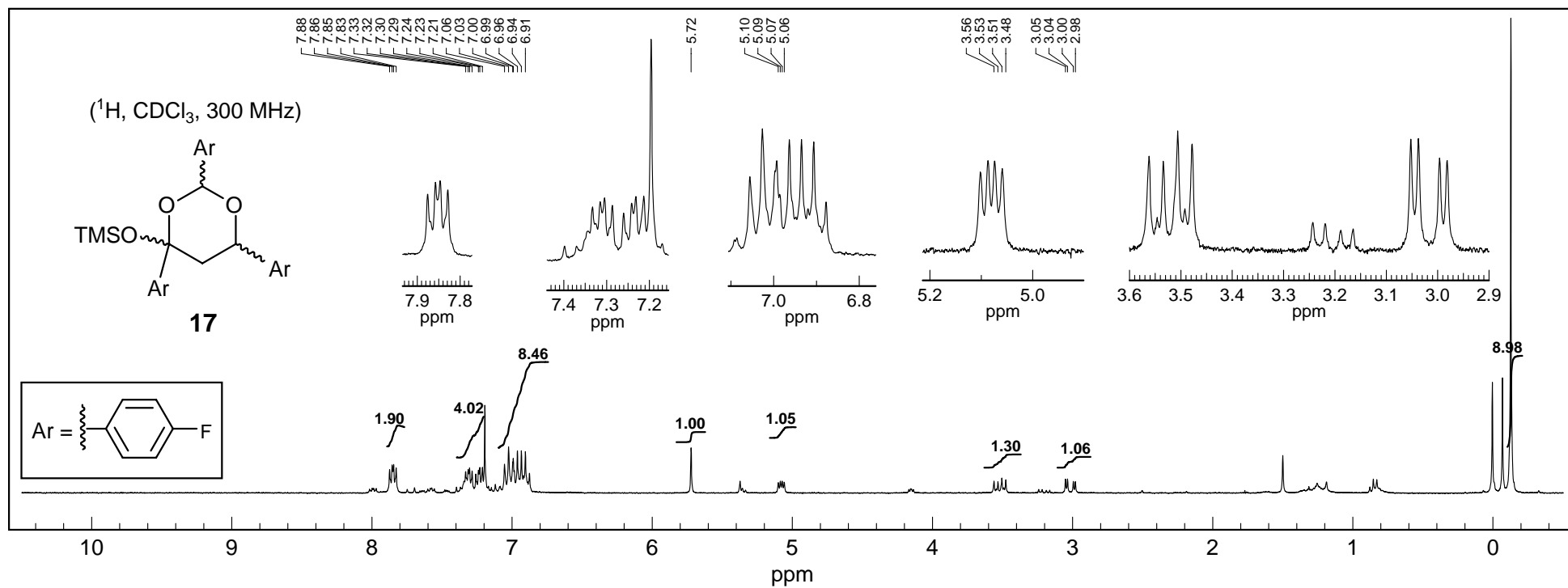












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