

Supporting Information for:

Anhydrous Tetrabutylammonium Fluoride

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Experimental Details

Materials

All reagents were handled under N₂. Hexafluorobenzene (C₆F₆) (99%, SynQuest) was passed through a column of activated (130 °C for 5 h) silica gel and distilled from CaH₂. Acetonitrile (HPLC grade, Aldrich) was distilled from P₂O₅ and redistilled under reduced pressure from CaH₂. THF (anhydrous, Aldrich) was distilled from LiAlH₄. Purified solvents were stored under N₂ in Schlenk-style flasks under N₂. Tetra-*n*-butylammonium cyanide (TBACN) (97%) was obtained from Fluka Chemical Co. TBACN was dried under vacuum at 40 °C overnight prior to use. For initial work, TBACN was recrystallized from THF/Hexane by layering, subsequent studies showed that this purification step was unnecessary. Tetramethylammonium hexafluorophosphate (TMAPF₆) was obtained from Fluka and dried under vacuum. All other reagents were of analytical grade, from Aldrich. All chemical handling was performed under N₂ in a glove box.

Instruments

¹H, ¹³C and ¹⁹F NMR spectra were determined in the Instrumentation Center at the University of Nebraska-Lincoln. 400 MHz (QNP probe for ¹H, ¹³C and ¹⁹F NMR spectra), 500 MHz (QNP probe for ¹H, ¹³C and ¹⁹F NMR spectra) and 600 MHz (HF probe for ¹H and ¹⁹F NMR spectra) NMR spectrometers were used in this study. ¹⁹F NMR chemical shifts were referenced to an internal standard, hexafluorobenzene.

General Note Regarding Choice of Solvents

The three solvents discussed in this communication (THF, acetonitrile, and DMSO) may be used interchangeably for the generation of anhydrous TBAF *in situ*. The principal differences are that 1) in THF the generation of TBAF is considerably slower, which can be an advantage in large scale preparations, and 2) the solubility of TBAF is much lower in THF than in the higher dielectric solvents. This latter fact aids the isolation of the purified salt.

General Note Regarding the Basicity of TBAF

The data that follow show (Figures S-5 to S-10) show that water is not deprotonated to a significant extent by large concentrations TBAF. Furthermore, the studies show that deuterium exchange of DMSO

by fluoride ion does not occur under anhydrous conditions, and that deuterium exchange is slow with acetonitrile. Qualitatively, these data indicate that the ion pair basicity of fluoride is not exceptional under these conditions. The impact of added water is easily seen, as $(\text{CD}_3)_2\text{SO}$ or CD_3CN begin to undergo H/D exchange when TBAF solutions are spiked with H_2O . The origin of the increased kinetic basicity of fluoride under these conditions is impossible to discern from the existing data. In principle, an undetected small amount of hydroxide could be acting as the catalytic base. Alternatively, the added water could vary the ion-pairing or aggregation equilibria for TBAF in these solvents. In either event, added water is implicated as a factor increasing the basicity of such solutions.

Syntheses of TBAF

Warning: The reaction of tetrabutylammonium cyanide and hexafluorobenzene is exothermic; care must be exercised to control the temperature for large-scale reactions.

Warning: In fluorodenitration reactions the temperature should be kept below 20 °C to prevent decomposition of TBANO_2 and gas release.

Anhydrous tetrabutylammonium fluoride (TBAF):

Small Scale

TBACN (0.67 g) was dissolved in 2.5 ml THF and the resulting solution was cooled to -65 °C. A chilled solution (-65 °C) of 0.3 ml hexafluorobenzene (C_6F_6) in 0.5 ml THF was added, and the mixture was allowed to warm gradually (over 4 hours) to -15 °C. During this time the solution changed from colorless to yellow-green, and a white solid precipitated. The mixture was again cooled to -65 °C, the solid was filtered and washed two times with cold THF. (All isolation procedures were kept below -35 °C.) The white or light yellow TBAF solid was collected and put into a -36 °C freezer for short term storage. Total TBAF yield was over 95% (based upon TBACN, confirmed by quenching experiments with benzyl chloride) if the mixture was used directly. Isolated yields of the solid material varied from 40% to 70% depending on the rapidity of the wash and filtration steps. ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 3.23 (8H, m), 1.56 (8H, m), 1.28 (8H, sext, $J = 7.31$ Hz), 0.86 (12H, t, $J = 7.31$ Hz); ^{19}F NMR ($(\text{CD}_3)_2\text{SO}$) δ -72.6 ppm (s); ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$) δ : 57.5, 23.1, 19.2, 13.5 ppm.

Large Scale

TBACN (5.7 g, 21 mmol) was dissolved in 12 ml anhydrous THF. The solution was cooled to -55 °C. Hexafluorobenzene (0.65 ml, 5.6 mmol) was added slowly with stirring at -55 °C. Upon completion of the addition, the solution was allowed to warm gradually to -15 °C (4 h). The mixture was cooled to -65 °C, the solid was filtered and washed several times with a small amount of cold THF. All isolation procedures were kept below -35 °C. The salt was dried under reduced pressure to yield 4.2 g (77%) TBAF isolated as a colorless solid. The material was stored in a -35 °C freezer.

Generation of TBAF in CH_3CN : TBACN (0.134 g, 0.5 mmol) was dissolved in anhydrous acetonitrile (0.5 ml). At 25 °C, 9.6 μl (0.083 mmol) C_6F_6 was added, and the initially colorless solution changed to dark-red immediately. The reaction was monitored by ^{19}F NMR spectroscopy. Fluoride generation was complete within 1 h. A representative ^{19}F NMR spectrum is shown in figure S-1.

Large Scale

TBACN (5.4 g, 20 mmol) was dissolved in 5 ml anhydrous acetonitrile. The solution was cooled to -35 °C in the freezer. Hexafluorobenzene (0.5 ml, 4.3 mmol) was added into TBACN solution under

stirring at $-35\text{ }^{\circ}\text{C}$, and the solution was held at this temperature for 1~1.5 h, then at room temperature for 0.5 h. NMR spectra were comparable to the small-scale reaction. This TBAF solution was sufficiently pure for direct use in fluorinations.

Generation of TBAF in DMSO: A very similar procedure was used to generate TBAF in DMSO. TBACN (0.134 g, 0.5 mmol) was dissolved in anhydrous DMSO (0.5 ml). At $25\text{ }^{\circ}\text{C}$, $9.6\text{ }\mu\text{l}$ (0.083 mmol) C_6F_6 was added, and the mixture was allowed to stand for one h. The solubility of TBAF in both CH_3CN and DMSO was excellent (up to 2 M). The solution was directly used in the fluorination reaction.

TMACN

TMACN was prepared by metathetical ion-exchange of TBACN with TMAPF_6 in acetonitrile/THF. 110 mg (0.5 mmol) TMAPF_6 was dissolved in a minimum amount of acetonitrile, and a saturated acetonitrile solution of TBACN (134 mg, 0.5 mmol) was added. The precipitated TMACN was filtered, washed with a small amount of acetonitrile, and the residual solvents were evaporated. ^1H NMR (CD_3CN) δ 3.11 ppm (s), ^{13}C NMR (CD_3CN) δ 54.27, 167.20.

TMAF

TMAF was synthesized from TMACN and C_6F_6 in $(\text{CD}_3)_2\text{SO}$ by a method similar to that described for TBAF. 4.6 mg TMACN dissolve in 0.6 ml of $(\text{CD}_3)_2\text{SO}$ at room temperature. $1.0\text{ }\mu\text{l}$ hexafluorobenzene (C_6F_6) was and the mixture was allowed to stand at room temperature for 12 h.

General Procedure for Fluorination Reactions

The general procedure given below was used for all fluorination reactions employing *in situ* generated TBAF. Yields were calculated by integration of the relevant peaks in the ^1H and ^{19}F NMR spectra.

In an NMR tube equipped with a PTFE resealable closure, TBACN (0.134 g, 0.5 mmol) was dissolved in anhydrous CD_3CN (or $(\text{CD}_3)_2\text{SO}$) (0.5 ml). At $25\text{ }^{\circ}\text{C}$, $9.6\text{ }\mu\text{l}$ (0.083 mmol) C_6F_6 was added, and the mixture was held at room temperature for 1 h. The mixture was cooled to $-40\text{ }^{\circ}\text{C}$ and the substrate (0.25 – 0.5 mmol) was added. The solution was mixed vigorously and the tube was transferred to a precooled ($-35\text{ }^{\circ}\text{C}$) NMR probe and spectra were gathered. The time elapsed from the sample mixing until completion of the first NMR spectrum was approximately 3 min. The reaction was monitored by ^{19}F NMR spectra every 2 minutes until no further change was observed.

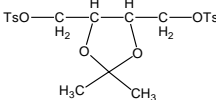
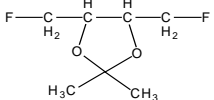
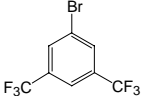
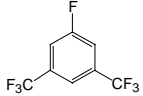
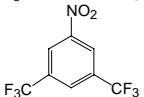
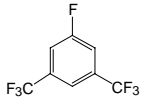




Example of a Larger Scale Fluorination

A solution of 20 mmol TBAF in acetonitrile was cooled to $0\text{ }^{\circ}\text{C}$ in an ice-bath. 3,5-Bis(trifluoromethyl)nitrobenzene (2.5 ml, 15 mmol) was added into the stirred solution over 15 min. After completion of the addition, the ice-bath was removed and the solution was stirred at room temperature for 8 h (monitored by NMR, ^1H NMR indicated 97% yield). The acetonitrile was removed at reduced pressure. The remainder was triturated with diethyl ether and the ether solution was extracted with water to remove residual salts. The collected organic layers were combined and dried over anhydrous Na_2SO_4 . The solution was fractionally distilled to give a colorless oil, 3,5-bis(trifluoromethyl)fluorobenzene, 75%. ^1H NMR (CD_3CN): 7.88 ppm (1H, s), 7.77 ppm (2H, d, $J_{\text{F-H}}=8.5\text{ Hz}$); ^{19}F NMR (CD_3CN): -63.5 ppm (6F, s), -109.1 ppm (1F, t, $J_{\text{H-F}}=8.5\text{ Hz}$); ^{13}C NMR (CD_3CN): 162.5 ppm (d, $J_{\text{F-C}}=250\text{ Hz}$), 133.1 ppm (q(d), $J_{\text{F-C}}(\text{q})=34\text{ Hz}$, $J_{\text{F-C}}(\text{d})=8.0\text{ Hz}$), 122.8 ppm (q(d), $J_{\text{F-C}}(\text{q})=272\text{ Hz}$, $J_{\text{F-C}}(\text{d})=3.0\text{ Hz}$), 118.5 ppm (o, $J_{\text{F-C}}=4.0\text{ Hz}$), 117.0 ppm (d(q), $J_{\text{F-C}}(\text{d})=25\text{ Hz}$, $J_{\text{F-C}}(\text{q})=3.5\text{ Hz}$).

Fluorination Results:

Table S-1 shows results of fluorination of various substrates under different conditions. For comparison, the literature results by other fluorinating reagents are listed in the table.

Table S-1. Additional fluorination results by using TBAF

Run	Substrate	Reagent	Solvent	Temp and Time	Product	Yield (%)	Comments	Ref.
1	PhCH ₂ Br	1.3~1.5 eq. TBAF	acetonitrile	-35 °C, <5 min	PhCH ₂ F	100	No PhCH ₂ OH	This work
2	PhCH ₂ Br		DMSO	RT, <2 min	PhCH ₂ F	100		This work
3	PhCH ₂ Br		THF	RT, <2 min	PhCH ₂ F	100		This work
4	PhCH ₂ Br	2 eq. TBAF "anhydrous"	THF	RT, 8 hours	PhCH ₂ F	>90	PhCH ₂ OH (5%)	¹
5	PhCH ₂ Cl	1.5 eq. TBAF	THF	RT, <2 min	PhCH ₂ F	100		This work
6	PhCH ₂ Cl	2 eq. TBAF "anhydrous"	THF	40 °C, 12 hours	PhCH ₂ F			¹
7	PhCH ₂ Cl	CoCp ₂ F	THF	RT, 90 min	PhCH ₂ F	95		²
8	CH ₃ I	1.5 eq. TBAF	acetonitrile	-40 °C, <5 min	CH ₃ F	100		This work
9	CH ₃ I	CoCp ₂ F	THF	RT, 6 hours	CH ₃ F	100		²
10	CH ₃ (CH ₂) ₇ Br	TBAF	THF	RT, <5 min	CH ₃ (CH ₂) ₇ F	40~50	No octanol	This work
11	CH ₃ (CH ₂) ₇ Br	6 eq. TBAT	acetonitrile	Reflux, 24 h	CH ₃ (CH ₂) ₇ F	85		³
12	CH ₃ (CH ₂) ₇ Br	2 eq. TBAF "anhydrous"	THF	RT, 1 hour	CH ₃ (CH ₂) ₇ F	48	40% octanol	¹
13	CH ₃ (CH ₂) ₁₇ (p-Cl-benzenesulfonate)	TBAF	THF	RT, <5 min	CH ₃ (CH ₂) ₁₇ F	100		This work
14	CH ₃ (CH ₂) ₇ OTs	2 eq. TBAF "anhydrous"	none	RT, 1 hour	CH ₃ (CH ₂) ₇ F	98	2% alkene	¹
15	CH ₃ (CH ₂) ₇ OTs	4 eq. TBAT	acetonitrile	Reflux, 24 h	CH ₃ (CH ₂) ₇ F	99	Trace alkene	³
16		4 eq. TBAF	THF, or acetonitrile	RT, <5 min		>80		This work
17		1.3 eq TBAF	DMSO, or acetonitrile	RT, <8 hours		>90		This work
18		1.3 eq TBAF	acetonitrile	RT, <2 min		~95		This work
19	PhCOCl	1 eq. TBAF	THF	RT or below RT, <2 min	PhCOF	100		This work
20	PhCOCl	2 eq. TBAF "anhydrous"		RT, 1 hour	PhCOF	81*		¹
21	Tosyl-Cl	1 eq. TBAF	THF	RT, <2 min	Tosyl-F	100		This work
22		2.5 eq. TBAF, 3 h; followed by add H ₂ O	DMSO or acetonitrile	RT, ~3 hours				This work
23		TBABF-KHF ₂	none	120 °C, 2 hours		86	Contains 10% PhCHFCH ₂ OH	⁴

- (1) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216-3219.
- (2) Bennett, B. K.; Harrison, R. G.; Richmond, T. G. *J. Am. Chem. Soc.* **1994**, *116*, 11165-11166.
- (3) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166-5167.
- (4) Akiyama, Y.; Fukuhara, T.; Hara, S. *Synlett* **2003**, 1530-1532.

NMR spectra

Generation of TBAF

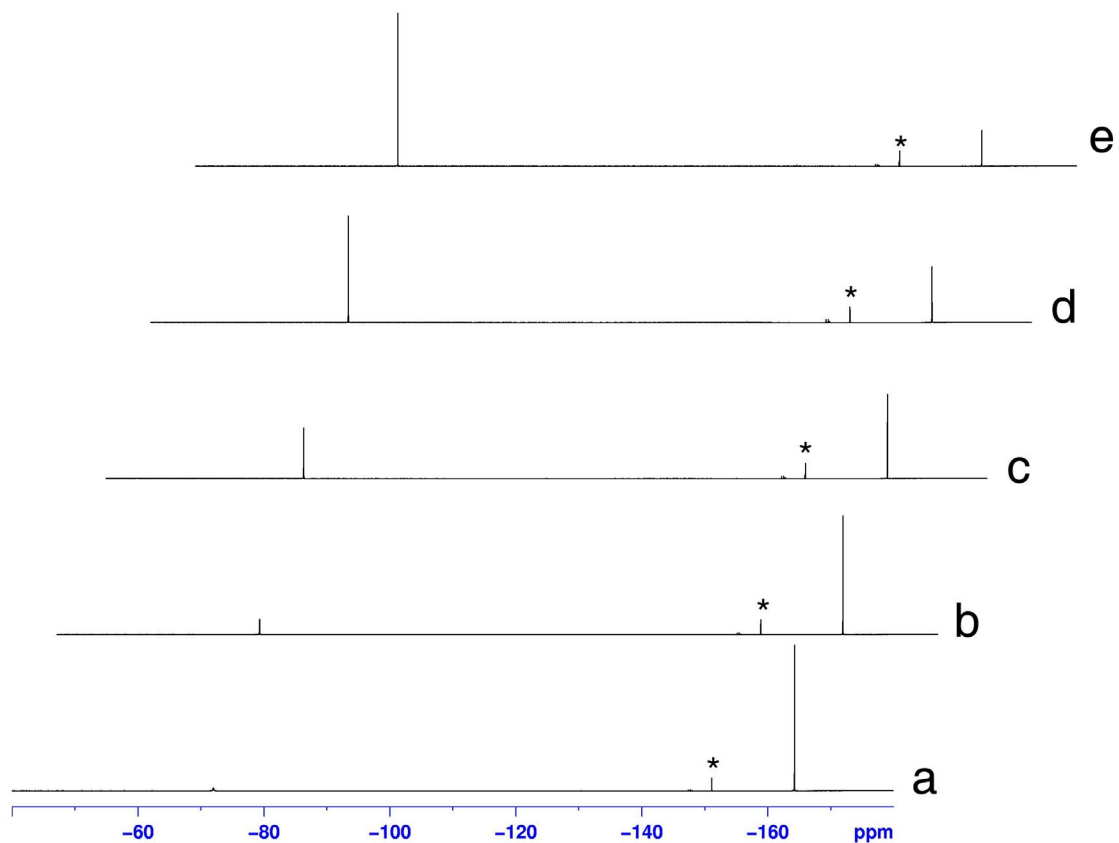


Figure S-1. ^{19}F NMR spectra recorded over the course of 40 minutes following the mixing of 134 mg TBACN and 9.6 μl C_6F_6 in CD_3CN . The peak at $\delta = -72$ ppm is due to fluoride ion; the peak at $\delta = -164$ ppm peak is the C_6F_6 ; the small peak at $\delta = -147$ ppm (d, $J_{\text{HF}}=148$ Hz) is due to HF_2^- (The signal marked with * at -151 ppm is an artifact).

Debromofluorination of an aromatic compound

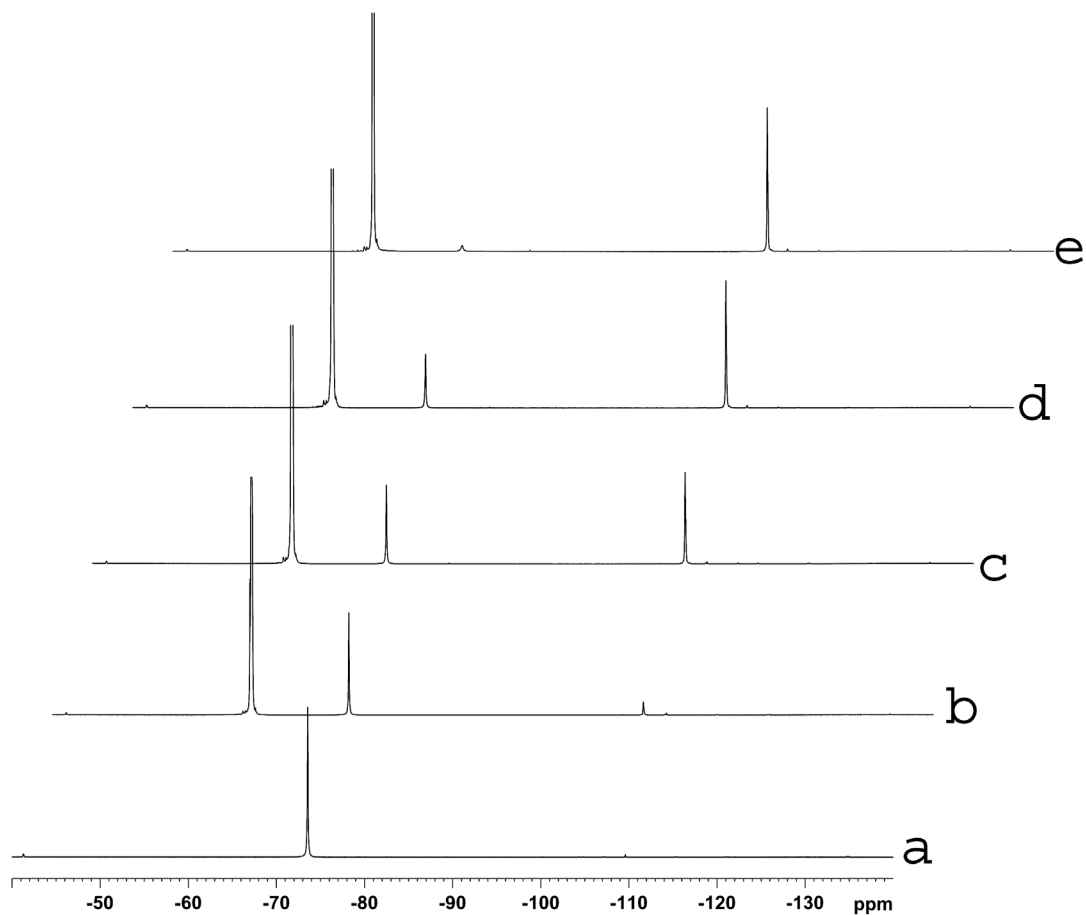


Figure S-2. Conversion of 3,5-bis(trifluoromethyl)bromobenzene to 3,5-bis(trifluoromethyl)fluorobenzene by TBAF in $(\text{CD}_3)_2\text{SO}$. **a**: ^{19}F NMR spectrum before the addition of 3,5-bis(trifluoromethyl)bromobenzene; **b-e**: ^{19}F NMR spectrum after the addition of 3,5-bis(trifluoromethyl)bromobenzene. The total elapsed time was 8 h. Chemical shift assignments: $\delta = -74$ ppm (F), $\delta = -64$ ppm (CF_3), $\delta = -108$ ppm (Ar-F).

Removal of protic solvent by hexacyanobenzene

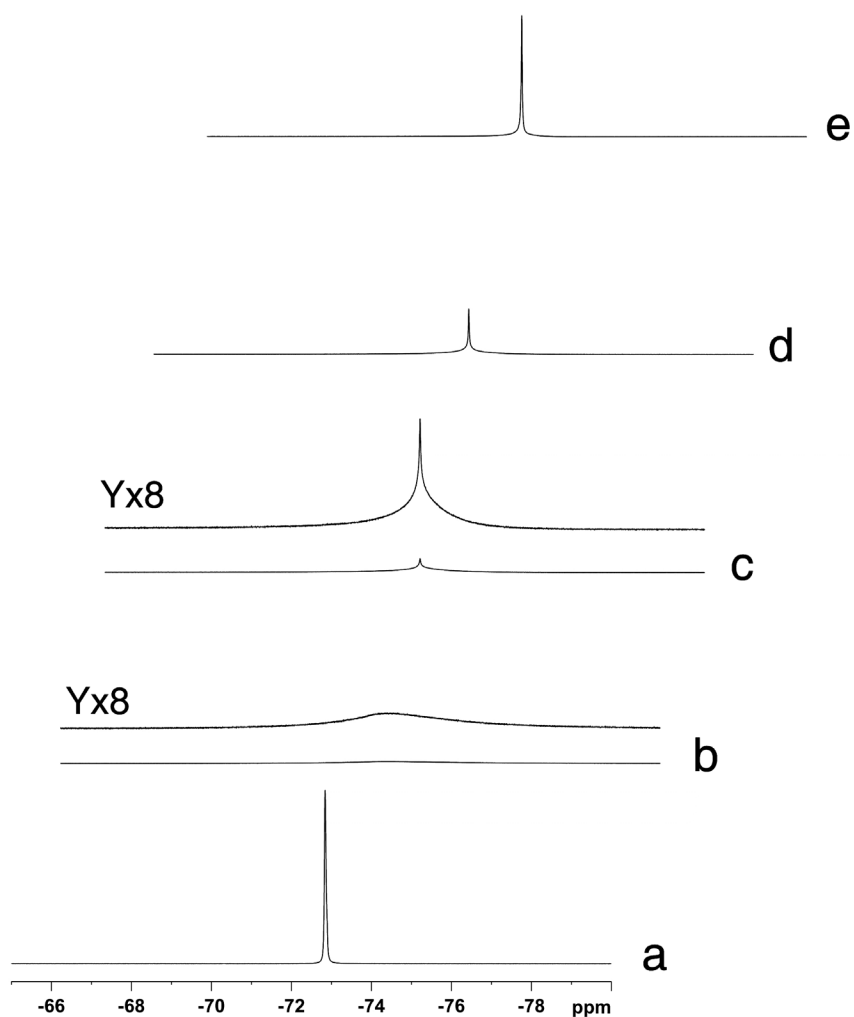


Figure S-3. ^{19}F NMR spectra showing the effect of adding .08 eq. benzyl alcohol to a solution of *in-situ* generated TBAF (CD_3) $_2\text{SO}$. **a**: Spectrum recorded before the addition of benzyl alcohol; **b**: 5 min after addition of benzyl alcohol; **c**: 1 h after addition; **d**: 4 h after addition; **e**: 20 h after addition. For spectra **b** and **c** the bottom spectrum is presented with the normal Y-scale, the top spectrum has the Y-scale multiplied by 8.

Impact of protic solvent in the absence of hexacyanobenzene

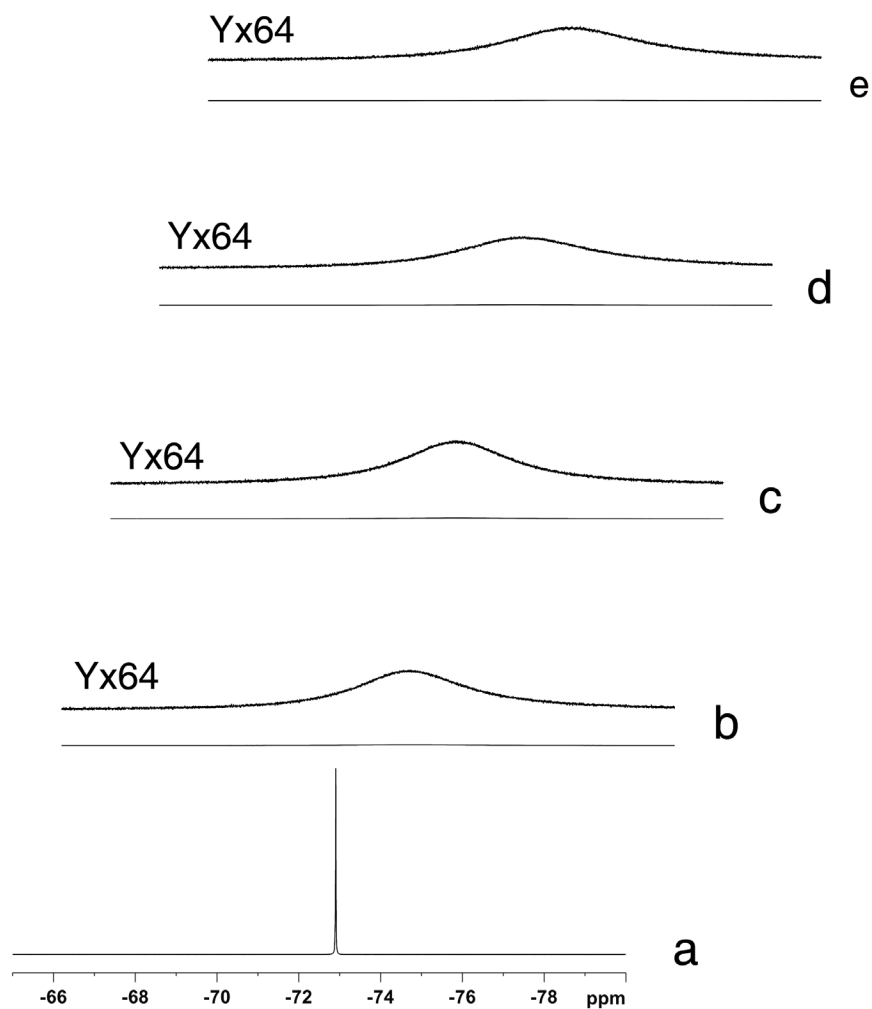


Figure S-4. ^{19}F NMR spectra showing the effect of adding .08 eq. benzyl alcohol to a solution of *purified* TBAF (CD_3) $_2\text{SO}$. **a:** Spectrum recorded before the addition of benzyl alcohol; **b:** 10 min after addition of benzyl alcohol; **c:** 1 h after addition; **d:** 7 h after addition; **e:** 20 h after addition. For spectra **b** and **c** the bottom spectrum is presented with the normal Y-scale, the top spectrum has the Y-scale multiplied by 64.

Reaction of *in-situ* generated TBAF with water

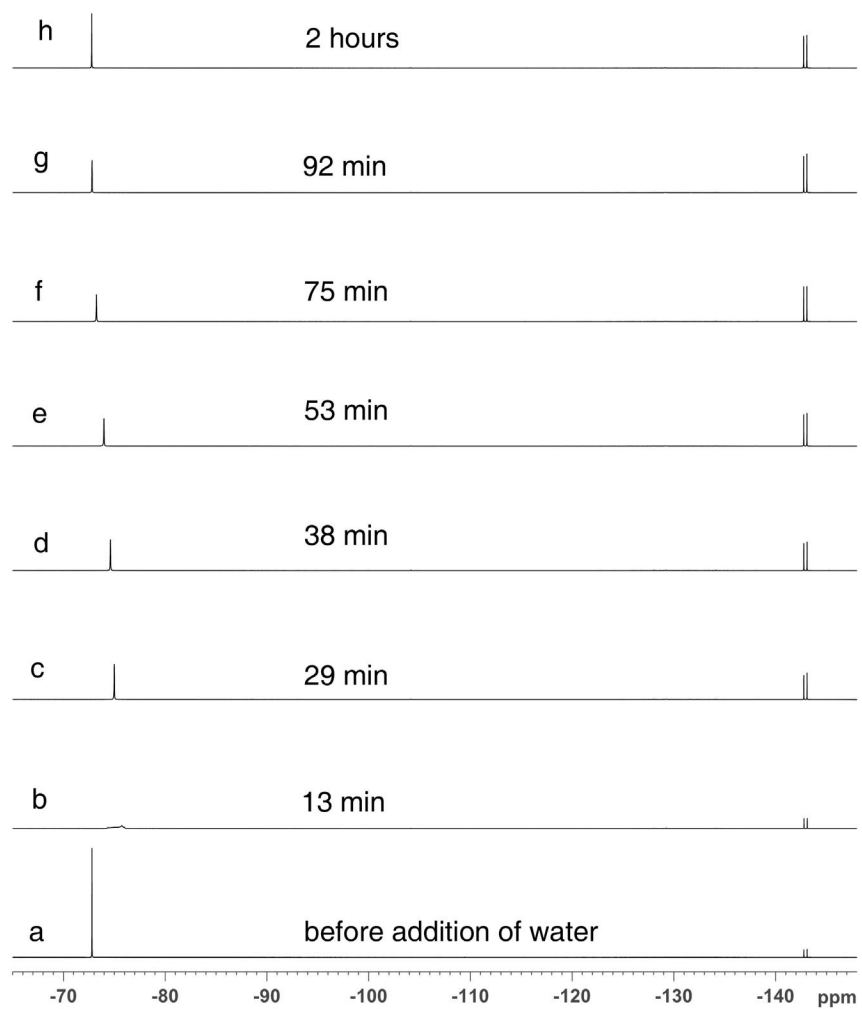


Figure S-5. ^{19}F NMR spectra of the reaction of in situ generated TBAF with 0.083 eq. water in $(\text{CD}_3)_2\text{SO}$. a, before addition of water; b~h, after addition of water.

^{19}F NMR (Detail of Figure S-5)

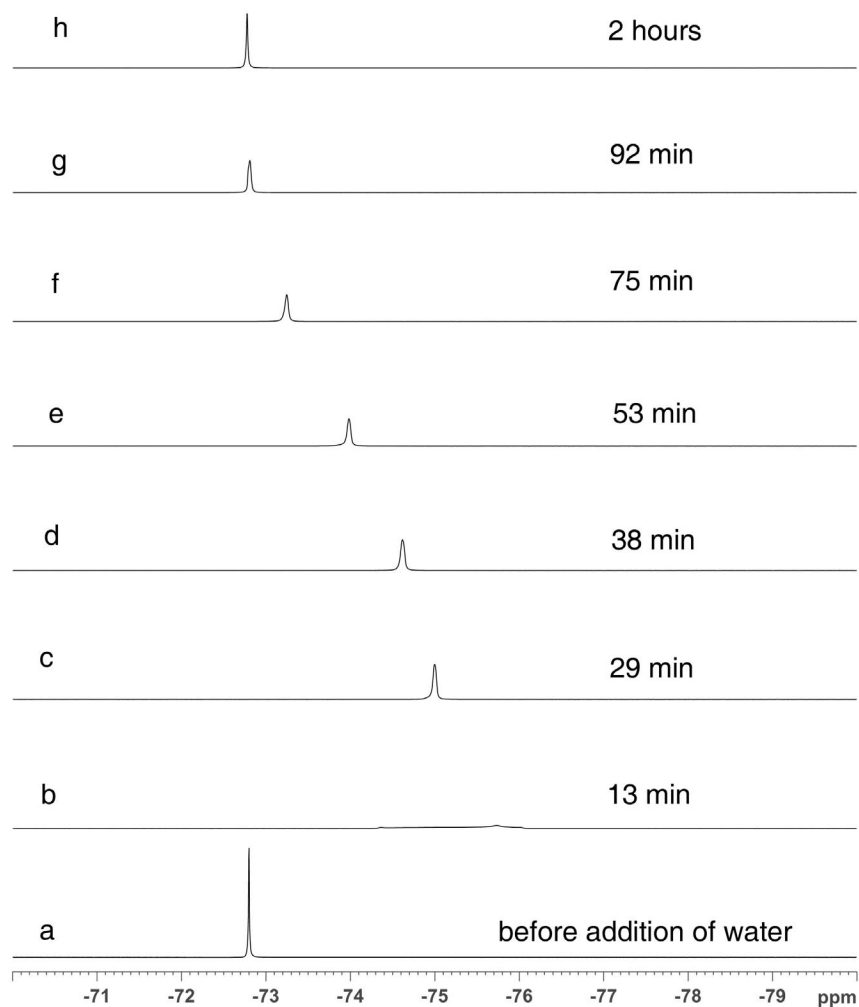


Figure S-6. ^{19}F NMR spectra (expanded area from Figure S-5) of the reaction of *in-situ* generated TBAF with 0.083 eq water in DMSO-d_6 . a, before addition of water; b~h, after addition of water.

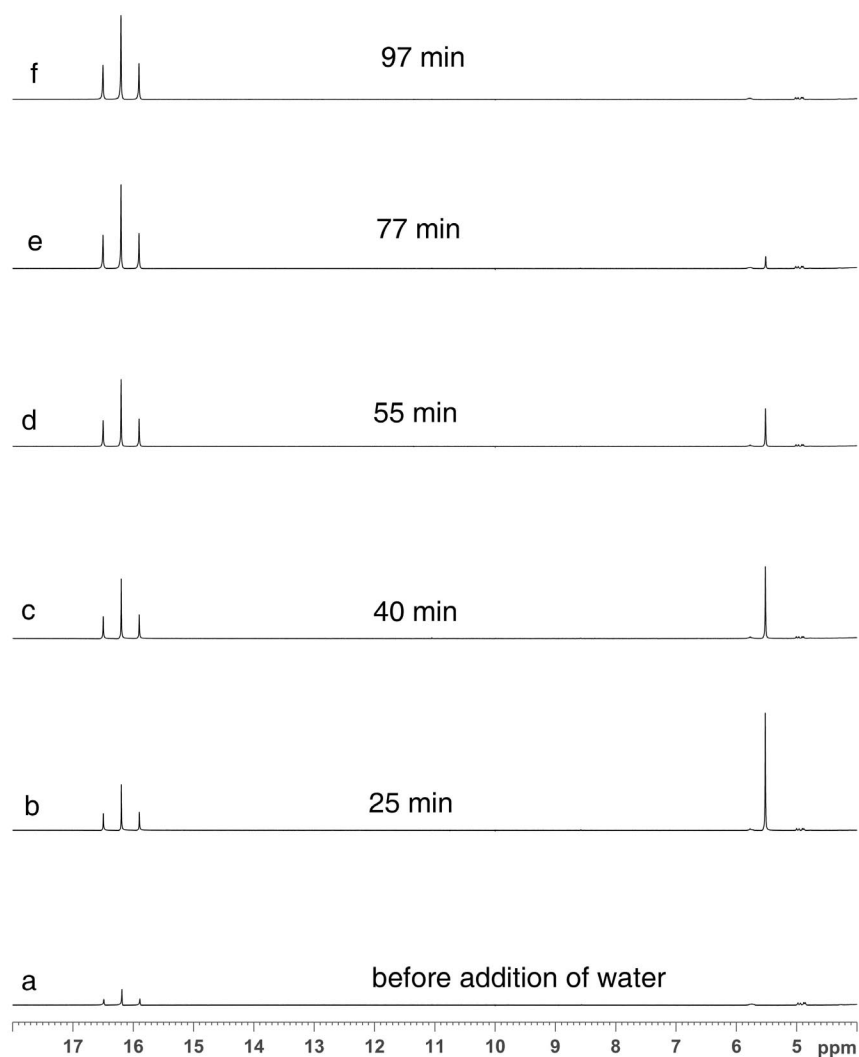


Figure S-7. ^1H NMR spectra of the reaction of *in-situ* generated TBAF with 0.083 eq water in $(\text{CD}_3)_2\text{SO}$. a, before addition of water; b~f, after addition of water. The signal at 5.6 ppm is assigned to H_2O .

Reaction of isolated TBAF with water

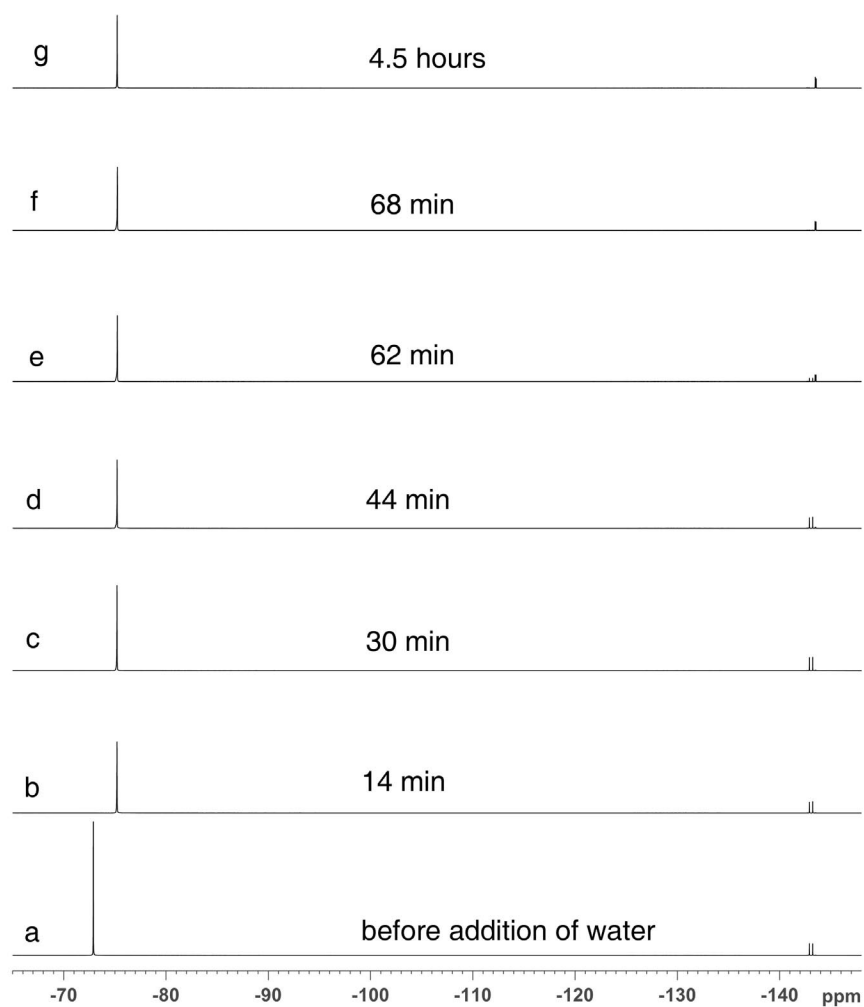


Figure S-8. ^{19}F NMR spectra of the reaction of isolated TBAF with 0.083 eq water in $(\text{CD}_3)_2\text{SO}$. a, before addition of water; b~g, after addition of water.

^{19}F NMR (Detail of Figure S-8)

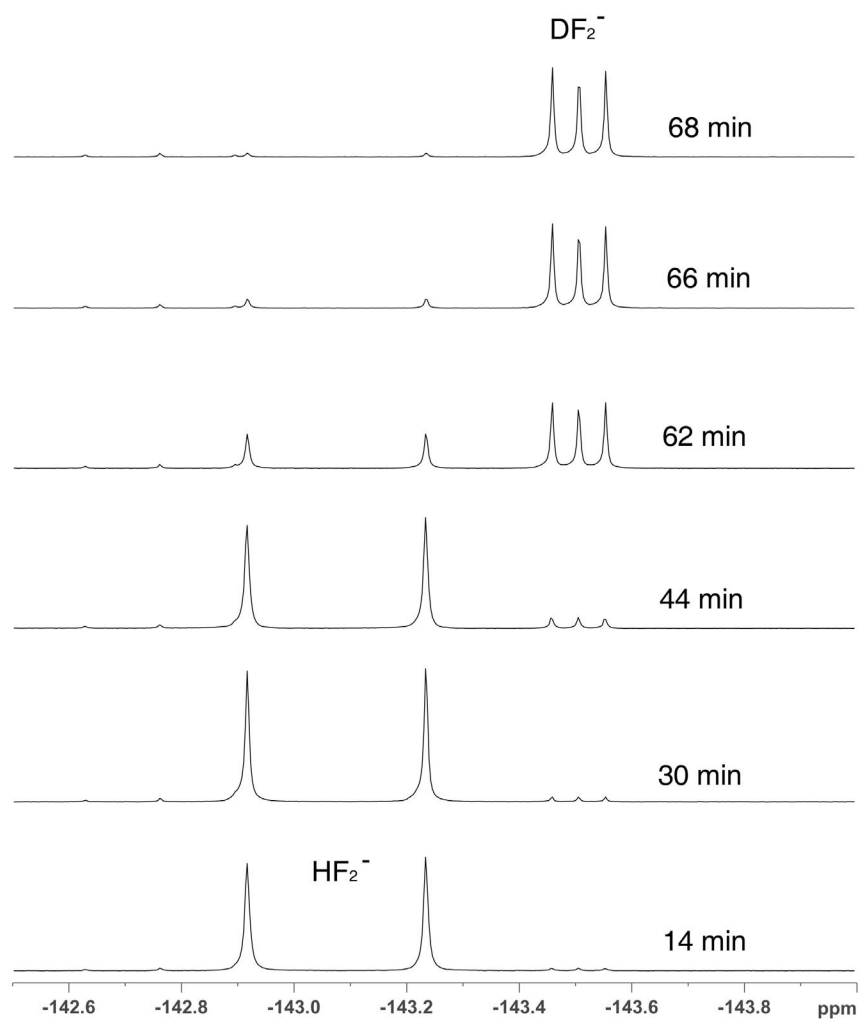


Figure S-9. ^{19}F NMR spectra of the reaction of isolated TBAF with 0.083 eq water in $(\text{CD}_3)_2\text{SO}$. (Detail from Figure S-8.)

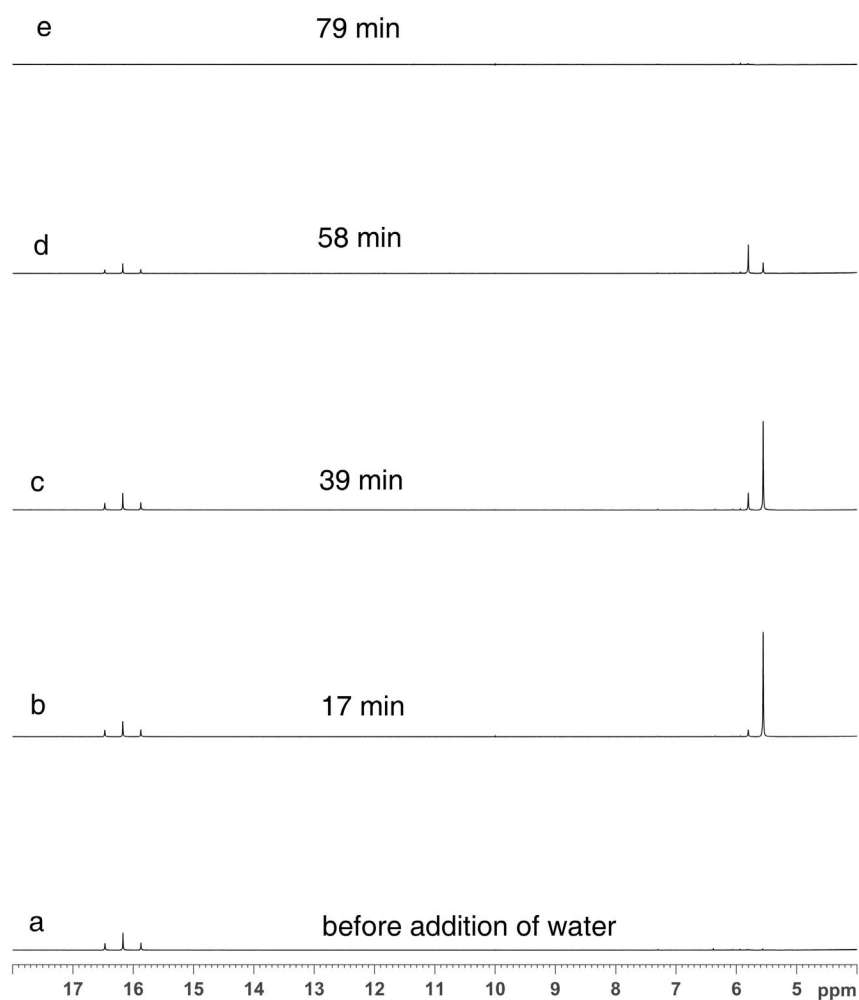


Figure S-10. ^{19}F NMR spectra of the reaction of isolated TBAF with 0.083 eq water in $(\text{CD}_3)_2\text{SO}$. a, before addition of water; b~e, after addition of water. The signal at 5.6 ppm is assigned to H_2O ; the signal at 5.8 ppm is assigned to HOD.