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Facile preparation of di- and monofluoromethyl ketones from trifluoromethyl ketones via fluorinated enol silyl ethers

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Dedicated to our colleague and friend, Karl O. Christe, on the occasion of his 65th birthday

Abstract

Di- and monofluoromethyl ketones were prepared from the readily available trifluoromethyl ketones in high yields. Magnesium metal mediated reductive defluorination readily generates fluorinated enol silyl ethers, which upon fluoride or acid assisted hydrolysis give the respective ketones in good to excellent yields. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Difluoromethyl; Monofluoromethyl; Trifluoromethyl ketones; Synthesis; Silyl ethers; Magnesium; Defluorination

1. Introduction

Difluoromethyl and monofluoromethyl ketones are potential biologically active compounds of increasing interest. These compounds have found use as potential protease and enzyme inhibitors due to the unique properties of the fluorinated methyl group [1–3]. These compounds are commonly prepared either by Friedel–Crafts acylation [4,5], or by reaction between difluoro- or monofluoroacetic acid derivatives and organometallic reagents [6–8]. However, both difluoro- and monofluoroacetic acid derivatives are rather expensive, and the monofluoroacetic acid derivatives are highly toxic. Recently, several other approaches for the preparation of difluoromethyl ketones have been reported, such as using 1,1-difluoro-2-lithioalkenes obtained from trifluoroethanol [9,10], 2,2-difluoroalkenylboranes from 2,2,2-trifluoro ethyl to sylate [11], difluoroenol silyl ethers obtained through nucleophilic trifluoromethylation of acylsilanes with Ruppert's reagent [12], difluoromethyl-β-ketophosphonate [13], and electrophilic fluorination of acetylenes [14]. Enol silyl ethers react with electrophilic fluorinating agents such as trifluoromethyl hypofluorite, acetyl hypofluorite, elemental fluorine and Selectfluor® to provide monofluoromethyl ketones [15–18]. Stereoselective monofluorinations of enol silyl ethers have been recently developed [19–21]. Diazoketones or α-haloketones also react with HF to provide monofluoromethyl ketones [22,23]. However, none of these methods uses trifluoromethyl ketones as precursor to prepare di- and monofluoromethyl ketones through selective successive defluorinations.

Trifluoromethyl ketones can be obtained from inexpensive trifluoroacetic acid derivatives [24,25]. Recently, we reported the direct preparation of trifluoromethyl ketones from carboxylic esters with (trifluoromethyl)trimethyl silane ($TMS\text{-}CF_3$) [26]. The method has been further extended by Shreeve and coworkers with CsF catalyzed trifluoromethylation of esters [27]. Uneyama and coworkers have elegantly shown magnesium metal promoted selective defluorination of trifluoromethyl ketones in the presence of chlorotrimethyl silane (TMSCl) to 2,2-difluoroenol silyl ethers [28]. Such silyl ether intermediates have found use in synthesis of difluorinated compounds by Aldol type chemistry [29,30].

We now report the preparation of di- and monofluoromethyl ketones from trifluoromethyl ketones via fluorinated enol silyl ethers. Through magnesium mediated selective defluorination followed by hydrolysis, trifluoromethyl ketones are transformed into difluoromethyl ketones. The difluoromethyl ketones are further transformed into monofluoromethyl ketones through their respective monofluoroenol silyl ethers. A significant advantage of this methodology is that it uses only inexpensive and readily available reagents, and the reactions are mild and facile.

2. Results and discussion

Table 1 summarizes the reaction conditions and yields of the preparation of difluoromethyl ketones from trifluoromethyl

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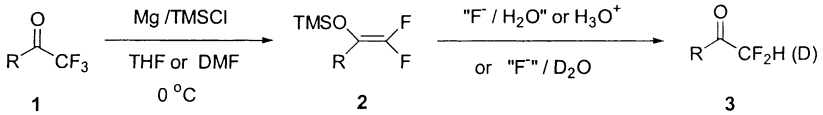
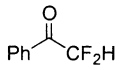
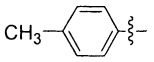
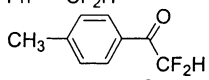
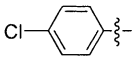
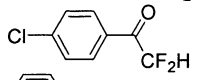
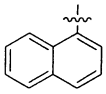
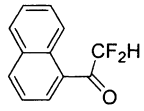
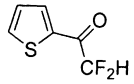
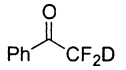
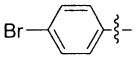
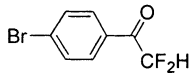
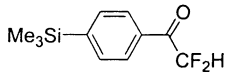
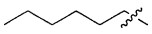
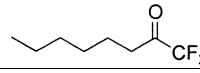
Table 1
Preparation of difluoromethyl ketones (**3**) from trifluoromethyl ketones (**1**) via difluoroenol silyl ethers (**2**)



Entry	R	Solvent[a]	Time (h)[a]	Hydrolysis method[b]	Product **3**	Yield (%)[c]
a	Ph	THF	1.0	TBAF/H_2O/THF		83
b		THF	2.0	5 M HCl		81
c		THF	1.5	TBAF/H_2O/THF		80
d		THF	2.0	3 M HCl		87
e		THF	2.0	3 M HCl		92
f	Ph	THF	1.0	TBAT/D_2O/THF		88
g		THF	1.5	3 M HCl		14[d]
						65
h		DMF	2.0	3 M HCl		33[e]

[a] For the first step **1** → **2**.
[b] For the second step **2** → **3**.
[c] Isolated yield.
[d] Determined by GC–MS.
[e] Determined by ^{19}F NMR.

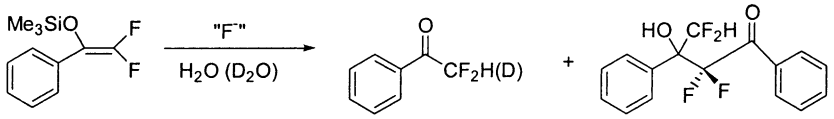
ketones. Aromatic and heteroaromatic trifluoromethyl ketones **1a–e** can be smoothly transformed into corresponding 2,2-difluoroenol silyl ethers in THF [28]. After hydrolysis, difluoromethyl ketones were obtained in good to excellent yields. The presence of either electron-withdrawing or electron-donating groups has little effect on the overall yields. By using TBAT (tetrabutylammonium fluoride) with D_2O in THF, deuterium-labeled difluoromethyl ketone (**2f**) was successfully obtained. Interestingly, chloroarene functionality in **1c** is compatible with the reaction conditions, while bromoarene group in **1g** is not; a silylated Barbier by-product is formed in major amounts. In the case of aliphatic trifluoromethyl ketone, more polar solvent DMF has to be used to facilitate the formation of difluoroenol silyl ether in moderate yield [28].

During our investigation on the hydrolysis of 2,2-difluoroenol silyl ethers (**2**), we found a dramatic effect of fluoride ion sources on the desilylative hydrolysis process. Silyl ether (**2a**) was treated with KF, tetrabutylammonium fluoride (TBAF), benzyltrimethylammonium fluoride (BTAF), tetrabutylammonium triphenyldifluorosilicate (TBAT), respectively. As shown in Table 2, aqueous KF needs prolonged time and gives self Aldol condensation by-product **4a** in significant amounts. TBAF and BTAF in wet THF give only small amounts of the Aldol product. It turns out that TBAT in wet TUF and dilute HCl (3–5 M) are the ideal hydrolysis media. Both systems generate the desired 2,2-difluoromethyl ketone **3a** (**3f**) cleanly without any Aldol by-product **4a**.

We have also found that difluoromethyl ketones react with Mg–TMSCl system to produce isomeric 2-fluoroenol silyl ethers (**5**) in excellent yields (vide supra). 2-Fluoroenol silyl ethers (**5**) can be easily hydrolyzed to the corresponding monofluoromethyl ketones. The reaction conditions and the yields are similar to the conversion from **1** to **3**. The results are shown in Table 3.

2-Fluoroenol silyl ethers (**5**) prepared from **3** are obtained as mixtures of *Z*- and *E*-isomers, as shown in Table 4. It is

Table 2
The effect of fluoride ion sources on the desilylative hydrolysis



2a **3a (3f)** **4a**

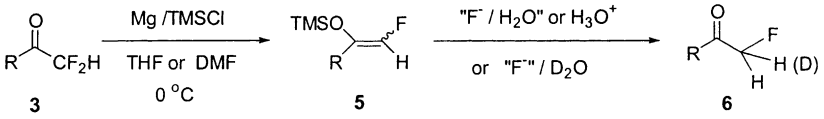
Fluoride source	Reaction time	Temperature (°C)	Yield (%)[a]	
			3a (3f)	**4a**
KF/H_2O	48 h	RT	32	46
TBAF/H_2O/THF	15 min	0	83	~5
$BnN^+Ne_3F^-$/H_2O/THF	15 min	0	82	~5
TBAT/D_2O/THF	15 min	0	88	0
3 M HCl (no fluoride)	Overnight	RT	85	0

[a] Isolated yields based on trifluoroacetophenone used to prepare enol silyl ethers.

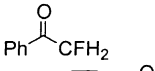
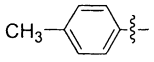
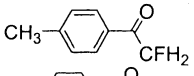
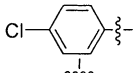
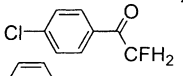
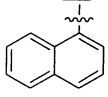
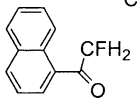
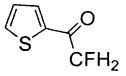
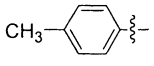
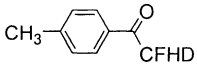
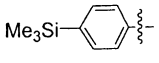
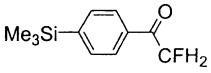
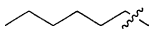
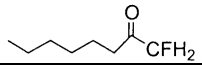
remarkable that aromatic and heteroaromatic ketones (**3a–f**) all give isomers with a *Z*:*E* ratio about 2:1, while the aliphatic ketone (**3g**) gives the opposite ratio (*Z*:*E* = 0.7:1). This is probably due to the steric as well as electronic effect of the different aryl and alkyl groups.

The mechanism of Mg-promoted defluorination of difluoromethyl ketones is not clear. It is possible that the C–F bond cleavage is facilitated by a two-electron transfer process as suggested by Uneyama and coworkers in the case of trifluoromethyl ketones [28]. As shown in Scheme 1, the first electron transfer from Mg to ketone gives a ketyl species **8**, which is further reduced to an anionic species **9** by Mg. After β-elimination [28,32], 2-fluoroenol silyl ether (**5**) is formed which readily reacts with protic acid to generate **6**.

Table 3
Preparation of monofluoromethyl ketones (**6**) from difluoromethyl ketones (**3**)

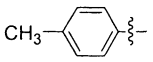
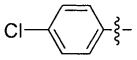
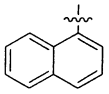
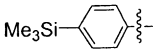
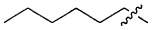


3 **5** **6**

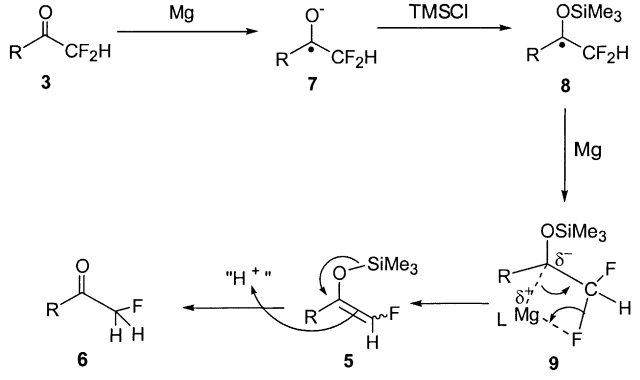
Entry	R	Solvent[a]	Time (h)[a]	hydrolysis method[b]	Product **6**	Yield (%)[c]
a	Ph	THF	1.0	TBAF/H_2O/THF		89
b		THF	1.0	5 M HCl		78
c		THF	2.0	TBAF/H_2O/THF		80
d		THF	2.0	3 M HCl		84
e		THF	2.0	3 M HCl		95
f		THF	1.0	TBAT/D_2O/THF		91
g		THF	1.0	3 M HCl		91
h		DMF	2.0	3 M HCl		35[d]

[a] For the first step **3** → **5**.
[b] For the second step **5** → **6**.
[c] Isolated yield.
[d] Determined by ^{19}F NMR.

Table 4
The *Z*:*E* isomers of 2-fluoroenol silyl ethers (**5**)

Entry	R	*Z*:*E* ratio[a]	Yield (%)[a]
a	Ph	2.2:1	94
b		2.2:1	92
c		2.0:1	96
d		2.1:1	Quantitative
e		2.0:1	Quantitative
f		2.2:1	94
g		0.72:1	50

[a] Determined by ^{19}F NMR [31].



Scheme 1. Proposed mechanism of transformation of **3**–**6**.

3. Conclusion

In conclusion, Mg metal mediated reductive successive defluorinations provide an effective methodology to prepare di- and monofluoromethyl ketones from readily available trifluoromethyl ketones.

4. Experimental

4.1. Materials and measurement

Unless otherwise mentioned, all the other reagents were purchased from commercial sources. THF was distilled under nitrogen over sodium/benzophenone ketyl prior to use. DMF was distilled over calcium hydride. Except for α,α,α-trifluoroacetophenone, all the other trifluoromethyl ketones were simply prepared according to the reported procedures [25,26]. Column chromatography was carried out using silca gel (60–200 mesh) and hexanes/ethyl acetate (commonly v/v = 4:1). All Mg mediated defluorination reactions were carried out by Schlenk technique, and the reactions were monitored by ^{19}F NMR. All the fluorinated enol silyl ethers were directly hydrolyzed shortly after work-up and solvent removal [28]. The ratio of *Z*:*E* isomers of 2-fluoroenol silyl ethers were determined from ^{19}F NMR.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker AMX 500 and AM 360 NMR spectrometers. TMS and $CFCl_3$ are used as internal standards for these spectra, respectively. Mass spectra were recorded on Hewlett-Packard 5971 Series GC–MS.

4.2. Typical experimental procedures

1. The typical procedure for the preparation of difluoromethyl ketones from trifluoromethyl ketones is as follows. Under an argon atmosphere, to the mixture of 0.27 g (11 mmol) magnesium turning and 2.4 g (22 mmol) TMSCl in 25 ml dry THF at 0 °C, was added 1.0 g (5.3 mmol) 4′-methyl-2,2,2-trifluoroacetophenone (**1b**). Then the mixture was stirred at 0 °C for 2 h. THF and excess TMSCl were removed under vacuum and to the residue was added 30 ml hexanes. The solid was removed by suction filtration, and the filtrate was condensed under vacuum to give about 1.4 g crude product **2b**. To **2b**, 20 ml 5 M HCl was added and the mixture was stirred at room temperature overnight. Then the mixture was extracted successively with 20 ml ether thrice. Combined ether phase was further washed with 20 ml brine successively thrice, and then washed with 20 ml water. The organic phase was dried over anhydrous $MgSO_4$ and 0.85 g crude product was collected after removal of the solvent. The product was purified by silica gel column chromatography (hexanes/ethyl acetate (v/v = 4:1)) to give 0.73 g **3b** as a white solid, yield 81%.
2. The typical procedure for the preparation of monofluoromethyl ketones from difluoromethyl ketones is as follows. Under an argon atmosphere, to the mixture of 28 mg (1.17 mmol) magnesium turning and 260 mg (2.35 mmol) TMSCl in 3 ml dry THF at 0 °C, was added 100 mg (0.588 mmol) 4′-methyl-2,2-difluoroacetophenone (**3b**). Then the mixture was stirred at 0 °C for 1 h. THF and excess TMSCl were removed under vacuum and to the residue was added 15 ml hexanes. The solid was removed by suction filtration, and the filtrate was condensed under vacuum to give about 140 mg crude product **5b**. To **5b**, 10 ml 5 M HCl was added and the mixture was stirred at room temperature overnight. Then the mixture was saturated with NaCl and extracted successively with 10 ml ether three times. Combined ether phase was further washed with 10 ml brine twice, and the organic phase was dried over anhydrous $MgSO_4$. After removal of the solvent, 89.6 mg crude product was collected. The product was purified by silica gel column chromatography (hexanes/ethyl acetate (v/v = 4:1)) to give 69.8 mg **6b** as a white solid, yield 78%.

4.3. 2,2-Difluoro-1-phenyl-1-trimethylsiloxyethene (**2a**)

^{1}H NMR (500 Hz, $CDCl_3$): $\delta = 0.60$ (s, 9H), 7.38 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.61 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 0.02$, 114.09 (q, $^2J_{CF} = 18.0$ Hz), 125.84, 127.72, 128.25, 132.71, 154.87 (t, $^1J_{CF} = 286.8$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -112.16$ (d, $^2J_{HF} = 68.0$ Hz). GC–MS: 228, 213, 197, 186, 177, 165, 149, 143, 131, 115, 105, 89, 81, 73.

4.4. 2-Fluoro-1-phenyl-1-trimethylsiloxyethene (**5a**)

Z-isomer: ^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 0.31$ (s, 9H), 7.04 (d, $^2J_{HF} = 78.2$ Hz, 1H), 7.34–7.49 (m, 3H), 7.71 (d, $J = 7.8$ Hz, 2H); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = 158.83$ (d, $^2J_{HF} = 79.4$ Hz). *E-isomer*: ^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 0.25$ (s, 9H), 6.99 (d, $^2J_{HF} = 79.6$ Hz, 1H), 7.34–7.49 (m, 3H), 7.71 (d, $J = 7.8$ Hz, 2H); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -164.63$ (d, $^2J_{HF} = 79.5$ Hz).

4.5. 2,2-Difluoroacetophenone (**3a**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 6.30$ (t, $^2J_{HF} = 53.8$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 2H), 7.67 (t, $J = 7.5$ Hz, 1H), 8.08 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 110.98$ (t, $^1J_{CF} = 253.7$ Hz), 128.88, 129.50, 131.45, 134.83, 187.46 (t, $^2J_{CF} = 25.2$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -122.51$ (d, $^2J_{HF} = 56.4$ Hz).

4.6. 2,2-Difluoro-4′-methylacetophenone (**3b**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 2.45$ (s, 3H), 6.26 (t, $^2J_{HF} = 53.8$ Hz, 1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.97 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 21.71$, 111.03 (t, $^1J_{CF} = 253.4$ Hz), 128.98, 129.59, 133.27, 146.15, 187.03 (t, $^2J_{CF} = 25.1$ Hz); ^{19}C NMR (338 MHz, $CDCl_3$): $\delta = -122.62$ (d, $^2J_{HF} = 55.1$ Hz).

4.7. 4′-Chloro-2,2-difluoroacetophenone (**3c**)

^{1}H NMR (500 Hz, $CDCl_3$): $\delta = 6.28$ (t, $^2J_{HF} = 53.5$ Hz, 1H), 7.49 (d, $J = 8.9$ Hz, 2H), 8.01 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 111.27$ (t, $^1J_{CF} = 254.3$ Hz), 129.34, 129.72 (t, $^3J_{CF} = 2.1$ Hz), 130.96, 141.61, 186.53 (t, $^2J_{CF} = 25.9$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -122.11$ (d, $^2J_{HF} = 53.4$ Hz).

4.8. 2,2-Difluoro-1′-acetonaphthone (**3d**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 6.47$ (t, $^2J_{HF} = 53.8$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.58 (t, $J = 7.5$ Hz, 1H), 7.67 (t, $J = 7.8$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 1H), 8.07 (d, $J = 8.3$ Hz, 1H), 8.16 (dm, $J = 7.5$ Hz, 1H), 8.90 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 110.64$ (t, $^1J_{CF} = 254.9$ Hz), 124.08, 125.24, 126.87, 128.74, 129.06, 131.10 (t, $^3J_{CF} = 4.3$ Hz), 133.87, 135.40, 189.52 (t, $^2J_{CF} = 23.8$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -121.18$ (d, $^2J_{HF} = 52.0$ Hz).

4.9. 2,2-Difluoro-2′-acetothienone (**3e**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 6.24$ (t, $^2J_{HF} = 53.9$ Hz, 1H), 7.27 (m, 1H), 7.89 (m, 1H), 8.05 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 110.69$ (t, $^1J_{CF} = 253.5$ Hz), 128.87, 135.51, 136.75, 137.68 (t, $^3J_{CF} = 2.5$ Hz), 180.98 (t, $^2J_{CF} = 26.9$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -122.21$ (d, $^2J_{HF} = 55.9$ Hz).

4.10. 2-Deutero-2,2-difluoroacetophenone (**3f**)

^{1}H NMR (500 Hz, $CDCl_3$): $\delta = 7.54$ (t, $J = 8.0$ Hz, 2H), 7.68 (t, $J = 7.5$ Hz, 1H), 8.08 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 110.85$ (tt, $^1J_{CF} = 252.4$ Hz, $^2J_{CF} = 29.2$ Hz), 128.94, 129.61, 131.51 (t, $^3J_{CF} = 1.7$ Hz), 134.87, 187.57 (t, $^2J_{CF} = 25.5$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -123.10$ (t, $^2J_{DF} = 7.6$ Hz).

4.11. 2,2-Difluoro-4′-trimethylsilylacetophenone (**3g**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 0.33$ (s, 9H), 6.31 (t, $^2J_{HF} = 53.5$ Hz, 1H), 7.70 (d, $J = 8.3$ Hz, 2H), 8.04 (d, $J = 8.3$ Hz, 2H); ^{13}C MMR (90 MHz, $CDCl_3$): $\delta = -1.54$, 111.09 (t, $^1J_{CF} = 253.6$ Hz), 128.32 (t, $^3J_{CF} = 2.8$ Hz), 131.46, 133.74, 149.91, 187.72 (t, $^2J_{CF} = 25.0$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -122.62$ (d, $^2J_{HF} = 53.4$ Hz).

4.12. 2-Fluoroacetophenone (**6a**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 5.51$ (d, $^2J_{HF} = 47.0$ Hz, 2H), 7.46 (t, $J = 7.4$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.86 (d, $J = 7.4$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 83.38$ (d, $^1J_{CF} = 183.2$ Hz), 127.66 (d, $^3J_{CF} = 2.5$ Hz), 128.81, 133.48, 134.02, 193.31 (d, $^2J_{CF} = 15.9$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -231.69$ (t, $^2J_{HF} = 47.0$ Hz).

4.13. 2-Fluoro-4′-methyl-acetophenone (**6b**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 5.50 (d, $^2J_{HF} = 47.5$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 21.77$, 83.45 (d, $^1J_{CF} = 182.0$ Hz), 127.91 ($^3J_{CF} = 2.5$ Hz), 129.56, 131.16, 145.16, 192.90 (d, $^2J_{CF} = 15.9$ Hz; ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -231.31$ (t, $^2J_{HF} = 47.7$ Hz).

4.14. 4′-Chloro-2-fluoroacetophenone (**6c**)

^{1}H NMR (500 Hz, $CDCl_3$): $\delta = 5.48$ (d, $^2J_{HF} = 47.0$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.85 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 83.57$ (d, $^1J_{CF} = 183.1$ Hz), 129.27, 129.40 (d, $^3J_{CF} = 2.5$ Hz), 132.07, 140.65, 192.48 (d, $^2J_{CF} = 16.1$ Hz); ^{19}F NMR (470 MHz, $CDCl_3$): $\delta = -230.25$ (t, $^2J_{HF} = 46.7$ Hz).

4.15. 2-Fluoro-1′-acetonaphthone (**6d**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 5.58$ (d, $^2J_{HF} = 47.4$ Hz, 2H), 7.54 (t, $J = 7.8$ Hz, 1H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.71 (t, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 7.5$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 1H), 8.82 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 83.74$ (d, $^1J_{CF} = 184.8$ Hz), 124.04, 125.21, 126.67, 128.02, 128.05, 128.40, 128.44, 133.79, 133.88, 196.81 (d, $^2J_{CF} = 17.1$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = 225.78$ (t, $^2J_{HF} = 45.9$ Hz).

4.16. 2-Fluoro-2′-acetothienone (**6e**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 5.30$ (d, $^2J_{HF} = 47.5$ Hz, 2H), 7.12 (m, 1H), 7.69 (m, 1H), 7.79 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 83.46$ (d, $^1J_{CF} = 184.4$ Hz), 128.32, 132.93, 134.77, 139.55 (d, $^3J_{CF} = 2.4$ Hz), 186.87 (d, $^2J_{CF} = 17.1$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -127.99$ (d, $^2J_{HF} = 45.9$ Hz).

4.17. 2-Deutero-2-fluoro-4′-methylacetophenone (**6f**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 5.48 (dt, $^2J_{HF} = 46.8$ Hz, $^3J_{DH} = 2.5$ Hz, 1H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.79 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = 21.72$, 83.13 (dt, $^1J_{CF} = 181.1$ Hz, $^2J_{CD} = 23.3$ Hz), 127.90 (d, $^3J_{CF} = 2.5$ Hz), 129.55, 131.16, 145.15, 193.01 (d, $^2J_{CF} = 16.0$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -231.95$ (dt, $^2J_{HF} = 45.8$ Hz, $^2J_{DF} = 7.6$ Hz).

4.18. 2-Fluoro-4′-trimethylsilylacetophenone (**6g**)

^{1}H NMR (360 Hz, $CDCl_3$): $\delta = 0.30$ (s, 9H), 5.52 (d, $^2J_{HF} = 47.3$ Hz, 2H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.84 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$): $\delta = -1.49$, 83.47 (d, $^1J_{CF} = 181.7$ Hz), 126.60, 133.59, 133.70, 148.75, 193.63 (d, $^3J_{CF} = 15.2$ Hz); ^{19}F NMR (338 MHz, $CDCl_3$): $\delta = -231.60$ (t, $^2J_{HF} = 47.7$ Hz). GC–MS: 210, 195, 177, 149, 134, 119, 105, 91, 77, 73, 67, 53.

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