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Defluorination—silylation of alkyl trifluoroacetates to 2,2-difluoro-2-(trimethylsilyl)acetates by copper-deposited magnesium and trimethylsilyl chloride

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ABSTRACT

Reductive defluorination—silylation of alkyl trifluoroacetates with copper-deposited magnesium and trimethylsilyl chloride (TMS-Cl) gave 2,2-difluoro-2-(trimethylsilyl)acetates, potential difluoromethylene building blocks, in 60–68% yields.

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1. Introduction

Reductive defluorination-silvlation of trifluoromethyl compounds into difluoroorganic compounds using magnesium metal and trimethylsilyl chloride (TMS-Cl) has become a popular synthetic method in organofluorine chemistry.¹ The magnesium method is easier to use than electrolysis, which requires an electric power supply unit, electrodes, and a specialized reaction cell.^{1,2} However, the magnesium method is sometimes less powerful than electrolysis. Electrolysis has been shown to reduce alkyl (ethyl, *tert*-butyl, and *n*-hexyl) trifluoroacetates into the corresponding 2,2-difluoro-2-(trimethylsilyl)acetates,^{2a} while only the alkyl trifluoroacetates were recovered using the magnesium method (Scheme 1).³ A successful metal-reduction method requires an alteration of the acetate structure, i.e., an alkyloxycarbonyl moiety to an aryloxycarbonyl moiety³ or a trifluoromethyl group to a bromodifluoromethyl group via reduction by Zn.⁴ Here, we describe a device with a stronger reducing ability than the magnesium metal, which requires the deposition of copper metal on the surface of magnesium metal powder. The copper-deposited magnesium powder could reduce commercially available alkyl trifluoroacetates. Alkyl 2,2-difluoro-2-(trimethylsilyl)acetates 2a-d, the products of the reductive defluorination—silylation of various alkyl trifluoroacetates, are potential building blocks for difluoromethylene compounds.^{2b,c,5}

2. Results and discussion

Optimization of the reductive defluorination of ethyl trifluoroacetate (**1a**) by copper-deposited magnesium $(Mg-Cu)^7$ in *N*,*N*-dimethylimidazolidinone (DMI) with LiCl as an additive gave ethyl 2,2-difluoro-2-(trimethylsilyl)acetate (**2a**) in 62% isolated yield (Scheme 2). The Mg–Cu was prepared by mixing 4 molar equiv of Mg powder and 0.5 molar equiv of CuCl in a solution of LiCl in DMI just prior to the reaction. The silyl ketal byproduct, **3a**, was difficult to separate from **2a** by distillation because of a small difference in boiling points.⁶ However, decomposing **3a** by adding





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anhydrous HCl/EtOH (prepared from TMS-Cl and EtOH) enabled the isolation of **2a** by distillation. Details on the optimization of the reaction conditions are described below.



Scheme 2.

The effects of the transition metal deposits and the shape of the magnesium metal are summarized in Table 1. The reaction without the addition of any transition metals resulted in the recovery of ethyl trifluoroacetate, as was previously reported (entry 1).³ Magnesium powder activated by FeCl3 and NiCl2 led to the decomposition of **1a** and gave the target compound **2a** in 1% and 2% yield, respectively (entry 3 and 4). Magnesium powder activated by 0.25 molar equiv of CuCl gave 2a in 25% yield, and 48% of 1a was recovered (entry 2). The use of 4 molar equiv of the Mg powder activated by 0.5 molar equiv of CuCl resulted in the complete consumption of **1a**.⁷ The reaction gave compounds **2a** and **3a** in a 50% and 45% yield, respectively (entry 5). The use of 4 molar equiv of magnesium powder activated by 1.0 molar equiv of CuCl resulted in the formation of the compound **2a** in a 26% yield, and recovery of **1a** in 39% (entry 6). A mixture of Cu(0) and Mg powder reduced 1a to 2a in a 3% yield (entry 7). These results suggest that 'the Cu(0) attached on magnesium surface' is essential for efficient reduction of 1a. The use of powdered magnesium metal was also found to be essential. Magnesium turnings and magnesium ribbon resulted in a lower conversion of the substrate (entries 8, 9, and 10). Use of commercially available Zn dust or Zn–Cu dust resulted in complete recovery of the substrate **1a** (entry 11 and 12). Mg with a large surface area was necessary for the complete consumption of **1a** in the reaction.

Table 1

Effects of metals on defluorination-silylation of ethyl trifluoroacetate (1a)

	TMS-Cl (8 eq.)	0 TMS-F-C [⊥] OFt	+	OTMS /-OEt
F ₃ C OEt	DMI	2-		F3C TMS
1a i	25 °C 5 h	Za		Ja

Metal reducing	Activation	Recov. of	Yields ^a	Yields ^a (%)	
agent	of Mg (equiv)	1a ^a [%]	2a	3a	
Mg powder	_	100	0	0	
Mg powder	CuCl (0.25)	48	(25)	(23)	
Mg powder	FeCl ₃ (0.25)	84	(1)	(0)	
Mg powder	NiCl ₂ (0.25)	38	(2)	(1)	
Mg powder	CuCl (0.5)	0	(50)	(45)	
Mg powder	CuCl (1.0)	39	(26)	(15)	
Mg powder	Cu(0) (0.5) ^c	93	(3)	(2)	
Mg turnings	CuCl (0.5)	70	(9)	(9)	
Mg turnings ^d	CuCl (0.5)	44	(24)	(18)	
Mg ribbon	CuCl (0.5)	45	(25)	(23)	
Zn dust	_	100	0	0	
Zn–Cu dust	_	100	0	0	
	Metal reducing agent Mg powder Mg powder Mg powder Mg powder Mg powder Mg powder Mg turnings Mg turnings ^d Mg tibbon Zn dust Zn-Cu dust	Metal reducing agent Activation of Mg (equiv) Mg powder — Mg powder FcCl ₃ (0.25) Mg powder NiCl ₂ (0.25) Mg powder CuCl (0.5) Mg turnings CuCl (0.5) Mg turnings ^d CuCl (0.5) Mg ribbon CuCl (0.5) Zn dust — Zn-Cu dust —	$\begin{array}{c c} \mbox{Metal reducing} \\ \mbox{agent} & \mbox{Activation} \\ \mbox{agent} & \mbox{of } Mg \ (equiv) & \mbox{1a}^a \ [\%] \\ \mbox{Mg powder} & - & 100 \\ \mbox{Mg powder} & \mbox{CuCl } (0.25) & 48 \\ \mbox{Mg powder} & \mbox{FeCl}_3 \ (0.25) & 84 \\ \mbox{Mg powder} & \mbox{NiCl}_2 \ (0.25) & 38 \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & 0 \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & 0 \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & 0 \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & 70 \\ \mbox{Mg turnings} & \mbox{CuCl } (0.5) & 44 \\ \mbox{Mg tribbon} & \mbox{CuCl } (0.5) & 44 \\ \mbox{Mg ribbon} & \mbox{CuCl } (0.5) & 44 \\ \mbox{Mg ribbon} & \mbox{CuCl } (0.5) & 45 \\ \mbox{Zn dust} & - & 100 \\ \mbox{Zn-Cu dust} & - & 100 \\ \end{tabular}$	$\begin{array}{c cccc} \mbox{Metal reducing} \\ \mbox{agent} & \mbox{Activation} \\ \mbox{agent} & \mbox{of } Mg \ (equiv) & \mbox{1a}^a \ [\%] & \mbox{Yields}^a \\ \hline \mbox{1a}^a \ [\%] & \mbox{2a} \\ \hline \mbox{2a} \\ \mbox{2a} \\ \mbox{Mg powder} & \mbox{CuCl } (0.25) & \mbox{48} & (25) \\ \mbox{Mg powder} & \mbox{FeCl}_3 \ (0.25) & \mbox{84} & (1) \\ \mbox{Mg powder} & \mbox{NiCl}_2 \ (0.25) & \mbox{84} & (1) \\ \mbox{Mg powder} & \mbox{NiCl}_2 \ (0.25) & \mbox{84} & (1) \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & \mbox{0} & (50) \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & \mbox{0} & (50) \\ \mbox{Mg powder} & \mbox{CuCl } (0.5) & \mbox{70} & (9) \\ \mbox{Mg turnings} & \mbox{CuCl } (0.5) & \mbox{44} & (24) \\ \mbox{Mg ribbon} & \mbox{CuCl } (0.5) & \mbox{45} & (25) \\ \mbox{Zn Aust} & - & \mbox{100} & \mbox{0} \\ \mbox{Zn-Cu dust} & - & \mbox{100} & \mbox{0} \\ \end{tabular}$	

^a Yields in parentheses and recoveries of **1a** were determined by ¹⁹F NMR with 4-(trifluoromethyl)anisole as an internal standard.

^b Reaction time is 24 h.

^c Cu(0) powder was added to the suspension of Mg powder.

^d Mg (12 equiv) turnings were used.

Results for the optimization of reaction conditions by changing the solvent are summarized in Table 2. The use of the highly polar solvent DMF resulted in the formation of **2a** in 8% yield (entry 1). The use of DMI, whose dielectric constant is similar to that of DMF, resulted in the effective formation of the difluoroacetate **2a** in a 50% yield (entry 2). The use of a similar cyclic amidic solvent, *N*-methylpyrrolidone (NMP), resulted in the formation of **2a** in only a 14% yield (entry 3). The use of THF resulted in the formation of the difluoroacetate **2a** in only a 2% yield (entry 4). Using DMI resulted in the highest yields for the solvents examined.

Table 2

Solvent effect on defluorination-silylation of 1a

O H F ₃ C [^] OEt Mg-Cu ^a TMS-Cl (8 eq.) solvent, 5 h		O TMS-F₂C [⊥] OEt ⁺ 2a	0 F ₃ C 1 3	TMS -OEt -MS a	
Entry	Solvent	Temp [°C]	Recov. of 1a^b [%]	Yields ^b	[%]
				2a	3a
1	DMF	25	70	(8)	(5)
2	DMI	25	0	(50)	(45)
3	NMP	25	36	(14)	(14)
4	THF	50	76	(2)	(0)

^aMg—Cu was in situ prepared from Mg powder (4 equiv) and CuCl (0.5 equiv). ^b Yields in parentheses and recoveries of **1a** were determined by ¹⁹F NMR with 4-(trifluoromethyl)anisole as an internal standard.

Electrochemical reduction of **1a** gave compound **2a** in a 68% yield by ¹⁹F NMR analysis of the crude mixture, ^{2a} which was higher than the best reaction by conditions present in Table 2 (entry 2, 50%). In order to determine if the electrolyte present in the electrochemical reaction was the reason for the higher yields, we decided to add 'supporting electrolyte' to the magnesium metal reaction. The results are summarized in Table 3. The reaction with Et₄NCl added resulted in a lower conversion of **1a**. The reaction with an 8 equiv amount of LiCl additive resulted in a 62% isolated yield (69% by ¹⁹F NMR analysis, entry 4).⁸ The reaction with a 12 equiv amount of LiCl resulted in the formation of **2a** in the same yield with the ketal **3a** in lower yield (20%; entry 5). Reactions with other lithium salt (LiBr, LiClO₄, Li(OTf)) additives resulted in



Effects of additives on the defluorination-silylation reaction of 1a

	Mg-Cu ^a			
	TMS-CI			
Q	additive	U L	+	
F ₃ C [™] OEt		TMS-F ₂ C [^] OEt		F ₃ C TMS
1a	25 °C, 5 h	2a		3a

Entry	Additive (equiv)	Recov. of 1a ^b (%)	Yields ^c [%]	
			2a	3a
1	_	0	(50)	(45)
2	Et ₄ NCl (16)	68	(18)	(14)
3	LiCl (4.0)	0	(62)	(26)
4 ^e	LiCl (8.0)	0	62 ^d (69)	(22)
5	LiCl (12)	2	(69)	(20)
6	LiBr (4.0)	56	(25)	(11)
7	LiBr (8.0)	100	(0)	(0)
8	$Li(ClO_4) (4.0)^{f}$	100	(0)	(0)
9	Li(OTf) (4.0) ^f	95	(4)	(0)
10	$MgBr_2 \cdot OEt_2(0.5)$	20	(43)	(34)
11	MgBr ₂ ·OEt ₂ (2.0) ^f	100	(0)	(0)
12	KCl (4)	59	(19)	(15)

^aMg-Cu was in situ prepared from Mg powder (4 equiv) and CuCl (0.5 equiv).

^b Values were determined by ¹⁹F NMR of crude mixture containing solvent with 4-(trifluoromethyl)anisole as an internal standard.

^c Values in parentheses were yields determined by ¹⁹F NMR of crude mixture after extractions with benzotrifluoride as an internal standard.

^d The yield is the isolated yield.

^e Reaction time is 4 h.

^f The additives were not completely dissolved.

lower conversions of the substrate **1a** than that with LiCl (entry 4), although these additives suppressed the formation of the ketal **3a** (entries 6–9). Other metal salt additives (MgBr₂·OEt₂ and KCl) did not suppress the formation of **3a** (entry 10–12). Thus, the reaction in DMI with an 8 equiv amount of LiCl was found to be the best conditions for the preparation of **2a**, which is shown in Scheme 2.

The defluorination—silylation reaction with another silylating agent, TES-Cl, resulted in a low yield of difluoroacetate (a 5% yield determined by ¹⁹F NMR of the crude mixture, Scheme 3).

$$\begin{array}{c} & \underset{\textbf{H}_{25}}{\overset{\textbf{M}_{25}}{\text{TES-Cl}}} & \underset{\textbf{LiCl 8 eq.}}{\overset{\textbf{O}}{\text{TES-F}_{2}C} & \underset{\textbf{OEt}}{\overset{\textbf{O}}{\text{OEt}}} & + & \text{others} \\ \hline & \underset{\textbf{1a}}{\overset{\textbf{DMI}}{\text{25 °C, 5 h}}} & \underset{\textbf{5\%}}{\overset{\textbf{S}\%} & 11\% \end{array}$$

(1a (48%) was recovered)

Scheme 3.

While variation in the silyl moiety led to reduced yields, variation in the alkyl moiety was successful; two primary (R=Et, *n*-C₆H₁₃) and two secondary (R=*i*-Pr, Cy) 2,2-difluoro-2-(trimethylsilyl)acetates **2a**–**d** were similarly produced from the corresponding trifluoroacetate under the optimized conditions (Table 4). The *i*-propyl 2,2-difluoro-2-(trimethylsilyl)acetate **2c** was produced in a 65% isolated yield using a similar procedure as that for **2a** (entry 3). The *n*-hexyl and the cyclohexyl 2,2-difluoro-2-(trimethylsilyl) acetates were isolated in a 60% and 68% yield, respectively, by distillation followed after the decomposition of the silyl ketals **3b** and **3d** by reacting them with TFA (entries 2, 4). The yields for products **2a**–**d** were comparable to those of electrochemical reductions.

Table 4

Defluorination-silylation of alkyl trifluoroacetates (1)

C F ₃ C	M TM OR [1	g-Cu ^a /IS-CI _iCI 	۲MS-F ₂ C) OR ⁺ 2	F ₃ C	OTMS ↓ OEt TMS 3
Entry	R	Temp (°C)	Time (h)	Yields ^c (%	5)	Ref. 2a
				2 ^b	3	(2) ^d
1	Et (a)	rt (25)	4	62 (69)	(22)	[47]
2	$n-C_{6}H_{13}(\mathbf{b})$	rt (25)	4	60 (68)	(24)	[62]
3	<i>i</i> -Pr (c)	rt (29)	3.5	65 (77)	(11)	_
4	Cy (d)	rt (23)	4	68 (73)	(18)	—

^aMg—Cu was in situ prepared from Mg powder (4 equiv) and CuCl (0.5 equiv). ^b Isolated yields by distillation after decomposition of silyl ketals **3** under acidic conditions (on 5 mmol scale).

^c Values in parentheses are yields in crude product mixture determined by ¹⁹F NMR with benzotrifluoride as an internal standard.

Reported isolated yields by electrochemical reductions [Ref. 2a].

A plausible mechanism is illustrated in Scheme 4. Initial electron transfer(s) from magnesium to the trifluoroacetates would give some anion species, followed by defluorination—silylation or double silylations.^{2e} The enolate form of the product would be thermally rearranged to the ester **2**.^{2b}



3. Conclusions

In summary, alkyl 2,2-difluoro-2-(trimethylsilyl)acetates **2a–d** were produced by the reduction of alkyl trifluoroacetates **1** by copper-deposited magnesium, which can be easily prepared by the mixing of magnesium powder and CuCl in DMI with LiCl additive solution just prior to the reaction. Alkyl 2,2-difluoro-2-(trime-thylsilyl)acetates **2** were isolated by distillation after the decomposition of byproducts **3** under acidic conditions. Detailed mechanisms and the scope of the reduction ability of copper-deposited magnesium are now under investigation.

4. Experimental

4.1. General

All NMR spectra were recorded as CDCl₃ solutions. ¹H NMR (600 MHz) was recorded with Varian Unity INOVA AS600. ¹H NMR (400 MHz), ¹³C NMR (100 MHz), ¹⁹F NMR (376 MHz) spectra were recorded with Varian VNMRS-400 instrument. The chemical shifts are reported in TM (ppm) related to the CHCl₃ (7.26 ppm for ¹H NMR), CDCl₃ (77 ppm for ¹³C NMR), and C₆F₆ (0 ppm for ¹⁹F NMR: the relative chemical shift of C₆F₆ to CFCl₃ is – 162.2 ppm). Coupling constants (*J*) are reported in hertz (Hz). Infrared spectra were recorded on a Hitachi 270-30 spectrometer. Only selected absorbances are reported (*v* in cm⁻¹). MS analyses were performed on a Shimadzu GCMS-QP5050A. Elemental analyses were performed on a Perkin–Elmer series II CHNS/O Analyzer 2400.

4.2. Procedures for reductions of alkyl trifluoroacetates (1) by Cu-deposited Mg and trimethylsilyl chloride

4.2.1. Synthesis of ethyl 2,2-difluoro-2-(trimethylsilyl)acetate (**2a**). Mg powder (0.486 g, 20 mmol), copper(I) chloride (0.248 g, 2.5 mmol), and lithium chloride (1.7 g, 40 mmol) were stirred in DMI (10.0 ml) and TMS-Cl (5.0 ml, 40 mmol) for 15 min under an argon atmosphere at room temperature. Ethyl trifluoroacetate (5 mmol, 0.71 g) was added dropwise into the stirred suspension. The suspension was stirred for additional 4 h at room temperature. After removal of Mg–Cu by decantation, the DMI solution was extracted with Et₂O. The Et₂O layer was washed with 10% HCl aq and brine, dried over MgSO₄. Then, solvent was removed under a reduced pressure. The mixture of difluoro-compound **2a** and silyl ketal **3a** was obtained.

Procedure for removal of 3a from the mixture of 2a and 3a. Anhydrous HCl/EtOH was prepared from TMS-Cl (3.0 ml, 25 mmol) and ethanol (2 ml, 34 mmol). The prepared anhydrous HCl/EtOH was added dropwise into the mixture of difluoro-compound 2a and silvl ketal 3a. After stirring 90 min at room temperature, the solution was extracted with ether (5 ml \times 4). The combined organic layer was washed with brine. Organic layer was dried over MgSO₄, then, was concentrated under a reduced pressure. Kugelrohr distillation (100 °C/32 mmHg, bath temperature) of the crude product gave ethyl 2,2-difluoro-2-(trimethylsilyl)acetate (2a) in 62% (0.602 g) of isolated yield. Colorless oil. Bp=70 °C/20 mmHg (bath temperature). IR ν_{max} (neat) 2980, 1760 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.23 (s, 9H), 1.34 (t, *J*=7 Hz, 3H), 4.31 (q, *J*=7 Hz, 2H) ppm. [δ 0.16 (s, 9H), 1.27 (t, *J*=7 Hz, 3H), 4.24 (q, *J*=7 Hz 2H) ppm. (Ref. 2c)] ¹³C NMR (100 MHz, CDCl₃) δ -5.2 (s), 13.9 (s), 62.2 (s), 121.0 (t, *J*=268 Hz), 166.3 (t, *J*=26 Hz) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ 38.4 (s, 2F) ppm. [δ 38.7 (s, 2F) ppm. (Ref. 2c)] EI-MS m/z (% relative intensity) 181 ([M]⁺-CH₃, 1), 153 (4), 117 (5), 73 (100).

4.2.2. Ethyl silyl ketal (**3a**). Compound **3a** was isolated from the reaction mixture with **2a** by column chromatography on silica gel (hexane eluent). Colorless oil. Bp=80 °C/20 mmHg (bath

temperature). IR ν_{max} (neat) 2990, 2910 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.16 (q, *J*=1 Hz, 9H), 0.17 (s, 9H), 1.19 (t, *J*=7 Hz, 3H), 3.66 (m, 2H) ppm. [δ 0.18 (s, 9H), 0.19 (s, 9H), 1.21 (t, *J*=7.0 Hz, 3H), 3.68 (m, 2H) (Ref. 6)] ¹⁹F NMR (376 MHz, CDCl₃) δ 86.5 (s, 3F) ppm. [δ 86.7 (s, 3F) ppm. (Ref. 6)] EI-MS *m*/*z* (% relative intensity) 259 ([M]⁺-C₂H₅, 6), 73 (100).

4.2.3. Synthesis of *n*-hexyl 2,2-difluoro-2-(trimethylsilyl)acetate (**2b**). The procedure to obtain the mixture of difluoro-compound **2b** and silyl ketal **3b** was similar to that of the mixture of **2a** and **3a**.

TFA (20 mmol, 2 ml) was added to the mixture of difluorocompound **2b** and silvl ketal **3b**, and stirred additional 60 min at room temperature. The TFA solution of the crude mixture was extracted with *n*-hexane. The combined *n*-hexane solution was washed with 10% HCl ag and brine. The *n*-hexane solution was dried over MgSO₄. After removal of the solvent under a reduced pressure, Kugelrohr distillation afforded n-hexyl 2,2-difluoro-2trimethylsilylacetate (2b) in 60% (0.757 g) of isolated yield, respectively. Colorless oil. Bp=90 °C/2 mmHg (bath temperature). IR $\nu_{\rm max}$ (neat) 2970, 1760 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 0.23 (s, 9H), 0.89 (t, J=7 Hz, 3H), 1.28-1.34 (m, 4H), 1.34-1.40 (m, 2H), 1.69 (quint, J=7 Hz, 2H), 4.24 (t, J=7 Hz, 2H) ppm. [(200 MHz, CDCl₃) δ 0.23 (s, 9H), 0.89 (t, J=6.6 Hz, 3H), 1.30–1.41 (m, 6H), 1.62–1.72 (m, 2H), 4.23 (t, J=6.8 Hz, 2H) ppm. (Ref. 2a)] ¹⁹F NMR (376 MHz, CDCl₃) δ 38.4 (s, 2F) ppm. [δ 38.7 (s, 2F) (Ref. 2a)] EI-MS m/z (% relative intensity) 168 ([M]⁺-C₆H₁₂, 6), 152 (12), 77 (25), 73 (50), 43 (100).

4.2.4. *n*-Hexyl silyl ketal (**3b**). Compound **3b** was isolated from the reaction mixture by column chromatography on silica gel (hexane eluent). Yield (24%, determined by ¹⁹F NMR). Colorless oil. Bp=90 °C/2 mmHg (bath temperature). IR ν_{max} (neat) 2970 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.16 (br, 9H), 0.17 (s, 9H), 0.89 (t, *J*=7 Hz, 3H), 1.24–1.40 (m, 6H), 1.51–1.59 (m, 2H), 3.54–3.64 (m, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ –2.5 (s), 1.6 (s), 14.0 (s), 22.6 (s), 25.7 (s), 30.1 (s), 31.6 (s), 64.8 (s), 98.6 (q, *J*=34 Hz), 124.9 (q, *J*=288 Hz) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ 86.8 (s, 3F) ppm. EI-MS *m/z* (% relative intensity) 259 ([M]⁺–C₆H₁₃, 13), 73 (100). Elemental Anal. Calcd for C₁₄H₃₁F₃O₂Si₂: C, 48.80; H, 9.07. Found: C, 48.86; H, 8.96.

4.2.5. Synthesis of i-propyl 2,2-difluoro-2-(trimethylsilyl)acetate (**2c**). The procedure to obtain the mixture of difluoro-compound **2c** and silyl ketal **3c** was similar to that of the mixture of **2a** and **3a**.

Anhydrous HCl/i-PrOH was prepared from TMS-Cl (25 mmol) and H₂O (0.18 ml, 10 mmol) and *i*-PrOH (2.6 ml, 34 mmol). The lower layer of the acidic mixture (*i*-PrOH layer) was added to the mixture of 2c and 3c, and stirred for additional 10 h. The *i*-PrOH solution was extracted with Et₂O (5 ml×5). The combined organic layer was washed with diluted HCl aq and brine. Organic layer was dried over MgSO₄, and was concentrated under a reduced pressure. The mixture of the products was purified by Kugelrohr distillation (80 °C/20 mmHg, bath temperature), which provided isopropyl difluoro(trimethylsilyl)acetate 2c in 65% (0.684 g) of isolated yield. Colorless oil. Bp=80 °C/20 mmHg (bath temperature). IR ν_{max} (neat) 2990, 1760 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.23 (s, 9H), 1.32 (d, J=6 Hz, 6H), 5.15 (sep, J=6 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ -5.2 (s), 21.4 (s), 70.1 (s), 120.8 (t, J=267 Hz), 165.5 (t, J=25 Hz) ppm. $^{19}{\rm F}$ NMR (376 MHz, CDCl_3) δ 38.4 (s, 2F) ppm. EI-MS m/z (% relative intensity) 168 ([M]⁺–C₃H₆, 5), 153 (11), 117 (12), 77 (42), 73 (100). Elemental Anal. Calcd for C₈H₁₆F₂O₂Si: C, 45.69; H, 7.67. Found: C, 45.80; H, 7.85.

4.2.6. Isopropyl silyl ketal (**3c**). Compound **3c** was isolated from the reaction mixture by column chromatography on silica gel (hexane eluent). Yield (11%, determined by ¹⁹F NMR). Colorless oil. Bp=85 °C/20 mmHg (bath temperature). IR ν_{max} (neat) 2990 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 0.13 (s, 9H), 0.18 (s, 9H), 1.13 (dd, *J*=16, 6 Hz, 6H), 4.19 (sep(q), *J*=6 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ -3.2 (s), 1.8 (s), 23.3(s), 24.7 (s), 66.4 (s), 97.7 (q, *J*=34 Hz), 125.1 (q, *J*=289 Hz) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ 87.4 (s, 3F). EI-MS *m/z* (% relative intensity) 259 ([M]⁺-C₃H₇, 7), 73 (100). Elemental Anal. Calcd for C₁₁H₂₅F₃O₂Si₂: C, 43.68; H, 8.33. Found: C, 43.59; H, 8.28.

4.2.7. Synthesis of cyclohexyl 2,2-difluoro-2-(trimethylsilyl)acetate (2d). The procedure to obtain the mixture of difluoro-compound 2d and silyl ketal 3d is similar to that of the mixture of 2a and 3a.

Procedure to remove **3d** from the mixture of **2d** and **3d** is the same to that of *n*-hexyl acetate **2b**. Yield (68%). Colorless oil. Bp=90 °C/2 mmHg (bath temperature). IR ν_{max} (neat) 2950, 1750 cm⁻¹. ¹H NMR (600 MHz, CDCl₃) δ 0.23 (s, 9H), 1.29 (dtt, *J*=13, 10, 4 Hz, 1H), 1.39 (dtt, *J*=14, 10, 4 Hz, 2H), 1.48–1.52 (m, 2H), 1.55 (dtt, *J*=13, 8, 4 Hz, 1H), 1.74–1.78 (m, 2H), 1.88–1.91 (m, 2H), 4.92 (tt, *J*=4, 10 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ –5.0(s), 23.5 (s), 25.1 (s), 31.3 (s), 74.8 (s), 120.8 (t, *J*=267 Hz), 165.6 (t, *J*=25 Hz) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ 38.6 (s, 2F) ppm. El-MS *m/z* (% relative intensity) 168 ([M]⁺-C₆H₁₀, 14), 152 (19), 83 (74), 77 (31), 73 (57), 55 (100). Elemental Anal. Calcd for C₁₁H₂₀F₂O₂Si: C, 52.77; H, 8.05. Found: C, 52.49; H, 8.31.

4.2.8. Cyclohexyl silyl ketal (**3d**). Compound **3d** was isolated from the reaction mixture by column chromatography on silica gel (hexane eluent). Yield (18%, determined by ¹⁹F NMR). Colorless oil. Bp=90 °C/2 mmHg (bath temperature). IR ν_{max} (neat) 2940, 2860 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 0.13 (br, 9H), 0.17 (s, 9H), 1.20–1.48 (m, 6H), 1.71–1.78 (m, 4H), 3.84–3.89 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ –3.1 (s), 1.8 (s), 24.0 (s), 24.3 (s), 25.7 (s), 33.3 (s), 34.7 (s), 71.7 (s), 97.7 (q, *J*=34 Hz), 125.1 (q, *J*=289 Hz) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ 87.4 (s, 3F) ppm. El-MS *m/z* (% relative intensity) 259 ([M]⁺–C₆H₁₁, 4), 147 (2), 73 (100). Elemental Anal. Calcd for C₁₄H₂₉F₃O₂Si₂: C, 49.09; H, 8.53. Found: C, 48.98; H, 8.52.

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