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Direct aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with ketones by use of the combination of amines and acids

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Abstract—Trifluoroacetaldehyde ethyl hemiacetal reacts with unmodified ketones in the presence of 30–50 each mol % of amines and acids at ambient temperature, affording the corresponding β-hydroxy-β-trifluoromethylated ketones in good yields with good to excellent diastereoselectivities.

1. Introduction

Despite significant progress in the area of efficient synthesis of trifluoromethylated molecules using trifluoroacetaldehyde (CF_3CHO), the method for the generation of CF_3CHO from its hemiacetal or hydrate is still dependent on the early protocol, which includes a serious indispensable condition such as use of an excess amount of concentrated sulfuric acid under high reaction temperature.[1] Therefore, an environmentally-friendly, practical, and efficient method for the in situ generation of CF_3CHO attended by its simultaneous stereoselective carbon–carbon bond formation reaction is really required. Recently, we have found that a stoichiometric amount of enamines or imines react well with CF_3CHO ethyl hemiacetal via the regio- and/or stereoselective carbon–carbon bond formation reaction under mild conditions without any additives, producing β-hydroxy-β-trifluoromethylated ketones in good to excellent yields.[3] This reaction can serve as a new expedient method for the general, practical, and regio- and/or stereoselective synthesis of β-hydroxy-β-trifluoromethylated ketones. However, in this method a couple of steps for the preparation of enamines and imines as well as for the hydrolysis of the intermediates producing β-hydroxy-β-trifluoromethylated ketones are absolutely necessary. For the further development of a new atom-economical method for the synthesis of β-trifluoromethylated aldol adducts, we describe herein the direct aldol reaction of CF_3CHO ethyl hemiacetal with unmodified ketones by the use of the combination of a small amount (30–50 mol %) of amine and acid,[3–6] affording the good yields of β-hydroxy-β-trifluoromethyl ketones with good to excellent *syn*-diastereoselectivities. Importantly, this method could achieve a reduction of the steps for in situ generation of CF_3CHO and successive carbon–carbon bond formation reactions. That is, a single manipulation may include multi steps in the reaction, such as (1) the formation of enamine or imine, (2) the enamine- or imine-assisted in situ generation of CF_3CHO, (3) the successive carbon–carbon bond formation reaction of CF_3CHO, and (4) the hydrolysis of the intermediates, producing β-hydroxy-β-trifluoromethylated ketones as well as reproduction of amine and acid.

2. Results and discussion

CF_3CHO ethyl hemiacetal **1a** reacted smoothly with acetone **2a** in the presence of 50 each mol % of piperidine and acetic acid at room temperature for 24 h to produce the β-hydroxy-β-trifluoromethylated ketone **3a** in 60% yield, together with a trace amount of 1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-heptanone **4** (Table 1, entry 3). The direct aldol reactions of CF_3CHO ethyl hemiacetal **1a** with acetone **2a** under the various reaction conditions are summarized in Table 1.

The use of only piperidine gave no product **3a** with a trace amount of bis-adduct **4** at various temperatures (entries 1 and 2). Other organic acids, such as trifluoroacetic acid and *p*-toluenesulfonic acid were not effective to give a trace amount of or no product (entries 4 and 5). Among the solid acids examined, such as silica gel (Wakogel C200),[5] Montmorillonite K10, $H_4SiW_{12}O_{40}$, and Nafion R-50 (entries 6–9), Wakogel C200 was most effective for the direct aldol reaction with acetone to provide the aldol product **3a** in 58% yield, along with a 10% yield of **4** (entry 6). Out of a variety of amines screened in both cases of acetic acid and Wakogel C200, cyclic secondary amines, such as morpholine and

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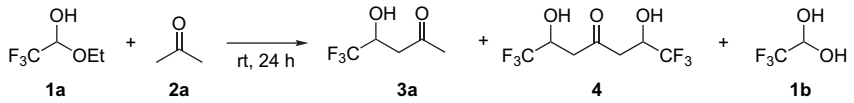
Table 1. In situ generation of trifluoroacetaldehyde from its hemiacetal **1a** and successive direct aldol reaction with acetone using the combination of amines and acids under the various conditions[a]



1a **2a** **3a** **4** **1b**

Entry	Amine	Acid	Solvent	Yield (%)[b]
1	Piperidine (50 mol %)	None	Acetone	**3a** (0), **4** (10), **1b** (22), **1a** (16)
2[c]	Piperidine (50 mol %)	None	Acetone	**3a** (0), **4** (6), **1b** (17), **1a** (13)
3	Piperidine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (60), **4** (5), **1b** (0), **1a** (0)
4	Piperidine (50 mol %)	CF_3CO_2H (50 mol %)	Acetone	**3a** (1), **4** (0), **1b** (32), **1a** (14)
5	Piperidine (50 mol %)	*p*-TsOH·H_2O (50 mol %)	Acetone	**3a** (0), **4** (0), **1b** (45), **1a** (11)
6	Piperidine (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (58), **4** (10), **1b** (0), **1a** (0)
7	Piperidine (50 mol %)	Montmorillonite K 10 (120 mg)	Acetone	**3a** (32), **4** (22), **1b** (0), **1a** (0)
8	Piperidine (50 mol %)	$H_4SiW_{12}O_{40}$ (120 mg)	Acetone	**3a** (9), **4** (18), **1b** (18), **1a** (9)
9	Piperidine (50 mol %)	Nafion R-50 (120 mg)	Acetone	**3a** (0), **4** (8), **1b** (16), **1a** (19)
10	*n*-$PrNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (65), **4** (3), **1b** (0), **1a** (0)
11	*c*-$HexNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (65), **4** (1), **1b** (0), **1a** (0)
12	*t*-$BuNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (17), **4** (11), **1b** (19), **1a** (22)
13	Morpholine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (61), **4** (1), **1b** (0), **1a** (2)
14	1-Methylpiperazine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (53), **4** (7), **1b** (0), **1a** (0)
15[d]	Et_2NH (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (30), **4** (18), **1b** (0), **1a** (0)
16	*i*-Pr_2NH (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (1), **4** (1), **1b** (49), **1a** (22)
17	Ph_2NH (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (0), **4** (0), **1b** (21), **1a** (57)
18	Et_3N (50 mol %)	CH_3CO_2H (50 mol %)	Acetone	**3a** (0), **4** (0), **1b** (56), **1a** (24)
19	*n*-$PrNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (53), **4** (3), **1b** (0), **1a** (0)
20	*c*-$HexNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (50), **4** (14), **1b** (0), **1a** (0)
21	*t*-$BuNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (3), **4** (13), **1b** (23), **1a** (5)
22	Morpholine (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (52), **4** (0), **1b** (0), **1a** (0)
23	1-Methylpiperazine (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (67), **4** (0), **1b** (0), **1a** (0)
24	Et_2NH (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (28), **4** (27), **1b** (0), **1a** (0)
25	*i*-Pr_2NH (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (0), **4** (0), **1b** (28), **1a** (24)
26	Ph_2NH (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (0), **4** (0), **1b** (39), **1a** (8)
27	Et_3N (50 mol %)	Silica gel (120 mg)	Acetone	**3a** (0), **4** (0), **1b** (26), **1a** (9)
28	Piperidine (30 mol %)	CH_3CO_2H (30 mol %)	Acetone	**3a** (53), **4** (21), **1b** (0), **1a** (0)
29	*n*-$PrNH_2$ (30 mol %)	CH_3CO_2H (30 mol %)	Acetone	**3a** (62), **4** (3), **1b** (0), **1a** (0)
30	Piperidine (30 mol %)	Silica gel (72 mg)	Acetone	**3a** (38), **4** (21), **1b** (0), **1a** (0)
31	*n*-$PrNH_2$ (30 mol %)	Silica gel (72 mg)	Acetone	**3a** (16), **4** (14), **1b** (6), **1a** (17)
32	Piperidine (50 mol %)	CH_3CO_2H (50 mol %)	Acetone–DMSO	**3a** (23), **4** (34), **1b** (0), **1a** (0)
33	*n*-$PrNH_2$ (50 mol %)	CH_3CO_2H (50 mol %)	Acetone–DMSO	**3a** (18), **4** (23), **1b** (0), **1a** (0)
34	Piperidine (50 mol %)	Silica gel (120 mg)	Acetone–DMSO	**3a** (0), **4** (2), **1b** (19), **1a** (8)
35	*n*-$PrNH_2$ (50 mol %)	Silica gel (120 mg)	Acetone–DMSO	**3a** (14), **4** (23), **1b** (4), **1a** (2)

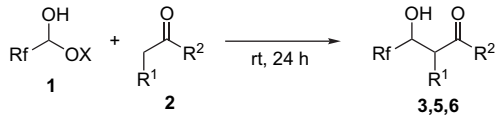
[a] All the reaction was carried out with trifluoroacetaldehyde ethyl hemiacetal **1a** (1 mmol) with amine **2** and organic acid or solid acid in dry acetone (10 ml) or in the mixed solvent of DMSO (8 ml) and dry acetone (2 ml).
[b] Yields were measured by ^{19}F NMR.
[c] Carried out at reflux.
[d] Many unidentified by-products were formed.

1-methylpiperazine (entries 13, 14, 22, and 23) as well as primary amines bearing *n*-propyl or *c*-hexyl group were suitable for the reaction to give acceptable yields of the aldol product **3a** (entries 10, 11, 19, and 20). The use of diethylamine as an acyclic secondary amine resulted in the increase of the formation of bis-adduct **4**, together with **3a** in 28–30% yields (entries 15 and 24).

The reaction with *tert*-butylamine (entries 12 and 21) or diisopropylamine (entries 16 and 25) having the bulky group produced only trace amount of the aldol product. Diphenylamine also was not effective for the reaction to afford no product, probably due to its low nucleophilicity (entries 17 and 26). The use of triethylamine also gave no product (entries 18 and 27). These results may suggest that (1) the reaction proceeds via enamine or imine, which is produced from the corresponding ketone in the presence of the acid and the corresponding secondary or primary amine, and (2) the resulting enamine or imine reacts with CF_3CHO ethyl hemiacetal **1a** via not only in situ generation of CF_3CHO but also carbon–carbon bond formation reaction to give the corresponding β-hydroxy-β-trifluoromethyl ketones.[2] The reaction of hemiacetal **1a** with acetone **2a** in the presence of 30 each mol % of piperidine or *n*-propylamine and acetic acid afforded the corresponding aldol product **3a** in acceptable yields (53–62%) (entries 28 and 29). Reducing the amount of amines to 30 mol % and the amount of silica gel to 60% of the former amount gave rise to lowering the yield of **2a**, together with the formation of bis-adduct **4** (entries 30 and 31). Irrespective of the amines as well as the acids, the use of DMSO as a polar co-solvent resulted in decreasing the yield of **3a**, along with the increase of bis-adduct **4**. In all cases, mass balances in the yield are not good, probably due to these high volatility and self-polymerization of CF_3CHO.

The results of cyclic ketones as well as other polyfluoroalkylaldehyde hemiacetal or hydrate are summarized in Table 2.

Table 2. In situ generation of polyfluoroalkylaldehyde from its hemiacetal or hydrate and successive direct aldol reaction with ketones using the combination of amines and acids[a]



Entry	1	R_f	X	2	R^1, R^2	Method[b]	3,5,6	Yield (%)[c]	*syn*:*anti*[d]
1	**1a**	CF_3	Et	**2a**	H, Me	A	**3a**	60	—
2	**1a**	CF_3	Et	**2b**	$-(CH_2)_3-$	A	**3b**	82 (41)	93:7
3	**1a**	CF_3	Et	**2c**	$-(CH_2)_4-$	A	**3c**	45	40:60
4	**1b**	CF_3	H	**2b**	$-(CH_2)_3-$	A	**3b**	88	92:8
5	**1c**	CHF_2	Et	**2b**	$-(CH_2)_3-$	A	**5**	47 (46)	78:22
6	**1d**	CF_3CF_2	H	**2b**	$-(CH_2)_3-$	A	**6**	77 (50)	94:6
7	**1a**	CF_3	Et	**2a**	H, Me	B	**3a**	58	—
8	**1a**	CF_3	Et	**2b**	$-(CH_2)_3-$	B	**3b**	86 (42)	90:10
9	**1a**	CF_3	Et	**2c**	$-(CH_2)_4-$	B	**3c**	33	54:46
10	**1b**	CF_3	H	**2b**	$-(CH_2)_3-$	B	**3b**	77 (40)	89:11
11	**1c**	CHF_2	Et	**2b**	$-(CH_2)_3-$	B	**5**	74 (71)	74:26
12	**1d**	CF_3CF_2	H	**2b**	$-(CH_2)_3-$	B	**6**	70 (61)	93:7
13	**1a**	CF_3	Et	**2b**	$-(CH_2)_3-$	C	**3b**	85	79:26

[a] All the reaction was carried out with polyfluoroalkylaldehyde ethyl hemiacetal (1 mmol) or hydrate (1 mmol) in the corresponding ketone (10 ml).
[b] Method A; piperidine (50 mol %) and acetic acid (50 mol %). Method B; piperidine (50 mol %) and Wakogel C200. Method C; *n*-$PrNH_2$ (50 mol %) and acetic acid (50 mol %).
[c] Measured by ^{19}F NMR using benzotrifluoride. Values in parentheses stand for the yields of isolated products.
[d] Determined by ^{19}F NMR.

Cyclopentanone **2b** could also participate well in the direct aldol reaction of CF_3CHO ethyl hemiacetal **1a** to produce the corresponding β-hydroxy-β-trifluoromethyl ketone **5** in good yields with high *syn*-diastereoselectivities by the use of acetic acid (Method A) or Wakogel C200 (Method B) (entries 2 and 8). Major diastereomer of **3b** could be assigned *syn*-isomer by comparison with the chemical shift of β-methine proton of aldol product attached to the hydroxyl group ($CF_3CH(OH)$–) in ^1H NMR according to the reported values.[4] This result could also be supported by the literature by Denmark.[7] The literature describes that in the aldol products, derived from cyclopentanone or cyclohexanone, the methine proton at β-carbon of *syn*-products appears in the lower field than those of *anti*-products in ^1H NMR. The reaction of CF_3CHO ethyl hemiacetal **1a** with cyclohexanone **2c** gave a 45% yield of the aldol product **3c** with low diastereoselectivity, because many unidentified by-products were produced (entries 3 and 9).

syn-Selective direct aldol reaction of CF_3CHO ethyl hemiacetal **1a** with cyclopentanone **2b** by using *n*-propylamine in place of piperidine also occurred to produce the aldol product **3b** in 85% yield with slight reduction of diastereoselectivity (entry 13). CF_3CHO hydrate **1b** also reacted well with cyclopentanone **2b** to produce the aldol product **3b** in the similar yields with similar diastereoselectivities (entries 4 and 10). The direct aldol reaction of difluoroacetaldehyde ethyl hemiacetal **1c** as well as pentafluoropropionaldehyde hydrate **1d** with cyclopentanone **2b**, also successfully occurred to produce the corresponding β-difluoromethyl or pentafluoroethyl aldol adduct **5** or **6** in good yields with good to excellent *syn*-diastereoselectivities in both cases of acetic acid and silica gel with piperidine (entries 5, 6, 11, and 12). The yields of isolated trifluoromethylated aldol product, derived from cyclopentanone, are lower than those of difluoromethylated or pentafluoroethylated aldol ones, because it is troublesome to isolate the trifluoromethylated aldol product from the reaction mixtures by column chromatography. Degree of *syn*-diastereoselectivities of the products **3b**, **5**, and **6**, derived from cyclopentanone, may depend on the bulkiness of the fluoroalkyl groups[8] in the following orders under the same conditions: the pentafluoroethyl (*syn*:*anti*=94:6, 88% de)>trifluoromethyl (*syn*:*anti*=93:7, 86% de)>difluoromethyl (*syn*:*anti*=78:22, 56% de) group (entries 2, 5, and 6), though the reason for this *syn*-selective outcome is not clear at this present.

3. Conclusions

In summary, we have achieved the direct aldol reaction of CF_3CHO ethyl hemiacetal, with unmodified ketones by the use of small amount of acids and amines without any strong acid and high reaction temperature, producing β-hydroxy-β-trifluoromethylated ketones in good yields. Studies addressing catalytic process for the asymmetric direct aldol reaction of CF_3CHO ethyl hemiacetal will be reported in due course.

4. Experimental

4.1. General

^1H NMR spectra were measured with a JEOL α-400 (400 MHz) FT-NMR spectrometer, a JNM-AL400 (400 MHz) FT-NMR spectrometer, or a JNM-ECA500 (500 MHz) FT-NMR spectrometer in deuteriochloroform ($CDCl_3$) solutions with tetramethylsilane (Me_4Si) as the internal standard. ^{13}C NMR spectra were measured with a JEOL α-400 (100 MHz) FT-NMR spectrometer, a JNM-AL400 (100 MHz) FT-NMR spectrometer, or a JNM-ECA500 (126 MHz) FT-NMR spectrometer in $CDCl_3$ solutions with tetramethylsilane (Me_4Si) as the internal standard. ^{19}F NMR spectra were recorded on a JEOL α-400 (376 MHz) FT-NMR spectrometer, a JNM-AL400

(372 MHz) FT-NMR spectrometer, or a JNM-ECA500 (471 MHz) FT-NMR spectrometer in $CDCl_3$ solutions using trifluoroacetic acid as the external standard.

4.2. A typical procedure

To a solution of a catalytic amount of silica gel (Wakogel C200) (0.120 g) and piperidine (0.043 g, 0.5 mmol) in dry acetone **2a** (10 ml) was added trifluoroacetaldehyde ethyl hemiacetal **1a** (0.144 g, 1 mmol) at room temperature under an inert atmosphere. After being stirred at room temperature for 24 h, the reaction mixture was quenched with NH_4Cl aq solution (40 ml), followed by extraction with Et_2O (30 ml×3). The organic layer was dried over Na_2SO_4 and the solvents were removed by distillation under reduced pressure with cold ice bath. After the measurement of the residue by ^{19}F NMR using benzotrifluoride (58% of **3a** and 10% of **4**), purification by flash chromatography on silica gel (hexane–Et_2O=3:1) gave **3a** (44%, 0.068 g) and trace amount of **4**.

4.2.1. 5,5,5-Trifluoro-4-hydroxy-2-pentanone (3a).[9] IR (KBr) 1716.9 (C=O), 3411.2 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.24 (3H, s), 2.78 (1H, dd, J=17.83, 3.01 Hz), 2.84 (1H, dd, J=17.83, 8.88 Hz), 3.41 (1H, br s), 4.44–4.51 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6 (s), 42.8 (s), 66.3 (q, J=32.2 Hz), 124.6 (q, J=280.6 Hz), 206.4 (s); ^{19}F NMR (471 MHz, $CDCl_3$) δ −1.8 (3F, d, J=6.9 Hz); HRMS (CI) Found: m/z 157.0476. Calcd for $C_5H_8F_3O_2$: M+H, 157.0479.

4.2.2. 1,1,1,7,7,7-Hexafluoro-2,6-dihydroxy-4-heptanone (4). Mp 70–71 °C; IR (KBr) 3392.9 (OH), 1732.3 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (1H×2, ddd, J=7.08, 2.69 Hz), 2.94 (1H×2, dd, J=17.57, 9.27 Hz), 3.06 (1H×2, br s), 4.50–4.60 (1H×2, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.0 (s), 66.4 (q, J=32.8 Hz), 66.4 (q, J=32.5 Hz), 124.3 (q, J=279.5 Hz), 204.7 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ −1.99 (3F, d, J=6.8 Hz), −2.02 (3F, d, J=6.8 Hz); HRMS (EI) Found: m/z 254.0374. Calcd for $C_7H_8O_3F_6$: M, 254.0377.

4.2.3. 2-(2,2,2-Trifluoro-1-hydroxyethyl)cyclopentanone (3b).[4] *syn Isomer*: IR (KBr) 1713.0 (C=O), 3458.8 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.72–1.89 (1H, m), 2.06–2.23 (4H, m), 2.34–2.51 (1H, m), 3.17–3.27 (1H, m), 4.58 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (s), 22.3 (s), 38.0 (s), 49.2 (s), 67.7 (q, J=31.7 Hz), 125.0 (q, J=282.0 Hz), 218.6 (s); ^{19}F NMR (471 MHz, $CDCl_3$) δ −0.3 (3F, d, J=7.5 Hz); HRMS (EI) Found: m/z 182.0555. Calcd for $C_7H_9F_3O_2$: M, 182.0555.

4.2.4. 2-(2,2,2-Trifluoro-1-hydroxyethyl)cyclohexanone (3c).[10] *anti Isomer*: IR (KBr) 1792.1 (C=O), 3447.2 (OH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64–1.81 (3H, m), 1.93–1.98 (1H, m), 2.14–2.24 (2H, m), 2.37–2.49 (2H, m), 2.74–2.80 (1H, m) 4.00–4.09 (1H, m), 4.38 (1H, d, J=5.85 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9 (s), 28.1 (s), 31.6 (s), 43.0 (s), 50.3 (s), 71.8 (q, J=31.4 Hz), 124.7 (q, J=282.9 Hz), 213.7 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ 2.0 (3F, d, J=7.6 Hz); HRMS (EI) Found: m/z 196.0711. Calcd for $C_8H_{11}F_3O_2$: M, 196.0711.

4.2.5. 2-(2,2-Difluoro-1-hydroxyethyl)cyclopentanone (5). IR (KBr) 3439.1 (OH), 1736.1 (C=O) cm^{-1}; *syn Isomer*: ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.88 (4H, m), 2.32–2.41 (2H, m), 3.74 (1H, br s), 4.26 (1H, br s), 5.76 (1H, dt, J=55.78, 4.59 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (s), 22.7 (s), 38.1 (s), 49.3 (t, J=2.5 Hz), 68.5 (t, J=24.6 Hz), 115.7 (t, J=244.1 Hz), 220.0 (d, J=6.6 Hz); ^{19}F NMR (372 MHz, $CDCl_3$) δ −52.9 (2F, ddd, J=55.8, 22.1, 11.5 Hz); *anti Isomer*: ^1H NMR (400 MHz, $CDCl_3$) δ 1.78–1.88 (2H, m), 2.10–2.31 (3H, m), 2.38–2.46 (2H, m), 3.87–3.95 (1H, m), 4.05 (1H, br s), 5.92 (1H, dt, J=55.78, 3.86 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (s), 27.0 (d, J=2.5 Hz), 39.1 (s), 48.8 (t, J=2.9 Hz), 72.4 (t, J=25.0 Hz), 116.0 (dd, J=245.0, 241.7 Hz), 222.4 (s); ^{19}F NMR (372 MHz, $CDCl_3$) δ −51.4 (1F, ddd, J=289.2, 55.8, 10.3 Hz), −55.6 (1F, ddd, J=289.2, 55.8, 11.4 Hz); HRMS (EI) Found: m/z 164.0656. Calcd for $C_7H_{10}O_2F_2$: M, 164.0649.

4.2.6. 2-(2,2,3,3,3-Pentafluoro-1-hydroxypropyl)cyclopentanone (6). *syn Isomer*: mp 58–58.5 °C; IR (KBr) 3457.0 (OH), 1736.1 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74–1.88 (1H, m), 2.05–2.27 (4H, m), 2.35–2.50 (2H, m), 3.50 (1H, d, J=6.28 Hz), 4.70 (1H, dt, J=20.77, 6.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5 (s), 22.6 (d, J=2.5 Hz), 37.8 (s), 49.3 (s), 66.5 (dd, J=27.4, 21.7 Hz), 114.0 (ddq, J=260.5, 255.6, 36.1 Hz), 118.7 (qt, J=286.7, 36.1 Hz), 218.8 (s); ^{19}F NMR (372 MHz, $CDCl_3$) δ −6.1 (3F, s), −45.9 (1F, dd, J=275.4, 20.6 Hz), −52.4 (1F, ddd, J=275.4, 20.6, 2.3 Hz); HRMS (EI) Found: m/z 232.0528. Calcd for $C_8H_9O_2F_5$: M, 232.0523.

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