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Metal-mediated Reformatsky reaction of bromodifluoromethyl ketone and aldehyde using water as solvent

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ABSTRACT

Water is demonstrated as a suitable solvent for an efficient and environmentally friendly method for the synthesis of α,α-difluorinated β-hydroxy carbonyl compounds through the Reformatsky reaction of bromodifluoromethyl ketones with aldehydes in the presence of Zn/CuCl at room temperature.

1. Introduction

Fluorine-containing compounds have received considerable attention for many years due to their unique physical, chemical, and biological properties [1]. Incorporation of fluorine as either a bioisosteric replacement for hydrogen or an isoelectronic replacement for hydroxy group has profound influence on the metabolic degradation, lipophilicity and reactivities of organic compounds [2]. Accordingly, deliberate introduction of fluorinated moieties into organic molecules has become one of the effective strategies in drug design. Among various fluorinated moieties, α,α-difluoroketone unit has found applications in many inhibitors of HIV-1 protease, elastase, rennin, and human heart chymase [1b,3]. Additionally, α,α-difluorinated β-hydroxy carbonyl compounds have been used to synthesize many fluorinated analogs of biochemically important compounds, such as sugars, nucleosides, amino acids or fatty acids [4]. Therefore, the development of practical methods for the introduction of α,α-difluoroketone unit is of great significance.

Aldol-type addition reaction of difluoroenol ethers has proven to be productive for the synthesis of difluorocarbonyl compounds [3,5]. Additionally, metal-mediated Reformatsky reactions of halodifluoroacetates and halodifluoroketones afford another effective approach [4,6]. However, fluorine-containing organometallic reagents often suffer from difficulties due to their intrinsic low nucleophilicity and thermal instability [7]. Moreover, these classic reactions generally require strict anhydrous and oxygen-free conditions.

Carrying out organic reaction in aqueous media has significant advantages from an economic and environmental standpoint [8]. Furthermore, the use of a moisture-resistant radical species would eliminate the cumbersome operations involved in conventional ionic reactions [9]. It has been demonstrated that metals, such as Zn, Sn and Bi, could mediate Reformatsky-type reaction in aqueous media [10]. For these reactions, a radical mechanism initiated by electron abstraction from organometallic reagent was proposed. In-mediated aqueous Reformatsky reaction of chlorodifluoromethyl ketones has also been reported, in which the mixture of organic solvent and water was employed and the scope of chlorodifluoromethyl ketone is quite limited [11]. Recently, it was found in our laboratory that the Reformatsky reaction of bromodifluoromethyl ketones with aldehydes could take place readily in water in the presence of Zn or In to give the corresponding α,α-difluorinated β-hydroxy carbonyl compounds. The results are reported in this paper.

2. Results and discussion

Initially, bromodifluoromethyl phenyl ketone (**1a**) was used as the substrate to investigate the Reformatsky reaction with benzaldehyde. When the reaction was carried out with 4.0 equiv. of benzaldehyde **2a** and 1.3 equiv. of zinc powder in

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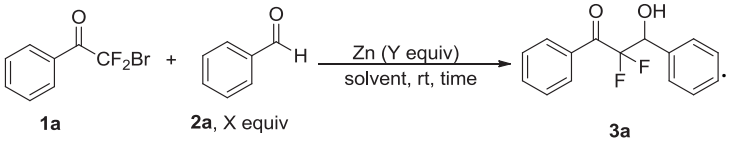
Table 1
Reformatsky reaction of **1a** and **2a** under different conditions.



1a **2a**, X equiv **3a**

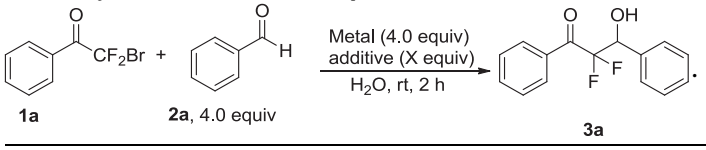
Entry[a]	*X* (equiv.)	*Y* (equiv.)	Solvent	Time (h)	Yield (**3a**, %)[b]
1	4.0	1.3	THF	4	8
2	4.0	1.3	DMF	4	27
3	4.0	1.3	DCM	4	39
4	4.0	1.3	THF/H_2O (3:1)	4	13
5	4.0	1.3	H_2O	2	81
6	4.0	1.3	H_2O	2	65[c]
7	1.3	1.3	H_2O	2	60
8	4.0	0.5	H_2O	2	35
9	2.0	2.0	H_2O	2	81
10	4.0	4.0	H_2O	2	90

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (*X* equiv.), zinc (*Y* equiv.) in solvent (2.0 mL) at room temperature for 2–4 h.
[b] Determined by ^{19}F NMR.
[c] The reaction was carried out at 55 °C.

tetrahydrofuran (THF) at room temperature, the desired adduct **3a** was obtained in 8% yield (Table 1, entry 1). ^{19}F NMR monitoring showed that difluoromethyl phenyl ketone was formed as major by-product. Other solvents such as *N*,*N*-dimethylformide (DMF) and dichloromethane (DCM) didn't give satisfactory result either (entries 2–3). Welch et al. [11a] have reported that water was essential to the In-mediated Reformatsky reaction. And Hammond's group also present that difluoropropargyl bromide could react with aldehydes in aqueous media [12]. Since there are many advantages to carry out reactions in aqueous media, we next used a mixed solvent of THF and H_2O with a ratio of 3:1 (v/v) and ran the reaction at room temperature. However, **3a** was still obtained in low yield (13%, entry 4). Surprisingly, when the reaction of **1a** and **2a** was carried out in pure water, full conversion was achieved and **3a** was obtained in 81% yield in spite of the occurrence of defluorination (entry 5). Increasing the temperature to 55 °C had a negative effect on the reaction, leading to a decreased yield of **3a** (65%, entry 6). Decreasing the amount of benzaldehyde or zinc resulted in the obvious drop of the yield (entries 7–8). Increasing the amount of zinc to 4.0 equiv. improved the yield significantly (90%, entry 10).

To investigate the Reformatsky reaction of **1a** in the aqueous media further, various metals were examined next. The results are summarized in Table 2. Indium could also mediate this reaction effectively and give **3a** in 90% yield (Table 2, entry 2). When aluminum was used, the reaction was very slow and undetermined by-products were formed (entry 3). In the case of magnesium, the reaction was complicated and no desired adduct was observed (entry 4). We noticed that the Reformatsky reaction of chlorodifluoromethyl ketones with aldehydes and ketones in the presence of zinc dust activated in situ by copper (I) gave adducts in good to excellent yields [4,6d]. So we tried to add CuCl in the reaction system. To our delight, the addition of 1.25 equiv. CuCl afforded a clean reaction system (entries 5–9). Other metals such as Ni and Sb failed to promote the reaction, resulting in full recovery of the starting material (entries 10–12). There was no distinct difference between zinc and indium, and zinc was chosen in the following investigation. Therefore, the optimal conditions were set to 4.0 equiv. of

Table 2
Reformatsky reaction of **1a** and **2a** in the presence of different metal.

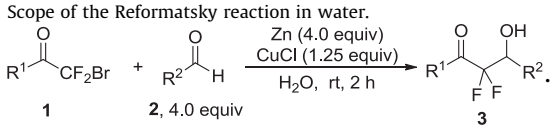


1a **2a**, 4.0 equiv **3a**

Entry[a]	Metal	Additive (*X* equiv.)	Yield (**3a**, %)[b]
1	Zn	–	90
2	In	–	90
3	Al	–	13
4	Mg	–	0[c]
5	Zn	CuCl (0.50)	90
6	Zn	CuCl (1.25)	>95
7	In	CuCl (1.25)	>95
8	Mg	CuCl (1.25)	44
9	Al	CuCl (1.25)	59
10	Ni	CuCl (1.25)	0[c]
11	Cu	CuCl (1.25)	0[c]
12	Sb	CuCl (1.25)	0[c]

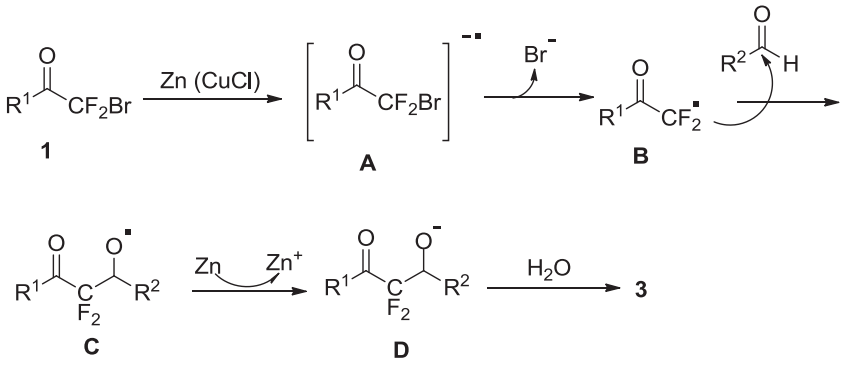
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mmol), metal (2.0 mmol) and *X* equiv. of additive in water (2.0 mL) at room temperature for 2 h.
[b] Determined by ^{19}F NMR.
[c] **1a** was recovered.

Table 3
Scope of the Reformatsky reaction in water.



Entry[a]	**1**, R^1	**2**, R^2	Product	Yield (**3**, %)[b]
1	**1a**, C_6H_5	**2a**, C_6H_5	**3a**	83
2	**1a**, C_6H_5	**2b**, 3-ClC_6H_4	**3b**	80
3	**1a**, C_6H_5	**2c**, 4-ClC_6H_4	**3c**	71
4	**1a**, C_6H_5	**2d**, 2,4-$(Cl)_2C_6H_3$	**3d**	72
5	**1a**, C_6H_5	**2e**, 4-BrC_6H_4	**3e**	64
6	**1a**, C_6H_5	**2f**, 4-FC_6H_4	**3f**	75
7	**1a**, C_6H_5	**2g**, 4-$NO_2C_6H_4$	**3g**	0[c]
8	**1a**, C_6H_5	**2h**, 4-$MeOC_6H_4$	**3h**	71
9	**1a**, C_6H_5	**2i**, 4-$CH_3C_6H_4$	**3i**	71
10	**1a**, C_6H_5	**2j**, 2-Furyl	**3j**	56
11	**1a**, C_6H_5	**2k**, *i*-C_4H_9	**3k**	65
12	**1a**, C_6H_5	**2l**, C_2H_5	**3l**	40
13	**1a**, C_6H_5	**2m**, *n*-C_3H_7	**3m**	56
14	**1b**, 4-$MeOC_6H_4$	**2a**, C_6H_5	**3n**	86
15	**1c**, 4-ClC_6H_4	**2a**, C_6H_5	**3o**	72
16	**1d**, $C_6H_5(CH_2)_3$–	**2a**, C_6H_5	**3p**	86
17	**1e**, EtO	**2a**, C_6H_5	**3q**	40

[a] Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), zinc (2.0 mmol), and CuCl (0.625 mmol) in water (2.0 mL) at room temperature for 2 h.
[b] Isolated yields.
[c] **1a** was recovered.



Scheme 1. Proposed mechanism for the Reformatsky reaction of bromodifluoromethyl ketone and aldehyde.

aldehyde, 4.0 equiv. of zinc and 1.25 equiv. of CuCl in water at room temperature.

Using the optimized conditions, a variety of aldehydes were investigated to evaluate the scope of this reaction. The results are summarized in Table 3. The procedure tolerated a broad range of functional groups. Halide substituted benzaldehydes reacted well with **1a** to give the corresponding adducts **3b-3f** in moderate to good yields (Table 3, entries 2–6). The use of a bromo substitution allows further modification of the adduct (entry 5). Reaction of **2g** with a nitro-substitutent failed to promote any adduct resulting in full recovery of the starting material (entry 7). Electron-rich benzaldehydes bearing methyl or methoxy-substitution worked well under the optimal reaction conditions (entries 8–9). 2-Furylaldehyde could also react with **1a** to afford product **3j** in 56% yield (entry 10). Reactions of aliphatic aldehydes were successful and the expected products **3k**-**3m** were formed in moderate yields (40–65%, entries 11–13).

The generality of the reaction was also surveyed with various bromodifluoro ketones **1** under the standard conditions. Both *p*-methoxy and *p*-chloro substituted phenyl ketones **1b** and **1c** reacted readily with benzaldehyde **2a** to give the desired products **3n** and **3o** in good yields (entries 14 and 15). The reaction of alkyl ketone **1d** also proceeded smoothly to afford the corresponding adduct **3p** in 86% yield (entry 16). In the case of bromodifluoroester **1e**, the expected product **3q** was obtained in only 40% yield and longer reaction time was required for the reaction to reach full conversion (entry 17).

Mechanistically, we postulate a reaction pathway based on our research results and literatures [10,13]. As illustrated in Scheme 1, bromodifluoromethyl ketone **1** was initiated by zinc (or activated by copper as in the case of the zinc-copper couple) to form a radical anion **A** which generated a radical **B**, then it attacked the aldehyde to furnish a radical intermediate **C**. Subsequent zinc-promoted reduction of intermediate **C** and the quenching of thus generated alkoxide anion **D** in the presence of water afforded the desired product **3**.

3. Conclusion

In summary, we have developed an environmentally friendly and efficient synthesis of α,α-difluorinated β-hydroxy carbonyl compounds under mild conditions. In the presence of Zn/CuCl, the reaction of various aldehydes and bromodifluoromethyl ketones took place readily in aqueous media at room temperature to give the corresponding difluorinated compounds in good yields. Further studies regarding the scope, mechanism and synthetic

application of this reaction are currently underway in our laboratory.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (300 MHz) with TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-400 spectrometer (100 MHz) with TMS as internal standard. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra and high resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 and a Finnigan MAT-8430 spectrometer. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. Bromodifluoromethyl ketones **1a-1d** were prepared according to the reported procedure [14].

4.2. Typical procedure

To a flask containing aldehyde **2** (2.0 mmol), bromodifluoromethyl ketone **1** (0.5 mmol) and water (2 mL) were added zinc powder (2.0 mmol) and CuCl (0.625 mmol) under stirring. The mixture was stirred at room temperature for 2 h, and then quenched with saturated aqueous NH_4Cl solution. The resulted mixture was stirred for additional 10 min, and extracted with ethyl acetate (3× 15 mL). The organic layer was dried over sodium sulfate. After the removal of solvent under reduced pressure, the residue was subjected to column chromatography on silica gel using ethyl acetate and petroleum ether as eluent to afford the corresponding product **3**.

4.2.1. 2,2-Difluoro-3-hydroxy-1,3-diphenylpropan-1-one (**3a**)

This is a known compound [3]; colorless oil, IR (neat): ν 3462, 1697, 1599, 1581, 1496, 1451 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 2H), 7.59–7.64 (m, 1H), 7.38–7.48 (m, 7H), 5.36 (dt, *J* = 18.9, 4.8 Hz, 1H), 3.12 (d, *J* = 4.8 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.6 (dd, *J* = 292.0, 8.2 Hz, 1F), −116.4 (dd, *J* = 292.0, 17.8 Hz, 1F). EI-MS (*m*/*z*, %): 263 (M+H$^+$, 0.61), 156 (29.79), 105 (89.89), 77 (100.00), 51 (52.82).

4.2.2. 3-(3-Chlorophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**3b**)

Colorless oil, IR (neat): ν 3497, 1694, 1599, 1579, 1558, 1480, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05–8.08 (m, 2H), 7.62–7.67 (m, 1H), 7.46–7.53 (m, 3H), 7.25–7.38 (m, 3H), 5.35 (dt, *J* = 19.8, 4.8 Hz, 1H), 3.23 (d, *J* = 4.8 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.3 (d, *J* = 296.2 Hz, 1F), −117.3 (dd, *J* = 296.2, 16.6 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.00 (t, *J* = 29.0 Hz), 136.69, 134.79, 134.26, 132.14, 130.29, 130.26, 129.47, 129.12, 128.71, 128.28, 115.42 (dd, *J* = 264.3, 256.1 Hz), 72.53 (dd, *J* = 29.1, 23.1 Hz). EI-MS (*m*/*z*, %): 296 (M$^+$, 1.08), 156 (49.70), 141 (14.42), 105 (100.00), 77 (76.83), 51 (22.83). HRMS calcd for $C_{15}H_{11}ClF_2O_2$ [M]$^+$: 296.0416, found: 296.0415.

4.2.3. 3-(4-Chlorophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**3c**)

This is a known compound [5b]; colorless oil, IR (neat): ν 3433, 1700, 1682, 1597, 1579, 1491 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 9.0 Hz, 2H), 7.62–7.67 (m, 1H), 7.35–7.51 (m, 6H), 5.36 (dt, *J* = 19.2, 4.2 Hz, 1H), 3.16 (d, *J* = 4.2 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.0 (dd, *J* = 295.5, 4.8 Hz, 1F), −116.63 (dd, *J* = 295.5, 18.6 Hz, 1F). EI-MS (*m*/*z*, %): 296 (M$^+$, 1.09), 156 (89.69), 141 (43.32), 105 (92.36), 77 (100.00), 51 (21.45).

4.2.4. 3-(2,4-Dichlorophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**3d**)

Solid, m.p.: 98–99 °C. IR (neat): ν 3443, 1696, 1600, 1589, 1564, 1469 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10–8.13 (m, 2H), 7.65–7.70 (m, 2H), 7.51–7.54 (m, 2H), 7.43–7.50 (m, 1H), 7.34–7.37 (m, 1H), 5.95 (ddd, *J* = 21.1, 4.5, 1.5 Hz, 1H), 3.16 (d, *J* = 4.5 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −103.9 (d, *J* = 302.0 Hz, 1F), −118.5 (dd, *J* = 302.0, 21.4 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.13 (t, *J* = 31.0 Hz), 135.44, 134.90, 134.61, 131.85, 131.47, 131.05, 130.32, 129.14, 128.78, 127.37, 115.54 (dd, *J* = 246.4, 257.0 Hz), 68.46 (dd, *J* = 29.7, 21.8 Hz). ESI-MS (*m*/*z*): 353 (M+Na$^+$). Anal. Calcd for $C_{15}H_{10}Cl_2F_2O_2$: C, 54.41; H, 3.04. Found: C, 54.42; H, 3.15.

4.2.5. 3-(4-Bromophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**3e**)

Solid, m.p.: 96–97 °C. IR (neat): ν 3431, 1699, 1681, 1596, 1578, 1490 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.1 Hz, 2H), 7.63–7.68 (m, 1H), 7.47–7.55 (m, 4H), 7.39 (d, *J* = 8.1 Hz, 2H), 5.36 (dt, *J* = 19.2, 4.2 Hz, 1H), 3.10 (d, *J* = 4.2 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.5 (dd, *J* = 296.8, 4.5 Hz, 1F), −117.2 (dd, *J* = 296.8, 18.6 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.71 (t, *J* = 31.5 Hz), 134.80, 133.71, 132.17, 131.45, 130.27, 129.81, 128.74, 123.20, 115.39 (dd, *J* = 264.1, 255.6 Hz), 72.62 (dd, *J* = 28.5, 22.7 Hz). EI-MS (*m*/*z*, %): 341 (M$^+$, 0.24), 185 (41.17), 156 (100.00), 105 (82.21), 77 (78.90), 51 (24.82). Anal. Calcd for $C_{15}H_{11}BrF_2O_2$: C, 52.81; H, 3.25. Found: C, 52.59; H, 3.45.

4.2.6. 2,2-Difluoro-3-(4-fluorophenyl)-3-hydroxy-1-phenylpropan-1-one (**3f**)

Solid, m.p.: 73–74 °C. IR (neat): ν 3292, 1699, 1604, 1581, 1512, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–8.10 (m, 2H), 7.64–7.70 (m, 1H), 7.49–7.54 (m, 3H), 7.08–7.14 (m, 3H), 5.96 (dt, *J* = 18.9, 4.1 Hz, 1H), 3.70 (d, *J* = 4.1 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −83.7 (dd, *J* = 294.4, 18.9 Hz, 1F), −87.7–87.8 (m, 1F), −96.0 (dd, *J* = 294.4, 5.4 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.13 (t, *J* = 29.3 Hz), 164.60, 162.14, 134.95, 132.55, 130.78, 130.51, 128.94, 115.60, 116.14 (dd, *J* = 262.7, 256.6 Hz), 72.82 (dd, *J* = 28.9, 23.1 Hz). ESI-MS (*m*/*z*): 303 (M+Na$^+$). Anal. Calcd for $C_{15}H_{11}F_3O_2$: C, 64.29; H, 3.96. Found: C, 64.32; H, 4.01.

4.2.7. 2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**3h**)

Colorless oil, IR (neat): ν 3450, 1698, 1613, 1599, 1587, 1515, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04–8.08 (m, 2H), 7.62–7.67 (m, 1H), 7.41–7.51 (m, 4H), 6.92–6.95 (m, 2H), 5.33 (dt, *J* = 19.2, 4.5 Hz, 1H), 3.83 (s, 3H), 3.09 (d, *J* = 4.5 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ -104.5 (dd, *J* = 292.9, 8.2 Hz, 1F), −115.9 (dd, *J* = 292.9, 20.3 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.33 (t, *J* = 29.0 Hz), 160.07, 134.43, 132.52, 130.19, 129.32, 128.57, 126.83, 115.90 (dd, *J* = 262.4, 254.6 Hz), 113.71, 72.95 (dd, *J* = 28.3, 23.1 Hz), 55.20. EI-MS (*m*/*z*, %): 292 (M$^+$, 0.25), 155 (2.60), 137 (51.60), 105 (55.52), 77 (100.00), 51 (35.63). ESI-HRMS calcd for $C_{16}H_{14}F_2NaO_3$ [M+Na] $^+$: 315.0813, found: 315.0803.

4.2.8. 2,2-Difluoro-3-hydroxy-1-phenyl-3-p-tolylpropan-1-one (**3i**)

Solid, m.p.: 72–73 °C. IR (neat): ν 3438, 1687, 1615, 1596, 1516, 1448 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.5 Hz, 2H), 7.61–7.66 (m, 1H), 7.37–7.50 (m, 4H), 7.19–7.25 (m, 2H), 5.34 (dt, *J* = 18.9, 4.5 Hz, 1H), 2.96 (d, *J* = 4.5 Hz, 1H), 2.37 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −105.2 (dd, *J* = 291.9, 3.95 Hz, 1F), −1117.2 (dd, *J* = 291.9, 20.6 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.05 (t, *J* = 29.2 Hz), 138.91, 134.51, 132.54, 131.81, 130.25, 129.05, 128.64, 128.01, 115.90 (dd, *J* = 262.8, 254.6 Hz), 73.24 (dd, *J* = 28.7, 23.2 Hz), 21.24. EI-MS (*m*/*z*, %): 276 (M$^+$, 0.23), 156 (23.10), 121 (100.00), 105 (46.47), 77 (46.67), 51 (11.41). Anal. Calcd for $C_{16}H_{14}F_2O_2$: C, 69.56; H, 5.11. Found: C, 69.48; H, 4.82.

*4.2.9. 2,2-Difluoro-3-(furan-2-yl)-3-hydroxy-1-phenylpropan-1-one (**3j**)*

Colorless oil, IR (neat): ν 3477, 1699, 1599, 1581, 1504, 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 7.5 Hz, 2H), 7.63–7.68 (m, 1H), 7.44–7.52 (m, 3H), 6.50 (d, J = 3.0 Hz, 1H), 6.40 (dd, J = 3.0, 1.8 Hz, 1H), 5.43 (dt, J = 15.9, 6.9 Hz, 1H), 3.07 (d, J = 6.9 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −106.5 (dd, J = 291.7, 8.2 Hz, 1F), −114.5 (dd, J = 291.7, 10.2 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.23 (t, J = 30.5 Hz), 148.35, 143.20, 134.58, 130.11, 130.05, 128.65, 115.43 (dd, J = 262.5, 256.8 Hz), 110.62, 110.10, 68.06 (dd, J = 28.6, 25.3 Hz). EI-MS (m/z, %): 252 (M^+, 0.36), 156 (34.29), 117 (0.59), 105 (100.00), 77 (44.37), 51 (20.27). HRMS calcd for $C_{13}H_{10}F_2NaO_3$ $[M+Na]^+$: 275.0500, found: 275.0490.

*4.2.10. 2,2-Difluoro-3-hydroxy-5-methyl-1-phenylhexan-1-one (**3k**)*

This is a known compound [3]; colorless oil, IR (neat): ν 3449, 2960, 2874, 1698, 1599, 1581, 1470, 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 7.8 Hz, 2H), 7.65–7.70 (m, 1H), 7.50–7.55 (m, 2H), 4.37–4.34 (m, 1H), 2.53 (d, J = 6.0 Hz, 1H), 1.98–1.93 (m, 1H), 1.74–1.64 (m, 1H), 1.54–1.47 (m, 1H), 1.04–0.97 (m, 6H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.2 (d, J = 300.3 Hz, 1F), −116.5 (dd, J = 300.3, 17.2 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.94 (t, J = 29.7 Hz), 134.81, 132.59, 130.48, 128.92, 116.93 (dd, J = 260.6, 256.1 Hz), 69.91 (dd, J = 27.4, 24.0 Hz), 37.73, 24.33, 23.85, 21.50. ESI-MS (m/z): 243 ($M+H^+$).

*4.2.11. 2,2-Difluoro-3-hydroxy-1-phenylpentan-1-one (**3l**)*

This is a known compound [15]; colorless oil, IR (neat): ν 3500, 2977, 2883, 1696, 1599, 1451 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 7.8 Hz, 2H), 7.62–7.67 (m, 1H), 7.47–7.53 (m, 2H), 4.20–4.11 (m, 1H), 2.54 (d, J = 6.0 Hz, 1H), 1.87–1.61 (m, 2H), 1.07 (t, J = 7.8 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −108.9 (d, J = 294.2 Hz, 1F), −116.2 (dd, J = 294.2, 20.30 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.01 (t, J = 30.5 Hz), 134.76, 132.40, 130.32, 128.77, 116.74 (dd, J = 260.2, 255.4 Hz), 72.84 (dd, J = 27.6, 23.8 Hz), 22.21, 10.03. EI-MS (m/z, %): 214 (M^+, 0.13), 156 (6.25), 105 (100.00), 77 (44.98), 59 (4.84), 51 (11.71).

*4.2.12. 2,2-Difluoro-3-hydroxy-1-phenylhexan-1-one (**3m**)*

This is a known compound [4a]; colorless oil, IR (neat): ν 3500, 2965, 2937, 2877, 1698, 1599, 1581, 1467, 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 7.8 Hz, 2H), 7.62–7.67 (m, 1H), 7.47–7.53 (m, 2H), 4.30–4.21 (m, 1H), 2.55 (d, J = 6.0 Hz, 1H), 1.71–1.42 (m, 4H), 0.98 (t, J = 6.6 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −107.0 (d, J = 302.0 Hz, 1F), −117.2 (dd, J = 302.0, 15.2 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.91 (t, J = 29.9 Hz), 134.51, 132.28, 130.16, 128.64, 116.60 (dd, J = 260.3, 256.3 Hz), 71.06 (dd, J = 26.8, 24.3 Hz), 30.80, 18.56, 13.73. ESI-MS (m/z): 229 (M^++1), 246 ($M+NH_4^+$).

*4.2.13. 2,2-Difluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (**3n**)*

This is a known compound [16]; colorless oil, IR (neat): ν 3448, 1681, 1662, 1600, 1570, 1508, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.95–8.03 (m, 2H), 7.37–7.41 (m, 2H), 7.27–7.30 (m, 3H), 6.83 (d, J = 8.7 Hz, 2H), 5.26 (dd, J = 19.05, 5.4 Hz, 1H), 3.77 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −103.9 (d, J = 291.9 Hz, 1F), −115.9 (dd, J = 291.9, 18.6 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.41 (t, J = 29.2 Hz), 164.72, 134.80, 132.92, 130.14, 128.87, 128.19, 128.11, 115.81 (dd, J = 263.0, 257.2 Hz), 113.95, 73.26 (dd, J = 28.5, 23.1 Hz), 55.54. EI-MS (m/z, %): 292 (M^+, 1.65), 186 (24.95), 135 (100.00), 107 (14.19), 77 (31.78), 51 (7.70).

*4.2.14. 1-(4-Chlorophenyl)-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one (**3o**)*

This is a known compound [17]; colorless oil, IR (neat): ν 3488, 1693, 1588, 1487, 1456, 1402 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 8.7 Hz, 2H), 7.58–7.63 (m, 1H), 7.36–7.45 (m, 5H), 5.34 (dd, J = 18.8, 5.7 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −104.7 (d, J = 282.8 Hz, 1F), −116.2 (dd, J = 282.8, 16.9 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.20 (t, J = 29.1 Hz), 141.29, 134.52, 133.78, 131.63, 130.72, 129.12, 128.33, 128.04, 115.79 (dd, J = 262.8, 255.1 Hz), 73.22 (dd, J = 28.6, 23.0 Hz). EI-MS (m/z, %): 296 (M^+, 0.62), 190 (43.19), 139 (100.00), 111 (49.47), 107 (34.94), 77 (35.15).

*4.2.15. 2,2-Difluoro-1-hydroxy-1,6-diphenylhexan-3-one (**3p**)*

Colorless oil, IR (neat): ν 3457, 3063, 3026, 2946, 2868, 1738, 1686, 1602, 1583, 1496, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.15–7.14 (m, 10H), 5.20 (dd, J = 16.8, 8.1 Hz, 1H), 2.66 (m, 4H), 1.91 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.07 (dd, J = 274.1, 8.7 Hz, 1F), −123.7 (dd, J = 274.1, 14.1 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.41 (t, J = 31.0 Hz), 141.21, 134.78, 129.21, 128.48, 127.78, 126.10, 114.84 (dd, J = 260.6, 255.3 Hz), 73.14 (dd, J = 28.8, 22.2 Hz), 37.34, 34.71, 23.97. EI-MS m/z: 304 (M^+, 1.36), 198 (23.65), 147 (53.76), 77 (23.03). HRMS Calcd for $C_{18}H_{18}F_2O_2$ (M^+): 304.1275. Found: 304.1279.

*4.2.16. Ethyl 2,2-difluoro-3-hydroxy-3-phenylpropanoate (**3q**)*

This is a known compound [5c]; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.39 (m, 5H), 5.22–5.13 (m, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.3 (dd, J = 262.4, 8.0 Hz, 1F), −120.43 (dd, J = 262.4, 15.3 Hz, 1F).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.08.012.

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