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# Synthesis of α,α-difluoro-β-hydroxy ketone *via* the La(OTf)$_3$-catalyzed aldol reaction of carbonyl compounds with difluoroenol *O*-Boc esters

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ABSTRACT

We herein present an efficient method for the construction of α,α-difluoro-β-hydroxy ketones. The La(OTf)$_3$-catalyzed aldol reaction between difluoroenol *O*-Boc (Boc = *tert*-butyloxycarbonyl) esters and carbonyl compounds affords α,α-difluoro-β-hydroxy ketones in good yield. The key reagents of this reaction are the difluoroenol *O*-Boc esters, which are easily synthesized from trifluoromethyl alcohols in two steps.



## 1. Introduction

Organic fluorine compounds often show unique bioactivities and behavior compared with their non-fluorinated counterparts [1]. Currently, approximately 20–30% of agrochemicals and pharmaceuticals owe their effectiveness to the presence of one or more fluorine atoms in their structure. Therefore, various biologically active organic fluorine compounds are used in or under development for application in these areas. In particular, α,α-difluoro-β-hydroxy ketones have received considerable attention due to their unique biological properties. For example, introduction of the α,α-difluoro-β-hydroxy ketone unit into a peptide can give renin inhibitors [2]. In addition, Hockerman et al. reported that α,α-difluoro-β-hydroxy ketone **1** is an agonist of the γ-aminobutyric acid type B ($GABA_B$) receptor (Fig. 1) [3]. Furthermore, numerous bioactive compounds containing the difluoromethylene ketone unit are inhibitors of enzymes such as HIV-1 protease [4], elastase [5], and human heart chymase [6].

The aldol reaction is one of the most important and useful reactions for carbon–carbon bond formation in organic synthesis, and significant efforts have focused on the development of this reaction [7]. In general, synthetic routes to α,α-difluoro-β-hydroxy ketones are based on difluoroenol silyl ethers [8], although a number of other routes have been developed by numerous research groups [9].

We herein report a novel catalytic difluoroalkylation method to give α,α-difluoro-β-hydroxy ketones **4** from the aldol reaction of carbonyl compounds **3** with difluoroenol *O*-Boc (Boc = *tert*-butyloxycarbonyl) esters **2** (Scheme 1).

## 2. Results and discussion

We first demonstrated the synthesis of difluoroenol *O*-Boc esters from 1-phenyl-2,2,2-trifluoroethanol **5** [10] in two steps. Protection of the hydroxyl group of **5** as an *O*-Boc ester was by treatment with $Boc_2O$ and a catalytic amount (10 mol%) of 4-dimethylaminopyridine (DMAP) in $CH_3CN$ at room temperature, to give Boc-protected alcohol **6**. Compound **6** subsequently underwent β-elimination of fluoride when treated with 1.5 eq. of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, giving compound **7** in 87% yield (Scheme 2).

We then chose to expand the scope of our synthetic method for a variety of different trifluoromethyl alcohols [11] using the optimized conditions as outlined in Table 1. The desired difluoroenol *O*-Boc esters **10a-g** were formed from **8** *via* **9** in moderate to high yields, with the exception of 1-aryl-2,2,2-trifluoroethanol derivatives containing the strongly electron-withdrawing trifluoromethyl group in the para position of the aromatic ring. In this case, a complex mixture was obtained instead of the desired product (entry 5).

We then used our optimized aldol reaction conditions (1.5 eq. (**7**) to benzaldehyde **11**) to screen Lewis acid catalysts (Table 2). In the presence of $Cu(OTf)_2$ (20 mol%, $OTf = CF_3SO_3$) in

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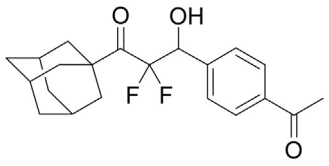
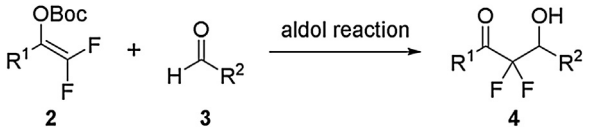


**Fig. 1.** The $GABA_B$ agonist α,α-difluoro-β-hydroxy ketone **1**.




**Scheme 1.** Difluoroalkylation *via* the aldol reaction of **2** with **3**.

dichloromethane (DCM) at r. t. for 24 h, the reaction yielded the desired product **12** in 50% yield (entry 1). In addition, when treated with $TiCl_4$ (20 mol%), **12** was obtained in 82% yield (entry 2). However, the use of $Sn(OTf)_2$ gave the desired product **12** along with the α,α-difluoro-β-hydroxy ketone *tert*-butyl ether **13** as a byproduct (entry 3; total aldol type product in 81% yield). Then, we also attempted the aldol reaction in the presence of $La(OTf)_3$, because lanthanum atom has the large ionic radius and high oxophilicity [12], to give both **12** and **13** in considerably higher yields (entry 4; total aldol type product ~99% yield). The general mechanism of the Boc deprotection involves coordination of the Lewis acid to the carbonyl oxygen atom of the *tert*-butyl carbamate, which results in degradation, initially producing carbon dioxide. The highly reactive *tert*-butyl cation can then decompose to isobutylene [13]. We therefore examined implementation of a higher reaction temperature to allow removal of isobutylene from the reaction system. In the presence of $La(OTf)_3$ (20 mol%) in DCM under reflux for 6 h, the desired product **12** was obtained as the sole product (entry 5). In addition, performing the reaction in 1,2-dichloroethane (DCE) under reflux for 20 min gave **12** alone in excellent yield (entry 6). We then examined the possibility of reducing the amount of catalyst, which resulted in slightly longer reaction times, but yielded the desired product in quantitative yield (entries 7 and 8). We could therefore conclude that the optimal reaction conditions for the catalytic difluoroalkylation

**Table 1**
Synthesis of difluoroenol *O*-Boc esters.

| Entry | R | Yield of **9** (%)[a] | Yield of **10** (%)[a] |
|---|---|---|---|
| 1 | 4-MeO-$C_6H_4$ | 97 (**9a**) | 64 (**10a**) |
| 2 | 4-Me-$C_6H_4$ | 90 (**9b**) | 80 (**10b**) |
| 3 | 4-F-$C_6H_4$ | 91 (**9c**) | 69 (**10c**) |
| 4 | 4-Cl-$C_6H_4$ | 94 (**9d**) | 78 (**10d**) |
| 5 | 4-$CF_3$-$C_6H_4$ | 84 (**9e**) | decomposed |
| 6 | 2-furyl | 91 (**9f**) | 65 (**10e**) |
| 7[b] | *c*-$C_6H_{11}$ | 76 (**9g**) | 95 (**10f**) |
| 8[c] | 1-adamantyl | 99 (**9h**) | 85 (**10g**) |

[a] Isolated yield.
[b] The reaction was performed with 2 eq. of LDA.
[c] The reaction was performed with 3 eq. of LDA.

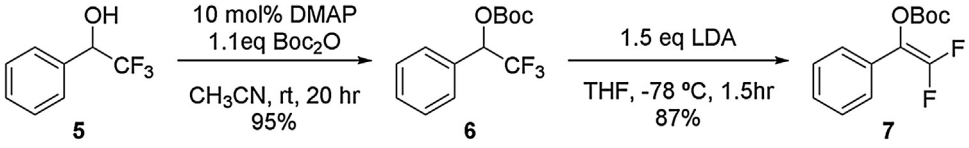
aldol reaction involved treatment of the difluoroenol *O*-Boc ester and carbonyl compounds with 1 mol% $La(OTf)_3$ in DCE under reflux.

To expand the scope of our novel difluoroalkylation reaction, we then investigated the reaction of 1.5 eq. of the difluoroenol *O*-Boc esters (**7**) with various aldehydes under the optimized conditions (Table 3).

The effect of substituents on the substrate aromatic ring was first investigated (entries 1–6). In all cases, the aldol reaction proceeded successfully and the desired adducts were obtained in good yield. For substrates containing aromatic oxygen or sulfur heterocycles, the desired adducts were recovered in good yield (entries 7 and 8). However, the presence of a nitrogen-based aromatic heterocycle had a detrimental effect on the reaction, with no trace of the desired product being detected (entries 9 and 10). We also applied the aldol reaction to aliphatic substrates (entries 11 – 14), with the reaction between heptanal and compound **7** giving the desired product in good yield (entry 11). Furthermore, the reaction also proceeded smoothly for α-branched aliphatic aldehydes (entries 12 and 13). However, using the α,α-disubstituted aliphatic pivalaldehyde, the reaction did not proceed due to steric hindrance (entry 14).

We continued to investigate the scope and limitations of the optimized aldol reaction by applying variety of different ketones **16**, as shown in Table 4.

The reaction of alkyl aromatic ketones with compound **7** provided the corresponding adduct in moderate to high yields (entries 1 and 2). However, using a di-aromatic ketone, the reaction did not proceed (entry 3). Furthermore, we explored the aldol




**Scheme 2.** Synthesis of difluoroenol *O*-Boc ester **7** from trifluoromethyl alcohol **5**.

**Table 2**
Optimization of the reaction conditions.

| Entry | Cat. | Amount of cat. (mol%) | Solvent | Temp. (°C) | Reaction time | Yield of **12** (%)[a] | Yield of **13** (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | 20 | DCM | r.t. | 24 h | 50 | N. D.[b] |
| 2 | $TiCl_4$ | 20 | DCM | r.t. | 12 h | 82 | N. D.[b] |
| 3 | $Sn(OTf)_2$ | 20 | DCM | r.t. | 24 h | 56 | 25 |
| 4 | $La(OTf)_3$ | 20 | DCM | r.t. | 12 h | 63 | 37 |
| 5 | $La(OTf)_3$ | 20 | DCM | reflux | 6 h | 81 | N. D.[b] |
| 6 | $La(OTf)_3$ | 20 | DCE | reflux | 20 min | 96 | N. D.[b] |
| 7 | $La(OTf)_3$ | 2.5 | DCE | reflux | 40 min | 99 | N. D.[b] |
| 8 | $La(OTf)_3$ | 1 | DCE | reflux | 50 min | 99 | N. D.[b] |

[a] Isolated yield.
[b] N. D.; Not detected.

**Table 3**
Aldol reaction of **7** with a range of aldehydes.

| Entry | R | Reaction time (h) | Yield of **15** (%)[a] |
|---|---|---|---|
| 1 | 2-MeO-$C_6H_4$ | 1.5 | 72 (**15a**) |
| 2 | 3-MeO-$C_6H_4$ | 3.5 | 85 (**15b**) |
| 3 | 4-MeO-$C_6H_4$ | 3.5 | 71 (**15c**) |
| 4 | 2-$NO_2$-$C_6H_4$ | 2 | 70 (**15d**) |
| 5 | 3-$NO_2$-$C_6H_4$ | 1 | 92 (**15e**) |
| 6 | 4-$NO_2$-$C_6H_4$ | 1 | 78 (**15f**) |
| 7 | 2-furyl | 2 | 77 (**15g**) |
| 8 | 2-thionyl | 4.5 | 73 (**15h**) |
| 9 | 2-pyrrolyl | 24 | N. D.[b] |
| 10 | 2-pyridyl | 24 | N. D. [b] |
| 11 | *n*-$C_6H_{13}$ | 0.5 | 80 (**15i**) |
| 12 | *c*-$C_5H_9$ | 1.2 | 87 (**15j**) |
| 13 | *c*-$C_6H_{11}$ | 1.5 | 79 (**15k**) |
| 14 | *t*-Bu | 24 | N. D. [b] |

[a] Isolated yield.
[b] N. D.; Not detected.

**Table 4**
Aldol reaction of **7** with a range of ketones.

| Entry | $R^1$ | $R_2$ | Reaction time (h) | Yield of **17**(%)[a] |
|---|---|---|---|---|
| 1 | Ph | Me | 3.5 | 81 (**17a**) |
| 2 | Ph | Et | 3 | 49 (**17b**) |
| 3 | Ph | Ph | 24 | N. D.[c] |
| 4 | Me | Me | 2.5 | 52 (**17c**) |
| 5 [b] | Me | Me | 0.3 | 74 (**17c**) |
| 6 | $-(CH_2)_4-$ | | 24 | Trace |
| 7 | $-(CH_2)_5-$ | | 0.5 | 99 (**17d**) |

[a] Isolated yield.
[b] The reaction was performed with 10 eq. of **16**.
[c] N. D.; Not detected.

reaction of an aliphatic ketone, namely acetone, which gave the desired product but in low yield due to the volatility of the ketone (entry 4). Increasing the amount of acetone from 1 to 10 eq., the yield of **17c** was increased to 81% (entry 5). We then explored the reactivity of cyclic ketones of different ring sizes, as cyclohexanone generally exhibits higher reactivity compared to cyclopentanone in carbonyl addition reactions [14]. Indeed, when cyclopentanone was used as the substrate, the reaction was unsuccessful (entry 6). However, when cyclohexanone was used, the reaction proceeded smoothly to afford the corresponding adduct in excellent yield (entry 7).

The aldol reaction of various difluoroenol *O*-Boc esters was also investigated to generalize the reaction using **11** as the model substrate (Table 5).

In all cases, the reaction of **10** with **11** was successful, giving the desired product **18a-g** in good to high yields with short reaction times (entries 1–7).

Using this procedure, we successfully prepared the $GABA_B$ agonist **1** (Table 6). However, the reaction of **10g** with 4-acetylbenzaldehyde **19** in the presence of 1 mol% catalyst resulted

**Table 5**
Aldol reaction of **11** with various difluoroenol *O*-Boc esters.

| Entry | R | Reaction time (h) | Yield of **18** (%)[a] |
|---|---|---|---|
| 1 | 4-MeO-$C_6H_4$ | 1.5 | 72 (**18a**) |
| 2 | 4-Me-$C_6H_4$ | 2 | 99 (**18b**) |
| 3 | 4-F-$C_6H_4$ | 0.3 | 86 (**18c**) |
| 4 | 4-Cl-$C_6H_4$ | 3.5 | 75 (**18d**) |
| 5 | 2-furyl | 2 | 96 (**18e**) |
| 6 | *c*-$C_6H_{11}$ | 2 | 80 (**18f**) |
| 7 | 1-adamantyl | 1.5 | 88 (**18g**) |

[a] Isolated yield.

**Table 6**
Synthesis of $GABA_B$ agonist **11.**

| Entry | Catalyst X (mol%) | Yield of **1** (%)[a] |
|---|---|---|
| 1 | 1 | 29 |
| 2 | 5 | 99 |

[a] Isolated yield.

in the formation of the desired product in low yield (entry 1). As substrate **19** contains two carbonyl oxygen atoms, we expect that the Lewis acid was being consumed in coordination with the carbonyl groups. An increase in the amount of catalyst used (from 1 to 5 mol%) confirmed this, with the yield of **1** increasing to 99% (entry 2).

## 3. Conclusion

In conclusion, we successfully developed a catalytic difluoroalkylation method to give α,α-difluoro-β-hydroxy ketones from carbonyl compounds and difluoroenol *O*-Boc esters using 1 mol% $La(OTf)_3$ catalyst. The current methodology is particularly well suited to the introduction of a difluoromethylene moiety to a wide range of carbonyl compounds in short reaction times. These structural classes enjoy significant application in the fields of biochemical, biomedical, and pharmaceutical research and it is envisaged that the current methodologies will be of significant use to researchers in these areas. In ongoing work, we are exploring the asymmetric aldol reaction of difluoroenol *O*-Boc esters with carbonyl compounds. In addition, we are screening catalysts with complexes of $La(OTf)_3$ and optically active ligands.

## 4. Experimental

### 4.1. General

All reactions were carried out under a nitrogen atmosphere. $La(OTf)_3$ was purchased from Tokyo Chemical Industry CO., LTD. Other reagents were obtained from commercial sources, and used as received. Anhydrous solvents were purified by usual methods. Melting points were measured using a Yanagimoto micro melting-point apparatus without correction. $^1H$, $^{13}C$, and $^{19}F$ NMR spectra were measured on a BRUKER BioSpin AVANCE-III-400 spectrometer at 400, 100, and 376 MHz, respectively. Chemical shifts were reported downfield from TMS (0 ppm) for $^1H$ NMR. For $^{13}C$ NMR, chemical shifts were reported relative to $CDCl_3$ (77.0 ppm). For $^{19}F$ NMR, chemical shifts were reported relative to $CF_3C_6H_5$ (−63.7 ppm). Infrared spectra were measured on a Perkin-Elmer Spectrum Two. Mass spectra were recorded on a JEOL JMS 600 mass spectrometer by either electron impact (EI) or chemical ionization (CI) methods. For electrospray ionization (ESI) a JEOL JMS-T100LP mass spectrometer was used. Purification was by column chromatography using 63-210 μm silica gel 60N (Kanto Chemical Co. Ltd.) or Chromatorex® NH-silica gel (NH-DM1020, Fuji Silysia Chemical Ltd.).

### 4.2. Typical procedure for Boc protection of trifluoromethyl alcohols

To a stirred solution of the desired 2,2,2-trifluoro-1-phenylethanol **5** (5.0 mmol) and DMAP (61.1 mg, 0.5 mmol) in dry $CH_3CN$ (12.5 mL) was added $(Boc)_2O$ (1.64 g, 7.5 mmol) in dry $CH_3CN$ (5.4 mL). The reaction mixture was stirred at room temperature for 20 h, after which time the mixture was concentrated *in vacuo*. Finally, the residue was purified by silica gel column chromatography (chloroform/*n*-hexane = 1: 2) to give product **6**.

*4.2.1. 2,2,2-Trifluoro-1-phenylethyl* tert*-butyl carbonate* ***(6)***

Colorless oil; 93% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (s, 9H), 5.91 (q, $J$ = 6.8 Hz, 1H), 7.40–7.45 (m, 3H), 7.46–7.51 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.5, 74.6 (q, $J$ = 33.2 Hz), 84.0, 123.1 (q, $J$ = 280.8 Hz), 127.9, 128.6, 129.9, 131.1, 151.7; $^{19}$F NMR (376 Hz, $CDCl_3$): δ −77.3 (d, $J$ = 6.8 Hz, 3F); IR (film): 2983, 1756, 1372, 1255, 1135, 700 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{16}O_3F_3$ [M+H$^+$]: 277.1046, found: 277.1051.

*4.2.2. 2,2,2-Trifluoro-1-(4-methoxyphenyl)ethyl tert-butyl carbonate (****9a****)*

Colorless oil; 97% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (s, 9H), 3.82 (s, 3H), 5.86 (q, $J$ = 6.8 Hz, 1H), 6.93 (d, $J$ = 8.6 Hz, 2H), 7.41 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.6, 55.2, 74.3 (q, $J$ = 33.3 Hz), 83.9, 114.1, 123.1, 123.1 (q, $J$ = 280.4 Hz), 129.4, 152.7, 160.7; $^{19}$F NMR (376 Hz, $CDCl_3$): δ −77.4 (d, $J$ = 6.8 Hz, 3F); IR (film): 2983, 1754, 1615, 1518, 1254, 1134 cm$^{-1}$; HRMS (CI): calcd. for $C_{14}H_{17}O_4F_3$ [M+H$^+$]: 306.1099, found: 306.1079.

*4.2.3. 2,2,2-Trifluoro-1-(4-methylphenyl)ethyl tert-butyl carbonate (****9b****)*

Colorless oil; 90% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (s, 9H), 2.37 (s, 3H), 5.88 (q, $J$ = 6.8 Hz, 1H), 7.22 (d, $J$ = 8.0 Hz, 2H), 7.37 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.1, 27.5, 74.5 (q, $J$ = 33.1 Hz), 83.8, 123.1 (q, $J$ = 280.7 Hz), 127.9, 128.1, 129.3, 139.9, 151.7; $^{19}$F NMR (376 Hz, $CDCl_3$): δ −77.3 (d, $J$ = 6.8 Hz, 3F); IR (film): 1618, 1755, 2984 cm$^{-1}$; HRMS (CI): calcd. for $C_{14}H_{18}O_3F_3$ [M+H$^+$]: 291.1208, found: 291.1220.

*4.2.4. 2,2,2-Trifluoro-1-(4-fluorophenyl)ethyl tert-butyl carbonate (****9c****)*

Colorless oil; 96% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (s, 9H), 5.89 (q, $J$ = 6.7 Hz, 1H), 7.08-7.15 (m, 2H), 7.47 (dd, $J$ = 5.3, 8.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.4, 73.9 (q, $J$ = 33.4 Hz), 84.1, 115.8 (d, $J$ = 21.9 Hz), 123.0 (q, $J$ = 280.6 Hz), 127.1 (d, $J$ = 3.1 Hz), 130.0 (d, $J$ = 8.5 Hz), 151.6, 163.6 (d, $J$ = 249.3 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −77.4 (d, $J$ = 6.1 Hz, 3F), −112.0 (tt, $J$ = 5.1, 8.1 Hz, 1F); IR (KBr): 2989, 1757, 1515, 1160, 1137 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{15}O_3F_4$ [M+H$^+$]: 295.0978, found: 295.0957.

*4.2.5. 2,2,2-Trifluoro-1-(4-chlorophenyl)ethyl tert-butyl carbonate (****9d****)*

Colorless oil; 94% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.48 (s, 9H), 5.88 (q, $J$ = 7.0 Hz, 1H), 7.38–7.44 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.6, 73.9 (q, $J$ = 33.5 Hz), 84.3, 122.8 (q, $J$ = 280.9 Hz), 129.0, 129.3, 129.6, 136.1, 151.5; $^{19}$F NMR (376 Hz, $CDCl_3$): δ −77.3 (d, $J$ = 6.8 Hz, 3F); IR (film): 3464, 2986, 1760, 1739, 1258, 1140, 822 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{15}O_3F_3Cl$ [M+H$^+$]: 311.0685, found: 311.0662.

*4.2.6. 2,2,2-Trifluoro-1-[4-(trifluoromethyl)phenyl]ethyl tert-butyl carbonate (****9e****)*

Colorless oil; 84% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.49 (s, 9H), 5.97 (q, $J$ = 6.6 Hz, 1H), 7.62 (d, $J$ = 8.2 Hz, 2H), 7.69 (d, $J$ = 8.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.5, 73.9 (q, $J$ = 33.5 Hz), 84.6, 122.7 (q, $J$ = 280.9 Hz), 123.7 (q, $J$ = 272.3 Hz), 125.7 (q, $J$ = 3.7 Hz), 128.4, 132.1 (q, $J$ = 32.8 Hz), 135.0, 151.5; $^{19}$F NMR (376 Hz, $CDCl_3$): −63.8 (s, 3F), −79.4 (d, $J$ = 6.8 Hz, 3F); IR (film): 2987, 2295, 1759, 850, 830 cm$^{-1}$; HRMS (CI): calcd. For $C_{14}H_{15}O_3F_6$ [M+H$^+$]: 345.0950, found: 345.0925.

*4.2.7. 2,2,2-Trifluoro-1-(furan-2-yl)ethyl tert-butyl carbonate (****9f****)*

Colorless oil; 91% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.50 (s, 9H), 6.07 (q, $J$ = 6.6 Hz, 1H), 6.43 (dd, $J$ = 1.8, 3.4 Hz, 1H), 6.62 (d, $J$ = 3.4 Hz, 1H), 7.49 (d, $J$ = 1.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.3, 68.3 (q, $J$ = 35.2 Hz), 84.2, 110.7, 112.0, 122.3 (q, $J$ = 280.7 Hz), 144.2, 144.3, 151.6; $^{19}$F NMR (376 Hz, $CDCl_3$): −76.5 (d, $J$ = 6.1 Hz, 3F); IR (film): 2985, 1759, 1256, 1156 cm$^{-1}$; HRMS (CI): calcd. for $C_{11}H_{14}O_4F_3$ [M+H$^+$]: 267.0849, found: 267.0844.

*4.2.8. 2,2,2-Trifluoro-1-cyclohexylethyl tert-butyl carbonate (****9g****)*

Colorless oil; 76% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.13–1.29 (m, 5H), 1.51 (s, 9H), 1.65–1.68 (m, 1H), 1.75–1.85 (m, 5H), 4.87 (dq, $J$ = 6.4, 7.3 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 25.5, 25.7, 25.8, 27.3, 27.5, 28.7, 37.2, 76.0 (q, $J$ = 30.7 Hz), 83.3, 123.9 (q, $J$ = 282.3 Hz), 152.7; $^{19}$F NMR (376 Hz, $CDCl_3$): −74.3 (d, $J$ = 7.5 Hz, 3F); IR (film): 2934, 2859, 1755 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{22}O_3F_3$ [M+H$^+$]: 283.1521, found: 283.1538.

*4.2.9. 2,2,2-Trifluoro-1-(adamantan-1-yl)ethyl tert-butyl carbonate (****9h****)*

Colorless oil; 96% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.51 (s, 9H), 1.66–1.76 (m, 12H), 2.01 (br s, 3H), 4.67 (q, $J$ = 8.1 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.6, 27.9, 35.6, 36.5, 37.5, 78.9 (q, $J$ = 29.3 Hz), 83.2, 124.2 (q, $J$ = 284.1 Hz), 152.9; $^{19}$F NMR (376 Hz, $CDCl_3$): −70.0 (d, $J$ = 8.2 Hz, 3F); IR (film):3421, 2910, 2854, 1754 cm$^{-1}$; HRMS (CI): calcd. for $C_{17}H_{26}O_3F_3$ [M+H$^+$]: 335.1834, found: 335.1846.

*4.3. Typical procedure for the synthesis of difluoroenol* O*-Boc esters*

To a solution of the Boc-protected trifluoromethyl alcohol **6** (1.0 mmol) in dry THF (5 mL) at −78 °C was added dropwise a freshly prepared [15] solution of LDA (0.7 M, 2.14 mL). After stirring for 1 h at −78 °C, the reaction mixture was stirred for an additional 1 h at room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL), dried over anhydrous $Na_2SO_4$, and the solvent evaporated to give a residue. Finally, the residue was purified by NH-silica gel chromatography (*n*-hexane) to give product **7**.

*4.3.1. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-phenylethene (****7****)*

Colorless oil; 87% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$1.51 (s, 9H), 7.30–7.34 (m, 1H), 7.38–7.46 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.4, 84.4, 112.9 (dd, $J$ = 19.1, 38.9 Hz), 125.3 (dd, $J$ = 3.6, 6.4 Hz), 128.4, 128.6, 129.2 (d, $J$ = 6.5 Hz), 150.8 (t, $J$ = 2.7 Hz), 154.8 (dd, $J$ = 289.9, 291.7 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −93.6 (d, $J$ = 47.3 Hz, 1F), −104.7 (d, $J$ = 47.3 Hz, 1F); IR (film): 2984, 1769, 1745, 1272, 1255, 1133 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{15}O_3F_2$ [M+H$^+$]: 257.1009, found: 257.0989.

*4.3.2. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-(4-methoxyphenyl) ethene (****10a****)*

White solid (mp 53–54 °C); 64% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.51 (s, 9H), 3.82 (s, 3H), 6.94 (d, $J$ = 8.9 Hz, 2H), 7.37 (d, $J$ = 8.9 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.5, 55.2, 84.2, 112.8 (dd, $J$ = 19.6, 39.7 Hz), 114.1, 121.2 (d, $J$ = 6.0 Hz), 127.0 (t, $J$ = 4.4 Hz), 150.8, 154.5 (dd, $J$ = 288.4, 289.8 Hz), 159.6; $^{19}$F NMR (376 Hz, $CDCl_3$): δ −95.7 (d, $J$ = 52.4 Hz, 1F), −106.8 (d, $J$ = 52.4 Hz, 1F); IR (KBr): 2983, 2938, 2841, 1768, 1612, 1517 cm$^{-1}$; HRMS (CI): calcd. for $C_{14}H_{17}O_4F_2$ [M+H$^+$]: 287.1076, found: 287.1095.

*4.3.3. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-(4-methylphenyl) ethene (****10b****)*

White solid (mp 30–33 °C); 80% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.51 (s, 9H), 2.36 (s, 3H), 7.20 (d, $J$ = 8.1 Hz, 2H), 7.33 (d, $J$ = 8.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.2, 27.5, 84.3, 113.0 (dd, $J$ = 19.1, 39.4 Hz), 125.3 (dd, $J$ = 3.6, 6.3 Hz), 126.3 (d, $J$ = 6.5 Hz), 129.3, 138.4, 150.8 (dd, $J$ = 2.3, 3.6 Hz), 154.6 (dd, $J$ = 289.1, 291.3 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −94.5 (d, $J$ = 49.1 Hz, 1F), −105.5 (d, $J$ = 49.1 Hz, 1F); IR (KBr): 3007, 2987, 2935, 1769, 1749, 1613 cm$^{-1}$; HRMS (CI): calcd. for $C_{14}H_{17}O_3F_2$ [M+H$^+$]: 271.1146, found: 271.1157.

*4.3.4. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-(4-fluorophenyl) ethene (**10c**)*

Colorless oil; 69% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ1.51 (s, 9H), 7.10 (t, $J$ = 8.7 Hz, 2H), 7.36–7.47 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.5, 84.7, 112.3 (dd, $J$ = 19.8, 40.0 Hz), 115.8 (d, $J$ = 22.0 Hz), 125.3 (dd $J$ = 3.5, 6.4 Hz), 127.5 (ddd, $J$ = 3.7, 6.2, 8.4 Hz), 150.7 (dd, $J$ = 2.2, 3.3 Hz), 154.7 (ddd, $J$ = 1.8, 289.0, 290.9 Hz), 162.5 (td, $J$ = 1.8, 248.7 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −94.0 (dd, $J$ = 3.4, 49.1 Hz, 1F), −105.4 (d, $J$ = 49.5 Hz, 1F), −113.3–−113.4 (m, 1F); IR (KBr): 1769, 1608, 1513 cm$^{-1}$; HRMS (CI): calcd. for $C_{14}H_{14}O_3F_3$ [M+H$^+$]: 275.0895, found: 275.0869.

*4.3.5. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-(4-chlorophenyl) ethene (**10d**)*

Colorless oil; 78% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 9H), 7.37 (s, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.4, 84.7, 112.3 (dd, $J$ = 19.8, 39.0 Hz), 126.6 (dd, $J$ = 3.7, 6.5 Hz), 127.8 (d, $J$ = 6.7 Hz), 128.9, 134.7 (t, $J$ = 1.8 Hz), 150.6 (dd, $J$ = 2.1, 3.4 Hz), 154.8 (dd, $J$ = 290.4, 292.7 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −92.7 (d, $J$ = 45.6 Hz, 1F), −103.8 (d, $J$ = 45.6 Hz, 1F); IR (film): 2984, 1770, 1744, 1274 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{14}O_3F_2Cl$ [M+H$^+$]: 290.0573, found: 291.0599.

*4.3.6. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-(furan-2-yl)ethene (**10e**)*

Colorless oil; 65% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 9H), 6.42 (dd, $J$ = 0.5, 3.4 Hz, 1H), 6.45 (dd, $J$ = 1.8, 3.4 Hz, 1H), 7.46 (d, $J$ = 0.5, 1.8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.1 (d, $J$ = 5.0 Hz), 84.5 (d, $J$ = 5.1 Hz), 107.3 (dd, $J$ = 23.5, 42.5), 108.6 (t, $J$ = 5.2 Hz), 111.2, 142.7 (d, $J$ = 8.2 Hz), 142.9, 150.4, 154.1 (t, $J$ = 292.0 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −95.6 (d, $J$ = 42.2 Hz), −102.3 (d, $J$ = 42.2 Hz); IR (film): 2985, 1772, 1278, 1258, 1135 cm$^{-1}$; HRMS (CI): calcd. for $C_{11}H_{13}O_4F_2$ [M+H$^+$]: 247.0803, found: 247.0782.

*4.3.7. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-cyclohexylethene (**10f**)*

Colorless oil; 95% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.10–1.41 (m, 5H), 1.51 (s, 9H), 1.65–1.79 (m, 5H), 2.20–2.34 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.4, 25.8, 27.1, 29.1 (t, $J$ = 2.3 Hz), 36.5 (d, $J$ = 2.4 Hz), 83.1, 115.7 (dd, $J$ = 12.7, 44.1 Hz), 150.8 (t, $J$ = 2.8 Hz), 153.8 (dd, $J$ = 280.8, 288.9 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −99.2 (d, $J$ = 64.7 Hz, 1F), −112.4 (dd, $J$ = 2.7, 64.7 Hz, 1F); IR (film): 2934, 2858, 1766 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{21}O_3F_2$ [M+H$^+$]: 263.1459, found: 263.1463.

*4.3.8. 1-(tert-Butoxycarbonyloxy)-2,2-difluoro-1-(adamantan-1-yl) ethene (**10g**)*

Colorless oil; 85% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 9H), 1.70 (brs, 6H), 1.82 (brs, 6H), 2.01 (brs, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 27.5, 28.0, 35.2 (d, $J$ = 4.0 Hz), 38.7 (dd, $J$ = 1.4, 4.1 Hz), 83.5, 119.0 (dd, $J$ = 13.0, 36.3 Hz), 151.2 (t, $J$ = 2.8 Hz), 154.5 (t, $J$ = 287.2 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −95.5 (d, $J$ = 66.1 Hz, 1F), −107.9 (d, $J$ = 66.1 Hz, 1F); IR (film): 3435, 2909, 2854, 1764 cm$^{-1}$; HRMS (CI): calcd. for $C_{17}H_{24}O_3F_2$ [M+H$^+$]: 315.1786, found: 315.1772.

*4.4. Typical procedure for the aldol reaction*

To a solution of La(OTf)$_3$ (1.5 mg, 2.6 μmol) and aldehyde (0.26 mmol) in dry DCE (2 mL) was added difluoroenol *O*-Boc ester (1.5 eq., 0.39 mmol) at room temperature. The reaction mixture was then heated to reflux, and stirred until the disappearance of difluoroenol *O*-Boc ester was observed by TLC. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$ solution (2 mL) and the organic layer separated. Th aqueous layer was extracted with chloroform (3 × 5 mL), and the combined organic layer dried with anhydrous $Na_2SO_4$ and evaporated to give a residue. Finally, the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 7: 1) to give product **12**.

*4.4.1. 2,2-Difluoro-3-hydroxy-1,3-diphenylpropan-1-one (**12**)*

99% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.04 (brs, 1H), 5.39 (dd, $J$ = 5.4, 18.8 Hz, 1H), 7.37–7.43 (m, 3H), 7.45–7.54 (m, 4H), 7.61-7.66 (m, 1H), 8.03–8.08 (m, 2H). The $^1$H NMR spectrum matched that reported in the literature [16].

*4.4.2. 2,2-Difluoro-3-hydroxy-3-(2-methoxyphenyl)-1-phenylpropan-1-one (**15a**)*

Colorless oil; 72% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.58 (d, $J$ = 7.2 Hz, 1H), 3.70 (s, 3H), 5.66 (td, $J$ = 7.2, 17.2 Hz, 1H), 6.87 (d, $J$ = 8.3 Hz, 1H), 7.04 (dt, $J$ = 0.9, 7.5 Hz, 1H), 7.32–7.37 (m, 1H), 7.45–7.49 (m, 3H), 7.60–7.64 (m, 1H), 8.04–8.06 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 55.2, 70.1 (dd, $J$ = 24.4, 28.2 Hz), 110.8, 116.8 (dd, $J$ = 258.0, 261.4 Hz), 120.9, 122.8, 128.5, 129.5, 130.0 (t, $J$ = 3.4 Hz), 130.1, 132.8, 134.1, 157.2, 190.0 (dd, $J$ = 28.2, 29.5 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −107.8 (dd, $J$ = 6.8, 275.2 Hz, 1F), −115.9 (dd, $J$ = 17.0, 275.2 Hz, 1F); IR (film): 3492, 2941, 1698, 1599 cm$^{-1}$; HRMS (CI): calcd. for $C_{16}H_{15}O_3F_2$ [M+H$^+$]: 293.0948, found: 293.0989.

*4.4.3. 2,2-Difluoro-3-hydroxy-3-(3-methoxyphenyl)-1-phenylpropan-1-one (**15b**)*

Colorless oil; 85% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.98 (brs, 1H), 3.82 (s, 3H), 5.36 (dd, $J$ = 5.4, 18.6 Hz, 1H), 6.91–6.94 (m, 1H), 7.05–7.09 (m, 2H), 7.31 (t, $J$ = 8.2 Hz, 1H), 7.48 (t, $J$ = 7.9 Hz, 2H), 7.61–7.66 (m, 1H), 8.06 (dd, $J$ = 1.0, 8.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 55.2, 73.1 (dd, $J$ = 23.0, 28.6 Hz), 113.4, 14.7, 115.8 (dd, $J$ = 256.5, 264.6 Hz), 120.4, 128.6, 129.2, 130.1 (t, $J$ = 3.2 Hz), 132.4 (t, $J$ = 2.2 Hz), 134.5, 136.2 (d, $J$ = 1.0 Hz), 159.4, 190.9 (dd, $J$ = 28.7, 31.5 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −105.8 (dd, $J$ = 5.5, 290.5 Hz, 1F), −117.4 (dd, $J$ = 18.4, 290.5 Hz, 1F); IR (film): 3488, 1706, 1597 cm$^{-1}$; HRMS (CI): calcd. for $C_{16}H_{14}O_3F_2$ [M+H$^+$]: 293.0964, found: 293.0989.

*4.4.4. 2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**15c**)*

71% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.96 (d, $J$ = 4.6 Hz, 1H), 3.82 (s, 3H), 5.33 (ddd, $J$ = 4.6, 5.5, 18.5 Hz, 1H), 6.90–6.95 (m, 2H), 7.43 (d, $J$ = 8.3 Hz, 2H), 7.45–7.51 (m, 2H), 7.61–7.66 (m, 1H), 8.03–8.08 (m, 2H). The $^1$H NMR spectrum matched that reported in the literature [16].

*4.4.5. 2,2-Difluoro-3-hydroxy-3-(2-nitrophenyl)-1-phenylpropan-1-one (**15d**)*

Yellow solid (mp 106–107 °C); 70% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.26 (d, $J$ = 5.0 Hz, 1H), 6.57 (ddd, $J$ = 2.0, 5.0, 20.4 Hz, 1H), 7.48–7.52 (m, 2H), 7.54–7.59 (m, 1H), 7.64–7.69 (m, 1H), 7.73 (dd, $J$ = 1.2, 7.7 Hz, 1H), 7.99-8.01 (m, 2H), 8.08–8.11 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 66.7 (dd, $J$ = 21.6, 28.8 Hz), 115.2 (dd, $J$ = 258.9, 266.7 Hz), 124.6, 128.8, 129.4, 129.6, 130.3, 130.3 (d, $J$ = 3.3 Hz), 131.6 (t, $J$ = 2.8 Hz), 133.1, 135.0, 148.9, 189.8 (t, $J$ = 27.6 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): −104.3 (dd, $J$ = 1.4, 303.1 Hz, 1F), −118.5 (dd, $J$ = 20.4, 303.1 Hz, 1F); IR (KBr): 3497, 1706, 1531 cm$^{-1}$; HRMS (CI): calcd. for $C_{15}H_{11}O_4NF_2$ [M+H$^+$]: 308.0744, found: 308.0734.

*4.4.6. 2,2-Difluoro-3-hydroxy-3-(3-nitrophenyl)-1-phenylpropan-1-one (**15e**)*

Yellow solid (mp 80.5-81.5 °C); 92% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.30 (brs, 1H), 5.53 (dd, $J$ = 3.7, 19.5 Hz, 1H), 7.49–7.54 (m, 2H), 7.60 (t, $J$ = 8.0 Hz, 1H), 7.65-7.71 (m, 1H), 7.87 (d, $J$ = 7.7 Hz, 1H), 8.09–8.13 (m, 2H), 8.27 (ddd, $J$ = 1.0, 2.3, 8.2 Hz, 1H), 8.42 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 72.0 (dd, $J$ = 23.1, 28.8 Hz), 115.1 (dd, $J$ = 257.4, 266.6 Hz), 123.1, 123.8, 128.7, 129.1, 130.2 (t, $J$ = 3.2 Hz), 131.8 (t, $J$ = 2.6 Hz), 134.2, 135.0, 136.8 (d, $J$ = 1.0 Hz), 148.0, 190.3 (dd,

$J$ = 29.1, 31.8 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −104.4 (dd, $J$ = 3.4, 303.5 Hz, 1F), −118.0 (dd, $J$ = 19.1, 303.5 Hz, 1F); IR (KBr): 3516, 1689, 1596, 1533 $cm^{-1}$; HRMS (CI): calcd. for $C_{15}H_{11}O_4NF_2$ [M+H$^+$]: 308.0715, found: 308.0734.

*4.4.7. 2,2-Difluoro-3-hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (**15f**)*

78% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.31 (d, $J$ = 4.2 Hz, 1H), 5.55 (td, $J$ = 4.2, 19.4 Hz, 1H), 7.51–7.56 (m, 2H), 7.67–7.77 (m, 3H), 8.12 (dd, $J$ = 1.1, 8.5 Hz, 2H), 8.27–8.32 (m, 2H). The $^1$H NMR spectrum matched that reported in the literature [16].

*4.4.8. 2,2-Difluoro-3-(furan-2-yl)-3-hydroxy-1-phenylpropan-1-one (**15g**)*

77% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.96 (d, $J$ = 7.1 Hz, 1H), 5.43 (td, $J$ = 7.1, 16.0 Hz, 1H), 6.41 (dd, $J$ = 1.9, 3.4 Hz, 1H), 6.52 (d, $J$ = 3.4 Hz, 1H), 7.46 (d, $J$ = 1.9 Hz, 1H), 7.48–7.54 (m, 2H), 7.63–7.69 (m, 1H), 8.06-8.12 (m, 2H). The $^1$H NMR spectrum matched that reported in the literature [16].

*4.4.9. 2,2-Difluoro-3-(thien-2-yl)-3-hydroxy-1-phenylpropan-1-one (**15h**)*

White solid (mp 56–58 °C); 73% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.07 (d, $J$ = 5.5 Hz, 1H), 5.66 (td, $J$ = 5.5, 17.2 Hz, 1H), 7.05 (dd, $J$ = 3.5, 5.1 Hz, 1H), 7.20 (d, $J$ = 3.5 Hz, 1H), 7.39 (dd, $J$ = 1.1, 5.1 Hz, 1H), 7.50 (t, $J$ = 7.8 Hz, 2H), 7.63–7.69 (m, 1H), 8.09 (d, $J$ = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 70.1 (dd, $J$ = 24.2, 29.4 Hz), 115.1 (dd, $J$ = 257.7, 264.8 Hz), 126.7, 126.8, 127.5, 128.7, 130.2 (t, $J$ = 3.2 Hz), 132.2 (t, $J$ = 2.6 Hz), 134.7, 137.1, 190.5 (dd, $J$ = 29.2, 31.5 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −106.0 (dd, $J$ = 5.5, 293.6 Hz, 1F), −116.7 (dd, $J$ = 17.7, 293.6 Hz, 1F); IR (KBr): 3420, 1669, 1596 $cm^{-1}$; HRMS (ESI−): calcd. for $C_{13}H_{10}O_2F_2S$ [M−H$^+$]: 267.02913, found: 267.03222.

*4.4.10. 2,2-Difluoro-3-hydroxy-1-phenylnonan-1-one (**15i**)*

Colorless oil; 65% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, $J$ = 3.4 Hz, 3H), 1.24–1.48 (m, 7H), 1.59–1.76 (m, 3H), 2.41 (d, $J$ = 6.2 Hz, 1H), 4.18–4.29 (m, 1H), 7.48-7.55 (m, 2H), 7.64–7.68 (m, 1H), 8.12 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 25.3, 28.8 (dd, $J$ = 1.5, 2.7 Hz), 29.0, 31.7, 71.4 (dd, $J$ = 24.2, 27.2 Hz), 116.6 (dd, $J$ = 257.2, 261.5 Hz), 128.7, 130.2 (t, $J$ = 3.3 Hz), 132.3 (t, $J$ = 2.6 Hz), 134.6, 190.6 (dd, $J$ = 30.1, 31.6 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −108.8 (ddd, $J$ = 1.0, 5.5, 296.0 Hz, 1F), −118.1 (dd, $J$ = 17.0, 296.0 Hz, 1F); IR (film): 3435, 2928, 1696, 1598 $cm^{-1}$; HRMS (CI+): calcd. for $C_{15}H_{21}O_2F_2$ [M+H$^+$]: 271.1509, found: 271.1492.

*4.4.11. 3-Cyclopentyl-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**15j**)*

Colorless oil; 87% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.38–1.62 (m, 4H), 1.63–1.73 (m, 2H), 1.80–1.94 (m, 2H), 2.23–2.35 (m, 1H), 2.39 (d, $J$ = 6.1 Hz, 1H), 4.19 (qd, $J$ = 6.1, 19.4 Hz, 1H), 7.49–7.53 (m, 2H), 7.63–7.67 (m, 1H), 8.10–8.12 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.0, 25.3, 27.9, 29.4 (d, $J$ = 2.7 Hz), 39.6, 74.0 (dd, $J$ = 23.7 Hz, $J$ = 26.8 Hz), 117.3 (dd, $J$ = 257.2 Hz, $J$ = 262.5 Hz), 128.6, 130.1 (t, $J$ = 3.3 Hz), 132.5, 134.4, 190.9 (dd, $J$ = 29.0 Hz, $J$ = 31.5 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$): δ −106.3 (dd, $J$ = 5.5, 289.5 Hz, 1F), −117.1 (dd, $J$ = 19.1, 289.5 Hz, 1F); IR (film): 3467, 2957, 2870, 1698, 1598 $cm^{-1}$; HRMS (CI): calcd. for $C_{14}H_{17}F_2O_2$ [M+H$^+$]: 255.1196, Found: 255.1207.

*4.4.12. 3-Cyclohexyl-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**15k**)*

Colorless oil; 79% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.12–1.43 (m, 6H), 1.64–1.90 (m, 4H), 1.94–2.02 (m, 1H), 2.29 (d, $J$ = 6.4 Hz, 1H), 4.01–4.12 (m, 1H), 7.47–7.54 (m, 2H), 7.62–7.68 (m, 1H), 8.07–8.14 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 25.8, 26.0, 26.1, 27.2, 29.9, 38.0, 74.6 (dd, $J$ = 23.0, 26.5 Hz), 117.8 (dd, $J$ = 257.8, 262.8 Hz), 128.5, 130.0 (t, $J$ = 3.2 Hz), 132.5, 134.2, 190.8 (dd, $J$ = 28.9, 31.4 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$): δ −106.0 (dd, $J$ = 6.1, 290.2 Hz, 1F), −115.6 (dd, $J$ = 20.4, 290.2 Hz, 1F); IR (film): 3453, 2928, 2854, 1698 $cm^{-1}$; HRMS (ESI+): calcd. for $C_{15}H_{19}F_2O_2$ [M+H$^+$]: 269.1353, Found: 269.1332.

*4.4.13. 2,2-Difluoro-3-hydroxy-1,3-diphenylbutan-1-one (**17a**)*

White solid (mp 74–75 °C); 81% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.83 (t, $J$ = 1.5 Hz, 3H), 3.53 (brs, 1H), 7.27–7.38 (m, 3H), 7.39-7.45 (m, 2H), 7.51–7.62 (m, 3H), 7.92 (dd, $J$ = 1.1, 8.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 24.0 (t, $J$ = 3.0 Hz), 76.4, (t, $J$ = 24.6 Hz), 116.4 (t, $J$ = 263.6 Hz), 126.3, 128.0, 128.1, 128.4, 130.2 (t, $J$ = 3.6 Hz), 133.1 (t, $J$ = 2.2 Hz), 134.3, 140.2, 191.6 (t, $J$ = 30.8 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −108.6 (s, 2F); IR (KBr): 3510, 1684, 1596 $cm^{-1}$; HRMS (CI): calcd. for $C_{16}H_{15}O_2F_2$ [M+H$^+$]: 277.1066, found: 277.1040.

*4.4.14. 2,2-Difluoro-3-hydroxy-1,3-diphenylpentan-1-one (**17b**)*

Colorless oil; 49% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, $J$ = 7.4 Hz, 3H), 2.14–2.38 (m, 2H), 3.45 (brs, 1H), 7.27–7.37 (m, 3H), 7.40 (t, $J$ = 7.9 Hz, 2H), 7.51 (d, $J$ = 7.3 Hz, 2H), 7.54–7.61 (m, 1H), 7.86–7.94 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 6.6, 27.3 (t, $J$ = 2.5 Hz), 79.1 (t, $J$ = 23.5 Hz), 116.7 (t, $J$ = 264.2 Hz), 126.8, 127.8, 128.1, 128.3, 130.2 (t, $J$ = 3.5 Hz), 133.2 (t, $J$ = 2.1 Hz), 134.2, 137.6, 191.9 (t, $J$ = 30.9 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −108.8 (s); IR (film): 3521, 1691, 1452 $cm^{-1}$; HRMS (CI): calcd. for $C_{17}H_{17}O_2F_2$ [M+H$^+$]: 291.1199, found: 291.1196.

*4.4.15. 2,2-Difluoro-3-hydroxy-3-methyl-1-phenylbutan-1-one (**17c**)*

Colorless oil; 74% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.45 (t, $J$ = 1.4 Hz, 6H), 2.88 (brs, 1H), 7.48–7.52 (m, 2H), 7.63–7.67 (m, 1H), 8.12 (dd, $J$ = 1.0, 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 23.6 (t, $J$ = 2.9 Hz), 73.3 (t, $J$ = 24.7 Hz), 117.1 (t, $J$ = 261.7 Hz), 128.6, 130.4 (t, $J$ = 3.6 Hz), 133.1 (t, $J$ = 2.6 Hz), 134.4, 191.2 (t, $J$ = 31.7 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −111.6 (s, 2F); IR (film): 3503, 2994, 1694, 1598 $cm^{-1}$; HRMS (CI): calcd. for $C_{11}H_{13}O_2F_2$ [M+H$^+$]: 215.0890, found: 215.0883.

*4.4.16. 2,2-Difluoro-2-(1-hydroxycyclohexyl)-1-phenylethan-1-one (**17d**)*

Colorless oil; 99% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.14-1.35 (m, 2H), 1.57–1.77 (m, 6H), 1.81–1.95 (m, 2H), 2.53 (brs, 1H), 7.49 (t, $J$ = 7.5 Hz, 2H), 7.63 (t, $J$ = 7.5 Hz, 1H), 8.11 (d, $J$ = 7.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 20.4, 25.2, 29.9 (t, $J$ = 2.8 Hz), 74.2 (t, $J$ = 23.7 Hz), 117.4 (t, $J$ = 261.3 Hz), 128.5, 130.4 (t, $J$ = 3.9 Hz), 133.4 (t, $J$ = 2.5 Hz), 134.2, 191.4 (t, $J$ = 31.3 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −113.7 (s, 2F); IR (film): 3514, 2939, 2863, 1692, 1598 $cm^{-1}$; HRMS (CI): calcd. for $C_{14}H_{16}F_2O_2$ [M+H$^+$]: 255.1196, Found: 255.1199.

*4.4.17. 2,2-Difluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (**18a**)*

White solid (mp 68–69 °C); 72% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.22 (d, $J$ = 4.6 Hz, 1H), 3.89 (s, 3H), 5.37 (td, $J$ = 4.6, 19.2 Hz, 1H), 6.92–6.96 (m, 2H), 7.36-7.43 (m, 3H), 7.48–7.54 (m, 2H), 8.04–8.10 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 55.6, 73.3 (dd, $J$ = 23.1, 28.6 Hz), 114.0, 115.8 (dd, $J$ = 256.9, 264.8 Hz), 125.1 (t, $J$ = 2.6 Hz), 128.1, 128.2, 128.9, 132.9 (t, $J$ = 3.3 Hz), 134.8, 164.8, 189.1 (dd, $J$ = 29.2, 31.3 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −104.9 (dd, $J$ = 4.8, 294.6 Hz, 1F), −117.0 (dd, $J$ = 19.1, 294.6 Hz, 1F); IR (KBr): 3429, 1669, 1594 $cm^{-1}$; HRMS (CI): calcd. for $C_{16}H_{15}O_3F_2$ [M+H$^+$]: 293.0991, found: 293.0989.

*4.4.18. 2,2-Difluoro-3-hydroxy-1-(4-methylphenyl)-3-phenylpropan-1-one (**18b**)*

White solid (mp 126–127 °C); 99% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.05 (d, $J$ = 4.7 Hz, 1H), 5.38 (td, $J$ = 4.7, 18.9 Hz,

1H), 7.2–7.31 (m, 2H), 7.37–7.44 (m, 3H), 4.47–7.54 (m, 2H), 7.97 (d, $J$ = 8.2 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.8, 73.2 (dd, $J$ = 23.3, 28.6 Hz), 115.7 (dd, $J$ = 256.7, 264.7 Hz), 128.1, 128.2, 128.9, 129.3, 129.8 (t, $J$ = 2.5 Hz), 130.4 (t, $J$ = 3.2 Hz), 134.7, 145.9, 190.4 (dd, $J$ = 29.0, 31.3 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −105.5 (dd, $J$ = 5.5, 293.9 Hz, 1F), −117.4 (dd, $J$ = 19.1, 293.9 Hz, 1F); IR (KBr): 3460, 1685 cm$^{-1}$; HRMS (CI): calcd. for $C_{16}H_{15}O_2F_2$ [M+H$^+$]: 277.1040, found: 277.1028.

*4.4.19. 2,2-Difluoro-3-hydroxy-1-(4-fluorophenyl)-3-phenylpropan-1-one (**18c**)*

White solid (mp 103–104 °C); 86% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.98 (d, $J$ = 4.7 Hz, 1H), 5.37 (td, $J$ = 4.7, 13.8 Hz, 1H), 7.15 (t, $J$ = 8.7 Hz, 2H), 7.38–7.44 (m, 3H), 7.47-7.53 (m, 2H), 8.07–8.14 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 73.2 (dd, $J$ = 23.0, 28.6 Hz), 115.7 (dd, $J$ = 256.6, 264.5 Hz), 115.9 (d, $J$ = 22.0 Hz), 128.1, 128.3, 128.8 (q, $J$ = 2.7 Hz), 129.1, 133.2 (ddd, $J$ = 2.9, 4.0, 9.8 Hz), 134.5, 166.5 (d, $J$ = 258.2 Hz), 189.4 (dd, $J$ = 29.2, 32.1 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −102.5 (tt, $J$ = 5.5, 8.2 Hz, 1F), −105.6 (dd, $J$ = 5.5, 292.5 Hz, 1F), −117.3 (dd, $J$ = 19.1, 292.5 Hz); IR (KBr): 3467, 3079, 2938, 1691, 1598 cm$^{-1}$; HRMS (CI): calcd. for $C_{15}H_{11}O_2F_3$ [M+H$^+$]: 280.0711, found: 280.0720.

*4.4.20. 2,2-Difluoro-3-hydroxy-1-(4-chlorophenyl)-3-phenylpropan-1-one (**18d**)*

White solid (mp 112–113 °C); 75% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.97 (d, $J$ = 4.6 Hz, 1H), 5.37 (td, 1H, $J$ = 4.6, 18.6 Hz, 1H), 7.38–7.52 (m, 7H), 7.99 (d, 2H, $J$ = 8.7 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 73.3 (dd, $J$ = 23.1, 28.7 Hz), 115.7 (dd, $J$ = 256.3, 264.0 Hz), 128.1, 128.4, 129.0, 129.1, 130.7, 131.6 (t, $J$ = 3.3 Hz), 134.5, 141.3, 189.8 (d, $J$ = 29.4 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −105.9 (dd, $J$ = 6.1, 291.9 Hz, 1F), −117.5 (dd, $J$ = 18.4, 291.9 Hz, 1F); IR (KBr): 3486, 2882, 1694, 1588 cm$^{-1}$; HRMS (CI): calcd. for $C_{15}H_{12}O_2F_2Cl$ [M+H$^+$]: 297.0513, found: 297.0494.

*4.4.21. 2,2-Difluoro-1-(furan-2-yl)-3-hydroxy-3-phenylpropan-1-one (**18e**)*

White solid (mp 68–69 °C); 96% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 3.12 (s, 1H), 5.34 (dd, $J$ = 6.6, 17.6 Hz, 1H), 6.57 (dd, $J$ = 1.6, 3.7 Hz, 1H), 7.35–7.44 (m, 4H), 7.44–7.50 (m, 2H), 7.73 (d, $J$ = 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 72.9 (dd, $J$ = 23.7, 28.3 Hz), 115.8 (dd, $J$ = 254.9, 261.5 Hz), 124.2 (dd, $J$ = 3.9, 7.8 Hz), 127.6, 127.8, 128.6, 134.6, 148.2 (d, $J$ = 1.2 Hz), 149.2, 178.0 (dd, $J$ = 28.7, 31.4 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −109.4 (dd, $J$ = 5.8, 277.6 Hz, 1F), −120.5 (dd, $J$ = 17.7, 277.6 Hz, 1F); IR (KBr): 3467, 3147, 2924, 1679 cm$^{-1}$; HRMS (CI): calcd. for $C_{13}H_{11}O_3F_2$ [M+H$^+$]: 253.0692, found: 253.0676.

*4.4.22. 1-Cyclohexyl-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one (**18f**)*

White solid (mp 58–60 °C); 80% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.17–1.46 (m, 6H), 1.65–1.84 (m, 4H), 2.65 (d, $J$ = 4.8 Hz, 1H), 2.75 (m, 1H), 5.19 (ddd, $J$ = 4.8, 7.7, 16.6 Hz, 1H), 7.37–7.46 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 25.1, 25.2, 25.4, 27.6, 27.8, 45.8, 72.8 (dd, $J$ = 23.9, 28.0 Hz), 115.2 (dd, $J$ = 256.7, 263.0 Hz), 127.8, 128.2, 128.9, 134.9, 205.7 (dd, $J$ = 26.1, 30.4 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): δ −113.6 (dd, $J$ = 7.5, 273.2 Hz, 1F), −123.4 (dd, $J$ = 17.0, 273.2 Hz, 1F); IR (KBr): 3497, 2939, 2857, 1718 cm$^{-1}$; HRMS (ESI +): calcd. for $C_{15}H_{19}F_2O_2$ [M+H$^+$]: 269.1353, Found: 269.1332.

*4.4.23. 3-Phenyl-1-(adamantan-1-yl)-2,2-difluoro-3-hydroxypropan-1-one (**18g**)*

White solid (mp 88–89 °C); 88% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.64–1.77 (brm, 6H), 1.84–1.91 (brm, 6H), 2.01 (brs, 3H), 2.76 (d, $J$ = 5.1 Hz, 1H), 5.25 (ddd, $J$ = 5.1, 7.1, 17.4 Hz, 1H) 7.35–7.45 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 27.5, 36.3, 36.7, 46.7 (t, $J$ = 2.2 Hz), 73.1 (dd, $J$ = 23.4, 27.5 Hz), 116.5 (dd, $J$ = 259.5, 266.5 Hz), 128.0, 128.2, 128.9, 135.0, (d, $J$ = 2.1 Hz), 205.7 (dd, $J$ = 26.0, 29.0 Hz); $^{19}$F NMR (376 Hz, $CDCl_3$): −108.4 (dd, $J$ = 7.5, 286.1 Hz, 1F), −119.0 (dd, $J$ = 18.4, 286.1 Hz, 1F); IR (film): 3498, 2907, 2850, 1711, 1700 cm$^{-1}$; HRMS (CI): calcd. for $C_{19}H_{23}F_2O_2$ [M+H$^+$]: 321.1666, found: 321.1676.

*4.4.24. GABA$_B$ agonist (**1**)*

99% yield; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.65–1.80 (m, 6H), 1.90 (brs, 6H), 1.99–2.06 (m, 3H), 2.62 (s, 3H), 3.00 (d, $J$ = 4.9 Hz, 1H), 5.33 (td, $J$ = 4.9, 18.0 Hz, 1H), 7.54 (d, $J$ = 8.0 Hz, 2H), 7.94–8.00 (m, 2H). The NMR data matched that reported in the literature [17].

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