Indium-Mediated Reformatsky Reaction of Iododifluoro Ketones with Aldehydes: Preparation of α,α -Difluoro- β -hydroxyketone Derivatives in Water

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Abstract Indium can efficiently mediate the Reformatsky reaction of iododifluoroacetylketones with aldehydes to afford the corresponding α,α -difluoro- β -hydroxyketones in high yield in pure water. This reaction has excellent substrate suitability and functional group selectivity and provides an efficient approach for the synthesis of bioactive molecules containing the α,α -difluoro- β -hydroxyketone pharmacophore.

Key words Indium, Reformatsky reaction, α -iodo- α,α -difluoroketone, α,α -difluoro- β -hydroxyketone

The traditional Reformatsky reaction utilizes zinc to mediate the addition of α -halogenated esters to carbonyl compounds and is an important method to prepare β -hydroxy esters.^{1–4} In addition to zinc, other metals (Sm, Cr, Cu, In, etc.) have also been developed to mediate the Reformatsky

reaction.^{5–10} Among them, indium has attracted much more attention because of its similar properties to zinc and the mildness of the reaction conditions when using it, especially the ability to react in the aqueous phase. Since Rieke *et al.*¹⁰ first applied indium in the Reformatsky reaction in 1975, research on indium-mediated organic synthesis reactions has made great progress.^{12–15}

In medicinal chemistry, the α,α -difluoro- β -hydroxyketone skeleton has received considerable attention due to the unique biological properties present in a variety of active pharmaceutical ingredients such as HMG-CoA inhibitors, analgesics, protease inhibitors, and GABA agonists (Figure 1).^{16–19} In 2016, Ogoshi and co-workers reported the β -F elimination of trifluoroacetophenone to obtain α -metalated alkoxides and aldehydes to give the corresponding α,α -difluoro- β -hydroxyketones.²⁰

Usually, α,α -difluoro- β -hydroxyketones are constructed by zinc-mediated Reformatsky reaction between halodifluoroketones and aldehydes, although there are some disadvantages with this reaction, such as harsh reaction conditions, low yields, or substrate-scope limitations. The zinc-mediated Reformatsky reaction reported by Liu and co-workers in 2013¹⁹ was applied to the synthesis of α,α -difluoro-

Figure 1 Bioactive α,α -difluoro- β -hydroxy compounds

orinated β -hydroxy carbonyl compounds through reaction of bromodifluoromethyl ketones with aldehydes in the presence of Zn/CuCl to give the corresponding difluorinated compounds in good yields. However, they noted that reaction of bromodifluoromethyl ketones with a nitro substituent failed to promote any adduct resulting in full recovery of the starting material (Scheme 1a). The indium-mediated Reformatsky reaction can provide an important method for the construction of α,α -difluoro- β -hydroxyketones using chloro-/bromodifluoroketones or esters as substrates.

However, those reactions are also restricted due to the problems of using aqueous medium, resulting in poor reaction yields, serious side reactions, and limited substrate scope. For example, Welch's group used 2-chloro-2,2-difluoro-1-furan-2-yl ethylenedione (**I**) to perform the Reformatsky reaction with various aldehydes. When pure water was used as the solvent, side products (the reduction product **II** and a small amount of condensation product **III**), accounting for 53% product yield, are observed²¹ (Scheme 1b). Médebielle et al. reported the use of β -aminovinylchlorodifluoromethyl ketones and a series of heteroaryl aldehydes in H₂O/THF (4:1) to obtain the corresponding α,α -difluoro-

β -hydroxyketones. It is worth noting that the reaction failed when 4-pyridinecarboxaldehyde or trifluoromethylbenzaldehyde is applied, which may be due to intervention of the nitrogen atom in the indium intermediate and the formation of pinacol coupling products²² (Scheme 1c). Meanwhile, Poisson *et al.* prepared α,α -difluoro- β -hydroxyesters through indium-mediated Reformatsky reaction, but the reaction needs to be carried out in THF²³ (Scheme 1d).

For many years, our group has been committed to investigating radical reactions of iododifluoroketone compounds.^{24–29} During an experiment to reduce the carbonyl group of 2-iodo-2,2-difluoroacetophenone with LiEt₃BH, we unexpectedly obtained the aldol self-condensation product and the corresponding α,α -difluoro- β -hydroxyketone in the presence of an aldehyde³⁰ (Scheme 1e). In this respect, it has been reported that alkyl iodides can react with alkenes through indium-mediated radical addition reactions.^{31–34} We envisaged that an indium-mediated Reformatsky reaction of iododifluoroketones would be advantageous compared with the previous use of α -Cl-/ α -Br- α,α -difluoroketones or esters for the preparation of α,α -di-

a) Liu et al.

b) Welch

c) M. Médebielle

d) T. Poisson et al.

e) Our previous work:

Scheme 1 The preparation of α,α -difluoro- β -hydroxy compounds

fluoro- β -hydroxyketones.^{35–37} Herein, we wish to describe a more convenient and useful synthetic method for the preparation of α,α -difluoro- β -hydroxyketones using the indium-mediated Reformatsky reaction of iododifluoroketones and aldehydes in tap water (Scheme 2).

Scheme 2 Indium-mediated Reformatsky reaction of iododifluoroketones and aldehydes in water

Firstly, we used iododifluoroacetophenone (**1a**) as substrate to examine the Reformatsky reaction with benzaldehyde (**2a**) in various solvents at room temperature in the presence of 2.0 equiv of indium (entries 1–12, Table 1). To our satisfaction, the reaction proceeded smoothly in water to afford **3a** in 91% yield (entry 1, Table 1). It is worth noting that the reduction product of **1a** and its self-condensed product were not observed in this reaction. However, **3a** was obtained in low yield together with several reduction byproducts and substantial quantities of self-condensation byproducts when the reaction was carried out in aprotic solvents such as DMF, NMP, and 1,4-dioxane (entries 2–4, Table 1). The yield was moderate in MeCN and THF; whereas when H₂O–THF (4:1) was used as a mixed solvent, the yield of **3a** was significantly improved to 82% yield compared to the yield obtained pure THF (entries 5–7, Table 1). Among alcohol solvents, MeOH and 50% MeOH–H₂O (v/v) worked well, resulting in 89% and 90% yield, respectively. However, when the reaction was carried out in absolute ethanol, 95% EtOH–H₂O (v/v) and *n*-BuOH as solvent, the yield of **3a** was extremely low, and **1a** was mainly converted into reduction byproducts (entries 8–12, Table 1).

Using water as reaction solvent, the influences of reaction temperature and the amount of indium were studied (entries 13–19, Table 1). When the reaction was carried out at 40–50 °C, the yield of **3a** was equal to that at room temperature, but the reaction time could be reduced to 2–5 h. Evaluating the reaction at 70–100 °C led to a decrease in yield due to the increase of reduction byproducts. Theoretically, 0.33 equiv of indium are required and we found that 0.50 equiv of indium were enough and gave the same yield of **3a** as when using 1.0 and 2.0 equiv of indium (entries 1, 16, 17, Table 1). Reducing the amount of indium further led to a dramatic drop in yield (entries 18 and 19, Table 1). We also examined the reaction of other halodifluoroacetophenone substrates and found that trifluoroacetophenone did not react, and chloro- or bromodifluoroacetophenone only gave **3a** in 24% and 36% yield, respectively, under the same conditions (entries 20–22, Table 1).

Under the optimized reaction conditions (0.5 equiv indium, 50 °C in water), we examined the scope and limitations of substrates **1** and **2** (Scheme 3). As shown in Scheme

Table 1 Optimization of Indium-Mediated Reformatsky Reaction of Iododifluoroketones and Aldehydes^a

Entry	Indium (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%) ^b
1	2.0	H ₂ O	RT	12	91
2	2.0	NMP	RT	12	39
3	2.0	DMF	RT	18	13
4	2.0	1,4-dioxane	RT	12	35
5	2.0	MeCN	RT	12	76
6	2.0	THF	RT	16	56
7	2.0	H ₂ O–THF (4:1)	RT	14	82
8	2.0	MeOH	RT	12	89
9	2.0	EtOH	RT	18	10
10	2.0	95% EtOH–H ₂ O	RT	18	16
11	2.0	50% MeOH–H ₂ O	RT	14	90
12	2.0	<i>n</i> -BuOH	RT	18	13
13	2.0	H ₂ O	40	5	91
14	2.0	H ₂ O	50	2	91
15	2.0	H ₂ O	100	1	72
16	1.0	H ₂ O	50	2	91
17	0.5	H ₂ O	50	2	91
18	0.2	H ₂ O	50	48	35
19	0.05	H ₂ O	50	48	4
20	0.5	H ₂ O	50	12	– ^c
21	0.5	H ₂ O	50	6	24 ^d
22	0.5	H ₂ O	50	6	36 ^e

^a Reaction conditions (unless otherwise specified): **1a** (0.2 g, 1.0 equiv), **2a** (1.2 equiv).

^b Isolated yield.

^c 1.2 equiv trifluoroacetophenone.

^d 1.2 equiv chlorodifluoroacetophenone.

^e 1.2 equiv bromodifluoroacetophenone.

3, this reaction is efficient with aromatic aldehydes, regardless whether the substituents are halogens (**2b–d**), electron-donating groups (**2e–i**), electron-withdrawing groups (**2j,k**), as well as with the heterocyclic aromatic aldehyde (**2o**). It should be emphasized that the yield of halogen-substituted aromatic aldehydes **2b–d** is relatively high, and the presence of an unprotected phenolic hydroxyl group has no effect on the reaction (**3n**). Aliphatic aldehydes **2p,q** and α,β -unsaturated aldehydes **2r,s** also react to obtain the corresponding products **3p–s** with a yield of 80–87%. It is worth noting that for α,β -unsaturated aldehydes products **3r** and **3s** are also obtained in good yields, and no Michael addition products are produced. Finally, under the same re-

Scheme 3 The indium-mediated Reformatsky reaction of iododifluoroketones with various aldehydes^{a,b}

action conditions, reaction of various α -iodo- α,α -difluoroketones **1t–aa** with aldehydes **2t–aa** proceeded smoothly to afford the desired products **3t–aa** in 81–91% yield.

To investigate the reaction mechanism, the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and a trivalent indium reagent were used as controls compared with the standard conditions. The reaction was completely inhibited by TEMPO and we isolated the radical scavenger adduct in 85% yield; whereas the trivalent indium reagent was ineffective. (Scheme 4) These results confirmed that

this reaction proceeds by a radical process. With reference to relevant literature,^{31–34,38} we propose the following possible mechanism: single-electron transfer (SET) reaction between **1** and indium firstly produces a difluoromethyl radical, which is further reduced by indium or indium iodide to give the difluoromethyl-indium reagent **i**, that further isomerizes to generate α,α -difluoroenol structure **ii**. Then, addition to an aldehyde forms intermediate **iii** to afford the Reformatsky reaction product on H_2O or D_2O quench (Scheme 5).

Scheme 4 Mechanistic investigation

Scheme 5 Proposed reaction mechanism

To demonstrate the efficiency and viability of our developed methodology, GABA_B agonist **7** was prepared on a gram-scale in 89% yield from **5** and **6**, and no addition product to the ketone group of **6** was isolated. In addition, we also examined the reaction of two nature product substrates, citral (**8**) and retinaldehyde (**10**), and the corresponding Reformatsky products **9** and **11** were obtained in 70% and 63% yield, respectively (Scheme 6).

These examples emphasize that the indium-mediated Reformatsky reaction of iododifluoroketones has good selectivity for aldehydes.

In addition to showing good reactivity with aldehydes, applying this strategy to the reaction of iododifluoroacetophenone and isatin worked well in water, allowing efficient

construction of the quaternary oxindoles **13** featuring a CF₂ group at C3 (Scheme 7). It should be noted that the synthesis of quaternary oxindoles is of current interest as they present privileged scaffolds in medicinal research.³⁹

In summary, we have demonstrated that indium is an efficient reagent for the Reformatsky reaction of iododifluoroketones with various aldehydes as well as isatin under mild conditions using water as the solvent. This reaction has extensive substrate scope and excellent selectivity. This environmentally friendly approach has been applied to the gram-scale preparation of GABA_B receptor agonist **7** and other molecules with the α,α -difluoro- β -hydroxyketone pharmacophore.

Scheme 6 Synthesis of GABA_B agonist **7**, fluorine-containing citral and retinol derivatives by indium-mediated Reformatsky reaction

Reactions were monitored by thin-layer chromatography using UV light to visualize the plates. Purification of reaction products was carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. NMR spectra were obtained at 500/400 MHz (^1H NMR), 376 MHz (^{19}F NMR), and 126/101 MHz (^{13}C NMR) using CDCl_3 or $(\text{CD}_3)_2\text{SO}$ with the residual proton solvent resonance as the internal standard. Chemical shifts are reported in ppm relative to TMS. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, J , are reported in hertz.

General Procedure for the Reaction of α -Iodo- α,α -Difluoro-ketones with Aldehydes

To a 20 mL vial α -iodo- α,α -difluoroketones **1** (200 mg, 0.7 mmol, 1.0 equiv), indium powder (0.5 equiv), and aldehyde **2** (1.2 equiv) were added, followed by H_2O (8 mL). The reaction mixture was stirred at 50 °C for 2 h (monitored by TLC). Then ethyl acetate (3×10 mL) was added to extract the aqueous layer, the organic phase was concentrated and purified by column chromatography to afford the products **3a-aa**.

2,2-Difluoro-3-hydroxy-1,3-diphenylpropan-1-one (**3a**)⁴⁰

White solid, mp 62–63 °C, 0.169 g, 91% yield.

^1H NMR (500 MHz, CDCl_3): δ = 8.09 (d, J = 8.0 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.54 (d, J = 4.1 Hz, 2 H), 7.49 (t, J = 7.8 Hz, 2 H), 7.44–7.40 (m, 3 H), 5.40 (dt, J = 18.4, 4.7 Hz, 1 H), 3.12 (1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 191.11 (dd, J = 31.5, 28.7 Hz), 134.91, 134.59, 132.58, 130.29 (t, J = 2 Hz), 129.06, 128.69, 128.35, 128.19, 116.03 (dd, J = 264.3, 256.4 Hz), 73.37 (dd, J = 28.5, 23.2 Hz).

^{19}F NMR (376 MHz, CDCl_3): δ = –104.4 (d, J = 79 Hz, 1 F), –116.8 (d, J = 79 Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2\text{Na}$ [$M + \text{Na}$] $^+$: 285.0698; found: 285.0699

2,2-Difluoro-3-(3-fluorophenyl)-3-hydroxy-1-phenylpropan-1-one (**3b**)

White solid, mp 78–79 °C, 0.182 g, 92% yield.

^1H NMR (500 MHz, CDCl_3): δ = 8.08 (d, J = 7.9 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 2 H), 7.36 (dd, J = 13.9, 7.6 Hz, 1 H), 7.28 (d, J = 7.8 Hz, 2 H), 7.12–7.05 (m, 1 H), 5.40 (dt, J = 18.6, 4.5 Hz, 1 H), 3.63 (d, J = 4.5 Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 190.86 (dd, J = 31.6, 28.8 Hz), 163.68, 161.73, 137.35 (d, J = 7.5 Hz), 134.76, 132.33, 130.29 (t, J = 2 Hz), 129.77 (d, J = 8.1 Hz), 128.73, 123.87, 115.92 (d, J = 21.1 Hz), 115.49 (t, J = 90 Hz), 115.23 (d, J = 22.7 Hz), 72.63 (t, J = 110 Hz).

^{19}F NMR (376 MHz, CDCl_3): δ = –104.1 (dd, J = 15.0, 263 Hz, 1 F), –112.3 (m, 1 F), –116.7 (dd, J = 19, 338 Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2\text{Na}$ [$M + \text{Na}$] $^+$: 303.0603; found: 303.0603.

2,2-Difluoro-3-(4-fluorophenyl)-3-hydroxy-1-phenylpropan-1-one (**3c**)⁴¹

White solid, mp 70–72 °C, 0.188 g, 95% yield.

^1H NMR (500 MHz, CDCl_3): δ = 8.07 (d, J = 7.9 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.5 Hz, 4 H), 7.09 (t, J = 8.6 Hz, 2 H), 5.38 (dt, J = 18.6, 4.5 Hz, 1 H), 3.55 (d, J = 4.3 Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 191.21–190.72 (dd, J = 115 Hz, 10 Hz), 163.16 (d, J = 247.5 Hz), 134.73, 132.37, 130.65, 130.28 (t, J = 6.4 Hz, 3.6 Hz), 129.98 (d, J = 8.3 Hz), 128.73, 117.82–113.68 (dd, J = 8.2 Hz), 115.28 (d, J = 21.6 Hz), 72.83–72.42 (dd, J = 162.83, 25 Hz).

^{19}F NMR (376 MHz, CDCl_3): δ = –104.1 (dd, J = 15.0, 263 Hz, 1 F), –112.3 (m, 1 F), –116.7 (dd, J = 19, 338 Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2\text{F}_2\text{Na}$ [$M + \text{Na}$] $^+$: 303.0603; found: 303.0603.

3-(4-Bromophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**3d**)⁴⁰

White solid, mp 79–81 °C, 0.212 g, 93% yield.

^1H NMR (500 MHz, CDCl_3): δ = 8.06 (d, J = 7.9 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.54–7.45 (m, 4 H), 7.38 (d, J = 8.2 Hz, 2 H), 5.35 (dd, J = 18.7, 5.0 Hz, 1 H), 3.70 (s, 1 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 190.84 (dd, J = 31.5, 28.8 Hz), 134.76, 133.94, 132.33, 131.45, 130.37–130.16 (m), 129.85, 128.75, 123.19, 115.67 (dd, J = 265.0, 256.7 Hz), 72.62 (dd, J = 28.7, 23.3 Hz).

^{19}F NMR (376 MHz, CDCl_3): δ = –104.6 (d, J = 184 Hz, 1 F), –116.7 (d, J = 248 Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{11}\text{O}_2\text{BrF}_2\text{Na}$ [$M + \text{Na}$] $^+$: 362.9803; found: 362.9806.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(*p*-tolyl)propan-1-one (**3e**)⁴¹

White solid, mp 67–69 °C, 0.162 g, 83% yield.

^1H NMR (500 MHz, CDCl_3): δ = 8.10 (d, J = 8.0 Hz, 2 H), 7.67 (t, J = 7.1 Hz, 1 H), 7.51 (t, J = 7.7 Hz, 2 H), 7.43 (d, J = 7.8 Hz, 2 H), 7.25 (d, J = 7.9 Hz, 2 H), 5.45–5.30 (m, 1 H), 3.31 (d, J = 3.2 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 191.06 (t, J = 31.5 Hz), 138.92, 134.53, 131.88, 130.33–130.23 (m), 129.25, 129.08, 128.66, 128.06, 115.99 (dd, J = 264.1, 256.1 Hz), 73.28 (dd, J = 28.6, 23.2 Hz), 21.27.

^{19}F NMR (376 MHz, CDCl_3): $\delta = -104.5$ (d, $J = 188$ Hz, 1 F), -116.5 (d, $J = 316$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 299.0854; found: 299.0851.

2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (3f)⁴⁰

White solid, mp 67–68 °C, 0.174 g, 84% yield.

^1H NMR (500 MHz, CDCl_3): $\delta = 8.07$ (d, $J = 7.9$ Hz, 2 H), 7.63 (t, $J = 7.4$ Hz, 1 H), 7.48 (t, $J = 7.7$ Hz, 2 H), 7.43 (d, $J = 8.4$ Hz, 2 H), 6.93 (d, $J = 8.5$ Hz, 2 H), 5.38–5.29 (m, 1 H), 3.81 (s, 3 H), 3.46 (d, $J = 4.4$ Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 191.19$ (t, $J = 30.24$ Hz), 160.11, 134.51, 132.68, 130.38–130.11 (m), 129.44, 128.66, 127.05, 116.15 (dd, $J = 263.7$, 255.8 Hz), 113.80, 73.04 (dd, $J = 28.8$, 23.1 Hz), 55.28.

^{19}F NMR (376 MHz, CDCl_3): $\delta = -104.5$ (d, $J = 252$ Hz, 1 F), -116.5 (d, $J = 263$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_3\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 315.0809; found: 315.0801.

2,2-Difluoro-3-hydroxy-3-(3-methoxyphenyl)-1-phenylpropan-1-one (3g)⁴²

White solid, mp 59–62 °C, 0.166 g, 80% yield.

^1H NMR (500 MHz, CDCl_3): $\delta = 8.07$ (d, $J = 8.0$ Hz, 2 H), 7.64 (t, $J = 7.4$ Hz, 1 H), 7.48 (t, $J = 7.7$ Hz, 2 H), 7.31 (t, $J = 8.1$ Hz, 1 H), 7.08 (s, 2 H), 6.96–6.91 (m, 1 H), 5.36 (dt, $J = 18.4$, 5.0 Hz, 1 H), 3.81 (s, 3 H), 3.38 (d, $J = 4.6$ Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 190.94$ (dd, $J = 31.4$, 28.5 Hz), 160.61 (s), 137.15 (s), 134.52 (s), 132.63 (s), 130.21 (s), 128.65 (s), 115.99 (dd, $J = 264.6$, 256.5 Hz), 106.16 (s), 101.13 (s), 73.36 (dd, $J = 28.0$, 23.2 Hz), 55.38 (s).

^{19}F NMR (376 MHz, CDCl_3): $\delta = -104.5$ (d, $J = 252$ Hz, 1 F), -116.0 (d, $J = 34$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_3$ [$\text{M} + \text{Na}$] $^+$: 315.0803; found: 315.0803.

3-(3,5-Dimethoxyphenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (3h)

White solid, mp 63–65 °C, 0.196 g, 86% yield.

^1H NMR (500 MHz, CDCl_3): $\delta = 8.06$ (d, $J = 7.9$ Hz, 2 H), 7.63 (t, $J = 7.4$ Hz, 1 H), 7.48 (t, $J = 7.8$ Hz, 2 H), 6.67 (d, $J = 1.6$ Hz, 2 H), 6.48 (t, $J = 2.1$ Hz, 1 H), 5.31 (dt, $J = 18.3$, 4.5 Hz, 1 H), 3.78 (s, 6 H), 3.44 (d, $J = 4.2$ Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 190.93$ (t, $J = 34.02$ Hz), 160.61, 137.15, 134.52, 132.63, 130.21, 128.65, 115.99 (dd, $J = 264.6$, 256.5 Hz), 106.16, 101.13, 73.32 (t, $J = 42.84$ Hz), 55.38.

^{19}F NMR (376 MHz, CDCl_3): $\delta = -103.9$ (d, $J = 45$ Hz, 1 F), -116.25 (d, $J = 297$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{16}\text{F}_4\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 345.0909; found: 345.0911.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(3,4,5-trimethoxyphenyl)propan-1-one (3i)

White solid, mp 93–95 °C, 0.195 g, 78% yield.

^1H NMR (500 MHz, CDCl_3): $\delta = 8.04$ (d, $J = 7.9$ Hz, 2 H), 7.62 (t, $J = 7.4$ Hz, 1 H), 7.47 (t, $J = 7.8$ Hz, 2 H), 6.68 (s, 2 H), 5.29 (dd, $J = 17.9$, 5.5 Hz, 1 H), 3.82 (s, 9 H), 3.54 (s, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 191.06$ (dd, $J = 31.0$, 28.3 Hz), 152.96, 138.19, 134.48, 132.74, 130.58, 130.17 (t, $J = 18.9$ Hz), 128.61, 116.11 (dd, $J = 264.3$, 256.0 Hz), 105.19, 73.44 (dd, $J = 28.5$, 23.4 Hz), 60.82, 56.08.

^{19}F NMR (376 MHz, CDCl_3): $\delta = -103.7$ (d, $J = 41$ Hz, 1 F), -115.6 (d, $J = 41$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{18}\text{F}_2\text{O}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 375.1015; found: 375.1018.

2,2-Difluoro-3-hydroxy-1-phenyl-3-[3-(trifluoromethyl)phenyl]propan-1-one (3j)

White solid, mp 77–79 °C, 0.192 g, 82% yield.

^1H NMR (501 MHz, CDCl_3): $\delta = 8.09$ (d, $J = 7.9$ Hz, 2 H), 7.84 (s, 1 H), 7.72 (d, $J = 7.7$ Hz, 1 H), 7.66 (t, $J = 7.5$ Hz, 2 H), 7.51 (dt, $J = 15.5$, 7.8 Hz, 3 H), 5.48 (dt, $J = 19.1$, 4.4 Hz, 1 H), 3.69 (d, $J = 4.5$ Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 190.75$ (dd, $J = 31.7$, 29.1 Hz), 135.86, 134.89, 132.13, 131.58, 130.83 (t, $J = 32.5$ Hz), 130.29 (t, $J = 11.34$ Hz), 128.76, 128.73, 125.76 (q, $J = 3.6$ Hz), 125.04 (d, $J = 3.8$ Hz), 124.02 (dd, $J = 189.0$, 272.16 Hz), 115.51 (dd, $J = 265.6$, 257.0 Hz), 72.58 (dd, $J = 28.7$, 23.3 Hz).

^{19}F NMR (376 MHz, CDCl_3): $\delta = -62.64$ (s, CF_3), -103.8 (d, $J = 297$ Hz, 1 F), -115.8 (d, $J = 301$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{11}\text{F}_5\text{O}_2\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 353.0577; found: 353.0568.

2,2-Difluoro-3-hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (3k)

Yellow liquid, 0.176 g, 81% yield.

^1H NMR (500 MHz, CDCl_3): $\delta = 8.26$ (d, $J = 8.5$ Hz, 2 H), 8.10 (d, $J = 8.0$ Hz, 2 H), 7.72 (d, $J = 8.5$ Hz, 2 H), 7.69 (t, $J = 7.5$ Hz, 1 H), 7.52 (t, $J = 7.7$ Hz, 2 H), 5.55 (dt, $J = 19.3$, 3.9 Hz, 1 H), 3.49 (d, $J = 4.3$ Hz, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 190.31$ (dd, $J = 31.7$, 29.3 Hz), 148.29, 141.76, 135.11, 131.82, 130.34 (t, $J = 3.1$ Hz), 129.18, 128.86, 123.30, 115.15 (dd, $J = 266.5$, 258.2 Hz), 72.25 (dd, $J = 27.7$, 23.6 Hz).

^{19}F NMR (376 MHz, CDCl_3): $\delta = -104.0$ (d, $J = 338$ Hz, 1 F), -116.0 (d, $J = 376$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{11}\text{F}_2\text{NO}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 330.0548; found: 330.0546.

2,2-Difluoro-3-hydroxy-3-(4-methoxy-3-nitrophenyl)-1-phenylpropan-1-one (3l)

Yellow liquid, 0.196 g, 82% yield.

^1H NMR (500 MHz, CDCl_3): $\delta = 8.09$ (d, $J = 7.8$ Hz, 2 H), 8.03 (d, $J = 1.3$ Hz, 1 H), 7.68 (dd, $J = 17.6$, 8.4 Hz, 2 H), 7.51 (t, $J = 7.8$ Hz, 2 H), 7.12 (d, $J = 8.7$ Hz, 1 H), 5.41 (dd, $J = 19.0$, 4.3 Hz, 1 H), 3.99 (s, 3 H), 3.50 (s, 1 H).

^{13}C NMR (126 MHz, CDCl_3): $\delta = 190.53$ (dd, $J = 31.9$, 29.1 Hz), 153.30, 139.27, 134.93, 133.90, 132.07, 130.28 (t, $J = 12.6$ Hz), 128.80, 127.31, 125.56, 115.33 (d, $J = 8.6$ Hz), 113.33, 71.78 (dd, $J = 29.5$, 23.4 Hz), 56.65.

^{19}F NMR (376 MHz, CDCl_3): $\delta = -103.8$ (d, $J = 331$ Hz, 1 F), -114.6 (d, $J = 331$ Hz, 1 F).

HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{13}\text{F}_2\text{NO}_5\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 360.0659; found: 360.0662.

2,2-Difluoro-3-hydroxy-3-(3-hydroxyphenyl)-1-phenylpropan-1-one (3m)

Yellow liquid, 0.173 g, 88% yield.

¹H NMR (501 MHz, DMSO): δ = 9.49 (s, 1 H), 8.05 (d, J = 7.8 Hz, 2 H), 7.73 (t, J = 7.4 Hz, 1 H), 7.60 (t, J = 7.8 Hz, 2 H), 7.19 (t, J = 7.8 Hz, 1 H), 6.97 (s, 1 H), 6.92 (d, J = 7.6 Hz, 1 H), 6.79 (dd, J = 8.0, 1.8 Hz, 1 H), 6.61 (s, 1 H), 5.18 (d, J = 3.0 Hz, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 191.48 (dd, J = 30.0, 25.7 Hz), 157.59, 138.47, 134.75, 133.53, 130.16, 129.38, 129.28, 119.20, 117.76 (d, J = 9.7 Hz), 115.95, 115.36, 72.87 (dd, J = 28.8, 23.5 Hz).

¹⁹F NMR (376 MHz, CDCl₃): δ = -103.4 (d, J = 353 Hz, 1 F), -116.7 (d, J = 353 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₅H₁₁O₂BrF₂Na [M + Na]⁺: 339.9910; found: 339.9912.

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

Yellow liquid, 0.194 g, 89% yield.

¹H NMR (500 MHz, CDCl₃): δ = 8.09 (d, J = 8.0 Hz, 2 H), 7.65 (t, J = 7.4 Hz, 1 H), 7.54 (d, J = 4.1 Hz, 2 H), 7.49 (t, J = 7.8 Hz, 2 H), 7.44–7.40 (m, 3 H), 5.40 (dt, J = 18.4, 4.7 Hz, 1 H), 3.46 (d, J = 4.4 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 191.11 (dd, J = 31.5, 28.7 Hz), 134.91, 134.59, 132.58, 130.29 (t, J = 2 Hz), 129.06, 128.69, 128.35, 128.19, 116.03 (dd, J = 264.3, 256.4 Hz), 73.37 (dd, J = 28.5, 23.2 Hz).

¹⁹F NMR (376 MHz, CDCl₃): δ = -103.5 (d, J = 331 Hz, 1 F), -114.8 (d, J = 316 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₆H₁₄F₂O₄Na [M + Na]⁺: 331.0752; found: 331.0754.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(pyridin-4-yl)propan-1-one (3o)

Yellow liquid, 0.143 g, 77% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.48 (d, J = 5.0 Hz, 2 H), 8.09 (d, J = 7.9 Hz, 2 H), 7.66 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.6 Hz, 4 H), 5.42 (dd, J = 18.9, 5.1 Hz, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 191.45 (dd, J = 31.9, 26.2 Hz), 154.68, 150.82, 137.79, 136.86, 129.57, 129.11, 128.49, 124.38, 117.64 (dd, J = 262.1, 253.0 Hz), 71.41 (t, J = 23.94, 3.78 Hz).

¹⁹F NMR (376 MHz, CDCl₃): δ = -103.5 (d, J = 305 Hz, 1 F), -114.8 (d, J = 305 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₄H₁₁F₂NO₂Na [M + Na]⁺: 286.0650; found: 286.0650.

2,2-Difluoro-3-hydroxy-1-phenylhexan-1-one (3p)

Colorless liquid, 0.133 g, 82% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.13 (d, J = 7.8 Hz, 2 H), 7.66 (t, J = 7.4 Hz, 1 H), 7.51 (t, J = 7.8 Hz, 2 H), 4.31–4.23 (m, 1 H), 2.67 (d, J = 5.9 Hz, 1 H), 1.75–1.63 (m, 3 H), 1.48 (dt, J = 14.4, 6.5 Hz, 1 H), 1.00 (t, J = 7.0 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 190.72 (t, J = 31.5), 134.51, 133.15, 132.56, 130.19 (t, J = 3.3 Hz), 128.68, 124.23, 116.22 (dd, J = 261.5, 257.0 Hz), 72.73 (dd, J = 28.0, 24.6 Hz), 17.97.

¹⁹F NMR (376 MHz, CDCl₃): δ = -103.6 (d, J = 263 Hz, 1 F), -114.4 (d, J = 263 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₂H₁₄F₂O₂ [M + Na]⁺: 228.0962; found: 228.0965.

2,2-Difluoro-3-hydroxy-1,5-diphenylpentan-1-one (3q)

Yellow liquid, 0.179 g, 87% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.15 (d, J = 7.8 Hz, 2 H), 7.68 (t, J = 7.4 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.27 (dd, J = 17.5, 7.0 Hz, 3 H), 4.37–4.25 (m, 1 H), 3.04 (ddd, J = 14.1, 9.4, 5.1 Hz, 1 H), 2.86–2.77 (m, 2 H), 2.19–2.01 (m, 2 H).

¹³C NMR (126 MHz, CDCl₃): δ = 190.59 (t, J = 30.24 Hz), 141.13, 134.70, 132.25, 130.29 (t, J = 3.1 Hz), 128.77, 128.57, 126.18, 116.63 (t, J = 262.08 Hz), 70.55 (t, J = 26.46 Hz), 31.40, 30.41.

¹⁹F NMR (376 MHz, CDCl₃): δ = -103.6 (d, J = 259 Hz, 1 F), -114.5 (d, J = 256 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₇H₁₆F₂O₂Na [M + Na]⁺: 313.1011; found: 313.1009.

(E)-2,2-Difluoro-3-hydroxy-1-phenylhex-4-en-1-one (3r)

Transparent liquid, 0.128 g, 80% yield.

¹H NMR (500 MHz, CDCl₃): δ = 8.10 (d, J = 7.9 Hz, 2 H), 7.64 (t, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.8 Hz, 2 H), 5.95 (dq, J = 13.1, 6.5 Hz, 1 H), 5.65 (dd, J = 15.4, 7.1 Hz, 1 H), 4.77–4.66 (m, 1 H), 2.99 (s, 1 H), 1.76 (d, J = 6.5 Hz, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 190.62 (t, J = 28.92 Hz), 134.51, 133.15, 132.56, 130.19 (t, J = 3.3 Hz), 128.68, 124.23, 116.22 (dd, J = 261.5, 257.0 Hz), 72.73 (dd, J = 28.0, 24.6 Hz), 17.97.

¹⁹F NMR (376 MHz, CDCl₃): δ = -106.0 (d, J = 368 Hz, 1 F), -115.6 (d, J = 368 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₂H₁₂F₂O₂Na [M + Na]⁺: 249.0698; found: 249.0700.

(E)-2,2-Difluoro-3-hydroxy-1,5-diphenylpent-4-en-1-one (3s)

Yellow liquid, 0.204 g, 81% yield.

¹H NMR (500 MHz, CDCl₃): δ = 8.17 (d, J = 6.8 Hz, 1 H), 7.66 (s, 1 H), 7.52 (d, J = 6.7 Hz, 1 H), 7.45 (d, J = 6.3 Hz, 1 H), 7.34 (dd, J = 16.7, 6.4 Hz, 2 H), 6.88 (d, J = 15.9 Hz, 1 H), 6.40 (dd, J = 15.7, 6.0 Hz, 1 H), 5.02 (d, J = 7.9 Hz, 1 H), 3.30 (d, J = 2.4 Hz, 1 H).

¹³C NMR (126 MHz, CDCl₃): δ = 191.11 (dd, J = 31.5, 28.7 Hz), 134.91, 134.59, 132.58, 130.29 (t, 2 H), 129.06, 128.69, 128.35, 128.19, 116.03 (dd, J = 264.3, 256.4 Hz), 73.37 (dd, J = 28.5, 23.2 Hz).

¹⁹F NMR (376 MHz, CDCl₃): δ = -106.0 (d, J = 368 Hz, 1 F), -115.4 (d, J = 368 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₇H₁₄F₂O₂Na [M + Na]⁺: 311.0854; found: 311.0859.

2,2-Difluoro-3-hydroxy-1-(pyridin-3-yl)-3-(p-tolyl)propan-1-one (3t)

Yellow liquid, 0.159 g, 81% yield.

¹H NMR (500 MHz, DMSO): δ = 9.21 (s, 1 H), 8.88 (d, J = 3.9 Hz, 1 H), 8.42 (d, J = 7.9 Hz, 1 H), 7.63 (dd, J = 7.9, 4.9 Hz, 1 H), 7.44 (d, J = 7.8 Hz, 2 H), 7.22 (d, J = 7.9 Hz, 2 H), 6.80 (d, J = 5.2 Hz, 1 H), 5.27 (dt, J = 20.1, 5.5 Hz, 1 H), 2.32 (s, 3 H).

¹³C NMR (101 MHz, DMSO): δ = 191.57 (dd, J = 31.8, 26.4 Hz), 154.60, 150.85, 138.45, 137.77, 133.91, 129.66, 129.08, 128.43, 124.33, 116.48 (t, J = 112.14 Hz), 72.81 (dd, J = 29.4, 23.5 Hz), 21.21.

¹⁹F NMR (376 MHz, CDCl₃): δ = -104.5 (d, J = 323 Hz, 1 F), -115.4 (d, J = 323 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₅H₁₃F₂NO₂Na [M + Na]⁺: 300.0807; found: 300.0810.

2,2-Difluoro-3-(4-fluorophenyl)-3-hydroxy-1-(pyridin-3-yl)propan-1-one (3u)

Yellow liquid, 0.169 g, 85% yield.

¹H NMR (501 MHz, DMSO): δ = 9.21 (s, 1 H), 8.88 (d, J = 4.0 Hz, 1 H), 8.41 (t, J = 11.2 Hz, 1 H), 7.62 (td, J = 8.2, 5.6 Hz, 3 H), 7.25 (t, J = 8.8 Hz, 2 H), 6.90 (dd, J = 17.5, 5.2 Hz, 1 H), 5.36 (dt, J = 20.1, 5.4 Hz, 1 H).

¹³C NMR (101 MHz, DMSO): δ = 191.28 (dd, J = 31.6, 26.4 Hz), 164.06, 161.62, 154.65, 150.86, 137.78, 133.11, 130.60, 130.52, 129.58, 124.33, 177.68 (t, J = 232.96 Hz), 115.46, 115.25, 72.17 (dd, J = 29.5, 23.4 Hz).

¹⁹F NMR (376 MHz, CDCl₃): δ = -105.4 (dd, J = 15.0, 331 Hz, 1 F), -111.9 (m, 1 F), -113.6 (dd, J = 15.0, 331 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₄H₁₀F₃NO₂Na [M + Na]⁺: 304.0556; found: 304.0556.

2,2-Difluoro-1-(4-fluorophenyl)-3-hydroxy-3-(4-methoxyphenyl)propan-1-one (3v)

White solid, mp 82–83 °C, 0.188 g, 91% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.09 (dd, J = 8.1, 5.6 Hz, 2 H), 7.41 (d, J = 8.5 Hz, 2 H), 7.13 (t, J = 8.6 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 5.29 (dd, J = 18.3, 6.1 Hz, 1 H), 3.80 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 189.68 (dd, J = 31.4, 28.9 Hz), 166.49 (d, J = 257.7 Hz), 160.17, 133.24 (dd, J = 6.1, 3.4 Hz), 132.34, 129.40, 129.13, 126.98, 115.93 (d, J = 22.0 Hz), 113.82, 73.00 (dd, J = 28.7, 23.3 Hz), 55.25.

¹⁹F NMR (376 MHz, CDCl₃): δ = -105.7 (dd, J = 15.0, 331 Hz, 1 F), -112.2 (m, 1 F), -116.3 (dd, J = 15.0, 331 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₆H₁₃F₃O₃Na [M + Na]⁺: 333.0709; found: 333.0711.

(E)-1-(4-Chlorophenyl)-2,2-difluoro-3-hydroxyhex-4-en-1-one (3w)

Pale yellow liquid, 0.145 g, 88% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.05 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 7.2 Hz, 2 H), 5.97 (dd, J = 14.9, 6.9 Hz, 1 H), 5.64 (dd, J = 15.3, 7.0 Hz, 1 H), 4.77–4.57 (m, 1 H), 2.65 (d, J = 4.5 Hz, 1 H), 1.79 (d, J = 6.3 Hz, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 189.48 (t, J = 29.5 Hz), 141.32, 133.44, 131.63, 130.85, 129.12, 124.04, 116.04 (t, J = 257.85 Hz), 72.70 (t, J = 24.85 Hz), 18.01.

¹⁹F NMR (376 MHz, CDCl₃): δ = -106.2 (d, J = 274 Hz, 1 F), -115.5 (d, J = 274 Hz, 1 F).

HRMS (ESI): m/z calcd for C₁₂H₁₁ClF₂O₂Na [M + Na]⁺: 283.0308; found: 283.0308.

1-[2-(Benzyloxy)-4-methoxyphenyl]-2,2-difluoro-3-hydroxy-3-(4-methoxy-3-nitrophenyl)propan-1-one (3x)

Yellow solid, mp 105–107 °C, 0.199 g, 88% yield.

¹H NMR (501 MHz, CDCl₃): δ = 7.85 (d, J = 1.4 Hz, 1 H), 7.68 (d, J = 8.6 Hz, 1 H), 7.51 (d, J = 8.6 Hz, 1 H), 7.43 (d, J = 7.4 Hz, 2 H), 7.35 (t, J = 7.4 Hz, 2 H), 7.30 (d, J = 7.3 Hz, 1 H), 6.95 (d, J = 8.8 Hz, 1 H), 6.52 (d, J = 1.8 Hz, 1 H), 6.48 (dd, J = 8.8, 1.9 Hz, 1 H), 5.34 (d, J = 18.1 Hz, 1 H), 5.08 (s, 2 H), 3.85 (s, 3 H), 3.78 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 190.52 (t, J = 30.24 Hz), 153.29, 139.26, 134.92, 133.89, 132.06, 128.78, 127.29, 125.54, 115.33 (t, J = 209.07 Hz), 71.77 (dd, J = 19.19, 5.05 Hz), 56.64.

¹⁹F NMR (376 MHz, CDCl₃): δ = -103.8 (d, J = 297 Hz, 1 F), -114.2 (d, J = 297 Hz, 1 F).

HRMS (ESI): m/z calcd for C₂₄H₂₁F₂NO₇Na [M + Na]⁺: 496.1178; found: 496.1182.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(pyridin-2-yl)propan-1-one (3y)⁴³

White solid, mp 70–72 °C, 0.152 g, 81% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.71 (d, J = 8 Hz, 1 H), 8.16–8.15 (m, 2 H), 7.90–7.87 (m, 1 H), 7.77–7.75 (m, 1 H), 7.69–7.63 (m, 3 H), 7.38–7.37 (m, 1 H), 5.55 (dt, J = 18.6, 4.5 Hz, 1 H), 3.50 (d, J = 4.5 Hz, 1 H).

HRMS (ESI): m/z calcd for C₁₄H₁₁F₂NO₂Na [M + Na]⁺: 286.0656; found: 286.0655.

2,2-Difluoro-3-(furan-2-yl)-3-hydroxy-1-phenylpropan-1-one (3z)⁴⁴

Yellow oil, 0.155 g, 86% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.11 (d, J = 1 Hz, 2 H), 7.62 (t, J = 1.5 Hz, 1 H), 7.37 (t, J = 2.5 Hz, 2 H), 7.26 (d, J = 1 Hz, 1 H), 6.63 (d, J = 5 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 5.56 (dt, J = 18.4, 5 Hz, 1 H), 3.30 (d, J = 7 Hz, 1 H).

HRMS (ESI): m/z calcd for C₁₃H₁₀F₂O₃Na [M + Na]⁺: 275.0496; found: 275.0497.

2,2-Difluoro-3-hydroxy-3-phenyl-1-(thiophen-2-yl)propan-1-one (3aa)⁴²

White solid, mp 60–61 °C, 0.169 g, 90% yield.

¹H NMR (500 MHz, CDCl₃): δ = 7.76 (d, J = 3 Hz, 1 H), 7.64–7.59 (m, 2 H), 7.49–7.47 (m, 4 H), 6.59 (dd, J = 18.7, 5.0 Hz, 1 H), 5.39 (dd, J = 18.7, 5.0 Hz, 1 H), 3.70 (s, 1 H).

HRMS (ESI): m/z calcd for C₁₃H₁₀F₂O₂SNa [M + Na]⁺: 291.0267; found: 291.0270.

Procedure for the Mechanistic Investigation

To a 20 mL vial, α -iodo- α,α -difluoroketone **1a** (200 mg, 0.7 mmol, 1.0 equiv), indium powder (0.5 equiv), benzaldehyde **2a** (1.2 equiv), and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.2 equiv) were added, followed H₂O (8 mL). The reaction mixture was stirred at 50 °C for 2 h (monitored by TLC). Then ethyl acetate (3 $\times$ 10 mL) was added to extract the aqueous layer, the organic phase was concentrated and purified by column chromatography to afford the product **4**, with no **3a** being detected.

2,2-Difluoro-1-phenyl-2-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]ethan-1-one (4)⁴⁵

Pale yellow liquid, 0.187 g, 85% yield.

¹H NMR (400 MHz, CDCl₃): δ = 8.15 (d, J = 7.7 Hz, 2 H), 7.68–7.62 (m, 1 H), 7.52 (t, J = 7.8 Hz, 2 H), 1.59 (dt, J = 10.0, 5.7 Hz, 5 H), 1.39 (s, 1 H), 1.25 (s, 3 H), 1.13 (s, 3 H).

¹³C NMR (101 MHz, CDCl₃): δ = 184.11 (t, J = 37.3 Hz), 134.42, 131.47, 130.39, 128.64, 117.13 (t, J = 278.0 Hz), 61.20, 40.20, 33.75 (t, J = 4.4 Hz), 20.94, 16.93.

¹⁹F NMR (376 MHz, CDCl₃): δ = -71.85.

Procedure for the Preparation of (GABA_B Agonist) 7

To a 20 mL vial, 1-[(3*r*,5*r*,7*r*)-adamantan-1-yl]-2,2-difluoro-2-iodoethan-1-one (**5**, 500 mg, 1.47 mmol), indium powder (85 mg, 0.74 mmol), and 4-acetylbenzaldehyde (**6**, 262 mg, 1.76 mmol) were added, followed by H₂O (10 mL). The reaction mixture was stirred at 50 °C

for 2 h (monitored by TLC). Then ethyl acetate (3 × 20 mL) was added to extract the aqueous layer, the organic phase was concentrated and purified by column chromatography to afford the product **7**.

3-(4-Acetylphenyl)-1-[(3*r*,5*r*,7*r*)-adamantan-1-yl]-2,2-difluoro-3-hydroxypropan-1-one (**7**)^{17b}

Pale yellow solid, mp 45–47 °C, 0.33 g, 89% yield.

¹H NMR (500 MHz, CDCl₃): δ = 7.99 (td, *J* = 8.5, 2.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 5.35 (dt, *J* = 18.0, 5.5 Hz, 1 H), 3.01 (d, *J* = 5.0 Hz, 1 H), 2.65 (s, 3 H), 2.05 (br s, 3 H), 2.01 (br s, 6 H), 1.72 (m, 6 H).

¹³C NMR (125 MHz, CDCl₃): δ = 205.52 (dd, *J* = 29.3, 25.9 Hz), 197.82, 140.12, 137.34, 129.08, 128.57, 116.15 (dd, *J* = 267, 259 Hz), 72.6 (dd, *J* = 27.9, 23.47 Hz), 46.85 (t, *J* = 2.3 Hz), 36.51, 36.55, 27.25, 26.71.

¹⁹F NMR (376 MHz, CDCl₃): δ = –106.0 (dd, *J* = 19, 173 Hz, 1 F), –118.2 (dd, *J* = 19, 173 Hz, 1 F).

HRMS (ESI): *m/z* calcd for C₂₁H₂₄F₂O₃Na [M + Na]⁺: 385.1591; found: 385.1593.

Procedure for the Preparation of **9**

To a 20 mL vial, α-iodo-α,α-difluoroketone **1a** (500 mg, 1.77 mmol), indium powder (102 mg, 0.89 mmol), and citral (**8**, 324 mg, 2.13 mmol) were added, followed by H₂O (10 mL). The reaction mixture was stirred at 50 °C for 2 h (monitored by TLC). Then ethyl acetate (3 × 20 mL) was added to extract the aqueous layer, the organic phase was concentrated and purified by column chromatography to afford the product **9**.

(*E*)-2,2-Difluoro-3-hydroxy-5,9-dimethyl-1-phenyldeca-4,8-dien-1-one (**9**)

Light yellow liquid, 0.382 g, 70% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.11 (d, *J* = 7.7 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 5.39 (dd, *J* = 28.7, 9.0 Hz, 1 H), 2.65 (dd, *J* = 50.3, 5.3 Hz, 1 H), 2.19–2.04 (m, 4 H), 1.82 (s, 1 H), 1.72 (s, 2 H), 1.70 (s, 1 H), 1.68 (s, 2 H), 1.62 (s, 1 H), 1.60 (s, 2 H).

¹³C NMR (126 MHz, CDCl₃): δ = 190.61 (t, *J* = 24.24 Hz), 145.54, 145.13, 134.41, 132.69, 132.50, 131.98, 130.15 (d, *J* = 3.3 Hz), 128.65, 123.54 (d, *J* = 5.3 Hz), 117.97, 116.75 (t, *J* = 199.48 Hz), 68.79 (t, *J* = 21.21 Hz), 39.72, 32.66, 26.45, 26.17, 25.63, 23.65, 17.66 (d, *J* = 2.9 Hz), 17.07.

¹⁹F NMR (376 MHz, CDCl₃): δ = –106.7 (d, *J* = 274 Hz, 1 F), –116.2 (d, *J* = 274 Hz, 1 F).

HRMS (ESI): *m/z* calcd for C₁₈H₂₂F₂O₂Na [M + Na]⁺: 331.1480; found: 331.1480.

Procedure for the Preparation of **11**

To a 20 mL vial, α-iodo-α,α-difluoroketone **1a** (200 mg, 0.71 mmol), indium powder (41 mg, 0.35 mmol), and retinaldehyde (**10**, 242 mg, 0.85 mmol) were added, followed by H₂O (8 mL). The reaction mixture was stirred at 50 °C for 2 h (monitored by TLC). Then ethyl acetate (3 × 10 mL) was added to extract the aqueous layer, the organic phase was concentrated and purified by column chromatography to afford the product **11**.

(4*E*,6*E*,8*E*,10*E*)-2,2-Difluoro-3-hydroxy-5,9-dimethyl-1-phenyl-11-(2,6,6-trimethylcyclohex-1-en-1-yl)undeca-4,6,8,10-tetraen-1-one (**11**)

Yellow liquid, 0.196 g, 63% yield.

¹H NMR (501 MHz, CDCl₃): δ = 8.11 (d, *J* = 7.7 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 6.71 (dd, *J* = 15.1, 11.4 Hz, 1 H), 6.32 (d, *J* = 15.1 Hz, 1 H), 6.22 (d, *J* = 16.1 Hz, 1 H), 6.16–6.09 (m, 2 H), 5.39 (dd, *J* = 28.7, 9.0 Hz, 1 H), 5.15–4.96 (m, 1 H), 2.70 (s, 1 H), 2.07–2.02 (m, 2 H), 1.98 (s, 3 H), 1.94 (s, 3 H), 1.74 (s, 3 H), 1.64 (dt, *J* = 8.8, 6.1 Hz, 2 H), 1.49 (dd, *J* = 7.7, 4.0 Hz, 2 H), 1.27 (t, *J* = 7.1 Hz, 1 H), 1.05 (s, 6 H).

¹³C NMR (126 MHz, CDCl₃): δ = 190.61 (t, *J* = 31.5 Hz), 145.13, 134.41, 132.69, 131.98, 130.15 (d, *J* = 3.3 Hz), 128.65, 123.52, 117.97, 116.68 (t, *J* = 250.11 Hz), 68.89 (dd, *J* = 23.94, 3.78 Hz), 39.72, 25.63, 17.07.

¹⁹F NMR (376 MHz, CDCl₃): δ = –106.6 (d, *J* = 368 Hz, 1 F), –116.3 (d, *J* = 368 Hz, 1 F).

HRMS (ESI): *m/z* calcd for C₂₈H₃₄F₂O₂Na [M + Na]⁺: 463.2419; found: 463.2413.

General Procedure for the Preparation of **13**

To a 20 mL vial, isatin derivative **12** (200 mg, 1.0 equiv), indium powder (0.5 equiv), and 2,2-difluoro-2-iodo-1-phenylethan-1-one (**1**, 1.2 equiv) were added, followed by H₂O (10 mL). The reaction mixture was stirred at 50 °C for 2 h (monitored by TLC). Then the mixture was filtered and washed with petroleum ether to afford the product **13**.

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-3-hydroxyindolin-2-one (**13a**)³⁸

Yellow solid, mp 117–118 °C, 0.392 g, 95% yield.

¹H NMR (501 MHz, DMSO): δ = 8.07 (d, *J* = 7.6 Hz, 1 H), 7.74 (t, *J* = 7.0 Hz, 1 H), 7.58 (t, *J* = 7.1 Hz, 1 H), 7.47 (s, 1 H), 7.41 (dd, *J* = 18.9, 7.7 Hz, 1 H), 7.08 (d, *J* = 7.2 Hz, 1 H), 3.14 (s, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 188.28 (t, *J* = 28.4 Hz), 172.14, 144.80, 135.14, 132.97, 131.31, 130.69, 129.62, 129.20, 126.06, 125.88, 117.34 (t, *J* = 262.4 Hz), 109.50, 76.01 (t, *J* = 25.4 Hz), 26.65.

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-5-fluoro-3-hydroxyindolin-2-one (**13b**)⁴⁶

Yellow solid, mp 135–137 °C, 0.373 g, 96% yield.

¹H NMR (501 MHz, DMSO): δ = 8.10 (d, *J* = 7.7 Hz, 2 H), 7.74 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 2 H), 7.17 (t, *J* = 8.2 Hz, 2 H), 6.90 (dd, *J* = 8.1, 4.1 Hz, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 188.16 (t, *J* = 29.0 Hz), 173.70, 159.15, 157.26, 139.72, 135.17, 132.97, 130.75, 129.19, 128.29 (d, *J* = 7.6 Hz), 117.53 (d, *J* = 23.4 Hz), 119.49–114.82 (m), 113.89 (d, *J* = 25.1 Hz), 111.53 (d, *J* = 7.5 Hz), 78.07–74.46 (m).

5-Chloro-3-(1,1-difluoro-2-oxo-2-phenylethyl)-3-hydroxyindolin-2-one (**13c**)⁴¹

Yellow solid, mp 82–84 °C, 0.353 g, 95% yield.

¹H NMR (501 MHz, DMSO): δ = 8.10 (d, *J* = 7.8 Hz, 1 H), 7.74 (t, *J* = 7.3 Hz, 1 H), 7.59 (t, *J* = 7.7 Hz, 1 H), 7.38 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.33 (s, 1 H), 6.92 (d, *J* = 8.3 Hz, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 188.15 (t, *J* = 29.3 Hz), 173.58, 142.75, 135.20, 132.93, 130.98, 130.77, 129.21, 128.81, 126.11 (d, *J* = 4.0 Hz), 119.42–114.80 (m), 112.18 (s), 76.40 (t, *J* = 24.8 Hz).

5-Bromo-3-(1,1-difluoro-2-oxo-2-phenylethyl)-3-hydroxyindolin-2-one (**13d**)⁴⁶

Yellow solid, mp 122–124 °C, 0.318 g, 94% yield.

¹H NMR (501 MHz, DMSO): δ = 8.11 (d, J = 7.8 Hz, 1 H), 7.75 (t, J = 7.3 Hz, 1 H), 7.60 (t, J = 7.7 Hz, 1 H), 7.39 (dd, J = 8.3, 1.7 Hz, 1 H), 7.35 (s, 1 H), 6.93 (d, J = 8.3 Hz, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 188.09 (t, J = 29.3 Hz), 173.52, 142.69, 135.14, 132.87, 130.92, 130.71, 129.14, 128.75, 126.05 (d, J = 4.0 Hz), 119.47–114.77 (m), 112.11 (s), 76.33 (t, J = 24.8 Hz).

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-3-hydroxy-5-methylindolin-2-one (13e)⁴¹

Yellow solid, mp 101–103 °C, 0.362 g, 92% yield.

¹H NMR (501 MHz, DMSO): δ = 8.10 (d, J = 7.7 Hz, 1 H), 7.73 (t, J = 7.2 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 1 H), 7.17 (s, 1 H), 7.11 (d, J = 7.8 Hz, 1 H), 6.77 (d, J = 7.8 Hz, 1 H), 2.24 (s, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 188.32 (t, J = 27.5 Hz), 173.80, 141.04, 134.97, 133.23, 131.30, 131.14, 130.77, 129.62, 129.10, 126.86, 117.44 (dd, J = 263.9, 259.7 Hz), 110.28 (s), 76.85–76.05 (m), 21.05.

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-3-hydroxy-5-methoxyindolin-2-one (13f)⁴⁷

Yellow solid, mp 131–132 °C, 0.346 g, 92% yield.

¹H NMR (501 MHz, DMSO): δ = 8.10 (d, J = 7.6 Hz, 1 H), 7.73 (t, J = 7.2 Hz, 1 H), 7.58 (t, J = 7.3 Hz, 1 H), 6.93 (s, 1 H), 6.90 (d, J = 8.5 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 3.70 (s, 2 H).

¹³C NMR (126 MHz, DMSO): δ = 188.45 (t, J = 16.6 Hz), 155.19, 136.66, 135.02, 133.21, 130.79, 129.62, 129.12, 127.89, 115.76, 113.11, 111.02, 55.97.

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-3-hydroxy-5,7-dimethylindolin-2-one (13g)⁴⁷

Yellow solid, mp 105–107 °C, 0.34 g, 90% yield.

¹H NMR (501 MHz, DMSO): δ = 10.59 (s, 1 H), 8.11 (d, J = 7.7 Hz, 2 H), 7.72 (t, J = 7.3 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 2 H), 7.28 (s, 1 H), 7.01 (s, 1 H), 6.94 (s, 1 H), 2.21 (s, 3 H), 2.18 (s, 3 H).

¹³C NMR (126 MHz, DMSO): δ = 188.31 (t, J = 28.6 Hz), 174.25, 139.50, 134.93, 133.28, 132.70, 131.10, 130.79, 129.07, 126.56, 124.16, 119.56, 119.66–115.30 (m), 77.05–76.12 (m), 20.96, 16.66.

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-3-hydroxy-1-methylindolin-2-one (13h)⁴¹

Yellow solid, mp 95–97 °C, 0.374 g, 95% yield.

¹H NMR (501 MHz, DMSO): δ = 8.07 (d, J = 7.6 Hz, 1 H), 7.74 (t, J = 7.0 Hz, 1 H), 7.58 (t, J = 7.1 Hz, 1 H), 7.47 (s, 1 H), 7.41 (dd, J = 18.9, 7.7 Hz, 1 H), 7.08 (d, J = 7.2 Hz, 1 H), 3.14 (s, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 188.28 (t, J = 28.4 Hz), 172.14, 144.80, 135.14, 132.97, 131.31, 130.69, 129.62, 129.20, 126.06, 125.88, 117.34 (t, J = 262.4 Hz), 109.50 (s), 76.01 (t, J = 25.4 Hz), 26.65.

3-(1,1-Difluoro-2-oxo-2-phenylethyl)-3-hydroxy-5-nitroindolin-2-one (13i)⁴⁷

Yellow solid, mp 112–114 °C, 0.33 g, 91% yield.

¹H NMR (501 MHz, DMSO): δ = 8.29 (d, J = 8.6 Hz, 1 H), 8.16–8.07 (m, 3 H), 7.76 (t, J = 7.0 Hz, 1 H), 7.60 (t, J = 7.5 Hz, 2 H), 7.12 (d, J = 8.4 Hz, 1 H).

¹³C NMR (126 MHz, DMSO): δ = 189.08–187.37 (m), 173.78, 143.45, 135.03, 133.14, 131.15, 130.76, 129.13, 126.76, 126.26, 122.27, 117.40 (dd, J = 263.4, 259.8 Hz), 110.52, 76.31 (t, J = 25.3 Hz).

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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