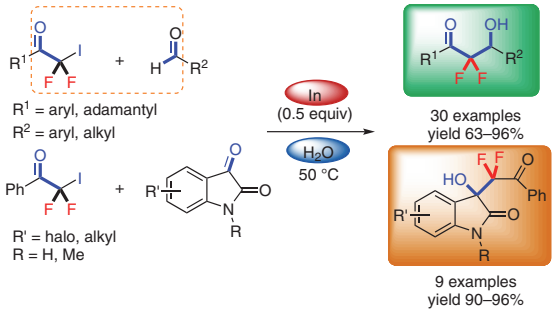
Indium-Mediated Reformatsky Reaction of Iododifluoro Ketones with Aldehydes: Preparation of α,α-Difluoro-β-hydroxyketone Derivatives in Water

Zhongyuan Li[a]
Jinwen Huang[*a,b]
Zhuang Ni[a]
Ran Sun[a]
Hui Nie[a]
Hui Tang[a]
Lixing Song[a]
Fanhong Wu[*a,b]

[a] School of Chemical and Environmental Engineering, Shanghai Institute of Technology, Shanghai 201418, P. R. of China
goldven@163.com
wfh@sit.edu.cn
[b] Shanghai Engineering Research Center of Green Fluoropharmaceutical Technology, Shanghai, P. R. of China



Received: 14.11.2021
Accepted after revision: 21.12.2021
Published online: 31.01.2022
DOI: 10.1055/s-0040-1719888; Art ID: so-2021-d0056-op

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 2013[19] was applied to the synthesis of α,α-difluo-

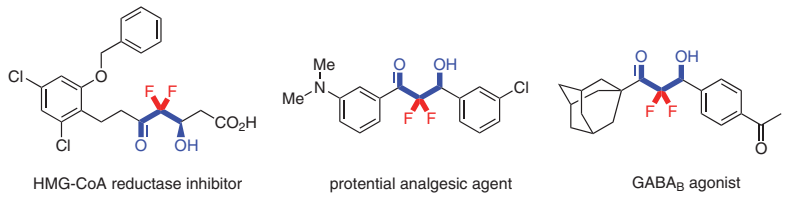
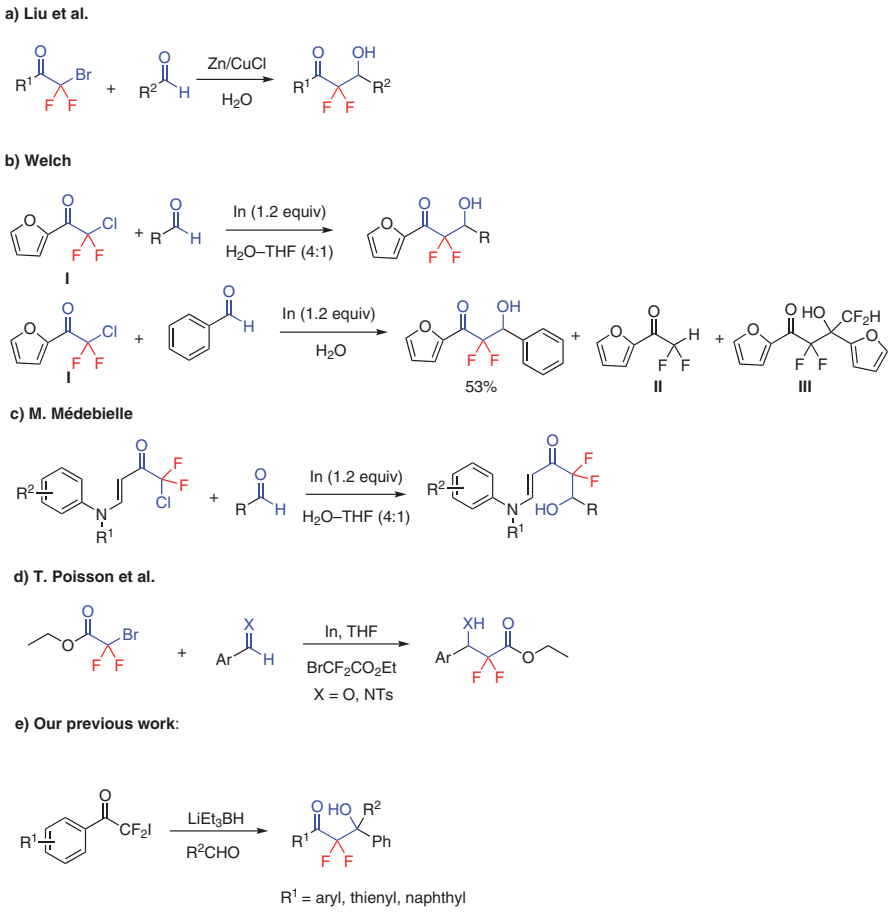


Figure 1 Bioactive α,α-difluoro-β-hydroxy compounds

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.

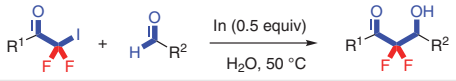
However, those reactions are also restricted due to the problems of using aqueous medium, resulting in poor reaction yields, serious side reactions, and limited substrate scope. For example, Welch's group used 2-chloro-2,2-difluoro-1-furan-2-yl ethylenedione (**I**) to perform the Reformatsky reaction 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 observed[21] (Scheme 1b). Médebielle et al. reported the use of β-aminovinylchlorodifluoromethyl ketones and a series of heteroaryl aldehydes in H_2O/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 products[22] (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 THF[23] (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 $LiEt_3BH$, we unexpectedly obtained the aldol self-condensation product and the corresponding α,α-difluoro-β-hydroxyketone in the presence of an aldehyde[30] (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-



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).



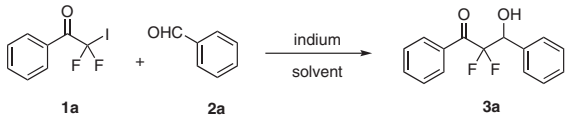
Scheme 2 Indium-mediated Reformatsky reaction of iododifluoroketones and aldehydes in water

Firstly, we used iododifluoroacetophenone (**1a**) as substate 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 H_2O–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–H_2O (v/v) worked well, resulting in 89% and 90% yield, respectively. However, when the reaction was carried out in absolute ethanol, 95% EtOH–H_2O (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 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-

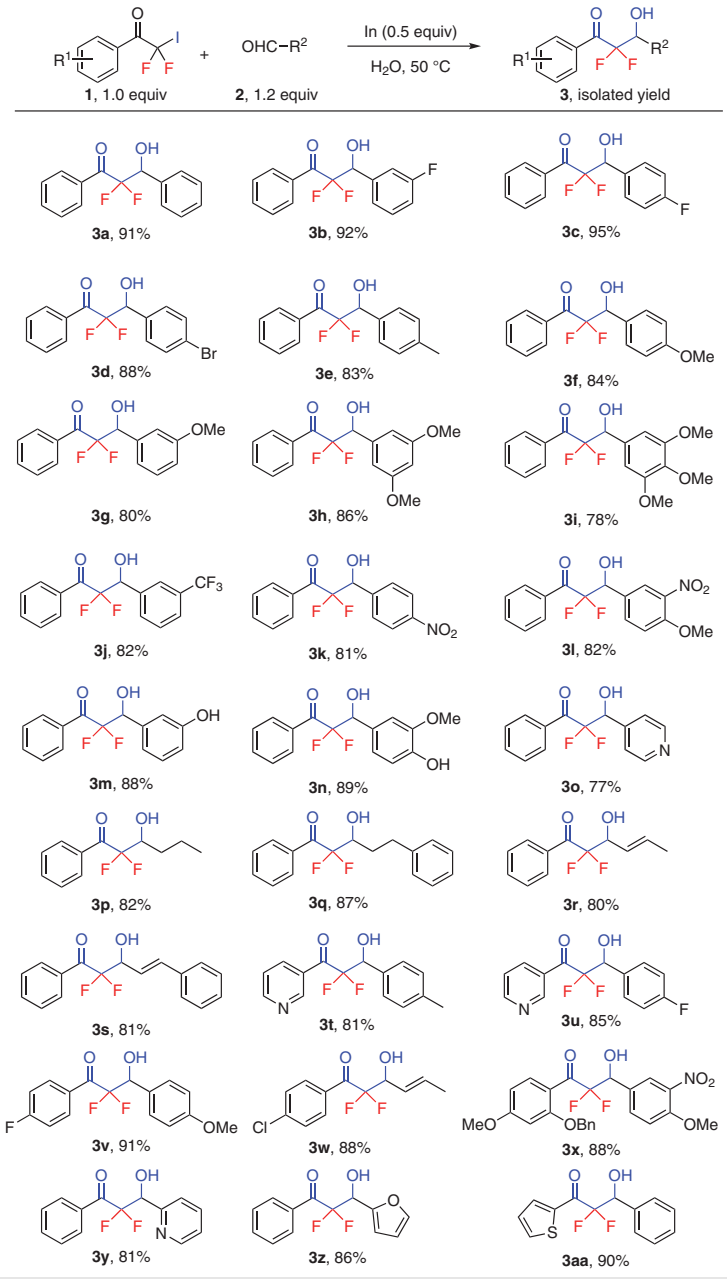
Table 1 Optimization of Indium-Mediated Reformatsky Reaction of Iododifluoroketones and Aldehydes[a]



1a 2a 3a

Entry	Indium (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	2.0	H_2O	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_2O–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_2O	RT	18	16
11	2.0	50% MeOH–H_2O	RT	14	90
12	2.0	*n*-BuOH	RT	18	13
13	2.0	H_2O	40	5	91
14	2.0	H_2O	50	2	91
15	2.0	H_2O	100	1	72
16	1.0	H_2O	50	2	91
17	0.5	H2O	50	2	91
18	0.2	H_2O	50	48	35
19	0.05	H_2O	50	48	4
20	0.5	H_2O	50	12	–[c]
21	0.5	H_2O	50	6	24[d]
22	0.5	H_2O	50	6	36[e]

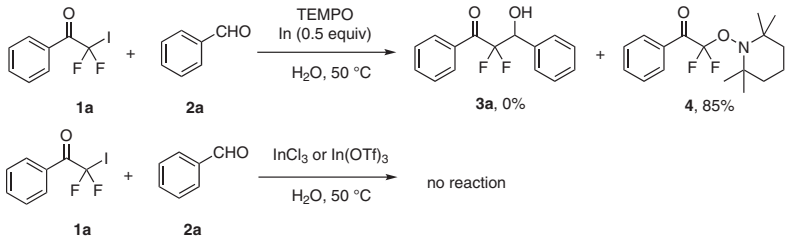
[a] Reaction conditions (unless otherwise specified): **1a** (0.2 g, 1.0 equiv), **2a** (1.2 equiv).
[b] Isolated yield.
[c] 1.2 equiv trifluoroacetophenone.
[d] 1.2 equiv chlorodifluoroacetophenone.
[e] 1.2 equiv bromodifluoroacetophenone.



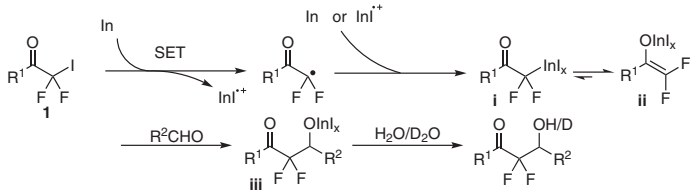
Scheme 3 The indium-mediated Reformatsky reaction of iododifluoketones with various aldehydes[a,b]

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



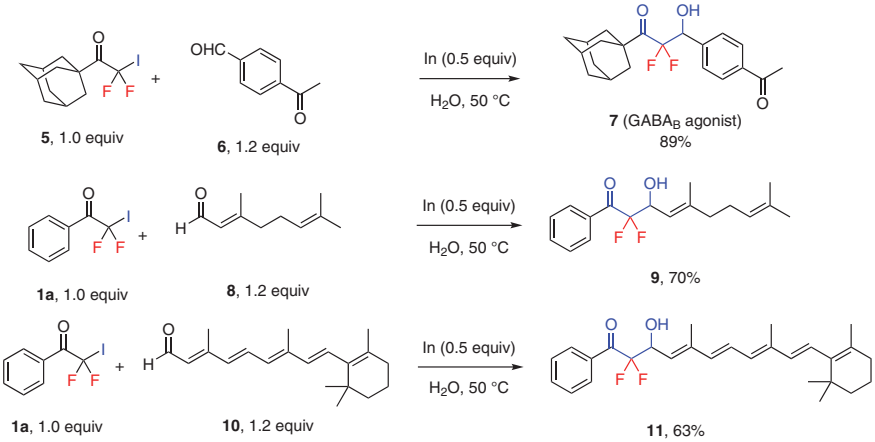
Scheme 5 Proposed reaction mechanism

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).

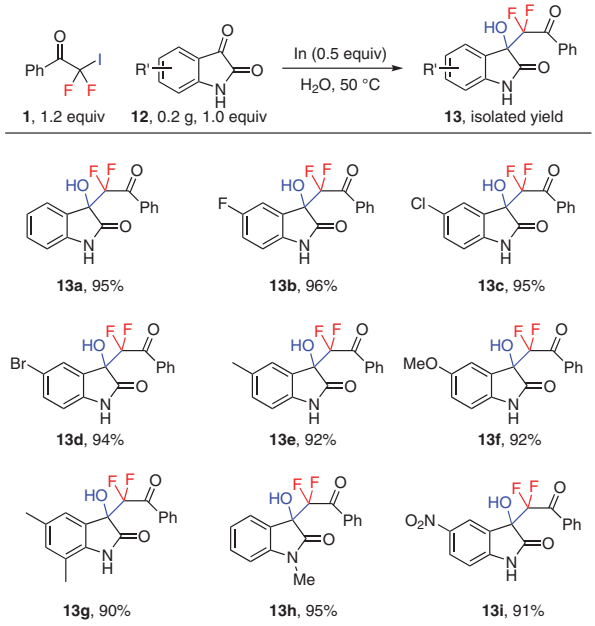
These examples emphasize that the indium-mediated Reformatsky reaction of iododifluoroketones has good selectivity for aldehydes.

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 CF_2 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



Scheme 7 Synthesis of isatin C-3 derivatives using **1**

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 (^{1}H NMR), 376 MHz (^{19}F NMR), and 126/101 MHz (^{13}C NMR) using $CDCl_3$ or $(CD_3)_2SO$ 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-Difluoroketones 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.

^{1}H 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 $C_{15}H_{12}O_2F_2Na$ [M + 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.

^{1}H 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 $C_{15}H_{12}O_2F_2Na$ [M + 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.

^{1}H 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 $C_{15}H_{12}O_2F_2Na$ [M + 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.

^{1}H 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 $C_{15}H_{11}O_2BrF_2Na$ [M + 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.

^{1}H 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, $CDCl_3$): δ = –104.5 (d, *J* = 188 Hz, 1 F), –116.5 (d, *J* = 316 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{16}H_{14}F_2O_2Na$ [M + 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.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –104.5 (d, *J* = 252 Hz, 1 F), –116.5 (d, *J* = 263 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{16}H_{14}F_2O_3Na$ [M + 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.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –104.5 (d, *J* = 252 Hz, 1 F), –116.0 (d, *J* = 34 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{16}H_{14}F_2O_3$ [M + 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.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –103.9 (d, *J* = 45 Hz, 1 F), –116.25 (d, *J* = 297 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{17}H_{16}F_4O_2Na$ [M + 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.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –103.7 (d, *J* = 41 Hz, 1 F), –115.6 (d, *J* = 41 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{18}H_{18}F_2O_5Na$ [M + 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.

^{1}H NMR (501 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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 $C_{16}H_{11\ F5}O_2Na$ [M + 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.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –104.0 (d, *J* = 338 Hz, 1 F), –116.0 (d, *J* = 376 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{15}H_{11}F_2NO_4Na$ [M + 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.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = –103.8 (d, *J* = 331 Hz, 1 F), –114.6 (d, *J* = 331 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{16}H_{13}F_2NO_5Na$ [M + 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.

^{1}H 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).

^{13}C 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).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.4 (d, *J* = 353 Hz, 1 F), –116.7 (d, *J* = 353 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{15}H_{11}O_2BrF_2Na$ [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.

^{1}H 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), 3.46 (d, *J* = 4.4 Hz, 3 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 = –103.5 (d, *J* = 331 Hz, 1 F), –114.8 (d, *J* = 316 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{16}H_{14}F_2O_4Na$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C 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).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.5 (d, *J* = 305 Hz, 1 F), –114.8 (d, *J* = 305 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{14}H_{11\ F2}NO_2Na$ [M + Na]$^+$: 286.0650; found: 286.0650.

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

Colorless liquid, 0.133 g, 82% yield.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (126 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.6 (d, *J* = 263 Hz, 1 F), –114.4 (d, *J* = 263 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{12\ H14}F_2O_2$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (126 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.6 (d, *J* = 259 Hz, 1 F), –114.5 (d, *J* = 256 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{17}H_{16}F_2O_2Na$ [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.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (126 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.0 (d, *J* = 368 Hz, 1 F), –115.6 (d, *J* = 368 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{12}H_{12}F_2O_2Na$ [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.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{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, 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 = –106.0 (d, *J* = 368 Hz, 1 F), –115.4 (d, *J* = 368 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{17}H_{14}F_2O_2Na$ [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.

^{1}H 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).

^{13}C 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –104.5 (d, *J* = 323 Hz, 1 F), –115.4 (d, *J* = 323 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{15}H_{13}F_2NO_2Na$ [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.

^{1}H 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).

^{13}C 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).

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{14}H_{10}F_3NO_2Na$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{16}H_{13}F_3O_3Na$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.2 (d, *J* = 274 Hz, 1 F), –115.5 (d, *J* = 274 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{12}H_{11}ClF_2O_2Na$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.8 (d, *J* = 297 Hz, 1 F), –114.2 (d, *J* = 297 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{24}H_{21}F_2NO_7Na$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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 $C_{14}H_{11}F_2NO_2Na$ [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.

^{1}H NMR (501 MHz, $CDCl_3$): 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 $C_{13}H_{10}F_2O_3Na$ [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.

^{1}H NMR (500 MHz, $CDCl_3$): 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 $C_{13}H_{10}F_2O_2SNa$ [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 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 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.

^{1}H NMR (400 MHz, $CDCl_3$): 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).

^{13}C NMR (101 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –71.85.

Procedure for the Preparation of ($GABA_B$ Agonist) 7

To a 20 mL vial, 1-[(3r,5r,7r)-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 H_2O (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-[(3r,5r,7r)-adamantan-1-yl]-2,2-difluoro-3-hydroxypropan-1-one (7)[17b]

Pale yellow solid, mp 45–47 °C,[5] 0.33 g, 89% yield.

^{1}H NMR (500 MHz, $CDCl_3$): 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).

^{13}C NMR (125 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): 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 $C_{21}H_{24}F_2O_3Na$ [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 H_2O (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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (126 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.7 (d, *J* = 274 Hz, 1 F), –116.2 (d, *J* = 274 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{18}H_{22}F_2O_2Na$ [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 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 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.

^{1}H NMR (501 MHz, $CDCl_3$): 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).

^{13}C NMR (126 MHz, $CDCl_3$): 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.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.6 (d, *J* = 368 Hz, 1 F), –116.3 (d, *J* = 368 Hz, 1 F).

HRMS (ESI): *m/z* calcd for $C_{28}H_{34}F_2O_2Na$ [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 H_2O (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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

^{1}H 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).

^{13}C 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.

Funding Information

We are grateful for financial support from the National Natural Science Foundation of China (21672151 and 21472126).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1719888.

References

(1) Choppin, S. L.; Medeiros, F.; Barbarotto, M.; Colobert, F. *Chem. Soc. Rev.* **2013**, *42*, 937.
(2) Cozzi, P. G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2568.
(3) Cozzi, P. G. *Angew. Chem.* **2007**, *119*, 2620.
(4) Sato, I.; Takizawa, Y.; Soai, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2825.
(5) Moslin, R. M.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 15106.
(6) Wessjohann, L. A.; Scheid, G. O.; Eichelberger, U.; Umbreen, S. *J. Org. Chem.* **2013**, *78*, 10588.
(7) Lambert, T. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 426.
(8) Grellepois, F. *J. Org. Chem.* **2013**, *78*, 1127.
(9) Chan, T.-H.; Li, C.-J.; Lee, M.-C.; Wei, Z.-Y. *Can. J. Chem.* **1994**, *72*, 1181.
(10) Chao, L.-C.; Rieke, R. D. A. *J. Org. Chem.* **1975**, *40*, 2253.
(11) Araki, S.; Hirashita, T. *Comprehensive Organometallic Chemistry, Vol. 9*; Crabtree, R. H.; Mingos, D. M. P., Ed.; Elsevier: Oxford, **2007**, 649–722.
(12) Roy, U. K.; Roy, S. *Chem. Rev.* **2010**, *110*, 2472.
(13) Shen, Z. L.; Wang, S. Y.; Chok, Y. K.; Xu, Y. H.; Loh, T. P. *Chem. Rev.* **2012**, *113*, 271.
(14) Pardoe, J. A.; Downs, A. J. *Chem. Rev.* **2007**, *107*, 2.
(15) Dreyer, G. B.; Metcalf, B. W. *Tetrahedron Lett.* **1988**, *29*, 6885.
(16) Hamer, R. L.; Freed, B.; Allen, R. C. US5006563, **1991**.
(17) (a) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. *J. Med. Chem.* **2013**, *56*, 2456. (b) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802.
(18) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302.
(19) Yao, H.; Cao, C.-R.; Jiang, M.; Liu, J.-T. *J. Fluorine Chem.* **2013**, *156*, 45.
(20) Doi, R.; Ohashi, M.; Ogoshi, S. *Angew. Chem.* **2016**, *128*, 349.
(21) Chung, W. J.; Higashiya, S.; Welch, J. T. *J. Fluorine Chem.* **2001**, *112*, 343.
(22) Médebielle, M.; Onomura, O.; Keirouz, R.; Okada, E.; Yano, H.; Terauchi, T. *Synthesis* **2002**, 2601.
(23) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277.
(24) Wang, J.-X.; Wu, J.-J.; Chen, H.; Zhang, S.-W.; Wu, F.-H. *Chin. Chem. Lett.* **2015**, *26*, 1381.
(25) Wang, D.-F.; Wu, J.-J.; Huang, J.-W.; Liang, J.-Q.; Peng, P.; Chen, H.; Wu, F.-H. *Tetrahedron* **2017**, *73*, 3478.
(26) Chen, H.; Wang, J.-X.; Wu, J.-J.; Kuang, Y.-J.; Wu, F.-H. *J. Fluorine Chem.* **2017**, *200*, 41.

(27) Liang, J.-Q.; Huang, G.-Z.; Peng, P.; Zhang, T.-Y.; Wu, J.-J.; Wu, F.-H. *Adv. Synth. Catal.* **2018**, *360*, 2221.
(28) Wang, X.; Hu, J.; Ren, J.; Wu, T.-C.; Wu, J.-J.; Wu, F.-H. *Tetrahedron* **2019**, *75*, 130715.
(29) Zhang, T.-Y.; Pan, J.; Duan, J.; Wu, J.-J.; Zhang, W.; Wu, F.-H. *ChemCatChem* **2019**, *11*, 5778.
(30) Peng, P.; Wu, J.-j.; Liang, J.-Q.; Zhang, T.-Y.; Huang, J.-W.; Wu, F.-H. *RSC Adv.* **2017**, *7*, 56034.
(31) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, *14*, 1454.
(32) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131.
(33) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *21*, 3835.
(34) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227.
(35) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277.
(36) Dewar, M. J. S.; Merz, K. M. Jr. *J. Am. Chem. Soc.* **1987**, *109*, 6553.
(37) Maiz, J.; Arrieta, A.; Lopez, X.; Ugalde, J. M.; Cossio, F. P. *Tetrahedron Lett.* **1993**, *34*, 6111.
(38) Yu, J.-S.; Liu, Y.-L.; Tang, J.; Wang, X.; Zhou, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9512.
(39) Zhou, F. Liu Y.-L. Zhou J. *Adv. Synth. Catal.* **2010**, *352*, 1381.
(40) Yuan, Z.-L.; Wei, Y.; Shi, M. *Tetrahedron* **2010**, *66*, 7361.
(41) Yu, J.-S. Liu Y.-L.; Tang, J.; Wang, X.; Zhou, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 9512.
(42) Sasaki, S.; Suzuki, T.; Uchiya, T.; Toyota, S.; Hirano, A.; Tanemura, M.; Teramoto, H.; Yamauchi, T.; Higashiyama, K. *J. Fluorine Chem.* **2016**, *192*, 78.
(43) Atsushi, T.; Mayuna, O.; Susumu, S.; Kazuyuki, S.; Masaaki, O. *RSC Adv.* **2018**, *8*, 20568.
(44) Yuan, J.-W.; Liu, S.-N.; Mai, W.-P. *Org. Biomol. Chem.* **2017**, *15*, 7654.
(45) Wu, P.-J.; Zheng, C.; Wang, X.; Wu, J.-J.; Wu, F.-H. *Eur. J. Org. Chem.* **2021**, 1420.
(46) Liu, Z.; Gao, Y.; Huang, D.; Gao, Y.; Yang, Z.; Hu, X. CN110156659A, **2019**.
(47) Li, Y.-L.; Wang, X.-L.; Xiao, D.; Liu, M.-Y.; Du, Y.; Deng, J. *Adv. Synth. Catal.* **2018**, *360*, 4147.