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Decarboxylative Aldol Reaction of α,α-Difluoro-β-keto Esters: Easy Access to Difluoroenolate

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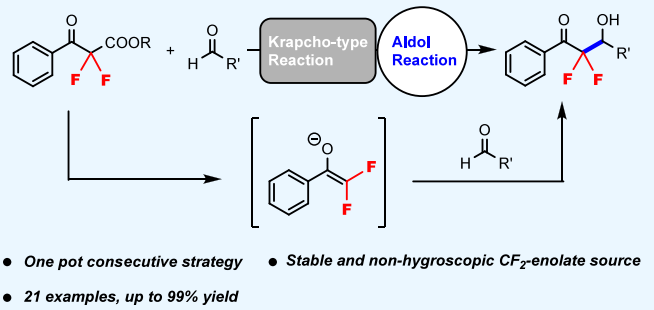
ABSTRACT: $Yb(OTf)_3$ promoted the Krapcho decarboxylation of 2,2-difluoro-3-oxopropanoate, and a subsequent aldol reaction was achieved. This process is the first example of generating difluoroenolates through a decarboxylation-type process, and a large number of carbonyl compounds are applicable to the aldol reaction. The protocol is a complete one-pot reaction that uses the bench-stable and nonhygroscopic 2,2-difluoro-3-oxopropanoate to generate the difluoroenolate. This strategy has been applied for the synthesis of CF_2-containing bioactive $GABA_B$ agonists, contributing to drug design.



INTRODUCTION

Fluorine-containing compounds play an important role in medicine, as they can contribute to increased lipophilicity, metabolic stability, and improved solubility.[1] In particular, the difluoromethylene unit has unique properties; it is considered a bioisostere of an oxygen atom and carbonyl group and can modify the p*K*a value of neighboring atoms.[2] The synthesis of α,α-difluoro-β-carbonyl compounds can be achieved via classical deoxyfluorination.[3] However, the requirement for the use of a highly toxic fluorine reagent amino sulfur trifluoride ((diethylamino)sulfur trifluoride) poses a drawback for the deoxyfluorination of ketones. Difluoromethylated carbonyl compounds are also accessible through the decarboxylation of β-oxo-α,α-difluorocarboxylic acids and their salts (**1**, Figure 1A).[4]

The synthesis of difluoromethylene compounds using decarboxylation has been expanded to include the introduction of an aryl group.[5] In this study, the decarboxylation method was expanded to include a wide range of skeletal transformations. Decarboxylation reactions are environmentally friendly chemical transformations that only involve the release of CO_2. Therefore, decarboxylative bond formation reactions of carboxylic acids have been utilized to introduce various substituents, including C−C bond formation.[6] Among them, the decarboxylative aldol reaction of β-oxocarboxylic acids has been widely investigated as a C−C bond formation reaction, which affords the formal enolate equivalents by releasing CO_2 from the carboxylic acids.[7]

We have also achieved the decarboxylative aldol reaction of **1b** (Figure 1B). According to these investigations, the generation of enolates from readily decarboxylatable carboxylic acids and their salts has been established for both nonfluorine and fluorine analogs and applied to bond formation reactions.

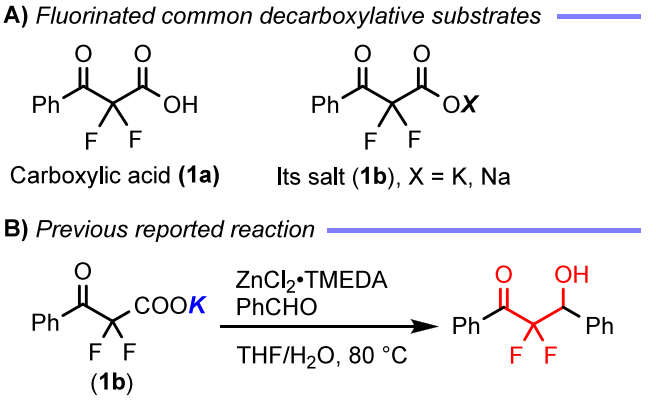


Figure 1. (A) Fluorine-containing decarboxylative substrates; (B) our reported decarboxylative aldol reaction of β-oxo-α,α-difluorocarboxylate potassium salt.

In contrast to the broadly applicable decarboxylation chemistry of carboxylic acids, reactions using β-ketoesters as direct substrates for decarboxylation reactions are scarce except for Krapcho decarboxylation. The reaction has been used as a simple skeletal transformation,[8] which is used to degrade ester

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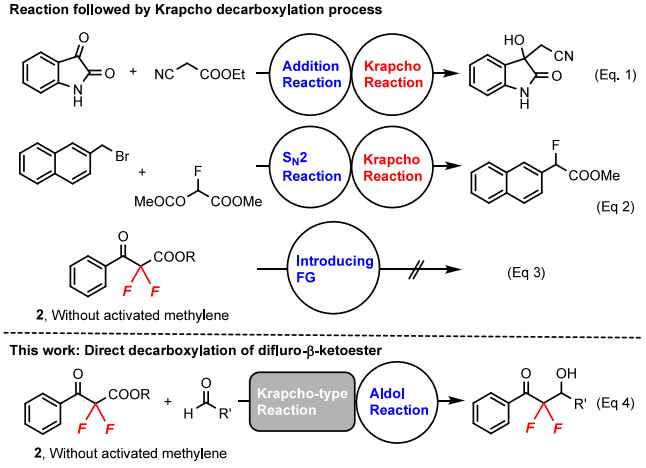
moieties from the carbon skeleton.[9] To the best of our knowledge, there is only one example of a bond formation reaction using Krapcho decarboxylation, in which CF_3 anions generated from trifluoroacetates are used for cross-coupling.[10] The most significant advantage of skeletal transformation reactions using β-ketoesters is that substituents can be introduced using the active methylene moiety, which is often used in combination with the Krapcho decarboxylation reaction for carbon chain elongation reactions by introducing substituents and removing unnecessary ester moieties (Scheme 1, eqs 1 and 2).[11] Unfortunately, a similar bond formation with

Scheme 1. Approaches for the Introduction of a Functional Group into the α-Position of β-Oxopropanoate Using Krapcho Decarboxylation: (1) Substituent Introduction Followed by Krapcho Decarboxylation for Nonfluorinated β-Oxopropanoate; (2) Substituent Introduction Followed by Krapcho Decarboxylation for Fluorinated β-Oxopropanoate; (3) Unsuccessful Similar Functionalization β-Oxo-α,α-Difluoropropanoate without Active Methylene; (4) This Study

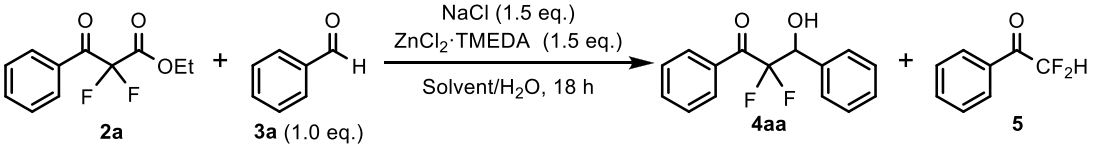


2 in which the two active hydrogens are replaced by fluorine atoms has not been achieved (Scheme 1, eq 3). In this study, we investigated the aldol reaction of compound **2**, which does not have an active methylene moiety, followed by the generation of a formal enolate from difluoro-β-ketoester directly. This offers a novel consecutive Krapcho-type decarboxylation/aldol reaction for the C−C bond formation (Scheme 1, eq 4). Indeed, the reaction of β-oxo-α,α-difluoropropanoate (**2**) with benzaldehyde, using metals and NaCl as additives, provided a direct aldol adduct via the enolate from **2**. Herein, we describe the first example of a decarboxylative aldol reaction of β-oxo-α,α-difluoropropanoate (**2**) using $Yb(OTf)_3$ to afford 2,2-difluoro-3-hydroxypropan-1-ones in excellent yields. The newly proposed difluoroenolate precursor **2**, unlike the corresponding carboxylic acids and their salts, is an easy-to-handle, chromatographically purifiable, and long-storable reactant. Furthermore, the synthesis of **2** is one step less than the corresponding carboxylic acids and their salts, allowing easier access to the difluoroenolate precursor.

RESULTS AND DISCUSSION

We commenced our investigation using the conditions employed in our previous decarboxylative aldol reaction with potassium 2,2-difluoro-3-oxo-3-phenylpropanoate. The reaction of ethyl 2,2-difluoro-3-oxo-3-phenylpropanoate (**2a**) with benzaldehyde (**3a**) using NaCl as a trigger for Krapcho decarboxylation provided the aldol product **4aa** in low yield (Table 1, entry 1). The reaction was performed in DMSO containing an equimolar ratio of both H_2O and **2a**, which is a commonly used condition in the Krapcho decarboxylation method. Next, the reaction solvents were screened (entries 2−7). As shown entries 2−4, polar solvents such as DMF, NMP, and DMA were not effective in this reaction, and the decarboxylated side product **5** was predominantly recovered. On the other hand, less polar solvents such as toluene and THF were not effective for this Krapcho decarboxylation, and the starting material **2a** was recovered in moderate-to-high yields (entries 5 and 6). However, acetonitrile was found to be effective in both the decarboxylation and aldol processes, affording the desired product in moderate yield (entry 7). To improve the yield of product **4aa**, further screening of the decarboxlative substrate **6a** and Lewis acid was investigated (Table 2). A further increase in yield was observed when methyl ester **6a** was used by shortening the carbon chain of the ester alkoxy moiety of substrate **2a** for a more efficient Krapcho decarboxylation (entry 1). The most effective improvements resulted from screening for Lewis acids. Several Lewis acids did not provide the desired product **4aa** (see the Supporting Information, Table S1).[12] The most effective metal additive was $Yb(OTf)_3$ hydrate, which afforded the product in 95% yield (entry 2). Finally, reagent-grade NaCl (99.5% purity) provided the optimal conditions for the quantitative yield of the product (entry 3). The reaction without $Yb(OTf)_3$ hydrate did not afford the desired product, and the moderate

Table 1. Screening of Solvents Using α,α-Difluoro-β-ketoester 2a



entry	solvent	temp. (°C)	isolated yield of **4aa** (%)	^{19}F NMR yield of **2a** (%)	^{19}F NMR yield of **5** (%)
1	DMSO	150	20	0	34
2	DMF	150	13	0	50
3	NMP	150	25	0	40
4	DMA	150	0	0	51
5	toluene	reflux	0	94	0
6	THF	reflux	20	48	7
7	CH_3CN	reflux	42	35	0

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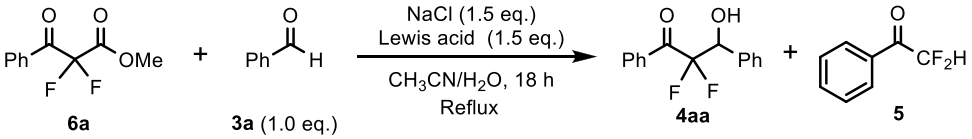
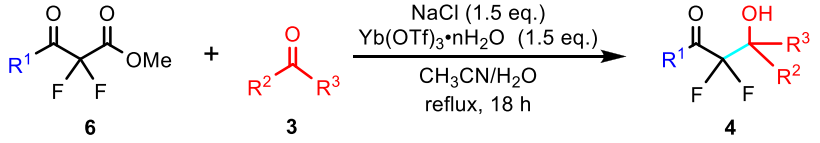
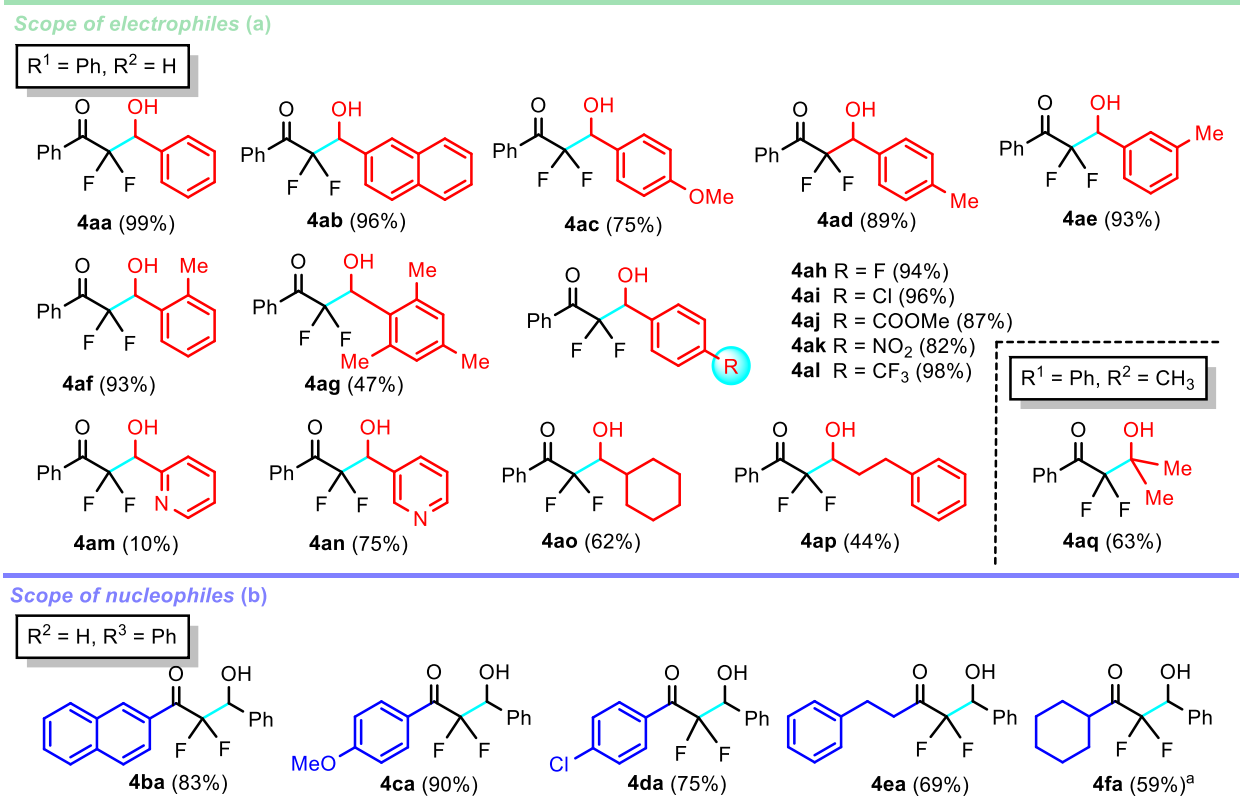
Table 2. Investigation of Methylester 6a and Further Screening of Reaction Condition



entry	Lewis acid	purity of NaCl (%)	isolated yield of **4aa** (%)	^{19}F NMR yield of **6a** (%)	^{19}F NMR yield of **5** (%)
1	$ZnCl_2$ TMEDA	95.0	55	16	16
2	$Yb(OTf)_3$ nH_2O	95.0	95	trace	0
3	$Yb(OTf)_3$ nH_2O	99.5	99	trace	0
4	none	99.5	0	50	18

Table 3. Scope and Limitations of Substrates





[a]The reaction was stirred for 48h.

yield of **6a** was recovered from the reaction mixture (entry 4). This indicates that a metal additive is necessary for the Krapcho decarboxylation/aldol reaction. The amount of additive was investigated with the aim of a catalyst loading of $Yb(OTf)_3$; however, a decrease in the yield of **4aa** was observed.[13]

Having established the optimal experimental conditions, the reactivities of various aldehydes were explored. As shown in Table 3a, this method was found to be applicable to a variety of aldehydes **3**, which underwent this decarboxylative aldol reaction successfully, affording the corresponding products **4aa**−**4ap** in 10−99% yields. The substituents of electron effects and substitution positions on the aromatic ring gave products without affecting their yields. Products **4ao** and **4ap** from aliphatic aldehydes were also obtained in moderate yields of 44−62%. In the cases of **4ag**, **4am**, and **4ap**, low conversion of **6a** and aldehydes was observed. The reaction of **6a** with ketones using an excess of an electrophile (1 mL) also provided the target product **4aq** in 63% yield. Subsequently, we further explored the scope of *α*,*α*-difluoro-*β*-ketoesters **6b**−**6f** (Table 3b). Different substituents on the benzene ring had good compatibility and afforded the desired products **4ca**−**4da** in 75−95% yields. Substrates bearing aliphatic ketoesters **6e** and **6f** provided the corresponding products in moderate yields.

This reaction is also applicable to the synthesis of $GABA_B$ agonist **12**. After synthesizing the corresponding *α*,*α*-difluoro-

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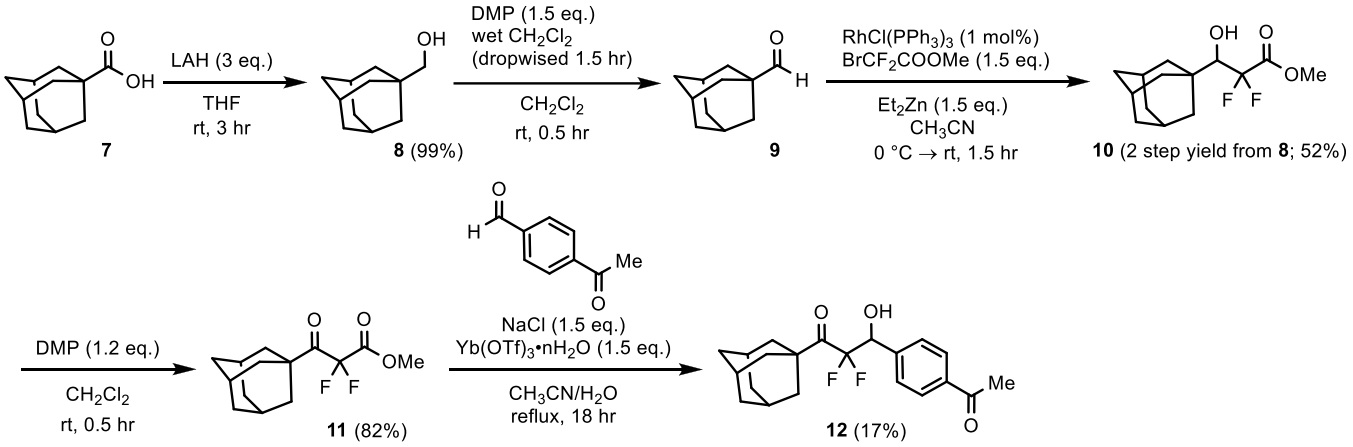
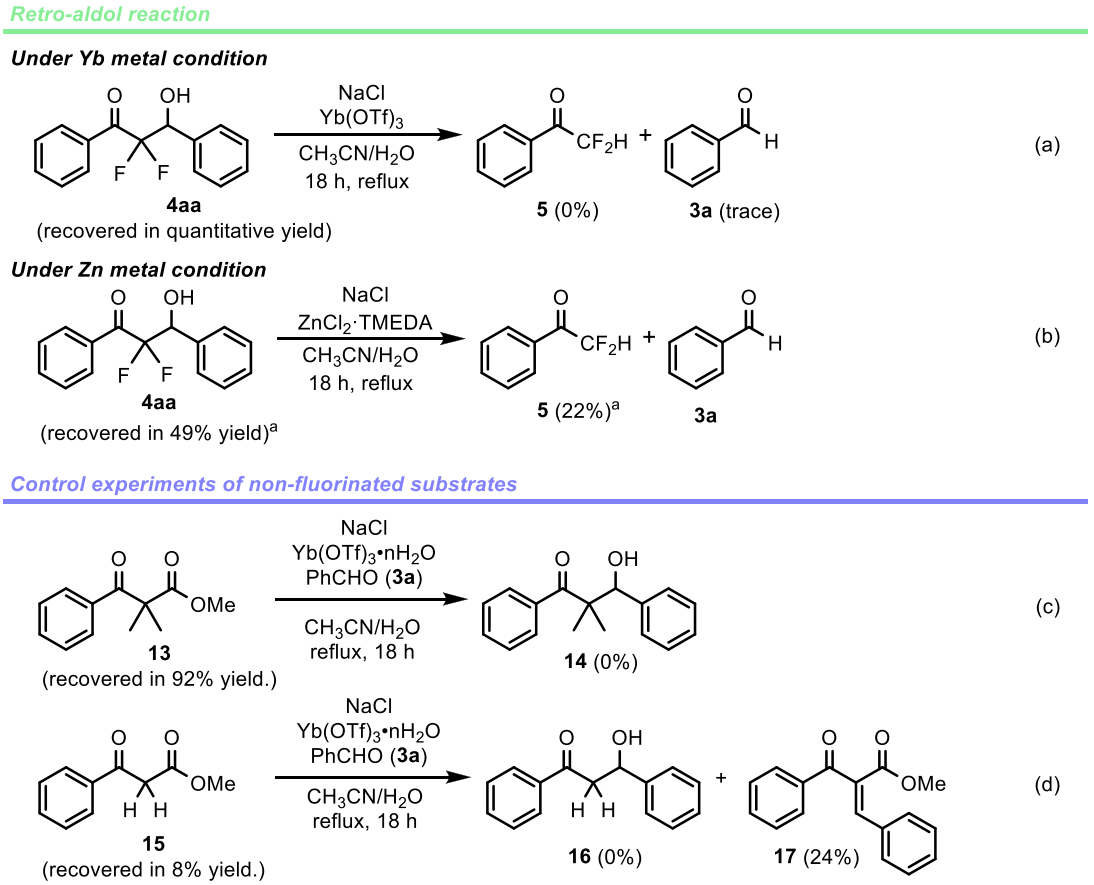
Scheme 2. Synthesis of Biological Active Compound toward $GABA_B$ Agonist 12



Scheme 3. Retro-Aldol Reactions and Control Experiments



[a]Yields determined by ^{19}F NMR using benzotrifluoride as an internal standard.

β-ketoester **11**, the method was applied to **11**, and the desired bioactive product **12** was successfully obtained (Scheme 2).

Several control experiments were performed to further investigate the reaction mechanism. The retro-aldol reaction of **4aa** was investigated in the presence of Zn and Yb (Scheme 3a,b). In the presence of $Yb(OTf)_3$, no retro-aldol process was observed with quantitative recovery of the substrate **4aa**. However, the Zn metal condition provided the retro-aldol product **5** with reduced recovery of **4aa**. The results suggest that $Yb(OTf)_3$ is the most effective additive for controlling the retro-aldol reaction in this system. Furthermore, nonfluorinated β-ketoesters **13** and **15** were used in the Krapcho/aldol reaction (Scheme 3c,d). α,α-Dimethyl substituted β-ketoester **13** did not provide the corresponding product **14**, and the Krapcho decarboxylation of **13** was not observed, with the recovery of **13** in 92% yield. Additionally, α-nonsubstituted β-ketoester **15** did not give rise to the corresponding product **16**. However, the nondecarboxylation and condensation products **17** were obtained in low yields in this case. They may have been generated by the reaction between the active methylene moiety of **15** and benzaldehyde **3a**. These results suggest that

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the difluoro substituents at the α-position are necessary and promote the Krapcho decarboxylation.

CONCLUSIONS

In conclusion, we succeeded in exploiting a novel and synthetically valuable method for the formation of C−CF_2 bonds via a Krapcho decarboxylative/aldol reaction between various carbonyl compounds and methyl α,α-difluoro-β-propanoate in the presence of $Yb(OTf)_3$. This transformation is the first that uses an α,α-difluoro-β-ketoester via Krapcho decarboxylation as the formal enolate equivalent, leading to C−C bond formation through the Krapcho/aldol consecutive reaction. The system was compatible with a wide range of methyl α,α-difluoro-β-propanoates, and a variety of carbonyl compounds bearing multifunctional groups were tolerated well. This methodology features a readily available β-ketoester and completely one-pot reaction. Furthermore, the developed method was applied to synthesize a CF_2-containing $GABA_B$ agonist as an example of its utility for the preparation of bioactive compounds. This research provides a path to the β-keto difluoromethylene unit, which is a valuable intermediate in the synthesis of many fine chemicals and naturally occurring compounds. Investigations to clarify the reaction mechanism and reactions with other electrophiles are currently underway.

EXPERIMENTAL SECTION

General Information. All commercially available reagents were purchased as reagent grades and were used without further purification unless otherwise stated. Solvents were heated to reflux over Na metal with benzophenone ketyl (THF), P_2O_5 (CH_2Cl_2), and CaH_2 (CH_3CN and *N*-methyl-2-pyrrolidone (NMP)) under an argon atmosphere and collected by distillation just before use. Anhydrous *N*,*N*-dimethylacetamide (DMA) was purchased from wako chemicals. All reactions were carried out under an Ar atmosphere and monitored by thin-layer chromatography (TLC) unless otherwise stated. TLCs were performed on silica gel 60 F254 and visualized by exposure to UV light. Flash column chromatography was performed using SiliCycle silica gel (SiliaFlash, 230−400 mesh). Melting points of the products obtained were measured using cover glass and were not corrected. NMR spectra were recorded at 400 MHz for ^1H, 100 MHz for ^{13}C, and 376 Hz for ^{19}F using $CDCl_3$ as a solvent. Chemical shifts of ^1H and ^{13}C NMR are reported in ppm downfield of TMS (^1H and ^{13}C = 0.00 ppm) and $CDCl_3$ (^{13}C δ = 77.2 ppm). Chemical shifts of ^{19}F NMR are reported in ppm from $CFCl_3$ as an internal standard. ^{13}C NMR spectra were obtained with ^1H decoupling. All data are reported as follows: chemical shifts, multiplicity (standard abbreviations), coupling constants (Hz), and relative integration value. HRMS experiments were measured on a double-focusing mass spectrometer with an ionization mode of EI.

Synthesis of β-Hydroxy-α,α-difluoro Ester via Honda−Reformatsky Reaction.[14] A flame-dried reaction vessel was cooled to room temperature and filled with argon. To this flask were added $RhCl(PPh_3)_3$ (1 mol %), the corresponding aldehyde (1.0 equiv), methyl bromodifluoroacetate (**18**, 1.5 equiv), and CH_3CN (8.0 mL/aldehyde). The reaction mixture was cooled at 0 °C with an ice bath. Finally, diethylzinc (1.5 equiv, 1.0 M in hexane) was added dropwise over a period of 20 min and the reaction mixture was stirred at room temperature. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with 10% aqueous HCl and extracted with ethyl acetate. The extract was washed with brine and dried with $MgSO_4$, and then the filtrate was collected and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/C6) to afford the desired product **19**.

*Methyl 2,2-Difluoro-3-hydroxy-3-phenylpropanoate (**19a**).*[15] Yield 91% (3.901 g), colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.39 (m, 5H), 5.18 (ddd, J = 15.7, 7.4, 5.2 Hz, 1H), 3.87 (s, 3H), 2.65 (brd, J = 5.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0 (t, J = 32.3 Hz), 134.3, 129.4, 128.5, 127.7, 113.8 (dd, J = 259.6, 253.8 Hz), 73.8 (dd, J = 27.9, 24.1 Hz), 53.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.1 (dd, J = 263.4, 7.4 Hz, 1F), −120.8 (dd, J = 263.4, 15.7 Hz, 1F). MS m/z = 216 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{10}H_{10}F_2O_3$: 216.0598; found: 216.0597.

*Methyl 2,2-Difluoro-3-hydroxy-3-(naphthalen-2-yl)-propanoate (**19b**).*[15] This reaction was carried out using 3 equiv of **18** and diethyl zinc, respectively. Yield 72% (576.1 mg), colorless solid, mp 92.3−93.3 °C (from $CHCl_3$−C6). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.84 (m, 4H), 7.55−7.50 (m, 3H), 5.34 (dd, J = 15.9, 7.5 Hz, 1H), 3.86 (s, 3H), 2.85 (brs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1 (dd, J = 32.8, 30.8 Hz), 133.7, 132.9, 131.7, 128.3, 128.2, 127.7, 127.5, 126.7, 126.5, 124.7, 113.9 (dd, J = 259.6, 253.8 Hz), 73.9 (dd, J = 28.4, 24.6 Hz), 53.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.7 (dd, J = 263.5, 7.5 Hz, 1F), −120.4 (dd, J = 263.5, 15.9 Hz, 1F). MS m/z = 266 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{12}F_2O_3$: 266.0755; found: 266.0759.

*Methyl 2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-propanoate (**19c**).* This reaction was carried out by using 3 equiv of **18** and diethyl zinc, respectively. Yield 97% (718.4 mg), colorless solid, mp 68.0−69.0 °C (from $CHCl_3$−C6). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.11 (ddd, J = 15.9, 7.9, 5.0 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.63 (d, J = 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1 (t, J = 31.8 Hz), 160.3, 129.0, 126.4, 113.9, 113.8 (dd, J = 261.9, 253.3 Hz), 73.4 (dd, J = 27.9, 24.1 Hz), 55.3, 53.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.5 (dd, J = 262.3, 7.9 Hz, 1F), −120.8 (dd, J = 262.3, 15.9 Hz, 1F). MS m/z = 246 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{11}H_{12}F_2O_4$: 246.0704; found: 246.0707.

*Methyl 3-(4-Chlorophenyl)-2,2-difluoro-3-hydroxypropanoate (**19d**).*[16] Yield 82% (612.2 mg), colorless solid, mp 52.0−53.0 °C (from C6). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 4H), 5.17 (ddd, J = 15.7, 7.2, 5.1 Hz, 1H), 3.88 (s, 3H), 2.68 (d, J = 5.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.9 (t, J = 32.3 Hz), 135.3, 132.8, 129.0, 128.7, 113.5 (dd, J = 260.1, 253.3 Hz), 73.1 (dd, J = 27.9, 24.1 Hz), 53.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.7 (dd, J = 265.2, 7.2 Hz, 1F), −120.9 (dd, J = 265.2, 15.7 Hz, 1F). MS m/z = 250 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{10}H_9ClF_2O_3$: 250.0208; found: 250.0213 (100), 252.0181 (33).

*Methyl 2,2-Difluoro-3-hydroxy-5-phenylpentanoate (**19e**).*[17] Yield 77% (562.1 mg), colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.29 (m, 2H), 7.23−7.20 (m, 3H), 4.08−3.97 (m, 1H), 3.89 (s, 3H), 2.93 (ddd, J = 13.9, 9.1, 5.1 Hz, 1H), 2.74 (ddd, J = 13.9, 8.6, 8.2 Hz, 1H), 2.10 (d, J = 6.9 Hz, 1H), 2.06−1.98 (m, 1H), 1.94−1.84 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.0 (dd, J = 33.2, 31.3 Hz), 140.7, 128.6, 128.5, 126.3, 114.6 (dd, J = 257.2, 254.3 Hz), 71.0 (dd, J = 27.0, 25.0 Hz), 53.5, 31.2, 30.7 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.2 (dd, J = 266.4, 7.6 Hz, 1F),

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−121.9 (dd, J = 266.4, 15.2 Hz, 1F). MS m/z = 244 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{12}H_{14}F_2O_3$: 244.0911; found: 244.0912.

*Methyl 3-Cyclohexyl-2,2-difluoro-3-hydroxypropanoate (**19f**).* Yield 88% (1.327 g), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 3.88−3.78 (m, 1H), 2.10 (d, J = 8.2 Hz, 1H), 1.93−1.90 (m, 1H), 1.81−1.65 (m, 5H), 1.32−1.08 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4 (dd, J = 32.8, 30.8 Hz), 115.5 (dd, J = 258.2, 255.3 Hz), 75.2 (dd, J = 26.5, 23.6 Hz) 53.4, 38.2, 29.6, 27.3, 26.1, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.9 (dd, J = 264.1, 7.6 Hz, 1F), −120.2 (dd, J = 264.1, 18.4 Hz, 1F). MS m/z = 222 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{10}H_{18}F_2O_3$: 222.1068; found: 222.1074.

Synthesis of β-Keto-α,α-difluoro Ester via Dess−Martin Oxidation.[18] To a vial containing β-hydroxy-α,α-difluoro ester (**19**, 1.0 equiv) and Dess−Martin periodinane (1.2 equiv) was added DCM (8 mL/**19**) at ambient temperature under air. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with 10% $Na_2S_2O_3$-saturated K_2CO_3 aqueous solution and the mixture was stirred for 30 min. Then, the whole mixture was extracted with $CHCl_3$. The extract was washed with saturated K_2CO_3 aqueous solution, followed by H_2O, and dried with $MgSO_4$, and then the filtrate was collected and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/C6) to afford the desired product **6**.

*Methyl 2,2-Difluoro-3-oxo-3-phenylpropanoate (**6a**).* Yield 85% (295.7 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.08 (m, 2H), 7.69−7.67 (m, 1H), 7.55−7.51 (m, 2H), 3.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.4 (t, J = 27.5 Hz), 162.3 (t, J = 30.3 Hz), 135.2, 130.9, 130.0, 129.0, 109.9 (t, J = 264.9 Hz), 54.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.2 (s, 2F). MS m/z = 214 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{10}H_8F_2O_3$: 214.0442; found: 214.0445.

*Methyl 2,2-Difluoro-3-(naphthalen-2-yl)-3-oxopropanoate (**6b**).* Yield 93% (493.0 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.07−7.89 (m, 4H), 7.68−7.61 (m, 2H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 185.3 (t, J = 27.5 Hz), 162.5 (t, J = 30.8 Hz), 136.3, 133.0 (m), 132.2, 130.2, 129.9, 129.0, 128.2, 127.9, 127.3, 124.2, 110.2 (t, J = 264.9 Hz), 54.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.6 (s, 2F). MS m/z = 264 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{10}F_2O_3$: 264.0598; found: 264.0601.

*Methyl 2,2-Difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (**6c**).* Yield 97% (340.4 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.7 (t, J = 27.5 Hz), 165.2, 162.6 (t, J = 30.8 Hz), 132.6, 123.7, 114.3, 110.2 (t, J = 264.9 Hz), 55.7, 54.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.9 (s, 2F). MS m/z = 244 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{11}H_{10}F_2O_4$: 244.0547; found: 244.0545.

*Methyl 3-(4-Chlorophenyl)-2,2-difluoro-3-oxopropanoate (**6d**).* Yield 73% (445.3 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 3.94 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 184.4 (t, J = 27.9 Hz), 162.1 (t, J = 30.3 Hz), 142.1, 131.4 (m), 129.5, 129.2 (m), 109.8 (t, J = 265.4 Hz), 54.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.2 (s, 2F). MS m/z = 248 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{10}H_7ClF_2O_3$: 248.0052; found: 248.0056 (100), 249.9994 (31.5).

*Methyl 2,2-Difluoro-3-oxo-5-phenylpentanoate (**6e**).* Yield 78% (437.0 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2H), 7.24−7.19 (m, 3H), 3.87 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H), 2.97 (t, J = 7.2 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 196.4 (t, J = 27.9 Hz), 161.7 (t, J = 30.8 Hz), 139.7, 128.7, 128.4, 126.5, 108.3 (t, J = 263.9 Hz), 54.0, 38.4, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.6 (s, 2F). MS m/z = 242 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{12}H_{12}F_2O_3$: 242.0755; found: 242.0751.

*Methyl 3-Cyclohexyl-2,2-difluoro-3-oxopropanoate (**6f**).* Yield 59% (336.3 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 2.94−2.88 (m, 1H), 1.92−1.69 (m, 5H), 1.46−1.22 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.1 (t, J = 27.0 Hz), 162.1 (t, J = 30.8 Hz), 108.7 (t, J = 264.9 Hz), 53.9, 45.3, 28.0, 25.5, 25.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.8 (s, 2F). MS m/z = 220 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{10}H_{14}F_2O_3$: 220.0911; found: 220.0911.

General Procedure for Krapcho Decarboxylative Aldol Reaction. A flame-dried reaction vessel was cooled to room temperature and filled with argon. To this flask containing the corresponding β-keto-α,α-difluoro ester (**6**, 0.5 mmol), $Yb(OTf)_3$·n-hydrate (0.75 mmol, 1.5 equiv), NaCl (0.75 mmol, 1.5 equiv), and aldehydes (0.5 mmol, 1.0 equiv) was added CH_3CN (2.0 mL/**6**). Then, H_2O (0.5 mmol, 1.0 equiv, 0.5 mL, 1.0 M in CH_3CN) was added to the reaction mixture. Finally, the reaction mixture was heated to 100 °C and stirred for 18 h. The reaction mixture was cooled to room temperature, quenched with 10% aqueous HCl, and extracted with ethyl acetate. The extract was washed with brine and dried with $MgSO_4$. The filtrate was collected and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/C6) to afford the desired product **4**.

*2,2-Difluoro-3-hydroxy-1,3-diphenylpropan-1-one (**4aa**).*[4c] Yield 95% (123.8 mg), colorless solid, mp 69.0−70.0 °C (from Et_2O-petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.05 (m, 2H), 7.66−7.62 (m, 1H), 7.51−7.39 (m, 7H), 5.39 (ddd, J = 18.8, 5.7, 4.6 Hz, 1H), 2.99 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.9 (dd, J = 31.3, 29.4 Hz), 134.7, 134.6, 132.4, 130.2 (m), 129.0, 128.6, 128.3, 128.1, 115.7 (dd, J = 264.4, 256.7 Hz), 73.3 (dd, J = 28.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.6 (dd, J = 293.0, 5.7 Hz, 1F), −116.4 (dd, J = 293.0, 18.8 Hz, 1F). MS m/z = 262 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{12}F_2O_2$: 262.0805; found: 262.0807.

*2,2-Difluoro-3-hydroxy-3-(naphthalen-2-yl)-1-phenylpropan-1-one (**4ab**).*[4b] Yield 96% (143.0 mg), colorless solid, mp 107.5−108.0 °C (from $CHCl_3$−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.3 Hz, 2H), 7.96 (s, 1H), 7.83−7.87 (m, 3H), 7.59−7.63 (m, 2H), 7.43−7.52 (m, 4H), 5.54 (ddd, J = 18.8, 5.8, 3.5 Hz, 1H), 3.19 (d, J = 3.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.9 (dd, J = 31.3, 29.4 Hz), 134.6, 133.6, 132.9, 132.4 (m), 132.2, 130.3 (m), 128.7, 128.3, 128.0, 127.8, 127.7, 126.5, 126.3, 125.3, 115.9 (dd, J = 264.9, 257.2 Hz), 73.4 (dd, J = 28.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.2 (dd, J = 293.0, 5.8 Hz, 1F), −116.1 (dd, J = 293.0, 18.8 Hz, 1F). MS m/z = 312 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{19}H_{14}F_2O_2$: 312.0962; found: 312.0961.

*2,2-Difluoro-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (**4ac**).*[4c,19] Yield 75% (109.8 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−8.06 (m, 2H), 7.61−7.65 (m, 1H), 7.41−7.50 (m, 4H), 6.92 (d, J = 6.6, 2.1 Hz, 2H), 5.33 (ddd, J = 18.3, 6.0, 4.6 Hz, 1H), 3.82 (s, 3H), 2.94 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ

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191.0 (dd, J = 31.8, 28.9 Hz), 160.1, 134.5, 132.5 (m), 130.2 (m), 129.4, 128.6, 126.8, 115.8 (dd, J = 263.9, 256.2 Hz), 113.8, 73.0 (dd, J = 27.9, 23.1 Hz), 55.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.0 (dd, J = 289.7, 6.0 Hz, 1F), −116.4 (dd, J = 289.7, 18.3 Hz, 1F). MS m/z = 292 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{14}F_2O_3$: 292.0911; found: 292.0907.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(p-tolyl)propan-1-one (**4ad**).[4b,c,19] Yield 89% (123.5 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.05 (m, 2H), 7.59−7.63 (m, 1H), 7.43−7.47 (m, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 5.32 (ddd, J = 18.8, 5.2, 3.6 Hz, 1H), 3.05 (brd, J = 3.6 Hz, 1H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.0 (dd, J = 31.8, 28.9 Hz), 138.9, 134.5, 132.5 (m), 131.8, 130.2 (m), 129.0, 128.6, 128.0, 115.8 (dd, J = 263.9, 256.2 Hz), 73.2 (dd, J = 28.9, 23.1 Hz), 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.8 (dd, J = 290.4, 5.2 Hz, 1F), −116.4 (dd, J = 290.4, 18.8 Hz, 1F). MS m/z = 276 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{14}F_2O_2$: 276.0962; found: 276.0964.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(m-tolyl)propan-1-one (**4ae**).[4b,c] Yield 93% (128.8 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−8.06 (m, 2H), 7.61−7.65 (m, 1H), 7.45−7.49 (m, 2H), 7.18−7.31 (m, 4H), 5.34 (ddd, J = 18.8, 5.4, 4.6 Hz, 1H), 2.99 (d, J = 4.6 Hz, 1H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.0 (dd, J = 31.8, 28.9 Hz), 138.0, 134.7, 134.5, 132.5 (m), 130.2 (m), 129.8, 128.7, 128.6, 128.2, 125.2, 115.9 (dd, J = 263.9, 256.2 Hz), 73.3 (dd, J = 28.9, 23.1 Hz), 21.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.6 (dd, J = 289.6, 5.4 Hz, 1F), −116.3 (dd, J = 289.6, 18.8 Hz, 1F). MS m/z = 276 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{14}F_2O_2$: 276.0962; found: 276.0966.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(o-tolyl)propan-1-one (**4af**).[4b,c] Yield 93% (128.4 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.3 Hz, 2H), 7.61−7.64 (m, 2H), 7.47 (m, 2H), 7.17−7.28 (m, 3H), 5.69 (dd, J = 19.9, 3.3 Hz, 1H), 2.97 (brs, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.1 (dd, J = 31.8, 28.9 Hz), 136.8, 134.6, 133.3, 132.4 (m), 130.4, 130.3 (m), 128.8, 128.7, 128.1 (m), 126.1, 116.4 (dd, J = 265.4, 255.8 Hz), 68.9 (dd, J = 29.9, 23.1 Hz), 19.6, 19.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.0 (dd, J = 293.7, 3.3 Hz, 1F), −116.9 (dd, J = 293.7, 19.9 Hz, 1F). MS m/z = 276 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{14}F_2O_2$: 276.0962; found: 276.0963.

2,2-Difluoro-3-hydroxy-3-mesityl-1-phenylpropan-1-one (**4ag**).[4c,19] Yield 47% (71.2 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.11 (m, 2H), 7.47−7.66 (m, 3H), 6.89 (s, 2H), 5.91 (ddd, J = 26.3, 4.6, 3.0 Hz, 1H), 2.80 (m, 1H), 2.46 (brs, 6H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.6 (dd, J = 32.8, 28.9 Hz), 138.2, 134.5, 132.5 (m), 130.3 (m), 128.7, 127.7, 117.7 (dd, J = 268.3, 252.9 Hz), 70.6 (dd, J = 30.8, 23.1 Hz), 21.2, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.0 (d, J = 292.6 Hz, 1F), −114.6 (dd, J = 292.6, 27.5 Hz, 1F). MS m/z = 304 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{18}H_{18}F_2O_2$: 304.1275; found: 304.1280.

2,2-Difluoro-3-(4-fluorophenyl)-3-hydroxy-1-phenylpropan-1-one (**4ah**).[19] Yield 94% (131.8 mg), colorless solid, mp 75.5−76.2 °C (from Et_2O−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.06 (m, 2H), 7.62−7.66 (m, 1H), 7.46−7.50 (m, 4H), 7.08 (m, 2H), 5.37 (dd, J = 18.8, 5.2 Hz, 1H), 3.13 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.8 (dd, J = 31.8, 29.9 Hz), 163.2 (d, J = 247.6 Hz), 134.8, 132.2 (m), 130.4 (m), 130.3 (m), 129.9 (d, J = 8.7 Hz), 128.7, 115.4 (dd, J = 264.9, 257.2 Hz), 115.3 (d, J = 22.2 Hz), 72.6 (dd, J = 28.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.5 (dd, J = 295.0, 5.2 Hz, 1F), −112.7 (m, 1F), −116.7 (dd, J = 295.0, 18.8 Hz, 1F). MS m/z = 280 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{11}F_3O_2$: 280.0711; found: 280.0709.

3-(4-Chlorophenyl)-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**4ai**).[4b] Yield 96% (143.0 mg), colorless solid, mp 96.5−97.0 °C (from Et_2O−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.62−7.66 (m, 1H), 7.43−7.50 (m, 4H), 7.36 (d, J = 8.4 Hz, 2H), 5.36 (dd, J = 18.8, 5.0 Hz, 1H), 3.18 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.7 (dd, J = 31.8, 28.9 Hz), 135.0, 134.8, 133.1, 132.2 (m), 130.3 (m), 129.5, 128.7, 128.5, 115.4 (dd, J = 264.9, 257.2 Hz), 72.6 (dd, J = 28.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.2 (dd, J = 296.2, 5.0 Hz, 1F), −116.6 (dd, J = 296.2, 18.8 Hz, 1F). MS m/z = 296 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{11}ClF_2O_2$: 296.0416; found: 296.0408 (100), 298.0394 (34.3).

Methyl 4-(2,2-Difluoro-1-hydroxy-3-oxo-3-phenylpropyl)-benzoate (**4aj**).[4c,19] Yield 87% (139.5 mg), colorless solid, mp 94.0−94.6 °C (from $CHCl_3$−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.8 Hz, 4H), 7.63−7.67 (m, 1H), 7.59 (d, J = 7.8 Hz, 2H), 7.47−7.51 (m, 2H), 5.46 (ddd, J = 19.2, 5.2, 4.6 Hz, 1H), 3.93 (s, 3H), 3.19 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ190.6 (dd, J = 31.8, 29.9 Hz), 166.8, 139.6, 134.8, 132.1 (m), 130.6, 130.3 (m), 129.5, 128.7, 128.2, 115.5 (dd, J = 265.9, 257.2 Hz), 72.8 (dd, J = 27.9, 23.1 Hz), 52.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.9 (dd, J = 296.0, 5.2 Hz, 1F), −116.4 (dd, J = 296.0, 19.2 Hz, 1F). MS m/z = 320 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{17}H_{14}F_2O_4$: 320.0860; found: 320.0866.

2,2-Difluoro-3-hydroxy-3-(4-nitrophenyl)-1-phenylpropan-1-one (**4ak**).[4b,c] Yield 82% (125.9 mg), colorless solid, mp 114.5−115.5 °C (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 6.9 Hz, 2H), 8.07−8.09 (m, 2H), 7.65−7.72 (m, 3H), 7.49−7.53 (m, 2H), 5.53 (ddd, J = 19.3, 4.3, 4.1 Hz, 1H), 3.38 (d, J = 4.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.3 (dd, J = 31.8, 29.9 Hz), 148.3, 141.7, 135.1, 131.7 (m), 130.3 (m), 129.2, 128.9, 123.3, 115.0 (dd, J = 266.8, 258.2 Hz), 72.2 (dd, J = 27.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.3 (dd, J = 302.0, 4.3 Hz, 1F), −116.5 (dd, J = 302.0, 19.3 Hz, 1F). MS m/z = 307 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{11}F_2NO_4$: 307.0656; found: 307.0659.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(4-(trifluoromethyl)-phenyl)propan-1-one (**4al**).[4c] Yield 98% (161.4 mg), colorless solid, mp 103.0−104.0 °C (from $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.3 Hz, 2H), 7.63−7.68 (m, 5H), 7.48−7.52 (m, 2H), 5.47 (ddd, J = 19.1, 5.1, 4.6 Hz, 1H), 3.20 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.5 (dd, J = 31.8, 29.9 Hz), 138.6, 134.9, 132.0 (m), 131.1 (q, J = 32.8 Hz), 130.3 (m), 128.8, 128.6, 125.2 (q, J = 3.5 Hz), 124.0 (q, J = 271.9 Hz), 115.28 (dd, J = 265.9, 257.2 Hz), 72.61 (dd, J = 28.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.6 (s, 3F), −103.8 (dd, J = 299.7, 5.1 Hz, 1F), −116.5 (dd, J = 299.7, 19.1 Hz, 1F). MS m/z = 330 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{11}F_5O_2$: 330.0679; found: 330.0673.

2,2-Difluoro-3-hydroxy-1-phenyl-3-(pyridin-2-yl)propan-1-one (**4am**).[4c] Yield 10% (13.0 mg), colorless solid, mp 70.5−71.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59−8.61 (m, 1H), 8.08−8.10 (m, 2H), 7.76−7.78 (m, 1H), 7.46−7.62 (m, 4H), 7.33−7.36 (m, 1H), 5.37 (dd, J = 17.8, 4.8 Hz, 2H) (Note: the OH and methine proton were overlapped); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.4 (dd, J = 29.9, 27.0 Hz), 152.4, 148.1, 137.0, 134.1, 133.3 (m), 130.3 (m),

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128.5, 124.0, 123.1 (m), 116.8 (dd, J = 263.9, 257.2 Hz), 71.84 (dd, J = 28.9, 25.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.8 (dd, J = 272.0, 4.8 Hz, 1F), −116.7 (dd, J = 272.0, 17.7 Hz, 1F). MS m/z = 263 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{11}F_2NO_2$: 263.0758; found: 263.0754.

*2,2-Difluoro-3-hydroxy-1-phenyl-3-(pyridin-3-yl)propan-1-one (**4an**).* Yield 75% (99.3 mg), colorless solid, mp 103.0−104.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.55 (d, J = 4.6 Hz, 1H), 8.09 (d, J = 7.3 Hz, 2H), 7.90 (d, J = 8.2 Hz, 1H), 7.64−7.68 (m, 1H), 7.48−7.52 (m, 2H), 7.33−7.36 (m, 1H), 5.43 (dd, J = 19.4, 4.8 Hz, 1H), 4.17 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.7 (dd, J = 31.3, 27.5 Hz), 149.1, 148.8, 136.6, 134.5, 132.7, 132.3, 130.2, 128.7, 123.5, 116.1 (dd, J = 264.9, 256.2 Hz), 70.8 (dd, J = 28.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.7 (dd, J = 297.3, 4.8 Hz, 1F), −116.8 (dd, J = 297.7, 19.4 Hz, 1F). MS m/z = 263 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{11}F_2NO_2$: 263.0758; found: 263.0760.

*3-Cyclohexyl-2,2-difluoro-3-hydroxy-1-phenylpropan-1-one (**4ao**).*[4c] Yield 62% (82.7 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.09 (m, 2H), 7.61−7.64 (m, 1H), 7.46−7.50 (m, 2H), 4.01−4.09 (m, 1H), 2.52 (brs, 1H), 1.96−1.98 (m, 1H), 1.65−1.83 (m, 5H), 1.12−1.39 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.9 (dd, J = 31.3, 29.4 Hz), 134.4, 132.53 (m), 130.2 (m), 128.7, 117.8 (dd, J = 263.0, 257.2 Hz,), 74.8 (dd, J = 27.0, 23.1 Hz), 38.1, 30.1, 27.3, 26.3, 26.1, 25.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.8 (d, J = 288.3 Hz, 1F), −114.5 (dd, J = 288.3, 20.2 Hz, 1F). MS m/z = 268 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{18}F_2O_2$: 268.1275; found: 268.1273.

*2,2-Difluoro-3-hydroxy-1,5-diphenylpentan-1-one (**4ap**).*[4b,c] Yield 44% (63.2 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.08 (m, 2H), 7.66−7.62 (m, 1H), 7.51−7.47 (m, 2H), 7.31−7.18 (m, 5H), 4.29−4.19 (m, 1H), 3.02−2.95 (m, 1H), 2.80−2.72 (m, 1H), 2.63 (d, J = 5.5 Hz, 1H), 2.12−1.95 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.5 (dd, J = 32.3, 30.3 Hz), 141.1, 134.7, 132.0, 130.3 (m), 128.7, 128.5, 126.1, 116.4 (dd, J = 262.0, 258.2 Hz), 70.4 (dd, J = 27.0, 24.1 Hz), 31.3, 30.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −107.3 (dd, J = 298.2, 5.4 Hz, 1F), −116.9 (dd, J = 298.2, 18.1 Hz, 1F). MS m/z = 290 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{17}H_{16}F_2O_2$: 290.1118; found: 290.1118.

*2,2-Difluoro-3-hydroxy-3-methyl-1-phenylbutan-1-one (**4aq**).*[4c] Yield 63% (66.4 mg), colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.11 (m, 2H), 7.65−7.61 (m, 1H), 7.51−7.47 (m, 2H), 3.01 (brs, 1H), 1.44 (t, J = 1.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.3 (t, J = 31.8 Hz), 134.6, 133.2 (m), 130.5 (m), 128.7, 117.2 (t, J = 262.0 Hz), 73.4 (t, J = 24.6 Hz), 23.7 (t, J = 2.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.5 (s, 2F). MS m/z = 214 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{11}H_{12}F_2O_2$: 214.0805; found: 214.0808.

*2,2-Difluoro-3-hydroxy-1-(naphthalen-2-yl)-3-phenylpropan-1-one (**4ba**).*[20] Yield 83% (129.9 mg), colorless solid, mp 122.5−123.5 °C (from $CHCl_3$−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.85−7.92 (m, 3H), 7.52−7.64 (m, 4H), 7.37−7.42 (m, 3H), 5.43 (ddd, J = 18.8, 5.8, 4.3 Hz, 1H), 3.15 (d, J = 3.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.7 (dd, J = 31.8, 28.9 Hz), 136.1, 134.7, 133.3 (m), 132.2, 130.2, 129.5, 129.1, 128.5, 128.3, 128.2, 127.8, 127.0, 124.7, 115.9 (dd, J = 264.4, 256.7 Hz), 73.4 (dd, J = 27.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.9 (dd, J = 291.9, 5.8 Hz, 1F), −115.4 (dd, J = 291.9, 18.8 Hz, 1F). MS m/z = 312 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{19}H_{14}F_2O_2$: 312.0962; found: 312.0965.

*2,2-Difluoro-3-hydroxy-1-(4-methoxyphenyl)-3-phenylpropan-1-one (**4ca**).*[4c,20] Yield 90% (130.7 mg), colorless solid, mp 119.5−120.5 °C (from Et_2O−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.07 (m, 2H), 7.37−7.50 (m, 5H), 6.93 (d, J = 9.2 Hz, 2H), 5.36 (ddd, J = 19.1, 5.5, 4.6 Hz, 1H), 3.88 (s, 3H), 3.21 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.1 (dd, J = 30.8, 28.9 Hz), 164.8, 134.8, 132.9 (m), 128.9, 128.3, 128.2, 125.1 (m), 115.8 (dd, J = 264.9, 257.2 Hz), 114.0, 73.4 (dd, J = 27.9, 23.1 Hz), 55.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −103.9 (dd, J = 293.5, 5.5 Hz, 1F), −115.8 (dd, J = 293.5, 19.1 Hz, 1F). MS m/z = 292 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{16}H_{14}F_2O_3$: 292.0911; found: 292.0905.

*1-(4-Chlorophenyl)-2,2-difluoro-3-hydroxy-3-phenylpropan-1-on (**4da**).*[4c,20] Yield 75% (111.2 mg), colorless solid, mp 111.5−112.5 °C (from Et_2O−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.7 Hz, 2H), 7.38−7.49 (m, 7H), 5.35 (ddd, J = 18.4, 5.8, 4.6 Hz, 1H), 3.00 (d, J = 4.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.9 (dd, J = 31.8, 28.9 Hz), 141.4, 134.5, 131.6 (m), 130.7 (m), 129.2, 129.1, 128.7, 128.5, 128.4, 128.1, 115.7 (dd, J = 263.9, 256.2 Hz), 73.2 (dd, J = 27.9, 23.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.7 (dd, J = 290.5, 5.8 Hz, 1F), −116.4 (dd, J = 290.5, 18.4 Hz, 1F). MS m/z = 296 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{11}ClF_2O_2$: 296.0416; found: 296.0420 (31.8), 298.0390 (11.7).

*2,2-Difluoro-1-hydroxy-1,5-diphenylpentan-3-one (**4ea**).*[21] Yield 69% (100.7 mg), colorless solid, mp 64.5−65.0 °C (from Et_2O−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.40 (m, 5H), 7.12−7.28 (m, 5H), 5.11 (dd, J = 16.5, 7.8 Hz, 1H), 2.84−3.01 (m, 4H), 2.70 (brs, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 201.5 (dd, J = 31.3, 27.5 Hz), 140.0, 134.6, 129.2, 128.5, 128.5, 128.3, 127.7, 126.3, 114.8 (dd, J = 261.5, 255.8 Hz), 73.2 (dd, J = 27.9, 24.1 Hz), 39.8, 28.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.3 (dd, J = 268.4, 7.8 Hz, 1F), −122.7 (dd, J = 268.4, 16.5 Hz, 1F). MS m/z = 290 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{17}H_{16}F_2O_2$: 290.1118; found: 290.1114.

*1-Cyclohexyl-2,2-difluoro-3-hydroxy-3-phenylpropan-1-one (**4fa**).*[4c,19] This reaction was stirred for 48 h. Yield 59% (78.5 mg), colorless solid, mp 62.0−63.0 °C (from Et_2O−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.42 (m, 5H), 5.17 (ddd, J = 16.6, 7.7, 3.8 Hz, 1H), 2.72−2.78 (m, 2H), 1.16−1.84 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 205.6 (dd, J = 30.3, 26.5 Hz), 134.8 (m), 129.1, 128.4, 127.8, 115.0 (dd, J = 263.0, 256.2 Hz), 73.0 (dd, J = 28.4, 23.6 Hz), 45.8, 27.9, 27.7, 25.5, 25.3, 25.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.4 (dd, J = 272.5, 7.7 Hz, 1F), −122.4 (dd, J = 272.5, 16.6 Hz, 1F). MS m/z = 268 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{15}H_{18}F_2O_2$: 268.1275; found: 268.1279.

*Synthetic Utility of α,α-Difluoro-β-keto Ester. Methyl 3-(Adamantan-1-yl)-2,2-difluoro-3-oxopropanoate (**11**).* 1-Adamantanemethanol (**8**) was obtained by a reported procedure.[22] The product **8** was purified via only filtration and solvent washing to afford 3.286 g of **8** in 99% yield as a colorless solid. To a vial containing 1-adamantanemethanol (**8**, 831.3 mg, 5 mmol) was added DCM (30 mL) at ambient temperature. Dess−Martin periodinane (DMP, 3.18 g, 7.5 mmol, 1.5 equiv) was added to the solution, and the mixture was stirred. To the whole mixture was added a wet DCM

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(0.4%, DCM/H_2O = 50/0.2 mL) dropwise over the period of 1.5 h. The reaction mixture was stirred for 0.5 h and then diluted to 200 mL with diethyl ether. The dilution was concentrated by rotary evaporation to approximately 30 mL. Unreacted DMP was removed through Celite filtration, and the filtrate was washed with 1:1 mixture of 10% $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with ether, and then the combined organic layers were washed with brine. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to afford 1-adamantane carboxaldehyde **9** as an oil.[22] The intermediate **9** was used immediately without any purification. The Reformatky reaction of **9** with methyl bromodifluoroacetate was conducted via above representative Honda−Reformatsky reaction (see the typical procedure of Honda−Reformatsky reaction). A solution of **9**, methyl bromodifluoroacetate (0.83 mL, 7.5 mmol), and $RhCl(PPh_3)_3$ (46.3 mg, 1 mol %) in CH_3CN (40 mL) was treated with Et_2Zn (7.5 mL, 1 M solution in C6). The Reformatsky product **10** was isolated and purified by column chromatography on silica gel (EtOAc/C6 = 1:4) to give a liquid in 52% yield (709.4 mg, 2.59 mmol, two steps from **8**). The obtaining **10** was oxidized via above representative Dess−Martin oxidation (See typical procedure of Dess−Martin oxidation reaction). A solution of **10** (685.8 mg, 2.5 mmol) in DCM (20 mL) was treated with DMP (1.27 g, 3 mmol, 1.2 equiv). The titled compound **11** was isolated and purified by column chromatography on silica gel (EtOAc/C6 = 1:9) to give a colorless liquid in 82% yield (555.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 2.07 (s, 3H), 1.98 (d, J = 2.7 Hz, 6H), 1.71−1.79 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.4 (t, J = 25.5 Hz), 162.3 (t, J = 30.8 Hz), 110.3 (t, J = 267.3 Hz), 53.8, 46.5, 37.1, 36.3, 27.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.5 (s, 2F). MS m/z = 272 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{14}H_{18}F_2O_3$: 272.1224; found: 272.1219.

3-(4-Acetylphenyl)-1-(adamantan-1-yl)-2,2-difluoro-3-hydroxypropan-1-one (12).[23] See representative procedure for the key Krapcho decarboxylative aldol reaction of **6**. Methyl 3-(adamantan-1-yl)-2,2-difluoro-3-oxopropanoate **11** (136.1 mg, 0.5 mmol) was used, and the title compound was obtained by column chromatography on silica gel (EtOAc/C6 = 1:3) to give a colorless solid in 17% yield (31 mg). Mp 88.0−88.5 °C (from $CHCl_3$−C6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 5.33 (dd, J = 18.3, 6.2 Hz, 1H), 3.31 (brs, 1H), 2.61 (s, 3H), 2.03 (brs, 3H), 1.90 (brs, 6H), 1.67−1.76 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 205.4 (dd, J = 29.4, 25.5 Hz), 198.1, 140.4, 137.3, 128.3, 128.1, 116.3 (dd, J = 267.8, 259.1 Hz), 72.6 (dd, J = 27.9, 23.1 Hz), 46.8 (t, J = 2.4 Hz), 36.8, 36.3, 27.6, 26.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.8 (dd, J = 290.4, 6.2 Hz, 1F), −118.7 (dd, J = 290.4, 18.3 Hz, 1F). MS m/z = 362 [M^+]; HRMS (EI): m/z [M^+] calcd for $C_{21}H_{24}F_2O_3$: 362.1694; found: 362.1699.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c02105.

Further detail screening of Lewis acids and the loading of it, spectral data of all compounds including ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

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