Highly C-selective difluoromethylation of β-ketoesters by using TMSCF2Br/lithium hydroxide/N,N,N-trimethylhexadecan-1-ammonium bromide

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1. General information:
All reactions were performed in a flame-dried glassware (10 mL) under positive pressure of nitrogen unless mentioned otherwise. Solvents were transferred via syringe and were introduced into reaction vessels though a rubber septum. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and KMnO₄ in water/heat. Column chromatography was carried out on columns packed with flash silica gel (60N spherical neutral size 40-50 μm). The ¹H-NMR (300 MHz), ¹⁹F-NMR (659 MHz or 282 MHz), ¹³C-NMR (125 MHz or 175 MHz) spectra for solution in CDCl₃ were recorded on a Bruker Avance 500, a Varian Mercury 300 and Jeol 700 NMR spectrometers. Chemical shifts (δ) are expressed in ppm downfield from internal TMS (δ = 0.00) as an internal standard. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A (EI-MS) and SHIMAZU LCMS-2020 (ESI-MS). High resolution mass spectrometry (HRMS) was recorded on a Waters Synapt G2 HDMS (ESI-MS) with a TOF analyzer. Solvents were dried and distilled before use.

2. General procedure for difluoromethylation of β-keto esters 1
The solution of β-ketoesters 1 (0.1 mmol), base (0.3 mmol), ammonium salts (additive) such as hexadecyltrimethylammonium bromide (10 mol%) in 1.0 mL dry solvent, was stirred at room temperature for 10 min. Then TMSCF₂Br (0.3 mmol) was added slowly, and the reaction mixture was monitored by TLC and upon the completion of the reaction at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to crude ¹⁹F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8.2 μL as internal standard). Subsequently, the desired difluoromethylated β-ketoesters 2 can be purified by chromatography on silica gel (hexane/ethyl acetate).
3. Table S-1 Optimization of Difluoromethylation of β-ketoesters 1a

![Chemical Reaction Image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>TMSCF&lt;sub&gt;2&lt;/sub&gt;Br (equiv)</th>
<th>LiOH (equiv)</th>
<th>Additive&lt;sup&gt;a&lt;/sup&gt; (Ammonium salts)</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>C/O&lt;sup&gt;c&lt;/sup&gt;</th>
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<td>DMSO</td>
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<sup>a</sup> Additive (Ammonium salts): A-1 = Hexadecyltrimethylammonium bromide; A-2 = tetra-n-butylammonium bromide; A-3 = didecyldimethylammonium bromide; A-4 = Methyl tri-octylammonium chloride; A-5 = Tetrabutylammonium iodide.  
<sup>b</sup> Yields of 2a were determined by crude <sup>19</sup>F-NMR and trifluoromethylbenzene as internal standard.  
<sup>c</sup> The C/O ratio of difluoromethylated β-ketoesters 2a and 3a was confirmed by crude <sup>19</sup>F-NMR.

After screening additives (ammonium salts)(entries 1-7, and entries 11-13), reaction temperature (entries 6-9), the equivalent of TMSCF<sub>2</sub>Br and activator LiOH (entries 10-17), reaction concentration (entry 18), and reaction solvents (entries 19-24), the combination of β-ketoesters I / TMSCF<sub>2</sub>Br (3.0 equiv) / LiOH (3.0 equiv) / Additive-1 (A-1, hexadecyltrimethylammonium bromide, 10 mol%) in toluene (0.1 M) at room temperature for 4 hours, was selected as the optimized reaction condition. Additionally, adding ammonium bromide A-1 as additive can shorten the reaction time effectively and have slight positive effect on yields and regionselectivity (entry 6 vs entry 7, entry 11 vs entries 12-13).
4. Table S2 The function of ammonium salt in controlling C/O selectivity\(^{[a,b]}\)

![Diagram of reaction]

<table>
<thead>
<tr>
<th>Entry</th>
<th>TMSCF(_2)Br (equiv)</th>
<th>LiOH (equiv)</th>
<th>Ammonium salt (10 mol%)</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
<th>C/O(^b)</th>
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<td>2.0</td>
<td>3.0</td>
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<td>90:10</td>
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<td>57</td>
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<td>(n-Bu)(_2)N(NO(_3))</td>
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<td>90</td>
<td>98:2</td>
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</table>

[a] Reaction was carried out as follows; TMSCF\(_2\)Br was added after 10 min mixing of 1a and LiOH in the presence or absence of ammonium salts in 1.0 mL toluene. Yields of 2a were determined by crude \(^{19}\)F-NMR and trifluoromethylbenzene as internal standard.

[b] The C/O ratio of difluoromethylated \(\beta\)-ketoesters 2a and 3a was confirmed by crude \(^{19}\)F-NMR.

[c] The simultaneous addition of TMSCF\(_2\)Br and LiOH into the solution of 1a and ammonium bromide in 1.0 mL toluene.

Evaluating the function of ammonium salt were shown on Table S1 (entries 1-7) and Table S2: (1). When 2.0 equiv of TMSCF\(_2\)Br was used in DCM or toluene, the ammonium salts with bromide counter ion showed higher C/O control than other anions such as Cl\(_-\), I\_-, ClO\(_4\)_-, PF\(_6\)_- and NO\(_3\)_- (Table S1, entries 1-7 and Table S2, entries 2-8); (2). When 3.0 equivalent of TMSCF\(_2\)Br was used in toluene, the halogen-based anions gave similar results with minor difference both in yield and selectivity (Table S2, entries 11-14) and tetrabutylammonium nitrate gave moderate yield (46%); (3). Adding hexadecyltrimethylammonium bromide as additive can shorten the reaction time to 4 hours, but only slightly increase both in the yield and C/O selectivity can be observed (Table S2, entries 1-2, entries 9-10) comparing to omitting the additive. For instance, when 2.0 equiv of TMSCF\(_2\)Br was used, comparing to the absence of additive (66% yield, C/O = 92:8), the desired difluoromethylated product 2a was obtained in 77% yield with high C/O control (C/O = 96:4). Meanwhile, although high yield (90%) with better C/O control (C/O = 98:2) was observed when 3.0 equivalent of TMSCF\(_2\)Br was used, good result both in yield (80%) and selectivity (C/O = 95:5) also can be found when omitting the additive. The results above indicated that the adding of ammonium salt probably prompted the generation of difluorocarbene from TMSCF\(_2\)Br, thereby accelerating the difluoromethylation process However, the exact role of ammonium salts and their bromide counter ion was still unclear.
5. The preparation of difluoromethylated β-ketoesters 2a-u

Methyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2a\(^{1,2,3}\)

![Structure of 2a](image)

The solution of methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1a (19.1 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH\(_3\)(CH\(_2\))\(_3\)(CH\(_3\))NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF\(_2\)Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na\(_2\)SO\(_4\), the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2a (18.5 mg, 77% yield) as colorless oil.

\([\text{Harmo:} 7.78 (d, J = 7.7 \text{ Hz}, 1H), 7.69 (t, J = 7.5 \text{ Hz}, 1H), 7.57 (d, J = 7.7 \text{ Hz}, 1H), 7.42 (t, J = 7.4 \text{ Hz}, 1H), 6.60 (t, J = 55.2 \text{ Hz}, 1H), 3.79 (s, 3H), 3.56 (ABq, J\_AB = 17.6 \text{ Hz}, 2H); \text{[\text{F NMR:} (-126.0 \text{ dd, J = 287.7, 55.1 Hz, 1F), -129.3 \text{ dd, J = 287.8, 55.4 Hz, 1F}.}]]\)

Methyl 2-(difluoromethyl)-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2b\(^{1,2}\)

![Structure of 2b](image)

The solution of methyl 6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1b (20.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH\(_3\)(CH\(_2\))\(_3\)(CH\(_3\))NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF\(_2\)Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na\(_2\)SO\(_4\), the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2b (18.5 mg, 71% yield) as white solid, Mp 65.0-66.1°C.

\([\text{Harmo:} 7.57 (s, 1H), 7.50 (d, J = 8.0 \text{ Hz}, 1H), 7.44 (d, J = 7.9 \text{ Hz}, 1H), 6.58 (t, J = 55.2 \text{ Hz}, 1H), 3.78 (s, 3H), 3.58 (ABq, J\_AB = 17.6 \text{ Hz}, 2H), 2.41 (s, 3H); \text{[\text{F NMR:} (-126.06 \text{ dd, J = 287.7, 55.1 Hz, 1F}, -129.3 \text{ dd, J = 287.8, 55.4 Hz, 1F}.}]]\)

Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2c\(^{1,2}\)

![Structure of 2c](image)

The solution of methyl 6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1c (22.0 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH\(_3\)(CH\(_2\))\(_3\)(CH\(_3\))NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF\(_2\)Br (60.9 mg, 0.3 mmol) was added slowly, and the
reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2c (20.0 mg, 74% yield) as white solid, Mp 76.0-77.9 °C. 1H NMR (300 MHz, CDCl₃) δ 7.45 (d, J = 8.4 Hz, 1H), 7.29-7.23 (m, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.58 (t, J = 55.2 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.55 (ABq, J_AB = 17.3 Hz, 2H); 19F NMR (282 MHz, CDCl₃) δ -126.04 (dd, J = 287.6, 55.1 Hz, 1F), -129.53 (dd, J = 287.6, 55.4 Hz, 1F).

Methyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2d

The solution of methyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1d (25.0 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₁₅(CH₃)₃NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 20:1) to afford 2d (26.0 mg, 85% yield) as white solid, Mp 101.6-103.4 °C. 1H NMR (300 MHz, CDCl₃) δ 7.16 (s, 1H), 6.97 (s, 1H), 6.58 (t, J = 55.3 Hz, 1H), 4.00 (s, 3H), 3.90 (s, 3H), 3.79 (s, 3H), 3.53 (ABq, J_AB = 17.4 Hz, 2H); 19F NMR (282 MHz, CDCl₃) δ -126.19 (dd, J = 286.8, 55.2 Hz, 1F), -129.76 (dd, J = 286.8, 55.5 Hz, 1F).

Methyl 5-chloro-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2e

The solution of methyl 5-chloro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1e (22.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₁₅(CH₃)₃NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 20:1) to afford 2e (17.3 mg, 63% yield) as yellow solid, Mp 86.4-87.5 °C. 1H NMR (300 MHz, CDCl₃) δ 7.71 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 7.41 (d, J = 8.3 Hz, 1H), 6.58 (t, J = 55.1 Hz, 1H), 3.80 (s, 3H), 3.62 (ABq, J_AB = 17.8 Hz, 2H); 19F NMR (282 MHz, CDCl₃) δ -125.98 (dd, J = 288.3, 54.9 Hz, 1F), -129.17 (dd, J = 288.3, 55.3 Hz, 1F).

Methyl 5-bromo-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2f

S5
The solution of methyl 5-bromo-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1f (26.9 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₃(CH₃)NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2f (22.2 mg, 68% yield) as yellow solid, Mp 85.3-86.3 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.75 (s, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 6.57 (t, J = 55.1 Hz, 1H), 3.79 (s, 3H), 3.61 (ABq, J_AB = 17.8, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -125.95 (dd, J = 288.3, 54.9 Hz, 1F), -129.15 (dd, J = 288.3, 55.3 Hz, 1F).

Ethyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2g

The solution of ethyl 6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1g (23.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₃(CH₃)NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2g (23.0 mg, 81% yield) as colorless oil. MS (ESI) calcd for C₁₄H₁₄F₂NaO₄⁺ [(M+Na)⁺]: 307.0758 found 307.0765; ¹H NMR (300 MHz, CDCl₃) δ 7.45 (d, J = 8.4 Hz, 1H), 7.26 (dd, J = 8.4, 2.6 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.58 (t, J = 55.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 3.54 (ABq, J_AB = 17.3, 2H), 1.27 (t, J = 7.1 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -126.18 (dd, J = 287.3, 55.1 Hz, 1F), -129.46 (dd, J = 287.3, 55.5 Hz, 1F); ¹³C NMR (126 MHz, CDCl₃) δ 195.8 (d, J = 6.9 Hz), 166.0 (d, J = 12.2 Hz), 159.8, 147.1, 135.3 (d, J = 3.7 Hz), 127.2, 125.8, 115.5 (dd, J = 247.2, 241.0 Hz), 105.9, 65.4 (dd, J = 23.9, 21.0 Hz), 62.7, 55.7, 29.3, 13.9; IR (neat): 3012, 2944, 1745, 1710, 1594, 1455, 1371, 1259, 1025, 765 cm⁻¹.

isopropyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2h¹²

The solution of isopropyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1h (21.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₃(CH₃)NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate,
and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2h (22.9 mg, 85% yield) as colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.77 (d, J = 7.7 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.4 Hz, 1H), 6.59 (t, J = 55.3 Hz, 1H), 5.19–4.99 (m, 1H), 3.62 (ABq, Jₐb = 17.6, 2H), 1.27 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.3 Hz, 3H); ¹⁹F NMR (282 MHz, CDCl₃) δ -126.35 (ddd, J = 287.2, 55.1, 7.4 Hz, 1F), -129.18 (ddd, J = 287.3, 55.6, 7.3 Hz, 1F).

tert-butyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2i

The solution of tert-butyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1i (23.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₁₅(CH₃)₃NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2i (23.9 mg, 83% yield) as colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 7.7 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 6.53 (t, J = 55.4 Hz, 1H), 3.58 (ABq, Jₐb = 17.5, 2H), 1.45 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) δ -126.63 (dd, J = 286.8, 55.1 Hz, 1F), -128.77 (dd, J = 286.8, 55.8 Hz, 1F).

Benzyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2j

The solution of benzyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1j (26.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₁₅(CH₃)₃NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to afford 2j (24.1 mg, 76% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, J = 7.7 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.38–7.26 (m, 5H), 6.62 (t, J = 55.2 Hz, 1H), 5.22 (d, J = 2.5 Hz, 2H), 3.65 (ABq, Jₐb = 17.6 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) δ -125.86 (dd, J = 287.8, 55.1 Hz, 1F), -129.12 (dd, J = 287.8, 55.4 Hz, 1F).

Allyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2k
The solution of allyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate \(1k\) (21.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), \(\text{CH}_3(\text{CH}_2)_{15}(\text{CH}_3)\)NBr (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF\(_2\)Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 5 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over \(\text{Na}_2\text{SO}_4\), the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 100:1) to give \(2k\) (21.8 mg, 80\% yield) as colorless oil. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.78 (d, \(J = 7.7 \text{ Hz}\), 1H), 7.68 (t, \(J = 7.4 \text{ Hz}\), 1H), 7.56 (d, \(J = 5.52 \text{ Hz}\), 1H), 6.61 (t, \(J = 5.56 \text{ Hz}\), 1H), 5.95–5.73 (m, 1H), 5.37–5.15 (m, 2H), 4.68 (d, \(J = 5.6 \text{ Hz}\), 2H), 3.65 (ABq, \(J_{AB} = 17.6, 2\text{H}\)); \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -125.95 (dd, \(J = 287.7, 55.1 \text{ Hz}\), 1F), -129.25 (dd, \(J = 287.8, 55.4 \text{ Hz}\), 1F).

Allyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate \(2l\)

The solution of allyl 5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate \(1l\) (27.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), \(\text{CH}_3(\text{CH}_2)_{15}(\text{CH}_3)\)NBr (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF\(_2\)Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over \(\text{Na}_2\text{SO}_4\), the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give \(2l\) (28.9 mg, 88\% yield) as colorless oil. MS (ESI-TOF) calcd for C\(_{16}\)H\(_{16}\)F\(_2\)NaO\(_5\)^+ [(M+Na)^+]: 349.0863 found 349.0870. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.15 (s, 1H), 6.96 (s, 1H), 6.59 (t, \(J = 55.3 \text{ Hz}\), 1H), 5.96–5.74 (m, 1H), 5.40–5.16 (m, 2H), 4.68 (dt, \(J = 5.5, 1.3 \text{ Hz}\), 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.53 (ABq, \(J_{AB} = 17.4, 2\text{H}\)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 193.9 (d, \(J = 7.0 \text{ Hz}\)), 166.0 (d, \(J = 12.3 \text{ Hz}\)), 156.7, 150.0, 149.9, 130.9, 126.6 (d, \(J = 3.8 \text{ Hz}\)), 118.9, 115.5 (d, \(J = 246.9, 241.1 \text{ Hz}\)), 107.2,105.1, 66.7, 65.1 (dd, \(J = 24.2, 20.6 \text{ Hz}\)), 56.5, 56.2, 29.59 (d, \(J = 2.6 \text{ Hz}\)). IR (neat): 3012, 2944, 2844, 1745, 1710, 1594, 1445, 1371, 1259, 1232, 1120, 1085, 765 cm\(^{-1}\).

Methyl 2-(difluoromethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate \(2m\)

The solution of methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate \(1m\) (20.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), \(\text{CH}_3(\text{CH}_2)_{15}(\text{CH}_3)\)NBr (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF\(_2\)Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over \(\text{Na}_2\text{SO}_4\), the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 100:1) to give \(2m\) (21.8 mg, 80\% yield) as colorless oil. MS (ESI-TOF) calcd for C\(_{16}\)H\(_{16}\)F\(_2\)NaO\(_5\)^+ [(M+Na)^+]: 349.0863 found 349.0870. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.15 (s, 1H), 6.96 (s, 1H), 6.59 (t, \(J = 55.3 \text{ Hz}\), 1H), 5.96–5.74 (m, 1H), 5.40–5.16 (m, 2H), 4.68 (dt, \(J = 5.5, 1.3 \text{ Hz}\), 2H), 4.00 (s, 3H), 3.90 (s, 3H), 3.53 (ABq, \(J_{AB} = 17.4, 2\text{H}\)); \(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -125.95 (dd, \(J = 287.7, 55.1 \text{ Hz}\), 1F), -125.88 (dd, \(J = 287.8, 55.4 \text{ Hz}\), 1F).
acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2m (21.6 mg, 83% yield) as colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, J = 7.9 Hz, 1H), 7.53 (td, J = 7.5, 1.3 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 6.60 (t, J = 55.3 Hz, 1H), 3.75 (s, 3H), 3.32 (ddd, J = 16.7, 11.5, 5.0 Hz, 1H), 3.07–2.98 (m, 1H), 2.71–2.62 (m, 1H), 2.46 (ddd, J = 14.0, 11.5, 5.2 Hz, 1H); ¹³F NMR (282 MHz, CDCl₃) δ -127.33 (dd, J = 283.3, 55.1 Hz, 1F), -131.80 (dd, J = 283.3, 55.5 Hz, 1F).

Methyl 2-(difluoromethyl)-5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2n

The solution of methyl 5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 1n (23.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₁₅(CH₃)₃NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2n (22.9 mg, 81% yield) as white solid, 89.5–91.2 °C. MS (ESI) calcd for C₁₅H₁₆F₂NaO₃: [(M+Na)⁺]: 305.0960 found 305.0966.

¹H NMR (300 MHz, CDCl₃) δ 7.72 (s, 1H), 7.23 (s, 1H), 6.59 (t, J = 55.3 Hz, 1H), 3.72 (s, 3H), 3.14–2.87 (m, 2H), 2.74–2.62 (m, 1H), 2.47–2.34 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 190.6 (d, J = 6.1 Hz), 166.6 (d, J = 8.4 Hz), 138.7, 136.4, 136.4, 130.8 (d, J = 2.4 Hz), 60.3 (t, J = 21.4 Hz), 53.2, 22.4 (t, J = 3.7 Hz), 21.9, 20.8, 19.2; IR (neat): 2965, 2929, 1745, 1685, 1602, 1467, 1371, 1236, 1072, 738 cm⁻¹.

Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2o

The solution of methyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 1o (23.4 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH₃(CH₂)₁₅(CH₃)₃NBr (10 mol%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF₂Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na₂SO₄, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2o (26.2 mg, 91% yield) as white solid, Mp 76.1–77.2 °C. MS (ESI) calcd for C₁₄H₁₄F₂NaO₄⁺ [(M+Na)⁺]: 307.0758 found 307.0764. ¹H NMR (300 MHz, CDCl₃) δ 8.01 (d, J = 8.8 Hz, 1H), 6.84 (dd, J = 8.8, 2.4 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.61 (t, J = 55.4 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H), 3.31 (ddd, J = 16.7, 11.5, 5.0 Hz, 1H), 3.05–2.91 (m, 1H), 2.68–2.56 (m, 1H), 2.44 (ddd, J = 13.9, 11.5, 5.1 Hz).
\[ \text{Methyl 6-(difluoromethyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate 2p} \]

The solution of methyl 5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate 1p (21.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH$_3$(CH$_2$)$_3$(CH$_3$)NBr (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF$_2$Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate and then washed with water and brine. After drying over Na$_2$SO$_4$, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2p (21.9 mg, 82% yield) as colorless oil. MS (ESI) calcd for C$_{19}$H$_{24}$F$_2$NaO$_3$\+: [M+Na]$^+$: 291.0803 found 291.0810. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.46 (dd, $J = 7.6, 1.1$ Hz, 1H), 7.40 (td, $J = 7.5, 1.5$ Hz, 1H), 7.32–7.24 (m, 1H), 7.15 (d, $J = 7.5$ Hz, 1H), 6.40 (t, $J = 55.2$ Hz, 1H), 3.66 (s, 3H), 3.08–2.81 (m, 2H), 2.55–2.38 (m, 1H), 2.28–2.04 (m, 2H), 2.04–1.84 (m, 1H); $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -126.20 (dd, $J = 266.9, 41.1$ Hz, 1F), -127.35 (dd, $J = 267.0, 41.3$ Hz, 1F); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 200.2 (d, $J = 3.9$ Hz), 167.3 (dd, $J = 6.1, 2.1$ Hz), 139.1, 138.5, 132.1, 129.3, 129.2, 126.7, 115.9 (t, $J = 248.9$ Hz), 65.6 (t, $J = 20.0$ Hz), 53.1, 32.7, 24.72 (t, $J = 3.4$ Hz), 23.0; IR (neat): 3008, 2952, 2877, 1749, 1625, 1598, 1442, 1243, 1149, 1120, 997 cm$^{-1}$.

\[ \text{Methyl 2-benzoyl-3,3-difluoro-2-methylpropanoate 2q} \]

The solution of methyl 2-methyl-3-oxo-3-phenylpropanoate 1q (19.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH$_3$(CH$_2$)$_3$(CH$_3$)NBr (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF$_2$Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate and then washed with water and brine. After drying over Na$_2$SO$_4$, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2q (17.1 mg, 70% yield) as colorless oil. MS (ESI) calcd for C$_{19}$H$_{24}$F$_2$NaO$_3$\+: [M+Na]$^+$: 265.0647 found 265.0648. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.91–7.75 (m, 2H), 7.64–7.53 (m, 1H), 7.50–7.40 (m, 2H), 6.52 (t, $J = 55.1$ Hz, 1H), 3.76 (s, 3H), 1.71 (s, 3H); $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -126.82 (dd, $J = 282.0, 54.8$ Hz, 1F), -129.81 (dd, $J = 282.0, 55.5$ Hz, 1F); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 193.2 (d, $J = 6.1$ Hz), 168.8 (dd, $J = 6.6, 1.4$ Hz), 134.6 (d, $J = 1.9$ Hz), 133.6, 128.8, 128.6, 115.2 (dd, $J = 250.3, 243.7$ Hz), 61.7 (t, $J = 21.1$ Hz), 53.5, 13.9 (dd, $J = 5.5, 3.3$ Hz); IR (neat): 3015, 2948, 1745, 1698, 1583, 1459, 1247, 1081, 997, 694.
Benzyl 2-benzoyl-3,3-difluoro-2-methylpropanoate 2r

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\begin{array}{c}
\text{O} \\
\text{CO}_2\text{Bn} \\
\text{Me} \\
\text{CF}_2\text{H}
\end{array}
\]

The solution of benzyl 2-methyl-3-oxo-3-phenylpropanoate 1r (26.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), \(\text{CH}_3(\text{CH}_2)_3(\text{CH}_3)\text{NBr}\) (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMS\text{CF}_2\text{Br} (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na\text{SO}_4, the solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2r (23.8 mg, 75\% yield) as colorless oil. MS (ESI) calcd for \(\text{C}_{18}\text{H}_{16}\text{F}_{2}\text{NaO}_3\) [(M+Na\(^+\)]: 341.0960 found 265.0963.

\(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.73 (d, \(J = 7.6\) Hz, 2H), 7.52 (t, \(J = 7.4\) Hz, 1H), 7.33 (t, \(J = 7.9\) Hz, 2H), 7.29–7.21 (m, 3H), 7.18–7.11 (m, 2H), 6.51 (t, \(J = 55.1\) Hz, 1H), 5.18 (s, 2H), 1.70 (s, 3H);

\(^19\text{F}\) NMR (282 MHz, CDCl\(_3\)) \(\delta\) -126.67 (dd, \(J = 282.0, 54.8\) Hz, 1F), -129.39 (dd, \(J = 282.0, 55.4\) Hz, 1F);

\(^{13}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 193.2 (d, \(J = 6.0\) Hz), 168.1 (dd, \(J = 6.4, 1.3\) Hz), 134.5 (d, \(J = 1.7\) Hz), 134.2, 133.5, 128.7, 128.60, 128.57, 128.5, 128.4, 115.2 (dd, \(J = 250.4, 244.0\) Hz), 68.2, 61.8 (t, \(J = 21.0\) Hz), 14.1 (dd, \(J = 5.5, 3.3\) Hz).

\(^{138}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 200.1 (d, \(J = 5.4\) Hz), 167.2 (dd, \(J = 7.6, 2.2\) Hz), 134.5, 128.6, 128.7, 128.2, 115.0 (dd, \(J = 246.6, 245.7\) Hz), 67.9, 63.8 (t, \(J = 21.4\) Hz), 26.9 (t, \(J = 1.6\) Hz), 12.4 (t, \(J = 4.1\) Hz).

IR (neat): 3035, 2944, 1749, 1685, 1587, 1494, 1452, 1388, 1251, 1085, 985, 746, 694 cm\(^{-1}\).

Benzyl 2-(difluoromethyl)-2-methyl-3-oxobutanoate 2s

\[
\begin{array}{c}
\text{O} \\
\text{CF}_2\text{H} \\
\text{Me} \\
\text{O}
\end{array}
\]

The solution of benzyl 2-methyl-3-oxobutanoate 1s (20.6 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), \(\text{CH}_3(\text{CH}_2)_3(\text{CH}_3)\text{NBr}\) (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMS\text{CF}_2\text{Br} (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na\text{SO}_4, the solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2s (15.5 mg, 52\% yield) as colorless oil. MS (ESI) calcd for \(\text{C}_{13}\text{H}_{14}\text{F}_{2}\text{NaO}_3\) [(M+Na\(^+\)]: 279.0809 found 279.0815.

\(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.41–7.28 (m, 5H), 6.37 (t, \(J = 55.1\) Hz, 1H), 5.22 (s, 2H), 2.16 (s, 3H), 1.54 (s, 3H); \(^{19}\text{F}\) NMR (282 MHz, CDCl\(_3\)) \(\delta\) -126.67 (dd, \(J = 282.0, 54.8\) Hz, 1F), -129.39 (dd, \(J = 282.0, 55.4\) Hz, 1F); \(^{13}\text{C}\) NMR (126 MHz, CDCl\(_3\)) \(\delta\) 200.1 (d, \(J = 5.4\) Hz), 167.2 (dd, \(J = 7.6, 2.2\) Hz), 134.5, 128.6, 128.7, 128.2, 115.0 (dd, \(J = 246.6, 245.7\) Hz), 67.9, 63.8 (t, \(J = 21.4\) Hz), 26.9 (t, \(J = 1.6\) Hz), 12.4 (t, \(J = 4.1\) Hz). IR (neat): 3035, 2944, 1749, 1685, 1587, 1494, 1452, 1388, 1251, 1085, 985, 746, 694 cm\(^{-1}\).

Ethyl 2-(difluoromethyl)-2-methyl-3-oxohexanoate 2t

\[
\begin{array}{c}
\text{O} \\
\text{CF}_2\text{H} \\
\text{Me} \\
\text{O}
\end{array}
\]

The solution of ethyl 2-methyl-3-oxohexanoate 1t (17.2 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), \(\text{CH}_3(\text{CH}_2)_3(\text{CH}_3)\text{NBr}\) (10 mol\%, 3.7 mg) in 1.0 mL dry toluene was stirred at room temperature for 10
min. Then TMSCF$_2$Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 6 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na$_2$SO$_4$, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2t (16.8 mg, 74% yield) as colorless oil. MS (ESI) calcd for C$_{10}$H$_{16}$F$_2$NaO$_3$: 245.0960 found 245.0970. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.38 (t, $J$ = 55.2 Hz, 1H), 4.25 (q, $J$ = 7.1 Hz, 2H), 2.60–2.31 (m, 2H), 1.66–1.55 (m, 2H), 1.52 (s, 3H), 1.28 (t, $J$ = 7.1 Hz, 3H), 0.90 (t, $J$ = 7.4 Hz, 3H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -126.86 (dd, $J$ = 284.9, 55.2 Hz, 1F), -129.83 (dd, $J$ = 284.8, 55.2 Hz, 1F); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.5 (d, $J$ = 5.3 Hz), 167.5 (dd, $J$ = 7.9, 1.9 Hz), 115.2 (dd, $J$ = 246.3, 245.1 Hz), 63.6 (t, $J$ = 21.2 Hz), 62.3, 40.8, 16.7, 13.9, 13.4, 12.1 (t, $J$ = 4.1 Hz). IR (neat): 2962, 2919, 2854, 1727, 1263, 1087 cm$^{-1}$.

Benzyl 1-(difluoromethyl)-2-oxocyclopentane-1-carboxylate 2u

The solution of benzyl 2-oxocyclopentane-1-carboxylate 1u (21.8 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol), CH$_3$CH$_2$Br (0.3 mol%), 3.7 mg in 1.0 mL dry toluene was stirred at room temperature for 10 min. Then TMSCF$_2$Br (60.9 mg, 0.3 mmol) was added slowly, and the reaction mixture was stirred for 4 h at the same temperature. The reaction mixture was diluted with ethyl acetate, and then washed with water and brine. After drying over Na$_2$SO$_4$, the solvent was removed under reduced pressure, and the residue was subject to chromatography on silica gel (hexane/ethyl acetate = 50:1) to give 2r (7.6 mg, 28% yield) as colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.43–7.28 (m, 5H), 6.37 (t, $J$ = 55.4 Hz, 1H), 5.20 (s, 2H), 2.70–2.27 (m, 4H), 2.20–1.83 (m, 2H); $^{19}$F NMR (282 MHz, CDCl$_3$) δ -126.55 (dd, $J$ = 288.2, 55.1 Hz, 1F), -128.00 (dd, $J$ = 288.3, 55.5 Hz, 1F).

Reference:

6. Copies of $^1$H, $^{19}$F and $^{13}$C NMR spectra of unknown compounds (2g, 2l, 2n-t)

Ethyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2g
Allyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2l
Methyl 2-(difluoromethyl)-5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2n
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2o
Methyl 6-(difluoromethyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate 2p
Methyl 2-benzoyl-3,3-difluoro-2-methylpropanoate 2q
Benzyl 2-benzoyl-3,3-difluoro-2-methylpropanoate 2r
Benzyl 2-(difluoromethyl)-2-methyl-3-oxobutanoate 2s
Ethyl 2-(difluoromethyl)-2-methyl-3-oxohexanoate 2t
7. Copies of $^1$H $^{19}$F NMR spectra of known compounds (2a-f, 2h-k, 2m, 2u)

Methyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2a
Methyl 2-(difluoromethyl)-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2b
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2c
Methyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2d
Methyl 5-chloro-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2e

\[
\text{Chemical Structure Image}
\]
Methyl 5-bromo-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2f
isopropyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2h
tert-butyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2i
Benzyl 2-(difluoromethyl)-1-o xo-2,3-dihydro-1H-indene-2-carboxylate 2j
Allyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2k
Methyl 2-(difluoromethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2m
Benzyl 1-(difluoromethyl)-2-oxocyclopentane-1-carboxylate 2u
8. Copies of $^{19}$F NMR spectra of crude mixtures for determining the C/O ratios

Methyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2a

Methyl 2-(difluoromethyl)-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2b
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2c

Methyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2d
Methyl 5-chloro-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2e

Methyl 5-bromo-2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2f
Ethyl 2-(difluoromethyl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2g

isopropyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2h
tert-butyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2i

Benzyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2j
Allyl 2-(difluoromethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2k

Allyl 2-(difluoromethyl)-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 2l
Methyl 2-(difluoromethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2m

Methyl 2-(difluoromethyl)-5,7-dimethyl-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2n
Methyl 2-(difluoromethyl)-6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate 2o

Methyl 6-(difluoromethyl)-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate 2p
Methyl 2-benzoyl-3,3-difluoro-2-methylpropanoate $2q$

![Chemical Structure Image]

Benzyl 2-benzoyl-3,3-difluoro-2-methylpropanoate $2r$

![Chemical Structure Image]
Benzyl 2-(difluoromethyl)-2-methyl-3-oxobutanoate 2s

Ethyl 2-(difluoromethyl)-2-methyl-3-oxohexanoate 2t
Benzyl 1-(difluoromethyl)-2-oxocyclopentane-1-carboxylate 2u
9. $^{19}$F-NMR study for encapsulation of free Lithium.

Methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate 1a (19.1 mg, 0.10 mol), LiOH (7.2 mg, 0.3 mmol) was added to one over-dried NMR tube sealed by a rubber septum with a N$_2$ balloon. After 1.0 mL CDCl$_3$ and 8.2 $\mu$L PhCF$_3$ (calculated 0.1 mmol for CF$_2$H group) and liquid 12-crown-4 (95 $\mu$L, 0.6 mmol) were added sequentially, the solution was strongly shaken for several minutes. Subsequently, TMSCF$_2$Br (60.9 mg, 0.3 mmol) was added dropwise accompanying with strongly shaking the NMR tube. Finally, rubber septum was removed very quickly under N$_2$ atmosphere and the tube was soon sealed by plastic cap. Then the cap was protected and wrapped by parafilm M. After strongly shaking for 4 hours, the HCF$_2$Br was detected in 59% yield and neither 2a nor 3a can be observed. Meanwhile, followed by the similar procedure without the addition of 12-crown-4 ether, $^{19}$F-NMR study of difluoromethylation of 1a was also investigated. After 48 hours shaking at room temperature, the unexpected protonated HCF$_2$Br was obtained in 5% yield and the desired carbon-difluoromethyalted product 2a was obtained in 80% yields with the C/O isomer ratio was determined as 95:5.