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# A facile synthetic route to 2-trifluoromethyl-substituted polyfunctionalized chromenes and chromones

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ABSTRACT

A method for the preparation of methyl 4-hydroxy-2-(trifluoromethyl)-4*H*-chromenes-3-carboxylate derivatives **3a–j** from readily available trifluoromethylated building block methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1** was described. Treatment of **3a–j** with Sarrett reagent in $CH_2Cl_2$ generated methyl 4-oxo-2-(trifluoromethyl)-chromene-3-carboxylate derivatives **4a–h** with moderate to good yields, which can be converted to 2-trifluoromethyl-substituted multifunctional benzoxepins through cyclopropanation and Lewis acid-catalyzed ring opening.



## 1. Introduction

2-Substituted 4*H*-chromenes and chromones are one of the main natural product scaffolds [1] displaying a broad range of biological and pharmacological activities [2], such as antiviral [3], antiallergic [4], anti-flammatory [5], and antifungal agents [6]. Not surprisingly, a variety of 4*H*-chromene and chromone analogs have been synthesized and evaluated as potential therapeutic agents [7]. On the other hand, although introduction of fluorine atom into organic compounds has been known as one of the major strategies for the enhancement or modification of their original biological activities [8], there are few reports on the preparation of perfluoroalkylated 4*H*-chromenes and chromones. Coppola reported that condensation of ethyl trifluoroacetoacetate with o-fluorobenzoyl chloride derivatives using sodium hydride as a base afforded the trifluoromethylchromones [9]. Laurent reported the synthesis of 4*H*-chromen-4-ones via the cyclization of substituted 3-aryloxy-3-perfluoroalkylpropenoic acids in high yield [10]. More recently, Cao reported an efficient and highly regio-selective synthesis of 4*H*-chromenes through $Et_3N$ mediated reactions of salicylaldyde derivatives with methyl 2-perfluoroalkynoates at room temperature [11]. Herein, we wish to report an alternative approach for the synthesis of 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene and 4-oxo-2-(trifluoromethyl)-chromene derivatives via condensation of salicylaldehyde derivatives with an easily available building block methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1** [12].

## 2. Results and discussion

We initially assessed the reaction conditions by reacting salicylaldehyde **2** with methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1**, a $CF_3$-containing building block developed in our group previously [12], using various bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), $K_2CO_3$, NaH, $Et_3N$ in a variety of solvents ($CH_2Cl_2$, THF, toluene, $CH_3CN$, DMF, DMSO) at room temperature. It was found that the reaction in the presence of 6.0 equivalents of $Et_3N$ in DMSO gave the best results. Reducing the amount of $Et_3N$ from 6.0 equivalents to 2.0 equivalents resulted in lower yields. Several other salicylaldehyde derivatives also reacted with (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1** under the optimized conditions to give the corresponding 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene in good to excellent yields. These results were summarized in Table 1. The structures of the products were determined by comparing the $^1H$ NMR spectra of the products with those reported previously [11]. Reactions of salicylaldehyde derivatives with halogen or an electron-donating group at 3 or 5-position occurred in excellent yields (Table 1, entries 1–6, 8 and 10). Reactions of salicylaldehyde derivatives containing an electron-withdrawing

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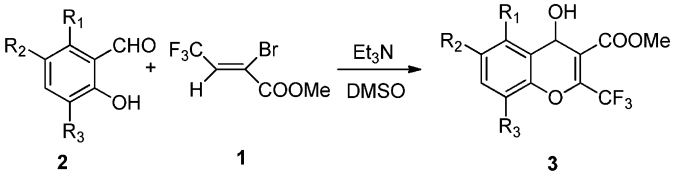
**Table 1**
$Et_3N$ mediated reaction of salicylaldehydes **2** with building block (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1**[a].




**2** **1** **3**

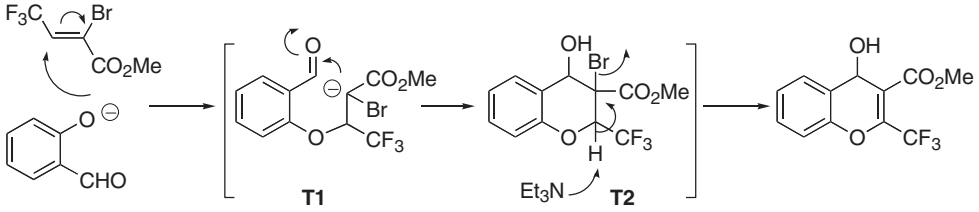
| Entry | $R_1$ | $R_2$ | $R_3$ | Time (h) | Product | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | H | H | H | 48 | **3a** | 85 |
| 2 | H | OMe | H | 72 | **3b** | 94 |
| 3 | H | F | H | 48 | **3c** | 90 |
| 4 | H | Cl | H | 48 | **3d** | 91 |
| 5 | H | Br | H | 48 | **3e** | 98 |
| 6 | H | $NO_2$ | H | 48 | **3f** | 85 |
| 7 | H | H | OMe | 72 | **3g** | 89 |
| 8 | H | Me | H | 48 | **3h** | 87 |
| 9 | H | $^t$Bu | $^t$Bu | 48 | **3i** | 83 |
| 10 | $(CH_2)_4$ | | H | 48 | **3j** | 84 |

[a] Reactions conducted with 0.5 mmol of salicylaldehyde, 0.5 mmol methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1**, 6.0 equiv of $Et_3N$ in DMSO (2.0 mL) at room temperature.
[b] Isolated yield.

nitro group, however, occurred in slightly lower yields due to the low nucleophilicity of the substrate (Table 1, entry 6). Likewise, sterically hindered *tert*-butyl group substituted salicylaldehyde also reacted to give the corresponding 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene in 83% yield (Table 1, entry 7).

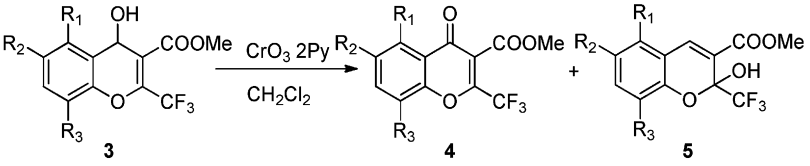
On the basis of our previous reports, we proposed a working mechanism as shown in Scheme 1. Presumably, the annulation reaction proceeds by a tandem oxa-Michael-aldol process. In the presence of $Et_3N$, salicylaldehyde first nucleophilically attacks β-position of methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate to form enolate **T1**, followed by aldol reaction of **T1** with the aldehyde to give intermediate **T2**. Finally, elimination of HBr under excessive $Et_3N$ leads to the corresponding 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene derivatives. An alternative mechanism through methyl 4,4,4-trifluorobutynoate is unlikely since reaction of methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate with $Et_3N$ in DMSO at room temperature did not form methyl 4,4,4-trifluorobutynoate as determined by $^{19}$F NMR spectroscopy.

We next focused on converting the 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene derivatives to 2-(trifluoromethyl)-chromones. We firstly attempted to oxidize 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene derivative **3a** by using PCC (pyridinium chlorochromate) as oxidant. However, the reaction was complicated even at −78 °C as determined by $^{19}$F NMR analysis of the crude solution, possibly due to the strong acidity of PCC. We then tried to use a neutral oxidant Sarrett reagent ($CrO_3$·2Py). To our delight, the methyl 2-(trifluoromethyl)-4-oxo-chromene-3-carboxylate **4a** was isolated with 76% yield, along with a rearranged product **5a** in 20% yield. Under similar conditions, other substrates (**3b**–**h**) were readily oxidized to give the corresponding 2-(trifluoromethyl)-chromones in good to excellent yield (Table 2, entries 1–8). When substrates with hindered substituted groups such as **3i** and **3j** were subjected to the reaction conditions, however, only the rearranged products were isolated in quantitative yields (Table 2, entries 9 and 10). Alternatively, 2-trifluoromethyl-2-hydroxychromenes can be obtained quantita-




**Scheme 1.** Proposed mechanism for annulation reaction of salicylaldehyde with building block (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1**.

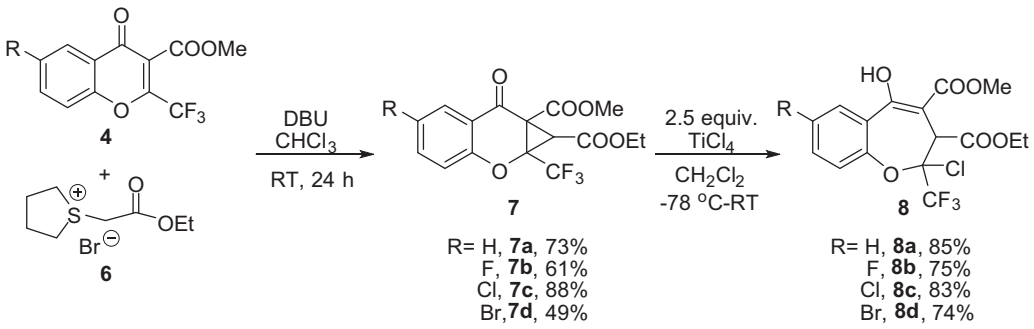
**Table 2**
Oxidation of 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene[a].




**3** **4** **5**

| Entry | Product | $R_1$ | $R_2$ | $R_3$ | **4** yield (%)[b] | **5** yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | H | H | 76 | 20 |
| 2 | **3b** | H | OMe | H | 56 | 34 |
| 3 | **3c** | H | F | H | 91 | 8 |
| 4 | **3d** | H | Cl | H | 85 | 14 |
| 5 | **3e** | H | Br | H | 79 | 10 |
| 6 | **3f** | H | $NO_2$ | H | 75 | 15 |
| 7 | **3g** | H | H | OMe | 65 | 28 |
| 8 | **3h** | H | Me | H | 51 | 43 |
| 9 | **3i** | H | $^t$Bu | $^t$Bu | – | 99[c] |
| 10 | **3j** | $(CH)_4$ | | H | – | 99[c] |

[a] Reactions conducted with 0.3 mmol of 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene, 1.5 mmol of $CrO_3$·2Py in $CH_2Cl_2$ (5.0 mL) at room temperature.
[b] Isolated yield.
[c] Determined by $^{19}$F NMR.




**Scheme 2.** Application in the synthesis of 2-trifluoromethylated benzoxepins.

tively by mixing 2-trifluoromethyl-4-hydroxychromene and 1.0 M HCl in DMSO at room temperature for 5 h.

To demonstrate the utility of the method for the preparation of 2-(trifluoromethyl)-chromones, we next investigated their applications in the synthesis of trifluoromethyl-containing benzoxepins. Treatment of 2-(trifluoromethyl)-chromones with sulfur ylides with DBU as base in chloroform afforded the desired cyclopropanation products **7a–d** in good yields. Further ring-opening reactions of compounds **7a–d** in the presence of Lewis acid titanium tetrachloride gave the desired 2-trifluoromethylated benzoxepins in good yields (Scheme 2). Benzoxepin derivatives are a class of important compounds which exhibit interesting antimicrobial and antifungal activities [13–15].

## 3. Conclusions

We have developed an efficient $Et_3N$-mediated reaction of salicylaldehyde with methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate that provides easy access to 4-hydroxy-2-(trifluoromethyl)-4*H*-chromene. We also discovered that 4-hydroxy-2-(trifluoromethyl)-4*H*-chromenes were readily oxidized to give the corresponding polyfunctional 2-(trifluoromethyl)-chromones under mild conditions. Furthermore, through cyclopropanation and ring-opening steps, 2-trifluoromethyl-substituted multifunctional benzoxepins were synthesized for the first time. The biological activities of these trifluoromethyl-substituted heterocycle compounds are currently under investigation in our laboratory.

## 4. Experimental

### 4.1. General information

Commercially obtained reagents were used without further purification. All solvents were purified by standard methods. $^1H$, $^{13}C$, $^{19}F$ NMR spectra were recorded on 300 MHz, 100 MHz, 282 MHz spectrometer. $^1H$ NMR and $^{13}C$ NMR chemical shifts were determined relative to internal standard TMS at $\delta$ 0.0 ppm, $^{19}F$ NMR chemical shifts were determined relative to $CFCl_3$ as internal standard. Infrared spectra were recorded by Shimadzu IR-440. Melting points of all solid products are uncorrected. Mass spectra were recorded on a mass spectrometer. All reactions were monitored by TLC or $^{19}F$ NMR. Flash column chromatograph was carried out using 300–400 mesh silica gel at medium pressure.

### 4.2. Typical procedure for synthesis of 2-(trifluoromethyl)-4H-chromenes

Salicyaldehyde (**2a**, 61 mg, 0.5 mmol), methyl (Z)-2-bromo-4,4,4-trifluoro-2-butenoate **1** (116 mg, 0.5 mmol), and $NEt_3$ (0.41 mL, 3.0 mmol) were added to dry DMSO (2.0 mL) in a Schlenk tube under Ar. The solution was stirred until the reaction was completed as determined by $^{19}F$ NMR spectra of the crude solution. The reaction mixture was then diluted with $CH_2Cl_2$ (3× 30 mL). The organic layer were combined and washed with water and brine, then dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: AcOEt/petroleum ether, 1:7) to give the corresponding product **3a**.

#### 4.2.1. Methyl 2-(trifluoromethyl)-4-hydroxy-4H-chromenes-3-carboxylate 3a

White solid; m.p.: 82–83 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.26 (d, $J$ = 6.0 Hz, 1H), 3.88 (s, 3H), 5.66 (d, $J$ = 6.0 Hz, 1H), 7.15 (d, $J$ = 8.1 Hz, 1H), 7.23 (dd, $J$ = 7.5 Hz, 1H), 7.35 (dd, $J$ = 7.2 Hz, 1H), 7.50 (d, $J$ = 7.5 Hz, 1H,); $^{19}F$ NMR (282 MHz) $\delta$ −67.0 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 53.0, 62.0, 111.6, 116.9, 117.8 (q, $J$ = 275.0 Hz), 120.8, 126.0, 129.7, 130.2, 143.1 (q, $J$ = 38.2 Hz), 148.7, 166.2; IR (KBr, $cm^{-1}$): $\nu$ = 3412, 1722, 1683, 1586, 1486, 1321; MS-EI ($m/z$, %) 274 ($M^+$, 11), 257 ($M^+$ −17, 25), 243 ($M^+$ −31, 14), 215 ($M^+$ −59, 45), 173 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_9F_3O_4$: 274.0453; Found: 274.0451.

#### 4.2.2. Methyl 4-hydroxy-6-methoxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate 3b

White solid; m.p.: 101–102 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.98 (d, $J$ = 6.3 Hz, 1H), 3.83 (s, 3H), 3.90 (s, 3H), 5.70 (d, $J$ = 6.3 Hz, 1H), 6.96 (m, 2H), 7.26 (d, $J$ = 9 Hz, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −67.1 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 52.7, 55.6, 62.2, 110.1, 113.1, 117.2, 117.6 (q, $J$ = 275.0 Hz), 117.8, 121.1, 142.5, 143.2 (q, $J$ = 38.2 Hz), 157.1, 166.0; IR (KBr, $cm^{-1}$): $\nu$ = 3477, 1707, 1654, 1505, 1440, 1320; EI-MS ($m/z$, %) 304 ($M^+$, 9.0), 287 ($M^+$ −17, 23), 273 ($M^+$ −31, 4.4), 203 ($M^+$ −101, 100); HRMS-EI calcd for $C_{13}H_{11}F_3O_5$: 304.0559; Found: 304.0554.

#### 4.2.3. Methyl 6-fluoro-4-hydroxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate 3c

White solid; m.p.: 91–92 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.09 (d, $J$ = 5.7 Hz, 1H), 3.90 (s, 3H), 5.68 (d, $J$ = 5.7 Hz, 1H), 7.10–7.24 (m, 3H); $^{19}F$ NMR (282 MHz) $\delta$ −116.0 (dd, $J$ = 8.4 Hz, 14.7 Hz, 1 F), −67.3 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 52.8, 61.6, 110.5, 114.9 (d, $J$ = 23.9 Hz), 117.2 (d, $J$ = 23.9 Hz), 118.2 (d, $J$ = 8.2 Hz), 120.2 (q, $J$ = 275.0 Hz), 122.0 (d, $J$ = 8.2 Hz), 142.3 (q, $J$ = 38.0 Hz), 144.4 (d, $J$ = 3.1 Hz), 158.4 (d, $J$ = 244.5 Hz), 165.8; IR (KBr, $cm^{-1}$): $\nu$ = 3418, 1726, 1599, 1490, 1314; MS-EI ($m/z$, %) 292 ($M^+$, 1.1), 261 ($M^+$ −31, 3.9), 191 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_8F_4O_4$: 292.0359; Found: 292.0361.

#### 4.2.4. Methyl 6-chloro-4-hydroxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate 3d

White solid; m.p.: 123–124 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.12 (d, $J$ = 6.3 Hz, 1H), 3.91 (s, 3H), 5.67 (d, $J$ = 6.3 Hz, 1H), 7.13 (d, $J$ = 9.0 Hz, 1H), 7.34 (d, $J$ = 2.4 Hz, 1H), 7.52 (d, $J$ = 2.4 Hz, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −67.2 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 53.2, 61.7, 111.4, 117.7 (q, $J$ = 275.0 Hz), 118.5, 122.2, 129.3, 130.5, 131.0,

143.1 (q, $J$ = 38.2 Hz), 147.2, 165.9; IR (KBr, $cm^{-1}$): $\nu$ = 3507, 1723, 1587, 1484, 1319; MS-EI ($m/z$, %) 308 ($M^+$, 17), 291 ($M^+$ −17, 25), 277 ($M^+$ −31, 23), 213 ($M^+$ −95, 58), 75 ($M^+$ −233, 100); HRMS-EI calcd for $C_{12}H_8ClF_3O_4$: 308.0063; Found: 308.0054.

#### 4.2.5. Methyl 6-bromo-4-hydroxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate **3e**

White solid; m.p.: 121–122 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.10 (d, $J$ = 5.7 Hz, 1H), 3.91 (s, 3H), 5.66 (d, $J$ = 5.4 Hz, 1H), 7.07 (d, $J$ = 8.7 Hz, 1H), 7.48 (dd, $J$ = 2.4 Hz, 9 Hz, 1H), 7.67 (d, $J$ = 2.7 Hz, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −67.2 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 53.2, 61.6, 111.6, 117.7 (q, $J$ = 275.0 Hz), 118.4, 118.7, 122.6, 132.3, 133.3, 143.0 (q, $J$ = 38.8 Hz), 147.7, 165.9; IR (KBr, $cm^{-1}$): $\nu$ = 3504, 1724, 1679, 1581, 1481, 1318; MS-EI ($m/z$, %): 352 ($M^+$, 33), 354 ($M^+$ +2, 34), 335 ($M^+$ −17, 47), 321 ($M^+$ −31, 89), 293 ($M^+$ −59, 69), 253 ($M^+$ −99, 100); HRMS-EI calcd for $C_{12}H_8BrF_3O_4$: 351.9558; Found: 351.9563.

#### 4.2.6. Methyl 4-hydroxy-6-nitro-2-(trifluoromethyl)-4H-chromene-3-carboxylate **3f**

White solid; m.p.: 125–126 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.50 (s, 1H), 3.93 (s, 3H), 5.78 (s, 1H), 7.34 (d, $J$ = 9.0 Hz, 1H), 8.27 (dd, $J$ = 3.0 Hz, 9.0 Hz, 1H), 8.50 (d, $J$ = 2.7 Hz, 1H); $^{19}F$ NMR(282 MHz) $\delta$ −67.2 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 53.2, 61.2, 112.0, 117.2 (q, $J$ = 275.0 Hz), 118.0, 121.5, 125.4, 126.0, 142.5 (q, $J$ = 38.8 Hz), 145.0, 152.2, 165.1; IR (KBr, $cm^{-1}$): $\nu$ = 3436, 1729, 1594, 1554, 1485, 1313; MS-EI ($m/z$, %) 319 ($M^+$, 2.5), 302 ($M^+$ −17, 16), 288 ($M^+$ −31, 8.6), 260 ($M^+$ −59, 27), 218 ($M^+$ −101, 55), 44 ($M^+$ −275, 100); HRMS-EI calcd for $C_{12}H_8F_3NO_6$: 319.0304; Found: 319.0289.

#### 4.2.7. Methyl 4-hydroxy-8-methoxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate **3g**

White solid; m.p.: 119–120 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.90 (d, $J$ = 6.3 Hz, 1H), 3.90 (s, 3H), 3.92 (s, 3H), 5.71 (d, $J$ = 6.0 Hz, 1H), 6.93 (dd, $J$ = 1.5 Hz, 8.4 Hz, 1H), 7.08 (dd, $J$ = 1.5 Hz, 7.8 Hz, 1H), 7.19 (t, $J$ = 8.1 Hz, 1H); $^{19}F$ NMR(282 MHz) $\delta$ −66.9 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 52.8, 56.2, 61.8, 111.1, 112.0, 117.6 (q, $J$ = 275.0 Hz), 120.3, 121.4, 125.6, 138.5, 143.0 (q, $J$ = 38.8 Hz), 147.7, 165.8; IR (KBr, $cm^{-1}$): $\nu$ = 3376, 1734, 1591, 1490, 1319; MS-EI ($m/z$, %): 304 ($M^+$, 5.63), 287 ($M^+$ −17, 3.9), 273 ($M^+$ −31, 2.5), 245 ($M^+$ −59, 3.8), 213 ($M^+$ −91, 59), 117 ($M^+$ −187, 98), 75 ($M^+$ −229, 100); HRMS-EI calcd for $C_{13}H_{11}F_3O_5$: 304.0559; Found: 304.0551.

#### 4.2.8. Methyl 4-hydroxy-6-methyl-2-(trifluoromethyl)-4H-chromene-3-carboxylate **3h**

White solid; m.p.: 109–110 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 2.34 (s, 3H), 3.12 (d, $J$ = 6 Hz, 1H), 3.86 (s, 3H), 5.61 (d, $J$ = 5.7 Hz, 1H), 7.02 (d, $J$ = 8.4 Hz, 1H), 7.14 (d, $J$ = 8.4 Hz, 1H), 7.28 (s, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −67.4 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 20.7, 52.8, 61.9, 111.0, 116.4, 117.6 (q, $J$ = 275.0 Hz), 120.1, 129.3, 130.8, 134.8, 143.2 (q, $J$ = 38.2 Hz), 146.5, 166.0; IR (KBr, $cm^{-1}$): $\nu$ = 3477, 1722, 1499, 1307; MS-EI ($m/z$, %): 288 ($M^+$, 7.4), 257 ($M^+$ −31, 7.1), 229 ($M^+$ −59, 8.9), 187 ($M^+$ −101, 100); HRMS-EI calcd for $C_{13}H_{11}F_3O_4$: 288.0609; Found: 288.0611.

#### 4.2.9. Methyl 6,8-di-tert-butyl-4-hydroxy-2-(trifluoromethyl)-4H-chromene-3-carboxylate **3i**

Colorless oil; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.33 (s, 9H), 1.42 (s, 9H), 2.91 (d, $J$ = 5.4 Hz, 1H), 3.90 (s, 3H), 5.68 (d, $J$ = 5.4 Hz, 1H), 7.35 (d, $J$ = 2.1 Hz, 1H), 7.40 (d, $J$ = 2.4 Hz, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −66.9 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 29.7, 31.3, 34.7, 35.0, 52.8, 62.6, 110.6, 117.8 (q, $J$ = 275.0 Hz), 120.0, 123.3, 125.4, 129.3, 136.6, 143.2 (q, $J$ = 38.2 Hz), 148.1, 166.0; IR (KBr, $cm^{-1}$): $\nu$ = 3484, 2967, 1725, 1604, 1479, 1367; MS-EI ($m/z$, %): 386 ($M^+$, 2.2), 369 ($M^+$ −17, 8.0), 355 ($M^+$ −31, 7.0), 339 ($M^+$ −47, 81), 285 ($M^+$ −101, 68), 57 ($M^+$ −329, 100); HRMS-EI calcd for $C_{20}H_{25}F_3O_4$: 386.1705; Found: 386.1711.

#### 4.2.10. Methyl 1-hydroxy-3-(trifluoromethyl)-1H-benzo[f]chromene-2-carboxylate **3j**

Light yellow solid; 117–118 °C; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 3.85 (s, 3H), 6.09 (d, $J$ = 6.9 Hz, 1H), 6.37 (d, $J$ = 6.9 Hz, 1H), 7.37 (d, $J$ = 6.6 Hz, 1H), 7.53 (dd, $J$ = 6.3 Hz, 1H), 7.62 (dd, $J$ = 6 Hz, 1H), 7.94 (m, 2H), 8.19 (d, $J$ = 6.3 Hz, 1H); $^{19}F$ NMR (282 MHz, DMSO-$d_6$) $\delta$ −66.6 (s, 3 F); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 53.4, 59.1, 114.5, 115.2, 117.1, 118.4 (q, $J$ = 274.2 Hz), 124.7, 126.2, 128.0, 129.1, 131.2, 131.5, 131.7, 139.7 (q, $J$ = 37.4 Hz), 146.7, 165.9; IR (KBr, $cm^{-1}$): $\nu$ = 3488, 1714, 1671, 1518, 1316; MS-EI ($m/z$, %) 324 ($M^+$, 3.6), 307 ($M^+$ −17, 11), 293 ($M^+$ −31, 4.0), 223 ($M^+$ −101, 100), 139 ($M^+$ −185, 63); HRMS-EI calcd for $C_{16}H_{11}F_3O_4$: 324.0609; Found: 324.0614.

### 4.3. Typical procedure for the oxidation of 2-trifluoromethyl-4H-chromenes

$CrO_3$·2Py (387 mg, 1.5 mmol) and new distilled $CH_2Cl_2$ (5.0 mL) were added to an oven-dried Schlenk tube (100 mL) under Ar at 0 °C. A solution of methyl 2-(trifluoromethyl)-4-hydroxy-4$H$-chromenes-3-carboxylate (**3a**, 82 mg, 0.30 mmol) in fresh $CH_2Cl_2$ (2.0 mL) was then added dropwise. The mixture was further stirred for an additional 3.5 h at room temperature. The mixture was filtered through a short plug of silica gel. The solvent of the filtrate was removed *in vacuo* and the crude product was further purified by column chromatography on silica gel (AcOEt/petroleum ether, 1:7) to afford the oxidized product **4a** and byproduct **5a**.

#### 4.3.1. Methyl 2-(trifluoromethyl)-4-oxo-4H-chromene-3-carboxylate **4a**

White solid; m.p.: 120–121 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.97 (s, 3H), 7.52 (m, 2H), 7.79 (dd, $J$ = 8.4 Hz, 15.6 Hz, 1H), 8.22 (d, $J$ = 8.4 Hz, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −68.9 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 53.6, 118.6, 119.7, 120.0 (q, $J$ = 275.8 Hz), 123.3, 126.3, 127.1, 135.8, 149.4 (q, $J$ = 38.8 Hz), 155.1, 162.1, 174.1; IR (KBr, $cm^{-1}$): $\nu$ = 1751, 1663, 1610, 1579, 1468, 1307; MS-EI ($m/z$, %) 272 ($M^+$, 22), 241 ($M^+$ −31, 100), 214 ($M^+$ −58, 40); HRMS-EI calcd for $C_{12}H_7F_3O_4$: 272.0296; Found: 272.0297.

#### 4.3.2. Methyl 2-(trifluoromethyl)-2-hydroxy-2H-chromenes-3-carboxylate 5a

White solid; m.p.: 78–79 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.90 (s, 3H), 7.01 (m, 2H), 7.23 (dd, $J$ = 1.8 Hz, 7.8 Hz, 1H), 7.35 (m, 2H), 7.79 (s, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −86.3 (s, 3 F); $^{13}C$ NMR (100 MHz): $\delta$ 53.0, 95.2 (q, $J$ = 35.0 Hz), 114.6, 116.1, 117.5, 121.5 (q, $J$ = 292.0 Hz), 122.7, 129.5, 134.1, 139.7, 152.7, 167.1; IR (KBr, $cm^{-1}$) $\nu$ = 3263, 1682; MS-EI ($m/z$, %) 274 ($M^+$, 0.91), 257 ($M^+$ −17, 1.4), 243 ($M^+$ −31, 2.9), 205 ($M^+$ −69, 21.9), 173 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_9F_3O_4$: 274.0453; Found: 274.0452.

#### 4.3.3. Methyl 6-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate **4b**

White solid; m.p.: 133–134 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.91 (s, 3H), 3.97 (s, 3H), 7.36 (m, 1H), 7.49 (s, 1H), 7.54 (m, 1H); $^{19}F$ NMR(282 MHz) $\delta$ −68.7 (s, 3 F); $^{13}C$ NMR (100 MHz): $\delta$ 53.6, 56.3, 105.3, 117.3 (q, $J$ = 280.1 Hz), 118.8, 120.0, 124.1, 125.8, 148.8 (q, $J$ = 39.5 Hz), 150.0, 158.3, 162.4, 174.1; IR (KBr, $cm^{-1}$): $\nu$ = 1743, 1656, 1614, 1489, 1284; MS-EI ($m/z$, %) 302 ($M^+$, 61), 271 ($M^+$ −31, 100), 244 ($M^+$ −58, 37); HRMS-EI calcd for $C_{13}H_9F_3O_5$: 302.0402; Found: 302.0412.

#### 4.3.4. Methyl 2-hydroxy-6-methoxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate **5b**

Yellow solid; m.p.: 90–91 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 3.77 (s, 3H), 3.90 (s, 3H), 6.74 (d, $J$ = 1.8 Hz, 1H), 6.94 (d, $J$ = 2.1 Hz, 1H), 7.37 (s, 1H), 7.75 (s, 1H); $^{19}F$ NMR (282 MHz) $\delta$ −86.5 (s, 3 F); $^{13}C$ NMR (100 MHz) $\delta$ 53.2, 55.9, 95.3 (q, $J$ = 34.4 Hz), 113.4, 115.3,

117.0, 118.0, 120.4, 121.5 (q, $J$ = 292.2 Hz), 140.0, 146.9, 155.0, 167.3; IR (KBr, $cm^{-1}$): $\nu$ = 3245, 1683; MS-EI ($m/z$, %) 304 ($M^+$, 6.9), 273 ($M^+$ −31, 2.909), 235 ($M^+$ −69, 20), 203 ($M^+$ −101, 100); HRMS-EI calcd for $C_{13}H_{11}F_3O_5$: 304.0559; Found: 304.0555.

*4.3.5. Methyl 6-fluoro-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate* **4c**

White solid; m.p.: 150–151 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.97 (s, 3H), 7.54 (m, 2H), 7.87 (m, 1H); $^{19}$F NMR (282 MHz) $\delta$ −68.8 (s, 3 F), −112, 1 (dd, $J$ = 7.1 Hz, 13.0 Hz, 1 F); $^{13}$C NMR (100 MHz) $\delta$ 53.7, 111.2 (d, $J$ = 23.9 Hz), 117.2 (q, $J$ = 275.8 Hz), 118.9, 121.0 (d, $J$ = 9.0 Hz), 124.1 (d, $J$ = 25.4 Hz), 124.5, 149.3 (q, $J$ = 39.5 Hz), 151.4 (d, $J$ = 2.3 Hz), 159.3, 161.7 (d, $J$ = 11.3 Hz), 173.5 (d, $J$ = 2.3 Hz); IR (KBr, $cm^{-1}$): $\nu$ = 1747, 1661, 1625, 1485, 1296; MS-EI ($m/z$, %) 290 ($M^+$, 23), 259 ($M^+$ −31, 100), 232 ($M^+$ −58, 33), 121 ($M^+$ −169, 23); HRMS-EI calcd for $C_{12}H_6F_4O_4$: 290.0202; Found: 290.0202.

*4.3.6. Methyl 6-fluoro-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate* **5c**

White solid; m.p.: 126–127 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.93 (s, 3H), 6.95–7.00 (m, 3H), 7.34 (s, 1H), 7.72 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.2 (s, 3 F), −119.7 (s, 1 F); $^{13}$C NMR (100 MHz) $\delta$ 53.2, 95.2 (q, $J$ = 35.1 Hz), 114.9 (d, $J$ = 24.2 Hz), 116.0, 117.2 (d, $J$ = 6.7 Hz), 120.4 (d, $J$ = 24.2 Hz), 121.0 (q, $J$ = 292.5 Hz), 138.6 (d, $J$ = 2.3 Hz), 148.6 (d, $J$ = 2.3 Hz), 156.4, 158.8, 166.8; IR (KBr, $cm^{-1}$): $\nu$ = 3302, 1693 $cm^{-1}$; MS-EI ($m/z$, %) 292 ($M^+$, 2.2), 261 ($M^+$ −31, 3.2), 223 ($M^+$ −69, 21), 191 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_8F_4O_4$: 292.0359; Found: 292.0369.

*4.3.7. Methyl 6-chloro-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate* **4d**

White solid; m.p.: 126–127 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.97 (s, 3H), 7.53 (d, $J$ = 9.0 Hz, 1H), 7.74 (dd, $J$ = 9.0 Hz, 2.7 Hz, 1H), 8.18 (d, $J$ = 2.1 Hz, 1H); $^{19}$F NMR(282 MHz) $\delta$ −68.9 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.7, 117.1 (q, $J$ = 275.7 Hz), 119.6, 120.4, 124.1, 125.6, 133.2, 136.1, 149.2 (q, $J$ = 38.8 Hz), 153.4, 161.7, 173.0; IR (KBr, $cm^{-1}$): $\nu$ = 1747, 1656, 1607, 1575, 1473, 1295; MS-EI ($m/z$, %) 306 ($M^+$, 31), 308 ($M^+$ +2, 10), 275 ($M^+$ −31, 100), 248 ($M^+$ −58, 45); HRMS-EI calcd for $C_{12}H_6ClF_3O_5$: 305.9907; Found: 305.9904.

*4.3.8. Methyl 6-chloro-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate* **5d**

White solid; m.p.: 127–128 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.94 (s, 3H), 7.00 (d, $J$ = 8.4 Hz, 1H), 7.23–7.34 (m, 3H), 7.71 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.2 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.2, 95.2 (q, $J$ = 35.2 Hz), 115.8, 117.4, 118.1, 120.9 (q, $J$ = 291.8 Hz), 127.7, 128.7, 133.6, 138.3, 151.0, 166.8; IR (KBr, $cm^{-1}$): $\nu$ = 3400, 1698, 1630, 1568; MS-EI ($m/z$, %) 308 ($M^+$, 2.7), 277 ($M^+$ −31, 2.7), 239 ($M^+$ −69, 17), 207 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_8ClF_3O_5$: 308.0063; Found: 308.0056.

*4.3.9. Methyl 6-bromo-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate* **4e**

White solid; m.p.: 135–136 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.97 (s, 3H), 7.47 (d, $J$ = 8.7 Hz, 1H), 7.88 (d, $J$ = 8.7 Hz, 1H), 8.32 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −68.9 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.8, 117.1 (q, $J$ = 275.7 Hz), 119.8, 120.5, 120.8, 124.5, 129.0, 138.9, 149.3 (q, $J$ = 39.5 Hz), 153.9, 161.7, 173.0; IR (KBr, $cm^{-1}$): $\nu$ = 1747, 1660, 1606, 1575, 1468, 1278; MS-EI ($m/z$, %) 350 ($M^+$, 40), 352 ($M^+$ +2, 39), 321 ($M^+$ −29, 100), 319 ($M^+$ −31, 99), 292 ($M^+$ −58, 51); HRMS-EI calcd for $C_{12}H_6BrF_3O_5$: 349.9402; Found: 349.9415.

*4.3.10. Methyl 6-bromo-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate* **5e**

White solid; m.p.: 120–121 °C; $^1$H NMR(300 MHz, $CDCl_3$) $\delta$ 3.93 (s, 3H), 6.93 (d, $J$ = 8.7 Hz, 1H), 7.38–7.49 (m, 2H), 7.71 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.3 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.3, 95.2 (q, $J$ = 35.2 Hz), 114.7, 115.8, 117.8, 119.2, 121.0 (q, $J$ = 291.8 Hz), 131.7, 136.5, 138.2, 151.5, 166.7; IR (KBr, cm): $\nu$ = 3403, 1696 $cm^{-1}$; MS-EI ($m/z$, %) 352 ($M^+$, 4.3), 354 ($M^+$ +2, 4.3), 321 ($M^+$ −31, 2.6), 283 ($M^+$ −69, 31), 251 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_8BrF_3O_5$: 351.9558; Found: 351.9555.

*4.3.11. Methyl 6-nitro-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate* **4f**

White solid; m.p.: 148–149 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.97 (s, 3H), 7.75 (d, $J$ = 6.9 Hz, 1H), 8.62 (dd, $J$ = 2.4 Hz, 6.9 Hz, 1H), 9.05 (d, $J$ = 1.8 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −68.9 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 52.3, 115.2 (q, $J$ = 275.8 Hz), 118.4, 118.9, 121.2, 121.8, 120.3, 144.2, 147.9 (q, $J$ = 40.4 Hz), 156.0, 159.3, 171.1; IR (KBr, $cm^{-1}$): $\nu$ = 1745, 1668, 1626, 1586; MS-EI ($m/z$, %) 317 ($M^+$, 19), 286 ($M^+$ −31, 100), 259 ($M^+$ −58, 69), 240 ($M^+$ −77, 61); HRMS-EI for calcd $C_{12}H_6F_3NO_6$: 317.0147; Found: 317.0147.

*4.3.12. Methyl 2-hydroxy-6-nitro-2-(trifluoromethyl)-2H-chromene-3-carboxylate* **5f**

Light yellow solid; m.p.: 125–126 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.98 (s, 3H), 7.16 (d, $J$ = 9.3 Hz, 1H), 7.84 (s, 1H), 8.22 (d, $J$ = 2.1 Hz, 1H), 8.27 (d, $J$ = 8.7 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.2 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.6, 95.8 (q, $J$ = 35.2 Hz), 116.9, 117.0, 117.4, 120.7 (q, $J$ = 290.0 Hz), 125.1, 129.0, 137.4, 142.9, 156.7, 166.3; MS-EI ($m/z$, %) 319 ($M^+$, 0.80), 288 ($M^+$ −31, 3.1), 250 ($M^+$ −69, 32), 218 ($M^+$ −101, 100); HRMS-EI calcd for $C_{12}H_8F_3NO_6$: 319.0304; Found: 319.0306.

*4.3.13. Methyl 8-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate* **4g**

White solid; m.p.: 139–140 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.94 (s, 3H), 3.99 (s, 3H), 7.24 (dd, $J$ = 0.6 Hz, 6.0 Hz, 1H), 7.38 (t, $J$ = 6.0 Hz, 1H), 7.70 (dd, $J$ = 0.9 Hz, 6.0 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −68.7 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.7, 56.7, 116.3, 116.7, 117.3 (q, $J$ = 275.8 Hz), 119.5, 124.4, 126.8, 145.6, 148.9 (q, $J$ = 39.6 Hz), 149.2, 162.3, 174.3; IR (KBr, $cm^{-1}$): $\nu$ = 1747, 1663, 1589; MS-EI ($m/z$, %) 302 ($M^+$, 57), 271 ($M^+$ −31, 100), 244 ($M^+$ −58, 47), 203 ($M^+$ −99, 81); HRMS-EI calcd for $C_{13}H_9F_3O_5$: 302.0402; Found: 302.0403.

*4.3.14. Methyl 2-hydroxy-8-methoxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate* **5g**

Light yellow solid; m.p.: 106–107 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.88 (s, 3H), 3.91 (s, 3H), 6.85–7.02 (m, 3H), 7.36 (s, 1H), 7.78 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.4 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.2, 56.7, 95.5 (q, $J$ = 35.1 Hz), 114.9, 117.3, 118.4, 121.5, 122.7, 124.3 (q, $J$ = 292.3 Hz), 140.1, 142.2, 147.8, 167.2; IR (KBr, $cm^{-1}$): $\nu$ = 3339, 1696; MS-EI ($m/z$, %) 304 ($M^+$, 4.5), 273 ($M^+$ −31, 4.4), 235 ($M^+$ −69, 15), 203 ($M^+$ −101, 100); HRMS-EI calcd for $C_{13}H_{11}F_3O_5$: 304.0559; Found: 304.0562.

*4.3.15. Methyl 6-methyl-4-oxo-2-(trifluoromethyl)-4H-chromene-3-carboxylate* **4h**

White solid; m.p.: 122–123 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.49 (s, 3H), 3.97 (s, 3H), 7.44 (d, $J$ = 8.4 Hz, 1H), 7.59 (dd, $J$ = 2.1 Hz, 8.7 Hz, 1H), 8.00 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −68.9 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 21.2, 53.6, 117.3 (q, $J$ = 275.8 Hz), 118.3, 119.5, 123.0, 125.6, 137.0, 137.4, 148.9 (q, $J$ = 38.8 Hz), 153.5, 162.4, 174.2; IR (KBr, $cm^{-1}$): $\nu$ = 1722, 1682, 1499, 1307; MS-EI ($m/z$, %) 286 ($M^+$, 34), 255 ($M^+$ −31, 100), 228 ($M^+$ −58, 50), 217 ($M^+$ −69, 10); HRMS-EI calcd for $C_{13}H_9F_3O_4$: 286.0453; Found: 286.0458.

*4.3.16. Methyl 2-hydroxy-6-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylate* **5h**

White solid; m.p.: 79–80 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.29 (s, 3H), 3.91 (s, 3H), 6.91 (d, $J$ = 8.7 Hz, 1H), 7.03 (s, 1H), 7.16 (d,

$J$ = 8.4 Hz, 1H), 7.75 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.4 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 20.6, 53.2, 95.3 (q, $J$ = 34.4 Hz), 114.6, 115.9, 117.5, 121.5 (q, $J$ = 292.3 Hz), 129.9, 132.4, 135.0, 140.2, 150.8, 167.4; IR (KBr, cm$^{-1}$): $\nu$ = 3365, 1702; MS-EI ($m/z$, %) 288 ($M^+$, 2.2), 257 ($M^+$ −31, 2.6), 219 ($M^+$ −69, 17), 187 ($M^+$ −101, 100); HRMS-EI calcd for $C_{13}H_{11}F_3O_4$: 288.0609; Found: 288.0614.

#### 4.3.17. Methyl 6,8-di-tert-butyl-2-hydroxy-2-(trifluoromethyl)-2H-chromene-3-carboxylate **5i**

Light yellow oil; yield: 97%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.29 (s, 9H), 1.41 (s, 9H), 3.89 (s, 3H), 7.06 (s, 1H), 7.22 (s, 1H), 7.44 (s, 1H), 7.77 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −86.7 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 29.8, 31.5, 34.6, 35.0, 53.1, 95.5 (q, $J$ = 35.1 Hz), 113.3, 117.3, 121.6 (q, $J$ = 292.6 Hz), 124.8, 129.5, 136.8, 141.3, 144.8, 149.1, 167.5; IR (film, cm$^{-1}$): $\nu$ = 3363, 1697; MS-EI ($m/z$, %) 386 ($M^+$, 4.4), 355 ($M^+$ −31, 4.1), 339 ($M^+$ −47, 54), 317 ($M^+$ −69, 38), 285 ($M^+$ −101, 100); HRMS-EI calcd for $C_{20}H_{25}F_3O_4$: 386.1705; Found: 386.1704.

#### 4.3.18. Methyl 3-hydroxy-3-(trifluoromethyl)-3H-benzo[f]chromene-2-carboxylate **5j**

Yellow solid; m.p.: 129–130 °C; yield: 96%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.98 (s, 3H), 7.23 (d, $J$ = 9.6 Hz, 1H), 7.43–7.64 (m, 3H), 7.80 (d, $J$ = 7.5 Hz, 1H), 7.89 (d, $J$ = 8.7 Hz, 1H), 8.04 (d, $J$ = 8.4 Hz, 1H), 8.53 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −88.0 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 53.3, 95.7 (q, $J$ = 35.1 Hz), 110.8, 112.3, 117.0, 121.1, 124.4 (q, $J$ = 291.5 Hz), 125.3, 128.6, 129.3, 129.8, 130.4, 135.3, 135.7, 152.6, 167.6; IR (KBr, cm$^{-1}$): $\nu$ = 3398, 1687; MS-EI ($m/z$, %) 324 ($M^+$, 5.9), 293 ($M^+$ −31, 3.1), 255 ($M^+$ −69, 17), 223 ($M^+$ −101, 100); HRMS-EI calcd for $C_{16}H_{11}F_3O_4$: 324.0609; Found 324.0612.

### 4.4. Typical procedure for transformation between 4H-chromene and 2H-chromene

**3e** (106 mg, 0.3 mmol) was added into the mixture of DMSO (2 mL) and HCl (1.0 M, 0.5 mL). The mixture was stirred for 5 h at room temperature. The reaction was then quenched by adding saturated $NaHCO_3$ aqueous. The mixture was extracted with $CH_2Cl_2$ three times (30 mL). The organic layer was combined and washed by brine, dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (AcOEt/petroleum ether, 1:7) to give pure **5e**; white solid; mp: 120–121; $^1$H NMR (300 MHz, $CDCl_3$, TMS) $\delta$ 3.93 (s, 3H), 6.93 (d, $J$ = 8.7 Hz, 1H), 7.38–7.49 (m, 2H), 7.71 (s, 1H); $^{19}$F NMR (282 MHz, $CFCl_3$) $\delta$ −86.3 (s, 3 F); $^{13}$C NMR (75 MHz, TMS) $\delta$ 53.3, 95.2 (q, $J$ = 26.5 Hz), 114.7, 115.8, 117.8, 119.2, 121.0 (q, $J$ = 219.4 Hz), 131.7, 136.5, 138.2, 151.5, 166.7; MS (EI) $m/z$352 ($M^+$, 4.32), 354 ($M^+$ +2, 4.29), 321 ($M^+$ −31, 2.59), 283 ($M^+$ −69, 31.89), 251 ($M^+$ −101, 100); HRMS for $C_{12}H_8BrF_3O_5$ Calcd: 351.9558; Found: 351.9555.

### 4.5. Typical procedure for the cyclopropanation of 2-trifluoromethyl-chromones

Under Ar atmosphere, to a solution of sulfur ylide **6** (26 mg, 0.1 mmol) dissolved in chloroform (2 mL) was added DBU (19 mg, 0.13 mmol). After the mixture was stirred for 30 min at room temperature, chromone **4a** was added and the reaction was monitored by $^{19}$F NMR. After the consumption of **4a**, the reaction was quenched by the addition of 2 M HCl (5 mL) and the aqueous phase was extracted with $CH_2Cl_2$ (10 mL × 3). The combined organic phases were washed with brine, dried over $Na_2SO_4$, the concentrated *in vacuo* to leave the residue, which was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 7/1) to give the product **7a**.

#### 4.5.1. 1-Ethyl 7a-methyl 7-oxo-1a-(trifluoromethyl)-1,1a,7,7a-tetrahydrocyclopropa[b]-chromene-1,7a-dicarboxylate **7a**

White solid; m.p.: 94–97 °C; yield: 73%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.07 (t, $J$ = 7.2 Hz, 3H), 3.26 (s, 1H), 3.81 (s, 3H), 4.02 (q, $J$ = 6.9 Hz, 2H), 7.09–7.21 (m, 2H), 7.56 (t, $J$ = 7.5 Hz, 1H), 7.97 (d, $J$ = 7.8 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −72.5 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.6, 27.2, 41.0, 53.9, 62.6, 68.2 (q, $J$ = 40.3 Hz), 117.0, 119.4, 119.8 (q, $J$ = 277.3 Hz), 123.4, 126.3, 136.5, 158.2, 163.3, 163.7, 180.9; IR (KBr, cm$^{-1}$): $\nu$ = 3038, 1739, 1609, 1464; EI-MS ($m/z$, %) 358 ($M^+$, 23), 327 ($M^+$ −31, 3.2), ($M^+$ −45, 1.2); HRMS-EI calcd for $C_{16}H_{13}F_3O_6$: 358.0664; Found: 358.0668.

#### 4.5.2. 1-Ethyl 7a-methyl 5-fluoro-7-oxo-1a-(trifluoromethyl)-1,1a,7,7a-tetrahydro-cyclopropa[b]chromene-1,7a-dicarboxylate **7b**

White solid; m.p.: 83–85 °C; yield: 61%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.12 (t, $J$ = 7.5 Hz, 3H), 3.27 (s, 1H), 3.81 (s, 3H), 4.05 (q, $J$ = 7.2 Hz, 2H), 7.09 (dd, $J$ = 3.9 Hz, 9.0 Hz, 1H), 7.27 (m, 1H), 7.62 (dd, $J$ = 3.0 Hz, 8.1 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −118.6 (q, $J$ = 3.9 Hz, F), −75.4 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.6, 27.4, 40.7, 53.9, 62.7, 68.6 (q, $J$ = 39.9 Hz), 111.5, 111.7, 118.7, 119.7 (q, $J$ = 277.7 Hz), 120.0, 123.7, 124.0, 154.3 (d, $J$ = 257.9 Hz), 159.3, 163.3, 180.4; IR (KBr, cm$^{-1}$): $\nu$ = 3037, 1738, 1486, 1440, 1313; EI-MS ($m/z$, %) 376 ($M^+$, 12), 345 ($M^+$ −31, 5.0), 210 ($M^+$ −166, 100); HRMS-EI calcd for $C_{16}H_{12}F_4O_6$: 376.0570; Found: 376.0574.

#### 4.5.3. 1-Ethyl 7a-methyl 5-chloro-7-oxo-1a-(trifluoromethyl)-1,1a,7,7a-tetrahydrocyclo-propa[b]chromene-1,7a-dicarboxylate **7c**

White solid; m.p.: 72–74 °C; yield: 88%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.15 (t, $J$ = 6.9 Hz, 3H), 3.27 (s, 1H), 3.81 (s, 3H), 4.08 (q, $J$ = 6.9 Hz, 2H), 7.06 (d, $J$ = 8.7 Hz 1H), 7.51 (dd, $J$ = 8.7 Hz, 2.4 Hz, 1H), 7.93 (d, $J$ = 2.4 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −74.3 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.9, 29.9, 41.0, 54.3, 63.0, 68.8 (q, $J$ = 40.0 Hz), 118.9, 119.9 (q, $J$ = 278.1 Hz), 120.6, 125.9, 129.4, 136.5, 156.9, 163.5, 163.6, 180.3; IR (KBr, cm$^{-1}$): $\nu$ = 3010, 1761, 1732, 1694, 1605, 1477; EI-MS ($m/z$, %) 392 ($M^+$, 11), 361 ($M^+$ −31, 1.8), 347 ($M^+$ −45, 1.4); HRMS-EI calcd for $C_{16}H_{12}ClF_3O_6$: 392.0275; Found: 392.0270.

#### 4.5.4. 1-Ethyl 7a-methyl 5-bromo-7-oxo-1a-(trifluoromethyl)-1,1a,7,7a-tetrahydrocyclopr-opa[b]chromene-1,7a-dicarboxylate **7d**

White solid; m.p.: 90–92 °C; yield: 49%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.13 (t, $J$ = 6.9 Hz, 3H), 3.27 (s, 1H), 3.81 (s, 3H), 4.08 (t, $J$ = 6.9 Hz, 2H), 7.02 (d, $J$ = 9.3 Hz, 1H), 7.65 (dd, $J$ = 2.4 Hz, 8.7 Hz, 1H), 8.08 (d, $J$ = 2.4 Hz, 1H); $^{19}$F NMR (282 MHz) $\delta$ −74.3 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 17.8, 31.7, 44.8, 58.1, 66.9, 72.7 (q, $J$ = 34.3 Hz), 120.3, 123.0, 123.7 (q, $J$ = 281.8 Hz), 124.8, 132.8, 143.1, 161.3, 167.4, 184.0; IR (KBr, cm$^{-1}$): $\nu$ = 2992, 1761, 1732, 1693; MS-EI ($m/z$, %) 438 ($M^+$ +2, 6.7), 436 ($M^+$, 7.2), 359 ($M^+$ −72, 4.0); HRMS-EI calcd for $C_{16}H_{12}BrF_3O_6$: 435.9769; Found: 435.9773.

### 4.6. Typical procedure for the ring-opening reaction of compounds **7a–7d**

Under Ar atmosphere, to a solution of cyclopropanation product **7a** (0.1 mmol) in $CH_2Cl_2$ (2 mL) was added a solution of $TiCl_4$ (1 M in $CH_2Cl_2$, 0.25 mL, 2.5 equiv.) dropwise at −78 °C. The mixture was stirred for 1.5 h at the same temperature and then allowed warm to room temperature with additional stirring for 30 min. The reaction mixture was quenched by addition of sat. ammonia chloride aqueous and extracted with $CH_2Cl_2$ (5 mL × 3). The combined organic phases were filtered through a short pad of Celite, dried over $Na_2SO_4$, the solution was removed under *vaccum* to give the desired product **8**.

*4.6.1. 3-Ethyl 4-methyl 2-chloro-5-hydroxy-2-(trifluoromethyl)-2,3-dihydrobenzo[b]oxe-pine-3,4-dicarboxylate* ***8a***

Yellow oil; yield: 85%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.02 (t, $J$ = 6.9 Hz, 3H), 3.86 (m, 5H), 4.91 (s, 1H), 7.22–7.52 (m, 3H), 7.56 (d, $J$ = 7.5 Hz, 1H), 13.3 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −79.7 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.6, 47.9, 52.9, 61.6, 97.8, 105.4 (q, $J$ = 31.1 Hz), 120.4 (q, $J$ = 284.9 Hz), 123.2, 125.0, 126.4, 127.5, 129.7, 151.2, 166.5, 169.6, 171.4; IR (film, cm$^{-1}$): $\nu$ = 2959, 1752, 1649, 1620; MS-EI ($m/z$, %) 396 ($M^+$ +2, 4.5), 394 ($M^+$, 12), 323 ($M^+$ −71, 26); HRMS-EI calcd for $C_{16}H_{14}F_3O_6Cl$: 394.0431; Found: 394.0432.

*4.6.2. 3-Ethyl 4-methyl 2-chloro-7-fluoro-5-hydroxy-2-(trifluoromethyl)-2,3-dihydroben-zo[b]oxepine-3,4-dicarboxylate* ***8b***

Light yellow oil; yield: 75%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.03 (t, $J$ = 7.2 Hz, 3H), 3.91 (s, 5H), 4.89 (s, 1H), 7.18 (d, $J$ = 4.8 Hz, 2H), 7.42 (d, $J$ = 8.4 Hz, 1H), 13.3 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −114.8 (q, $J$ = 5.9 Hz, F), −80.5 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.7, 47.9, 53.0, 61.8, 98.2, 115.2 (d, $J$ = 25.3 Hz), 118.9 (d, $J$ = 23.7 Hz), 120.3 (q, $J$ = 283.8 Hz), 124.6, 124.7, 130.3 (d, $J$ = 8.6 Hz), 147.1 (d, $J$ = 2.9 Hz), 159.3 (d, $J$ = 246.2 Hz), 166.5, 168.4, 171.2; IR (film, cm$^{-1}$): $\nu$ = 2989, 1752, 1654, 1585; MS-EI ($m/z$, %) 412 ($M^+$, 13), 341 ($M^+$ −71, 23), 307 ($M^+$ −105, 100); HRMS-EI calcd for $C_{16}H_{13}F_4O_6Cl$: 412.0337; Found: 412.0343.

*4.6.3. 3-Ethyl 4-methyl 2,7-dichloro-5-hydroxy-2-(trifluoromethyl)-2,3-dihydrobenzo-[b]oxepine-3,4-dicarboxylate* ***8c***

Yellow oil; yield: 83%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.96 (m, 3H), 3.79 (m, 5H), 4.83 (s, 1H), 7.08–7.65 (m, 3H), 13.2 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −80.0 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.6, 47.7, 52.9, 61.7, 98.1, 105.2 (q, $J$ = 30.7 Hz), 120.1 (q, $J$ = 285.0 Hz), 124.3, 128.5, 130.0, 132.0, 132.2, 149.5, 166.3, 186.1, 171.0; IR (film, cm$^{-1}$): $\nu$ = 2928, 1751, 1621, 1569; MS-EI ($m/z$, %) 430 ($M^+$ 2, 20), 428 ($M^+$, 30), 356 ($M^+$ −72, 15), 323 ($M^+$ −105, 78); HRMS-EI calcd for $C_{16}H_{13}F_3O_6Cl_2$: 428.0041; Found: 428.0042.

*4.6.4. 3-Ethyl 4-methyl 7-bromo-2-chloro-5-hydroxy-2-(trifluoromethyl)-2,3-dihydroben-zo[b]oxepine-3,4-dicarboxylate* ***8d***

Yellow oil; yield: 74%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.02 (t, $J$ = 6.9 Hz, 3H), 3.91 (m, 5H), 4.89 (s, 1H), 7.08 (d, $J$ = 8.4 Hz, 1H), 7.58 (dd, $J$ = 1.5 Hz, 8.7 Hz, 1H), 7.87 (s, 1H), 13.3 (s, 1H); $^{19}$F NMR (282 MHz) $\delta$ −80.4 (s, 3 F); $^{13}$C NMR (100 MHz) $\delta$ 13.7, 47.9, 53.0, 62.6, 98.2, 105.2 (q, $J$ = 31.0 Hz), 119.8, 120.2 (q, $J$ = 284.6 Hz), 124.7, 130.4, 131.5, 135.1, 150.2, 166.4, 168.0, 171.1; IR (film, cm$^{-1}$): $\nu$ = 3440, 1753, 1659, 1615; MS-EI ($m/z$, %) 474 ($M^+$ +2, 18), 472 ($M^+$, 14), 401 ($M^+$ −71, 81); HRMS-EI calcd for $C_{16}H_{13}BrF_3O_6Cl$: 471.9536; Found: 471.9532.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2011.10.011.

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