molecules

MDPI

Article

Silver-Promoted Radical Cascade Aryldifluoromethylation/Cyclization of 2-Allyloxybenzaldehydes for the Synthesis of 3-Aryldifluoromethyl-Containing Chroman-4-one Derivatives

Qianqian Sun [1], Hongxiao Li [1], Xingyu Chen [1], Jian Hao [1,*], Hongmei Deng [2] and Haizhen Jiang [1,3,*]

[1] Department of Chemistry, Shanghai University, Shanghai 200444, China
[2] Laboratory for Microstructures, Shanghai University, Shanghai 200444, China
[3] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China
* Correspondence: jhao@shu.edu.cn (J.H.); hzjiang@shu.edu.cn (H.J.)

Abstract: A convenient silver-promoted radical cascade aryldifluoromethylation/cyclization of 2-allyloxybenzaldehydes has been developed. Experimental studies disclosed that the addition of aryldifluoromethyl radicals in situ produced from easily accessible *gem*-difluoroarylacetic acids to unactivated double bonds in 2-allyloxybenzaldehyde was an effective route to access a series of 3-aryldifluoromethyl-containing chroman-4-one derivatives in moderate to good yields under mild reaction conditions.

Keywords: radical cascade; aryldifluoromethylation/cyclization; chroman-4-one derivatives

Citation: Sun, Q.; Li, H.; Chen, X.; Hao, J.; Deng, H.; Jiang, H. Silver-Promoted Radical Cascade Aryldifluoromethylation/Cyclization of 2-Allyloxybenzaldehydes for the Synthesis of 3-Aryldifluoromethyl-Containing Chroman-4-one Derivatives. *Molecules* **2023**, *28*, 3578. https://doi.org/10.3390/molecules28083578

Academic Editor: Wim Dehaen

Received: 23 March 2023
Revised: 12 April 2023
Accepted: 14 April 2023
Published: 19 April 2023

1. Introduction

The chroman-4-one framework belongs to the privileged class of heterocycles and acts as a major building block in many natural products, pharmaceuticals, and biologically active compounds [1,2]. In particular, the compounds with substituents at the 3-position of the chroman-4-one exhibit significant physiological and biological activities, such as GPR119 agonist (Figure 1, **a**) [3], anti-HIV agent (Figure 1, **b**) [4], and anti-tobacco mosaic virus agent (Figure 1, **c**) [5] etc. Thus, a number of approaches for the synthesis of 3-substituted chroman-4-one derivatives have been developed, such as transition-metal-catalyzed cross-coupling reaction [6], Stetter reaction [7], and cascade radical cyclization [8–12].

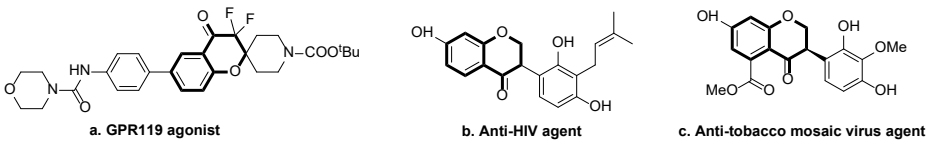
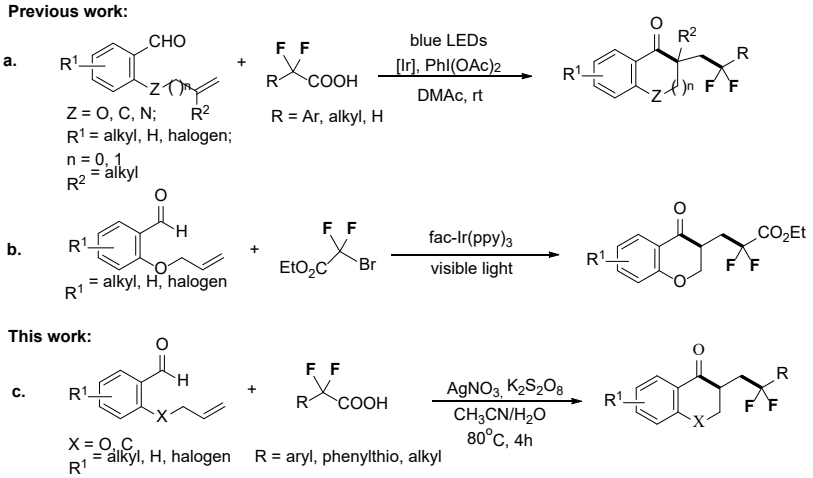


Figure 1. Examples of the bioactive compounds with a 3-substituent chroman-4-one moiety.

The introduction of difluoromethylene group into organic molecules can not only improve chemical, physical properties and the physiological activity of the parent molecule, but also affect their binding affinity, metabolic stability, lipophilicity, and membrane permeability and bioactivity, as well as modulate pharmacokinetic behavior and penetration in biological tissues [13–15]. Hence, *gem*-difluoromethylene group (CF_2) is regarded as a valuable fluorinated moiety that is extensively present in pharmaceuticals, biologically active compounds, and material molecules [16,17]. Therefore, the development of effective and general methodologies for the selective incorporation of a difluoromethylene group has become one of the hotspots in the field of organic chemistry. Traditional methods

for the synthesis of the difluoromethylene-containing compounds include the direct deoxyfluorination of the carbonyl group in corresponding aldehydes or ketones by using bis(2-methoxyethyl)aminosulfur trifluoride or DAST ($(C_2H_5)_2NSF_3$) [18–21] and the conversion of building blocks containing difluoromethylene under specific conditions. For example, visible light-promoted the difluoromethylenation of C–H bonds under xanthone catalyzed conditions [22–24], and transition-metal-catalyzed (Pd- or Ni-) difluoromethylenation can be achieved applying chlorodifluoromethane [25], and so on. However, some existing methods suffer from either functional group incompatibility or the use of toxic and explosive reagents [26–28]. Therefore, it remains highly desired to develop practical and mild synthetic methods by using stability and easily available substrates containing-difluoromethylene building blocks, such as α,α-difluoroarylacetic acids [29–32].

Radical cascade fluoroalkylation/cyclization of alkenes has been proved to be one of the effective methods to obtain fluoroalkyl-containing heterocycle products due to the advantages that it avoids the separation and purification of intermediates [33] and realizes the introduction a fluoroalkyl group while constructing the diversity and complexity of heterocyclic skeletons. However, some fluoroalkyl radicals, such as CF_3 radical, CF_2H, and C_nF_{2n+1} radical, are electron-deficient σ-radicals and thus prone to add to electron-rich alkenes. Due to electronically unfavorable conditions, it is difficult to realize the free radical cascade fluoroalkylation/cyclization of unactivated or electron-deficient alkenes. Therefore, there are only few reports on the cascade difluoromethylenation/cyclization regarding the synthesis of 3-difluoromethylene-containing chroman-4-one derivatives through the addition difluoromethyl radicals to unactivated alkenes in 2-allyloxybenzaldehydes. The reported methods include that of Zhu's group, which developed a visible light photocatalytic aryldifluoromethylation/cyclization of alkenes using α,α-difluoroarylacetic acids (Scheme 1a) [34], and Zhou's group and Ma's group, which described radical cascade cyclization of alkene aldehydes using a 1-bromo-2-difluoro-containing building block (Scheme 1b) [35,36] under the visible-light photoredox catalysis conditions. Therefore, it is highly desirable to develop new, convenient methods for the synthesis of 3-difluoromethylene-containing chroman-4-one derivatives, to avoid using a relatively expensive photocatalyst in the mild reaction. Our previous research on the decarboxylation of *gem*-difluoroarylacetic acids under silver-catalyzed condition revealed that aryldifluoromethyl radicals have a slightly electron-rich property relative to the CF_3 radical and could react with the electron-deficient activated double bond in allyl sulfones [37]. Herein, we further tried to use aryldifluoromethyl radicals from the decarboxylation of *gem*-difluoroarylacetic acids under the promotion of the catalytic amount of silver to explore the cascade aryldifluoromethylation/cyclization reaction with unactivated double bonds in 2-allyloxybenzaldehydes to synthesize 3-aryldifluoromethyl-containing chroman-4-one derivatives (Scheme 1c).

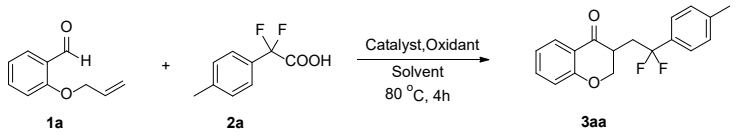


Scheme 1. Synthesis of 3-difluoromethylene-containing chroman-4-one derivatives.

2. Results and Discussion

Our previous research found that the system of silver salts and persulfate salts was effective in the decarboxylation of difluoroarylacetic acids in cross-coupling reactions with allyl sulfones [37]. Therefore, 4-methyl difluorophenylacetic acid **2a** and 2-(allyloxy)benzaldehyde **1a** which included unactivated double bonds were chosen as model substrates to participate in the reaction in the presence of $AgNO_3$ (20 mol%) and $K_2S_2O_8$ (2 equiv.) in CH_3CN/H_2O (v/v = 1:1) at 80 °C under a N_2 atmosphere, replacing visible light redox catalytic conditions [34]. To our delight, 3-(4-CH_3)phenyldifluoromethyl-containing chroman-4-one product **3aa** was observed in 56% ^{19}F NMR yield (Table 1, entry 1). Encouraged by the result, we try to optimize the reaction conditions. When solvent was shifted from CH_3CN/H_2O to $EtOH/H_2O$ or $DMSO/H_2O$, the reaction gave the desired product in lower yields (Entries 2 and 3). The product **3aa** was also produced when the solvent was pure H_2O, but the reaction efficiency was reduced (Entry 4). When the solvent was DMSO, the reaction could also produce the product in 32% yield (Entry 22). However, the desired product was obtained if the reaction was carried out in CH_3CN (Entry 5). Upon further screening of solvents, it was found that the reaction provided the highest yield (73%) in the solvent CH_3CN/H_2O (v/v = 1:3) when 2 equivalents of $K_2S_2O_8$ were used as oxidant (Entry 6). Other oxidants, including $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$, were also effective (Entries 7 and 8). In contrast, selectfluor failed to carry out this transformation (Entry 9). Additionally, when changing the amount of oxidant $K_2S_2O_8$ from 2 into 1.75 or 2.25 equiv., the reaction efficiency was slightly reduced (Entry 6 vs 17 and 18). Moreover, oxidant $K_2S_2O_8$ was actually required to bring about the cascade aryldifluoromethylation/cyclization (Entry 11). We also further evaluated the effect of the amount of $AgNO_3$ on the reaction. $AgNO_3$ could promote the reaction, but it was not necessary (Entry 10). A higher catalyst loading of $AgNO_3$ did not lead to a higher reaction efficiency, and 10 mol% of $AgNO_3$ as promoter resulted in 63% yield of **3aa** (Entries 12 and 13). The other Ag (I) sources, such as AgOAc, Ag_2O, or Ag_2CO_3, could also be used as the promoters, but they were less effective (Entries 19–21). Adjusting the ratio of **1a** and **2a**, it was found that **3aa** was provided in the highest yield when the ratio of **1a** and **2a** was 1:1.5 (Entries 6, 14–16) at 80 °C for 4 h (Supplementary Materials).

Table 1. Optimization of Reaction Conditions [a].



1a **2a** **3aa**

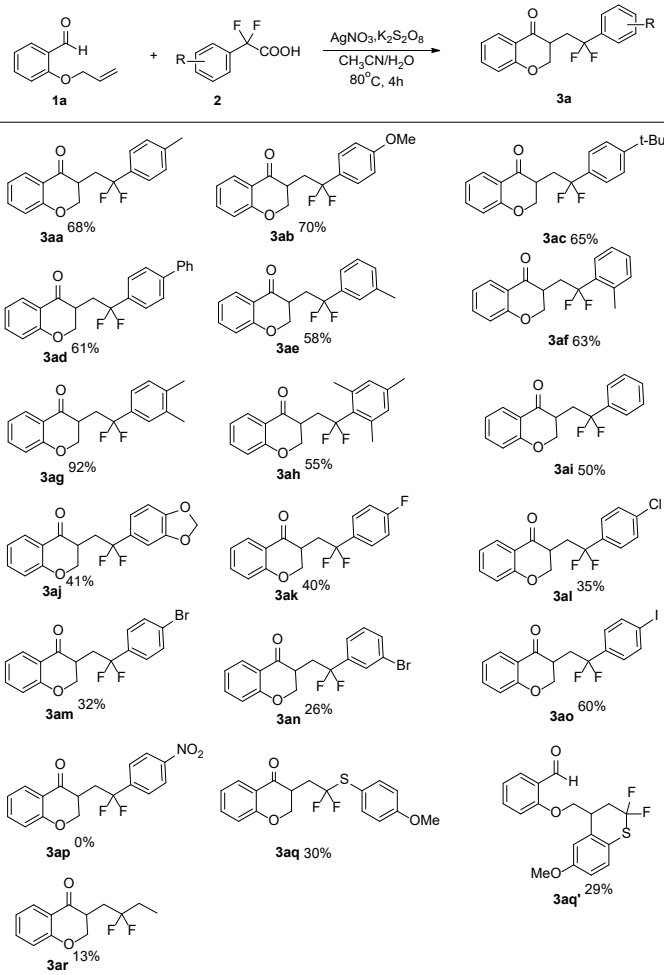
Entry	Catalyst (mol%)	Oxidant (equiv.)	Solvent	Yield (%) [b]
1	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:1)	56
2	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	$DMSO/H_2O$ (1:1)	45
3	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	$EtOH/H_2O$ (1:1)	5
4	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	H_2O	10
5	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	CH_3CN	N.R.
6	**$AgNO_3$ (20)**	**$K_2S_2O_8$ (2.0)**	**CH_3CN/H_2O (1:3)**	**73**
7	$AgNO_3$ (20)	$Na_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	66
8	$AgNO_3$ (20)	$(NH_4)_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	63
9	$AgNO_3$ (20)	Selectfluor (2.0)	CH_3CN/H_2O (1:3)	0
10	\	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	49
11	$AgNO_3$ (20)	\	CH_3CN/H_2O (1:3)	0
12	$AgNO_3$ (30)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	67
13	$AgNO_3$ (10)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	63
14 [c]	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	50
15 [d]	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	53
16 [e]	$AgNO_3$ (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	68
17	$AgNO_3$ (20)	$K_2S_2O_8$ (1.75)	CH_3CN/H_2O (1:3)	70
18	$AgNO_3$ (20)	$K_2S_2O_8$ (2.25)	CH_3CN/H_2O (1:3)	64
19	AgOAc (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	65
20	Ag_2O (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	68
21	Ag_2CO_3 (20)	$K_2S_2O_8$ (2.0)	CH_3CN/H_2O (1:3)	65
22 [f]	\	$(NH_4)_2S_2O_8$ (2.0)	DMSO	32

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv), catalyst (20 mol%) and oxidant (0.4 mmol) in 2.0 mL solvent at 80 °C for 4 h under N_2 atmosphere. [b] Yields determined by ^{19}F NMR analysis with $PhCF_3$ as the internal standard. [c] **1a**:**2a** = 1:1. [d] **1a**:**2a** = 1.5:1. [e] **1a**:**2a** = 1:2. [f] **1a** (0.2 mmol), **2** (0.3 mmol), $(NH_4)_2S_2O_8$ (0.4mmol) and DMSO (2.0 mL) at 40 °C for 6 h under N_2 atmosphere.

Having established the optimal experimental conditions, we explored the scope and limitation of this cascade aryldifluoromethylation/cyclization by the reaction of α,α-difluoroarylacetic acids and 2-allyloxybenzaldehydes. We first explored the scope with respect to the α,α-difluoroarylacetic acids **2**, as shown in Table 2. Difluoroarylacetic acids (**2a**–**2h**) bearing an electron-donating group, such as CH_3, OCH_3 etc., at different positions of benzene ring produced the desired product in moderate to excellent yields (**3aa**–**3ah**). When 2,2-difluoro-2-phenylacetic acid **2i** was used, the reaction gave the desired product **3ai** in 50% yield. The sterically hindered 2,2-difluoro-2-mesitylacetic acid **2h** was also a compatible substrate in the cascade aryldifluoromethylation/cyclization leading to **3ah** in 55% yield. Additionally, the α,α-difluoroarylacetic acids with different halogen groups at position-4 of the benzene ring could offer the desired products in 32 to 60% yields (**3ak**–**am** and **3ao**), and the halogen groups were well tolerated. However, no desired product **3ap** was obtained when the *para*-substituent of benzene ring in the α,α-difluoroarylacetic acid is strong electron-withdrawing nitro group. Difluoroarylacetic acids bearing a strong electron-withdrawing group, such as CN or CF_3 at benzene ring, also made it difficult to provide the desired product. The results showed that the substituents on the benzene ring of α,α-difluoroarylacetic acid have a great influence on the reaction activity. This could be attributed to the fact that the electron-donating group substituted aryldifluoromethyl radicals produced in situ under silver-promoted condition demonstrated greater electron-rich property than that of non-substituted or strong electron-withdrawing group substituted phenyldifluoromethyl radical. Thus, the electron-richer aryldifluoromethyl radicals were capable of facilitating addition to unactivated double bonds in 2-allyloxybenzaldehyde. To further investigate the reaction scope, 2,2-difluoro-2-((4-methoxyphenyl)thio)acetic acid **2q** was also employed as substrate, and an unexpected regio-selective product, **3aq′**, was achieved in 29% yield besides the desired product **3aq** in 30% yield. The structure of **3aq′** was further characterized by X-ray single crystal diffraction analysis (Figure 2) and the NMR and HR-MS etc. Additionally, when aliphatic 2,2-difluorobutanoic acid (**2r**) was employed in this transformation, the reaction also gave the desired product **3ar** in 13% yield.

The generality of this cascade aryldifluoromethylation/cyclization toward different 2-allyloxybenzaldehydes was also explored. As shown in Table 3, a variety of 2-allyloxybenzaldehydes **1** were employed to react with 2,2-difluoro-2-(4-methoxyphenyl) acetic acid (**2b**). This method successfully gave the corresponding products **3** in moderate to good yields. The substrates **1b**–**d** bearing electron-donating groups reacted smoothly, delivering the corresponding chroman-4-one derivatives **3bb**–**3db** in moderate yields (35–50%). Unexpectedly, the reaction of the di-*t*-Bu-substituted 2-allyloxybenzaldehyde (**1e**) provided the corresponding product **3eb** in trace amount in the aqueous CH_3CN solution (CH_3CN:H_2O = 1:3) under standard conditions, while it delivered **3eb** in 45% yield in the DMSO. The substrates monosubstituted by different halogens at different positions of the benzene ring in 2-allyloxybenzaldehydes (**1f**–**1k**) gave the desired product in moderate yields as well. Additionally, halogen functional groups were well tolerated in this protocol. The di-bromo-substituted substrate **1m** was not a good substrate for this transformation. However, the cascade aryldifluoromethylation/cyclization of 2-((2-methylallyl)oxy) benzaldehyde **1m** could afford the product **3mb** in 41% in DMSO. Notably, the reaction of 2-allylbenzaldehyde **1n** with 2,2-difluoro-2-(4-methylphenyl)acetic acid (**2a**) could also deliver the corresponding product **3na** in 37% yield.

Table 2. Scope of α,α-difluoroarylacetic acids [a,b].



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $AgNO_3$ (20 mol%) and $K_2S_2O_8$ (0.4 mmol) in 2.0 mL CH_3CN/H_2O (v/v = 1:3) solution at 80 °C for 4 h under N_2 atmosphere. [b] Isolated yields.

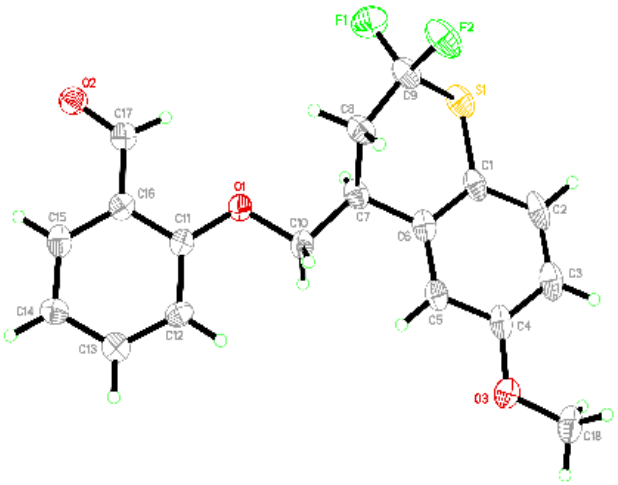
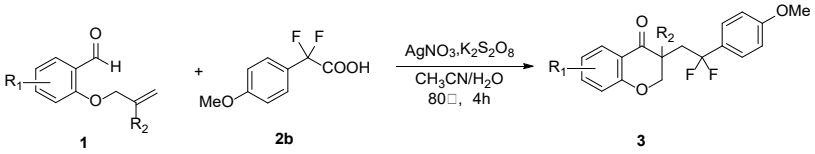
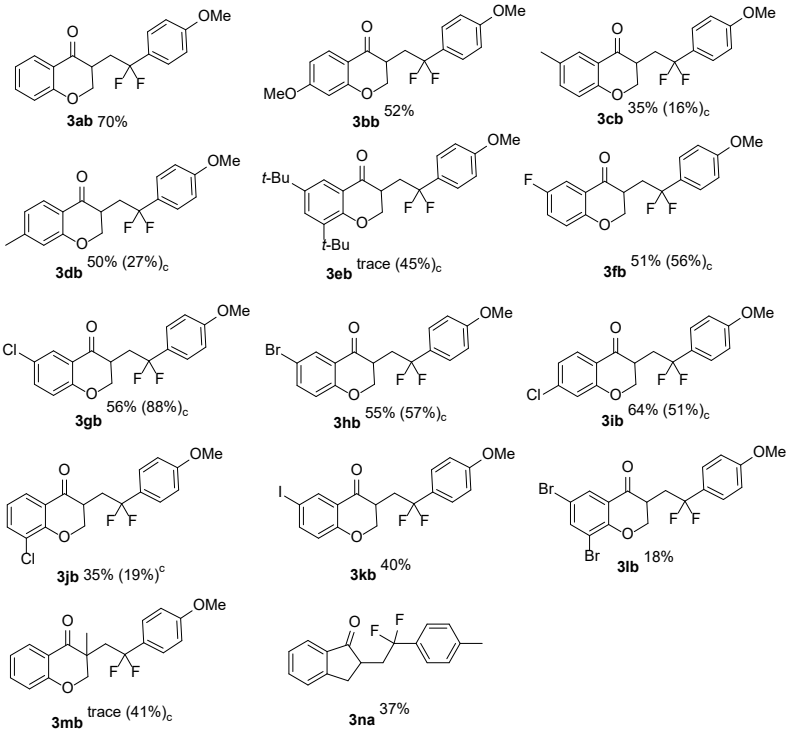


Figure 2. X-ray crystallography of **3aq′** (gray for carbon atoms, green for fluorine atom, yellow for sulfur atom and red for oxygen atom).

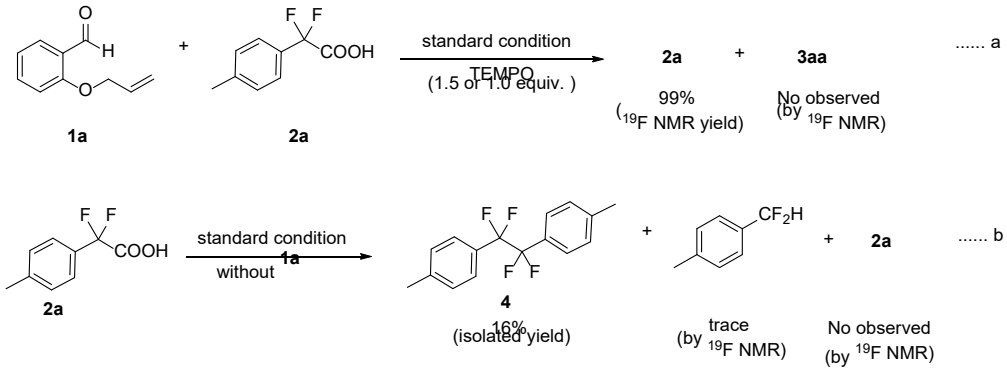
Table 3. Scope of 2-allyloxybenzaldehydes [a,b].





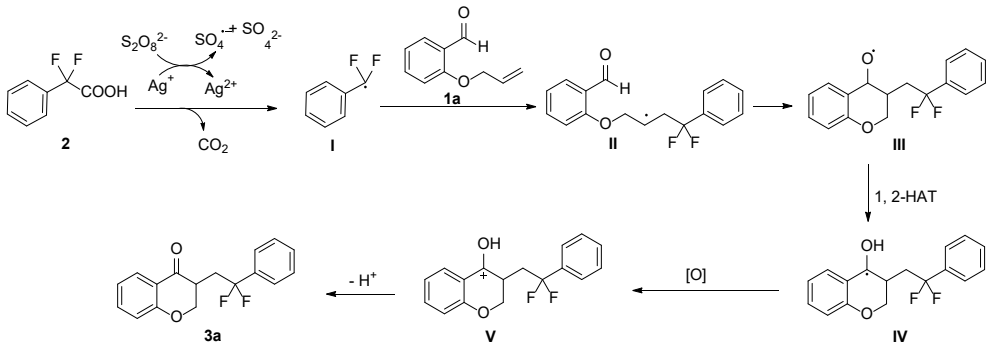
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $AgNO_3$ (20 mol%) and $K_2S_2O_8$ (0.4 mmol) in 2.0 mL CH_3CN:H_2O = 1:3 solution at 80 °C for 4 h under N_2 atmosphere. [b] Isolated yields. [c] **1a** (0.2 mmol), **2** (0.3 mmol), $(NH_4)_2S_2O_8$ (0.4mmol) in 2.0 mL DMSO at 40 °C for 6 h under N_2 atmosphere.

To gain more insight into the reaction mechanism and identify whether a radical pathway is involved in the silver promoted cascade aryldifluoromethylation/cyclization or not, some control experiments were carried out. When 1.0 or 1.5 equiv. of radical scavenger TEMPO were added into the reaction system of 4-methyl difluorophenylacetic acid (**2a**) and 2-allyloxybenzaldehyde **1a** under the standard conditions, the reaction provided neither the desired product **3aa** nor adduct of TEMPO with phenyldifluoromethyl radical based on ^{19}F NMR analysis. Additionally, the conversion of **2a** was completely inhibited under the standard conditions because **2a** almost totally remained in the above reaction system by ^{19}F NMR monitoring (Scheme 2a). We deduced from the results that the reaction may undergo a radical process. To further capture the phenyl difluoromethyl radical to verify this speculation, the reaction of only 4-methyl difluorophenylacetic acid (**2a**) used as substrate under the standard conditions in the absence of 2-allyloxybenzaldehyde **1a** was performed (Scheme 2b). The phenyl difluoromethyl radical self-coupling product **4** was obtained in 16% isolated yield. Thus, it was indicated that the phenyl difluoromethyl radical as intermediate could be involved in the reaction process (Scheme 2).



Scheme 2. Control experiments.

On the basis of the above-mentioned results and previous reports [35,37–42], a possible mechanism for the reaction is depicted in Scheme 3. First, α,α-difluorophenylacetic acid **2** undergoes an oxidative decarboxylation process under the promotion of Ag(I) to give the corresponding phenyldifluoromethyl radical **I** [43]. Then, the addition of **I** to the unactivated C=C double bond of 2-allyloxybenzaldehyde **1a** affords an alkyl radical **II**. The alkyl radical intermediate **II** attacking the C-O double bond led to an alkoxy radical intermediate **III**, realizing an intramolecular cyclization. Afterward, a formal 1,2-hydrogen atom transfer produces the α-hydroxy carbon-centered radical **IV**. Subsequently, radical **IV** is oxidized to give the carbocation intermediate **V** [43]. At last, the proton transfer of intermediate **V** leads to the final product **3a**. The product **3aq'** could be formed by the cyclization of the alkyl radical intermediate **II'** arising from a process similar to that of radical intermediate **II** to the benzene ring of **2q** instead of attacking the C-O double bond.



Scheme 3. Plausible reaction mechanism.

3. Conclusions

In conclusion, we established a facile radical cascade aryldifluoromethylation/cyclization method to synthesize a series of 3-aryldifluoromethyl-containing chroman-4-one derivatives in moderate to good yields. These reactions involved the addition of aryldifluoromethyl radicals in situ produced from easily accessible *gem*-difluoroarylacetic acids to unactivated double bonds in 2-allyloxybenzaldehydes under silver-promoted conditions. This benign protocol replaces the use of expensive photocatalysts in visible light redox catalytic conditions and provides a new perspective to construct pharmaceutically valuable, 3-difluoromethylene-containing chroman-4-one derivatives.

4. Materials and Methods

General Procedure for the Synthesis of Compounds ***3***

2-Allyloxyarylaldehyde **1** (0.20 mmol), $K_2S_2O_8$ (2.0 equiv, 0.40 mmol), $AgNO_3$ (20 mol%, 0.04 mmol) and α,α-difluoroarylacetic acid **2** (1.5 equiv, 0.30 mmol) were placed in a 10-mL round-bottom flask. Solvent CH_3CN/H_2O (v/v = 1:3, 2.0 mL) were then added under nitrogen atmosphere. The solution was stirred at 80 °C for 4 h. The resulting mixture

was cooled down to room temperature and extracted with EA (5 mL × 4). The combined organic phase was dried over anhydrous Na_2SO_4. After the removal of solvent under reduced pressure, the crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford pure 3-difluoromethylene-containing chroman-4-one **3**.

3-(2,2-Difluoro-2-(m-tolyl)ethyl)chroman-4-one (**3ae**), 35.1 mg, 58% yield, light yellow solid; mp 67.3–67.6 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.47 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.36–7.30 (m, 3H), 7.25 (s, 1H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 4.76 (dd, *J* = 11.4, 5.1 Hz, 1H), 4.26 (t, *J* = 11.7 Hz, 1H), 3.24–2.96 (m, 2H), 2.40 (s, 3H), 2.19–1.93 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −89.87 (ddd, *J* = 245.2, 24.6, 8.1 Hz), −97.24 (ddd, *J* = 245.1, 22.3, 16.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 161.6, 138.5, 136.5 (t, $^2J_{C\text{-}F}$ = 26.0 Hz), 136.0, 130.9, 128.6, 127.5, 125.5 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 122.8 (t, $^1J_{C\text{-}F}$ = 243.4 Hz), 122.0 (t, $^3J_{C\text{-}F}$ = 6.2 Hz), 121.5, 120.4, 117.8, 70.5, 41.3, 34.3 (t, $^2J_{C\text{-}F}$ = 28.1 Hz), 21.5; IR (KBr): 3065, 2924, 1687, 1606, 1460, 1369, 1149, 1077, 764, 702, 665; HRMS (ESI) calcd. for $C_{18}H_{16}F_2O_2$ $[M + H]^+$ 303.1197, found: 303.1193.

3-(2-(3,4-Dimethylphenyl)-2,2-difluoroethyl)chroman-4-one (**3ag**), 58.2 mg, 92% yield, light yellow solid; mp 84.5–84.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.47 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 7.31 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.01 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.75 (dd, *J* = 11.5, 5.1 Hz, 1H), 4.25 (t, *J* = 11.7 Hz, 1H), 3.27–2.89 (m, 2H), 2.31 (s, 3H), 2.29 (s, 3H), 2.14–1.99 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −88.88 (ddd, *J* = 245.1, 23.9, 8.1 Hz), −96.66 (dt, *J* = 245.1, 19.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 161.7, 138.8, 137.1, 136.0, 134.0 (t, $^2J_{C\text{-}F}$ = 26.2 Hz), 129.8, 127.5, 126.0 (t, $^3J_{C\text{-}F}$ = 6.0 Hz), 122.9 (t, $^1J_{C\text{-}F}$ = 242.8 Hz), 122.3 (t, $^3J_{C\text{-}F}$ = 6.2 Hz), 121.5, 120.4, 117.8, 70.6, 41.3, 35.3 (t, $^2J_{C\text{-}F}$ = 28.6 Hz), 19.9, 19.6; IR (KBr): 3051, 2925, 1688, 1607, 1467, 1393, 1138, 1028, 822, 767, 681; HRMS (ESI) calcd. for $C_{19}H_{18}F_2O_2$ $[M + H]^+$ 317.1353, found: 317.1359.

3-(2,2-Difluoro-2-(m-tolyl)ethyl)chroman-4-one (**3ae**), 36.3 mg, 55% yield, light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.5, 7.2, 1.8 Hz, 1H), 7.03 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.87 (s, 2H), 4.86 (dd, *J* = 11.3, 5.2 Hz, 1H), 4.34 (t, *J* = 11.6 Hz, 1H), 3.34 (dddd, *J* = 11.8, 8.5, 5.2, 2.7 Hz, 1H), 3.04 (dddd, *J* = 33.1, 15.9, 7.2, 2.7 Hz, 1H), 2.43 (t, *J* = 4.4 Hz, 6H), 2.27 (s, 3H), 2.16–2.01 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −85.20– −86.00 (m), −88.96 (dd, *J* = 250.6, 28.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 161.7, 139.0, 136.0, 136.0 (t, $^3J_{C\text{-}F}$ = 3.6 Hz), 131.2, 130.9 (t, $^2J_{C\text{-}F}$ = 23.6 Hz), 127.5, 125.4 (t, $^1J_{C\text{-}F}$ = 244.3 Hz), 121.5, 120.5, 117.9, 70.8 (d, $^3J_{C\text{-}F}$ = 4.7 Hz), 41.0, 33.7 (t, $^2J_{C\text{-}F}$ = 26.7 Hz), 22.2 (t, $^3J_{C\text{-}F}$ = 6.5 Hz), 20.7; IR (KBr): 3027, 2926, 1693, 1604, 1467, 1375, 1160, 1037, 860, 761; HRMS (ESI) calcd. for $C_{20}H_{20}F_2O_2$ $[M + H]^+$ 331.1510, found: 331.1511.

3-(2-(Benzo[d][1,3]dioxol-5-yl)-2,2-difluoroethyl)chroman-4-one (**3aj**), 27.6 mg, 41% yield, light yellow solid; mp 46.3–46.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.47 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H), 7.06–6.92 (m, 4H), 6.83 (d, *J* = 8.1 Hz, 1H), 5.99 (s, 2H), 4.72 (dd, *J* = 11.4, 5.0 Hz, 1H), 4.24 (t, *J* = 11.7 Hz, 1H), 3.17–2.93 (m, 2H), 2.11–1.98 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.57 (ddd, *J* = 244.5, 23.5, 8.1 Hz), −95.50 (ddd, *J* = 244.3, 21.7, 16.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.1, 161.6, 149.0, 148.0, 136.1, 130.4 (t, $^2J_{C\text{-}F}$ = 26.6 Hz), 127.5, 122.6 (t, $^1J_{C\text{-}F}$ = 243.1 Hz), 121.5, 120.4, 119.0 (t, $^3J_{C\text{-}F}$ = 6.8 Hz), 117.8, 108.2, 105.7 (t, $^3J_{C\text{-}F}$ = 6.2 Hz), 101.6, 70.5, 41.3, 34.3 (t, $^2J_{C\text{-}F}$ = 28.5 Hz); IR (KBr): 3045, 2920, 1691, 1604, 1498, 1447, 1101, 1038, 815, 758, 664; HRMS (ESI) calcd. for $C_{18}H_{14}F_2O_4$ $[M + H]^+$ 333.0938, found: 333.0934.

3-(2,2-Difluoro-2-(4-fluorophenyl)ethyl)chroman-4-one (**3ak**), 24.5 mg, 40% yield, white solid; mp 93.6–93.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.53 (dd, *J* = 8.8, 5.2 Hz, 2H), 7.48 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1H), 7.12 (t, *J* = 8.6 Hz, 2H), 7.06–6.99 (m, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 4.75 (dd, *J* = 11.3, 5.2 Hz, 1H), 4.26 (t, *J* = 11.6 Hz, 1H), 3.22–2.93 (m, 1H), 2.24–1.89 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −88.92 (ddd, *J* = 247.0, 24.8, 7.1 Hz), −96.62 (ddd, *J* = 246.6, 22.5, 15.7 Hz), −110.5; ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 163.6 (d, $^1J_{C\text{-}F}$ = 250.0 Hz), 161.6, 136.1, 132.6 (td, $^2J_{C\text{-}F}$ = 26.8 Hz, $^4J_{C\text{-}F}$ = 3.2 Hz), 127.5, 127.2 (dt, $^3J_{C\text{-}F}$ = 6.3 Hz, $^3J_{C\text{-}F}$ = 6.2 Hz), 122.9 (t, $^1J_{C\text{-}F}$ = 243.3 Hz), 121.6, 120.3, 117.8,

115.8 (d, $^{2}J_{C\text{-}F}$ = 22.0 Hz), 70.5, 41.2, 34.3 (t, $^{2}J_{C\text{-}F}$ = 28.0 Hz); IR (KBr): 3069, 2922, 1696, 1609, 1515, 1472, 1237, 1164, 1099, 832, 754; HRMS (ESI) calcd. for $C_{17}H_{13}F_3O_2$ $[M + H]^+$ 307.0946, found: 307.0945.

3-(2-(3-Bromophenyl)-2,2-difluoroethyl)chroman-4-one (**3an**), 19.1 mg, 26% yield, white solid; mp 60.1–60.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.69 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.51–7.45 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.77 (dd, *J* = 11.3, 5.2 Hz, 1H), 4.27 (t, *J* = 11.7 Hz, 1H), 3.21–2.94 (m, 2H), 2.17–1.97 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −90.78 (ddd, *J* = 246.6, 26.2, 7.6 Hz), −97.89 (ddd, *J* = 246.6, 23.7, 14.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 161.7, 138.7 (t, $^{2}J_{C\text{-}F}$ = 26.9 Hz), 136.2, 133.3, 130.3, 128.2 (t, $^{3}J_{C\text{-}F}$ = 6.4 Hz), 127.6, 123.6 (t, $^{3}J_{C\text{-}F}$ = 6.0 Hz), 122.8, 121.8 (t, $^{1}J_{C\text{-}F}$ = 243.9 Hz), 121.6, 120.3, 117.8, 70.5, 41.1, 34.3 (t, $^{2}J_{C\text{-}F}$ = 27.5 Hz); IR (KBr): 3035, 2923, 1693, 1603, 1470, 1120, 1064, 1001, 794, 753, 689, 591; HRMS (ESI) calcd. for $C_{17}H_{13}BrF_2O_2$ $[M + H]^+$ 367.0145, found: 367.0141.

3-(2,2-Difluoro-2-(4-iodophenyl)ethyl)chroman-4-one (**3ao**), 49.7 mg, 60% yield, light yellow solid; mp 116.0–116.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.47 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.01 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.74 (dd, *J* = 11.4, 5.1 Hz, 1H), 4.25 (t, *J* = 11.6 Hz, 1H), 3.16–2.96 (m, 2H), 2.10–1.99 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −90.34 (ddd, *J* = 246.9, 24.9, 7.7 Hz), −97.88 (ddd, *J* = 246.8, 22.8, 15.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 161.6, 137.9, 136.2, 136.2 (t, $^{2}J_{C\text{-}F}$ = 26.6 Hz), 127.6, 126.7 (t, $^{3}J_{C\text{-}F}$ = 5.8 Hz), 122.4 (t, $^{1}J_{C\text{-}F}$ = 243.6 Hz), 121.6, 120.3, 117.8, 96.6, 70.4, 41.1, 34.1 (t, $^{2}J_{C\text{-}F}$ = 27.8 Hz); IR (KBr): 3009, 2905, 1689, 1595, 1466, 1112, 1021, 826, 763, 555; HRMS (ESI) calcd. for $C_{17}H_{13}F_2IO_2$ $[M + H]^+$ 415.0007, found: 415.0011.

3-(2,2-Difluoro-2-((4-methoxyphenyl)thio)ethyl)chroman-4-one (**3aq**), 21.0 mg, 30% yield, white solid; mp 67.5–68.0 °C; ^{1}H NMR (500MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 7.49 (ddd, *J* = 8.8, 7.2, 1.8 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.3, 1.0 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.75 (dd, *J* = 11.4, 5.3 Hz, 1H), 4.22 (t, *J* = 11.8 Hz, 1H), 3.83 (s, 3H), 3.33–3.19 (m, 1H), 3.11–3.00 (m, 1H), 2.15–1.95 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.65 (ddd, *J* = 207.3, 19.6, 8.6 Hz), −74.59 (dt, *J* = 207.2, 17.4 Hz); ^{13}C NMR (125; MHz, $CDCl_3$) δ 191.6, 161.6, 161.3, 138.2, 136.1, 129.4 (t, $^{1}J_{C\text{-}F}$ = 278.2 Hz), 127.6, 121.6, 120.3, 117.8, 116.8, 114.8, 70.3, 55.4, 41.7, 33.8 (t, $^{2}J_{C\text{-}F}$ = 24.6 Hz); IR (KBr): 3052, 2929, 1688, 1596, 1469, 1394, 1153, 1026, 960, 823, 761; HRMS (ESI) calcd. for $C_{18}H_{16}F_2O_3S$ $[M + H]^+$ 351.0866, found: 351.0865.

2-((2,2-Difluoro-6-methoxythiochroman-4-yl)methoxy)benzaldehyde (**3aq'**), 20.3 mg, 29% yield, white solid; mp 64.0–64.5 °C; ^{1}H NMR (500MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.84 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.54 (ddd, *J* = 9.1, 7.4, 1.8 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.46–4.31 (m, 2H), 3.78 (s, 3H), 3.61–3.56 (m, 1H), 2.81–2.72 (m, 1H), 2.66–2.58 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.89 (ddd, *J* = 219.7, 22.1, 13.6 Hz), −64.51 (dt, *J* = 219.8, 12.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.2, 160.6, 158.4, 136.0, 134.5, 130.5 (t, $^{1}J_{C\text{-}F}$ = 268.7 Hz) 128.8, 128.3 (t, $^{3}J_{C\text{-}F}$ = 2.9 Hz), 125.0, 121.3, 120.8, 115.1, 113.7, 112.5, 68.2 (d, $^{3}J_{C\text{-}F}$ = 3.4 Hz), 55.5, 39.0 (d, ^{3}J = 5.6 Hz), 37.6 (t, $^{2}J_{C\text{-}F}$ = 23.8 Hz); IR (KBr): 3067, 2926, 1739, 1678, 1599, 1568, 1496, 1074, 1022, 990, 890, 806, 760; HRMS (ESI) calcd. for $C_{18}H_{16}F_2O_3S$ $[M + H]^+$ 351.0866, found: 351.0863.

3-(2,2-Difluorobutyl)chroman-4-one (**3ar**), 6.3 mg, 13% yield, light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.53–7.44 (m, 1H), 7.02 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.76 (dd, *J* = 11.4, 5.2 Hz, 1H), 4.24 (t, *J* = 11.7 Hz, 1H), 3.17 (dddd, *J* = 12.1, 8.9, 5.3, 3.0 Hz, 1H), 2.74 (dddd, *J* = 29.4, 15.4, 10.9, 3.0 Hz, 1H), 2.00–1.87 (m, 2H), 1.80 (dddd, *J* = 24.8, 15.8, 9.3, 6.9 Hz, 1H), 1.06 (t, *J* = 7.5 Hz, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −96.70–−98.13 (m), −100.51–−101.83 (m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 161.7, 136.0, 127.5, 125.0 (t, $^{1}J_{C\text{-}F}$ = 242.0 Hz), 121.5, 120.4, 117.8, 70.7, 40.9, 31.3 (t, $^{2}J_{C\text{-}F}$ = 25.4 Hz), 30.5 (t, $^{2}J_{C\text{-}F}$ = 26.0 Hz), 6.6 (t, $^{3}J_{C\text{-}F}$ = 5.7 Hz); IR (KBr): 3041, 2928, 1694, 1609, 1468, 1370, 1137, 1040, 764, 673; HRMS (ESI) calcd. for $C_{13}H_{14}F_2O_2$ $[M + H]^+$ 241.1040, found: 241.1037.

3-(2,2-Difluoro-2-(4-methoxyphenyl)ethyl)-7-methoxychroman-4-one (**3bb**), 36.2 mg, 52% yield, white solid; mp 105.9–106.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.57 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.39 (d, *J* = 2.3 Hz, 1H), 4.70 (dd, *J* = 11.2, 5.2 Hz, 1H), 4.22 (t, *J* = 11.5 Hz, 1H), 3.82 (s, 6H), 3.32–2.85 (m, 2H), 2.31–1.82 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.41 (ddd, *J* = 245.4, 23.5, 8.1 Hz), −95.84 (dt, *J* = 248.5, 20.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 166.0, 163.6, 160.8, 129.2, 128.8 (t, $^{2}J_{C\text{-}F}$ = 26.8 Hz), 126.4 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 123.0 (t, $^{1}J_{C\text{-}F}$ = 242.2 Hz), 114.2, 113.9, 110.1, 100.6, 70.9, 55.6, 55.4, 40.9, 34.3 (t, $^{2}J_{C\text{-}F}$ = 28.5 Hz); IR (KBr): 3021, 2957, 1690, 1614, 1511, 1460, 1374, 1614, 1167, 1026, 879, 830; HRMS (ESI) calcd. For $C_{19}H_{18}F_2O_4$ $[M + H]^+$ 349.1251, found: 349.1248.

3-(2,2-Difluoro-2-(4-methoxyphenyl)ethyl)-6-methylchroman-4-one (**3cb**), 23.3 mg, 35% yield, white solid; mp 69.6–70.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 8.9, 2.3 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 1H), 4.69 (dd, *J* = 11.2, 5.1 Hz, 1H), 4.21 (t, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.21–2.94 (m, 2H), 2.30 (s, 3H), 2.12–2.00 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.69 (ddd, *J* = 245.5, 23.3, 8.2 Hz), −95.74 (ddd, *J* = 245.5, 21.5, 16.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 160.8, 159.7, 137.1, 130.9, 128.8 (t, $^{2}J_{C\text{-}F}$ = 26.8 Hz), 127.0, 126.4 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 122.9 (t, $^{1}J_{C\text{-}F}$ = 242.2 Hz), 120.0, 117.6, 113.9, 70.5, 55.4, 41.4, 34.3 (t, $^{2}J_{C\text{-}F}$ = 28.8 Hz), 20.4; IR (KBr): 3027, 2916, 1697, 1617, 1501, 1424, 1302, 1169, 1028, 823, 735; HRMS (ESI) calcd. for $C_{19}H_{18}F_2O_3$ $[M + H]^+$ 333.1302, found: 333.1306.

3-(2,2-Difluoro-2-(4-methoxyphenyl)ethyl)-7-methylchroman-4-one (**3db**), 33.2 mg, 50% yield, white solid; mp 64.4–64.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.82 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1H), 6.76 (s, 1H), 4.70 (dd, *J* = 11.4, 5.2 Hz, 1H), 4.21 (t, *J* = 11.6 Hz, 1H), 3.82 (s, 3H), 3.20–2.88 (m, 2H), 2.35 (s, 3H), 2.05 (dddd, *J* = 22.4, 15.9, 9.7, 8.7 Hz, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.58 (ddd, J = 245.5, 23.2, 8.1 Hz), −95.75 (ddd, *J* = 245.4, 21.5, 16.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 161.7, 160.8, 147.6, 128.8 (t, $^{2}J_{C\text{-}F}$ = 26.9 Hz), 127.4, 126.4 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 122.9 (t, $^{1}J_{C\text{-}F}$ = 242.0 Hz), 122.9, 118.1, 117.8, 113.9, 70.5, 55.4, 41.2, 34.2 (t, $^{2}J_{C\text{-}F}$ = 28.6 Hz), 21.9; IR (KBr): 3019, 2934, 1684, 1612, 1513, 1319, 1167, 974, 827; HRMS (ESI) calcd. for $C_{19}H_{18}F_2O_3$ $[M + H]^+$ 333.1302, found: 333.1300.

6,8-Di-tert-butyl-3-(2,2-difluoro-2-(4-methoxyphenyl)ethyl)chroman-4-one (**3eb**), 38.8 mg, 45% yield, light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.5 Hz, 1H), 7.54 (d, *J* = 2.6 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.79 (s, 1H), 4.22 (t, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 3.18–2.97 (m, 2H), 2.18–2.00 (m, 1H), 1.40 (s, 9H), 1.30 (s, 9H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.06 (ddd, *J* = 245.5, 23.6, 7.9 Hz), −95.98 (ddd, *J* = 245.5, 21.8, 16.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 160.8, 158.8, 143.4, 138.3, 130.8, 128.9 (t, $^{2}J_{C\text{-}F}$ = 26.8 Hz), 126.5 (t, $^{3}J_{C\text{-}F}$ = 6.1 Hz), 123.0 (t, $^{1}J_{C\text{-}F}$ = 242.4 Hz), 121.5, 120.4, 113.9, 70.0, 55.4, 41.3, 35.1, 34.5, 34.4 (t, $^{2}J_{C\text{-}F}$ = 28.4 Hz), 31.3, 29.7; IR (KBr): 3006, 2920, 1682, 1613, 1471, 1364, 1171, 1023, 846, 758, 678; HRMS (ESI) calcd. for $C_{26}H_{32}F_2O_3$ $[M + H]^+$ 431.2398, found: 431.2395.

3-(2,2-Difluoro-2-(4-methoxyphenyl)ethyl)-6-fluorochroman-4-one (**3fb**), 34.3 mg, 51% yield, white solid; mp 112.4–112.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.3, 3.2 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.20 (ddd, *J* = 9.1, 7.7, 3.2 Hz, 1H), 6.95 (dd, *J* = 8.6, 5.0 Hz, 3H), 4.73 (dd, *J* = 11.7, 5.2 Hz, 1H), 4.23 (t, *J* = 11.8 Hz, 1H), 3.83 (s, 3H), 3.15–3.00 (m, 2H), 2.13–2.00 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.90 (ddd, *J* = 245.6, 23.8, 8.2 Hz), −95.81 (ddd, *J* = 245.5, 21.9, 16.3 Hz), -121.27 (td, *J* = 8.1, 4.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.5, 160.9, 158.2, 157.9 (d, $^{4}J_{C\text{-}F}$ = 1.7 Hz), 156.3, 128.6 (t, $^{2}J_{C\text{-}F}$ = 26.8 Hz), 126.4 (dd, $^{3}J_{C\text{-}F}$ = 6.4Hz, *J* = 5.6Hz), 123.6 (d, $^{2}J_{C\text{-}F}$ = 24.6 Hz), 122.7 (t, $^{1}J_{C\text{-}F}$ = 242.1 Hz), 120.7 (d, $^{3}J_{C\text{-}F}$ = 6.6 Hz), 119.5 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz), 112.4 (d, $^{2}J_{C\text{-}F}$ = 23.4 Hz), 70.7, 55.6, 41.2, 34.2 (dd, $^{2}J_{C\text{-}F}$ = 29.2, 28.0 Hz); IR (KBr): 3061, 2939, 1686, 1619, 1487, 1441, 1380, 1122, 1020, 897, 822, 744; HRMS (ESI) calcd. for $C_{18}H_{15}F_3O_3$ $[M + H]^+$ 337.1052, found: 337.1049.

6-Chloro-3-[2,2-difluoro-2-(4-methoxy-phenyl)-ethyl]-chroman-4-one (**3gb**), 39.5 mg, 56% yield, white solid; mp 116.1–116.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.7 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.41 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.93 (dd, *J* = 8.8, 5.7 Hz, 3H), 4.74 (dd,

J = 11.6, 5.2 Hz, 1H), 4.23 (t, *J* = 11.7 Hz, 1H), 3.83 (s, 3H), 3.15–3.00 (m, 2H), 2.12–1.98 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.93 (ddd, *J* = 245.8, 24.0, 8.1 Hz), −95.83 (ddd, *J* = 245.5, 22.0, 16.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.1, 160.9, 160.1, 135.9, 128.7 (t, $^2J_{C\text{-}F}$= 26.9 Hz), 127.0, 126.8, 126.4 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 122.7 (t, $^1J_{C\text{-}F}$ = 242.3 Hz), 121.1, 119.6, 114.0, 70.6, 55.4, 41.2, 34.2 (t, $^2J_{C\text{-}F}$ = 28.9 Hz); IR (KBr): 3087, 2921, 1698, 1610, 1571, 1515, 1472, 1381, 1104, 1022, 889, 826, 776, 426; HRMS (ESI) calcd. for $C_{18}H_{15}ClF_2O_3$ $[M + H]^+$ 353.0756, found: 353.0753.

6-Bromo-3-(2,2-difluoro-2-(4-methoxyphenyl)ethyl)chroman-4-one (**3hb**), 43.7 mg, 55% yield, white solid; mp 125.4–125.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.5 Hz, 1H), 7.54 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.75 (dd, *J* = 11.5, 5.1 Hz, 1H), 4.23 (t, *J* = 11.7 Hz, 1H), 3.83 (s, 3H), 3.18–2.96 (m, 2H), 2.19–1.91 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.93 (ddd, *J* = 245.7, 24.0, 8.0 Hz), −95.83 (ddd, *J* = 245.5, 22.0, 16.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 160.9, 160.5, 138.7, 129.9, 128.6 (t, $^2J_{C\text{-}F}$= 26.9 Hz), 126.4 (t, $^3J_{C\text{-}F}$ = 5.9 Hz), 122.7 (t, $^1J_{C\text{-}F}$ = 242.2 Hz), 121.6, 119.9, 114.1, 114.0, 70.6, 55.4, 41.1, 34.2 (t, $^2J_{C\text{-}F}$ = 28.7 Hz); IR (KBr): 3083, 2908, 1697, 1608, 1515, 1470, 1103, 1023, 889, 824, 777, 675; HRMS (ESI) calcd. for $C_{18}H_{15}BrF_2O_3$ $[M + H]^+$ 397.0251, found: 397.0253.

7-Chloro-3-(2,2-difluoro-2-(4-methoxyphenyl)ethyl)chroman-4-one (**3ib**), 45.2 mg, 64% yield, white solid; mp 116.3–116.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.00–6.97 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.75 (dd, *J* = 11.7, 5.2 Hz, 1H), 4.24 (t, *J* = 11.8 Hz, 1H), 3.82 (s, 3H), 3.17–2.97 (m, 2H), 2.15–1.95 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.90 (ddd, *J* = 245.6, 23.9, 8.2 Hz), −95.75 (ddd, *J* = 245.6, 21.9, 16.2 Hz); ^{13}C NMR (125MHz, $CDCl_3$) δ 191.2, 162.0, 160.9, 141.9, 128.8, 128.6 (t, $^2J_{C\text{-}F}$ = 26.8 Hz), 126.4 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 122.8 (t, $^1J_{C\text{-}F}$ = 242.0 Hz), 122.3, 118.9, 118.0, 114.0, 70.8, 55.4, 41.2, 34.2 (t, $^2J_{C\text{-}F}$ = 28.6 Hz); IR (KBr): 3012, 2949, 1674, 1605, 1516, 1468, 1379, 1069, 1025, 934, 834, 806, 705, 579, 448; HRMS (ESI) calcd. for $C_{18}H_{15}ClF_2O_3$ $[M + H]^+$ 353.0756, found: 353.0755.

8-Chloro-3-(2,2-difluoro-2-(4-methoxyphenyl)ethyl)chroman-4-one (**3jb**), 24.7 mg, 35% yield, light yellow solid; mp 76.1–76.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.56 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.46 (d, *J* = 9.2 Hz, 2H), 7.00–6.91 (m, 3H), 4.89 (dd, *J* = 11.2, 5.2 Hz, 1H), 4.31 (t, *J* = 11.6 Hz, 1H), 3.83 (s, 3H), 3.23–2.95 (m, 2H), 2.15–2.01 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.87 (ddd, *J* = 245.9, 23.0, 8.2 Hz), −95.55 (ddd, *J* = 246.0, 21.4, 16.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.3, 160.9, 157.1, 136.1, 128.5 (t, $^2J_{C\text{-}F}$ = 26.8 Hz), 126.4 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 126.1, 122.7 (t, $^1J_{C\text{-}F}$ = 242.4 Hz), 122.6, 121.6, 121.6, 114.0, 71.1, 55.4, 41.2, 34.1 (t, $^2J_{C\text{-}F}$ = 28.9 Hz); IR (KBr): 3074, 2924, 1682, 1608, 1450, 1515, 1374, 1115, 1023, 835, 767, 730, 595, 432; HRMS (ESI) calcd. for $C_{18}H_{15}ClF_2O_3$ $[M + H]^+$ 353.0756, found: 353.0759.

3-(2,2-Cifluoro-2-(4-methoxyphenyl)ethyl)-6-iodochroman-4-one (**3kb**), 35.5 mg, 40% yield, white solid; mp 130.1–131.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.2 Hz, 1H), 7.70 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 4.74 (dd, *J* = 11.5, 5.1 Hz, 1H), 4.22 (t, *J* = 11.7 Hz, 1H), 3.82 (s, 3H), 3.14–2.99 (m, 2H), 2.10–1.99 (m, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.86 (ddd, *J* = 245.8, 24.0, 7.8 Hz), −95.71 (ddd, *J* = 245.5, 21.8, 16.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 161.2, 160.9, 144.3, 136.1, 128.6 (t, $^2J_{C\text{-}F}$ = 26.7 Hz), 126.4 (t, $^3J_{C\text{-}F}$ = 6.1 Hz), 122.7 (t, $^1J_{C\text{-}F}$ = 242.3 Hz), 122.2, 120.2, 114.0, 83.8, 70.5, 55.4, 41.0, 34.2 (t, $^2J_{C\text{-}F}$ = 28.7 Hz); IR (KBr): 3078, 2902, 1692, 1592, 1514, 1101, 1027, 893, 823, 781, 571; HRMS (ESI) calcd. for $C_{18}H_{15}F_2IO_3$ $[M + H]^+$ 445.0122, found: 445.0124.

6,8-Dibromo-3-(2,2-difluoro-2-(4-methoxyphenyl)ethyl)chroman-4-one (**3lb**), 17.1 mg, 18% yield, white solid; mp 125.2–125.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.4 Hz, 1H), 7.83 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.90 (dd, *J* = 11.5, 5.4 Hz, 1H), 4.30 (t, *J* = 12.0 Hz, 1H), 3.83 (s, 3H), 3.21–2.97 (m, 2H), 2.20–1.96 (m, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −87.96 (ddd, *J* = 25.8, 23.4, 7.7 Hz), −95.58 (ddd, *J* = 245.8, 21.4, 16.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 160.9, 157.1, 141.1, 129.4, 128.4 (t, $^2J_{C\text{-}F}$ = 26.6 Hz), 126.4 (t, $^3J_{C\text{-}F}$ = 6.0 Hz), 122.6 (t, $^1J_{C\text{-}F}$ = 241.7 Hz), 122.2, 114.0, 112.6, 71.2, 55.4, 40.8, 34.1 (t, $^2J_{C\text{-}F}$ = 28.9 Hz); IR (KBr): 3063, 2939, 1685, 1614, 1515, 1438, 1114,

1022, 894, 837, 806, 767, 576; HRMS (ESI) calca. For $C_{18}H_{14}Br_2F_2O_3$ $[M + H]^+$ 474.9356, found: 474.9353.

3-(2,2-Difluoro-2-(4-methoxyphenyl)ethyl)-3-methylchroman-4-one (**3mb**), 27.3 mg, 41% yield, light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.48 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.03 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.98 (dd, *J* = 8.4, 0.7 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 11.7 Hz, 1H), 3.82 (s, 3H), 2.74 (ddd, *J* = 29.9, 15.7, 7.9 Hz, 1H), 2.42 (ddd, *J* = 26.9, 15.7, 11.5 Hz, 1H), 1.32 (s, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −89.01 (ddd, *J* = 243.5, 29.9, 11.5 Hz), −90.24 (ddd, *J* = 243.3, 26.7, 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.2, 161.0, 160.6, 135.7, 130.0 (t, $^2J_{C\text{-}F}$ = 26.7 Hz), 128.1, 126.3 (t, $^3J_{C\text{-}F}$ = 6.3 Hz), 122.9 (t, $^1J_{C\text{-}F}$ =244.2 Hz), 121.6, 119.3, 117.7, 113.7, 74.5, 55.3, 44.1, 41.7 (t, $^2J_{C\text{-}F}$ = 27.6 Hz), 19.8; IR (KBr): 3072, 2932, 1690, 1611, 1515, 1467, 1363, 1111, 1031, 829, 764; HRMS (ESI) calcd. for $C_{19}H_{18}F_2O_3$ $[M + H]^+$ 333.1302, found: 333.1306.

2-(2,2-Difluoro-2-(p-tolyl)ethyl)-2,3-dihydro-1H-inden-1-one (**3na**), 21.1mg, 37% yield, white solid; mp 122.8–123.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.38 (d, *J* = 7.1 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 3.44 (dd, *J* = 17.5, 8.1 Hz, 1H), 3.08–2.92 (m, 2H), 2.90–2.81 (m, 1H), 2.39 (s, 3H), 2.14 (dddd, *J* = 20.7, 14.9, 11.5, 8.0 Hz, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −90.63 (ddd, *J* = 244.7, 21.8, 7.9 Hz), −96.99 (ddd, *J* = 244.6, 20.3, 16.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 153.7, 140.0, 136.0, 135.0, 134.1 (t, $^2J_{C\text{-}F}$ = 26.4 Hz), 129.2, 127.5, 126.5, 124.8 (t, $^3J_{C\text{-}F}$ = 6.2 Hz), 124.0, 123.2 (t,$^1J_{C\text{-}F}$ = 242.7 Hz), 42.9, 40.2 (t, $^2J_{C\text{-}F}$ = 27.8 Hz), 33.9, 21.3; IR (KBr): 3054, 2924, 1711, 1597, 1460, 1080, 1021, 849, 811, 760; HRMS (ESI) calcd. for $C_{18}H_{16}F_2O$ $[M + H]^+$ 287.1247, found: 287.1243.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules28083578/s1, [34,42,44–46], Table S1: Screening the reaction time; Table S2: Screening the reaction temp; Figure S1: Crystal structure of 3aq′; Table S3: Sample and crystal data for 3aq′; Table S4: Bond lengths (Å) for 3aq′; Table S5: Bond angles (°) for 3aq′; Figure S2: Copies of ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra of all compounds.

Author Contributions: Conceptualization, H.J.; methodology, H.J. and J.H.; validation, H.J. and Q.S.; formal analysis, Q.S. and H.D.; investigation Q.S., H.L. and X.C.; writing—original draft preparation, H.J. and Q.S.; writing—review and editing, H.J. and J.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are contained in the article tables and Supplementary Materials.

Acknowledgments: We thank the Instrumental Analysis and Research Center of Shanghai University for assistance.

Conflicts of Interest: The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Sample Availability: Samples of the compounds 3 are available from the authors.

References

1. Emami, S.; Ghanbarimasir, Z. Recent advances of chroman-4-one derivatives: Synthetic approaches and bioactivities. *Eur. J. Med. Chem.* **2015**, *93*, 539–563. [CrossRef]
2. Fridén Saxin, M.; Seifert, T.; Landergren, M.R.; Suuronen, T.; Lahtela Kakkonen, M.; Jarho, E.M.; Luthman, K. Synthesis and evaluation of substituted chroman-4-one and chromone derivatives as sirtuin 2-selective inhibitors. *J. Med. Chem.* **2012**, *55*, 7104–7113. [CrossRef] [PubMed]
3. Godlewski, G.; Offertaler, L.; Wagner, J.A.; Kunos, G. Receptors for acylethanolamides-GPR55 and GPR119. *Prostag. Oth. Lipid Mediat.* **2009**, *89*, 105–111. [CrossRef]

4. McKee, T.C.; Bokesch, H.R.; McCormick, J.L.; Rashid, M.A.; Spielvogel, D.; Gustafson, K.R.; Alavanja, M.M.; Cardellina, J.H.; Boyd, M.R. Isolation and characterization of new anti-HIV and cytotoxic leads from plants, marine, and microbial organisms. *J. Nat. Prod.* **1997**, *60*, 431–438. [CrossRef]
5. Hu, Q.F.; Niu, D.Y.; Zhou, B.; Ye, Y.Q.; Du, G.; Meng, C.Y.; Gao, X.M. Isoflavanones from the stem of cassia siamea and their anti-tobacco mosaic virus activities. *Bull. Korean Chem. Soc.* **2013**, *34*, 3013–3016. [CrossRef]
6. Li, C.; Cao, Y.X.; Wang, R.; Wang, Y.N.; Lan, Q.; Wang, X.S. Cobalt-catalyzed difluoroalkylation of tertiary aryl ketones for facile synthesis of quaternary alkyl difluorides. *Nat. Commun.* **2018**, *9*, 4951. [CrossRef] [PubMed]
7. Hirano, K.; Biju, A.T.; Piel, I.; Glorius, F. N-Heterocyclic carbene-catalyzed hydroacylation of unactivated double bonds. *J. Am. Chem. Soc.* **2009**, *131*, 14190–14191. [CrossRef]
8. Hu, H.; Chen, X.; Sun, K.; Wang, J.; Liu, Y.; Liu, H.; Fan, L.; Yu, B.; Sun, Y.; Qu, L.; et al. Silver-Catalyzed radical cascade cyclization toward 1,5-/1,3-dicarbonyl heterocycles: An atom-/step-economical strategy leading to chromenopyridines and isoxazole-/pyrazole-containing chroman-4-ones. *Org. Lett.* **2018**, *20*, 6157–6160. [CrossRef]
9. Li, K.; Chen, J.; Yang, C.; Zhang, K.; Pan, C.; Fan, B. Blue light promoted difluoroalkylation of aryl ketones: Synthesis of quaternary alkyl difluorides and tetrasubstituted monofluoroalkenes. *Org. Lett.* **2020**, *22*, 4261–4265. [CrossRef]
10. Xie, L.-Y.; Peng, S.; Yang, L.-H.; Liu, X.-W. Metal-Free Synthesis of Carbamoylated Chroman-4-Ones via Cascade Radical Annulation of 2-(Allyloxy)arylaldehydes with Oxamic Acids. *Molecules* **2022**, *27*, 7049. [CrossRef]
11. Sheng, J.; Liu, J.; Chen, L.; Zhang, L.; Zheng, L.; Wei, X. Silver-catalyzed cascade radical cyclization of 2-(allyloxy)arylaldehydes with cyclopropanols: Access to chroman-4-one derivatives. *Org. Chem. Front.* **2019**, *6*, 1471–1475. [CrossRef]
12. Mei, Y.; Zhao, L.; Liu, Q.; Ruan, S.; Wang, L.; Li, P. Synthesis of sulfone-functionalized chroman-4-ones and chromans through visible-light-induced cascade radical cyclization under transition-metal-free conditions. *Green Chem.* **2020**, *22*, 2270–2278. [CrossRef]
13. Pan, X.; Xia, H.; Wu, J. Recent advances in photoinduced trifluoromethylation and difluoroalkylation. *Org. Chem. Front.* **2016**, *3*, 1163–1185. [CrossRef]
14. Hollingworth, C.; Gouverneur, V. Transition metal catalysis and nucleophilic fluorination. *Chem. Commun.* **2012**, *48*, 2929–2942. [CrossRef]
15. Ni, C.; Hu, M.; Hu, J. Good partnership between sulfur and fluorine: Sulfur-Based fluorination and fluoroalkylation reagents for organic synthesis. *Chem. Rev.* **2015**, *115*, 765–825. [CrossRef]
16. Hu, J.; Zhang, W.; Wang, F. Selective difluoromethylation and monofluoromethylation reactions. *Chem. Commun.* **2009**, 7465–7478. [CrossRef]
17. Tozer, M.J.; Herpin, T.F. Methods for the synthesis of gem-difluoromethylene compounds. *Tetrahedron* **1996**, *52*, 8619–8683. [CrossRef]
18. Wang, J.; Sánchez Roselló, M.; Aceña, J.L.; Del Pozo, C.; Sorochinsky, A.E.; Fustero, S.; Soloshonok, V.A.; Liu, H. Fluorine in pharmaceutical industry: Fluorine-Containing drugs introduced to the market in the last decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. [CrossRef]
19. Müller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: Looking beyond intuition. *Science* **2007**, *317*, 1881–1886. [CrossRef]
20. Gillis, E.P.; Eastman, K.J.; Hill, M.D.; Donnelly, D.J.; Meanwell, N.A. Applications of fluorine in medicinal chemistry. *J. Med. Chem.* **2015**, *58*, 8315–8359. [CrossRef]
21. Anderson, M.O.; Zhang, J.; Liu, Y.; Yao, C.J.; Phuan, P.W.; Verkman, A.S. Nanomolar potency and metabolically stable inhibitors of kidney urea transporter UT-B. *J. Med. Chem.* **2012**, *55*, 5942–5950. [CrossRef] [PubMed]
22. Middleton, W.J.; Bingham, E.M. α,α-Difluoroarylacetic acids: Preparation from (diethylamino)sulfur trifluoride and α-oxoarylacetates. *J. Org. Chem.* **1980**, *45*, 2883–2887. [CrossRef]
23. Umemoto, T.; Singh, R.P.; Xu, Y.; Saito, N. Discovery of 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride as a deoxofluorinating agent with high thermal stability as well as unusual resistance to aqueous hydrolysis, and its diverse fluorination capabilities including deoxofluoro-arylsulfinylation with high stereoselectivity. *J. Am. Chem. Soc.* **2010**, *132*, 18199–18205.
24. Lal, G.S.; Pez, G.P.; Pesaresi, R.J.; Prozonic, F.M.; Cheng, H. Bis(2-methoxyethyl)aminosulfur trifluoride: A new broad-spectrum deoxofluorinating agent with enhanced thermal stability. *J. Org. Chem.* **1999**, *64*, 7048–7054. [CrossRef]
25. Xia, J.B.; Zhu, C.; Chen, C. Visible light-promoted metal-free C-H activation: Diarylketone-Catalyzed selective benzylic mono- and difluorination. *J. Am. Chem. Soc.* **2013**, *135*, 17494–17500. [CrossRef] [PubMed]
26. Xu, C.; Guo, W.H.; He, X.; Guo, Y.L.; Zhang, X.Y.; Zhang, X.G. Difluoromethylation of (hetero)aryl chlorides with chlorodifluoromethane catalyzed by nickel. *Nat. Commun.* **2018**, *9*, 1170. [CrossRef] [PubMed]
27. Xiao, Y.L.; Min, Q.Q.; Xu, C.; Wang, R.W.; Zhang, X.G. Nickel-Catalyzed difluoroalkylation of (hetero)arylborons with unactivated 1-bromo-1,1-difluoroalkanes. *Angew. Chem. Int. Ed.* **2016**, *55*, 5837–5841. [CrossRef] [PubMed]
28. Min, Q.Q.; Yin, Z.S.; Feng, Z.; Guo, W.H.; Zhang, X.G. Highly selective gem-difluoroallylation of organoborons with bromodifluoromethylated alkenes catalyzed by palladium. *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233. [CrossRef]
29. Chen, F.; Hashmi, A.S.K. Silver-Catalyzed decarboxylative alkynylation of α,α-difluoroarylacetic acids with ethynylbenziodoxolone reagents. *Org. Lett.* **2016**, *18*, 2880–2882. [CrossRef]
30. Yuan, J.-W.; Zhang, M.-Y.; Liu, Y.; Hu, W.-Y.; Yang, L.-R.; Xiao, Y.-M.; Diao, X.-Q.; Zhang, S.-R.; Mao, J. Transition-metal-free radical difluorobenzylation/cyclization of unactivated alkenes: Access to $ArCF_2$-substituted ring-fused quinazolinones. *Org. Biomol. Chem.* **2022**, *20*, 9722–9733. [CrossRef]
31. Zhao, H.; Ma, G.; Xie, X.; Wang, Y.; Hao, J.; Wan, W. Pd(II)-Catalyzed decarboxylative meta-C-H difluoromethylation. *Chem. Commun.* **2019**, *55*, 3927–3930. [CrossRef] [PubMed]
32. Hong, G.; Yuan, J.; Fu, J.; Pan, G.; Wang, Z.; Yang, L.; Xiao, Y.; Mao, P.; Zhang, X. Transition-metal-free decarboxylative C3-difluoroarylmethylation of quinoxalin-2(1H)-ones with α,α-difluoroarylacetic acids. *Org. Chem. Front.* **2019**, *6*, 1173–1182. [CrossRef]

33. Wille, U. Radical cascades initiated by intermolecular radical addition to alkynes and related triple bond systems. *Chem. Rev.* **2013**, *113*, 813–853. [CrossRef]
34. Zhou, Y.; Xiong, Z.; Qiu, J.; Kong, L.; Zhu, G. Visible light photocatalytic acyldifluoroalkylation of unactivated alkenes for the direct synthesis of gem-difluorinated ketones. *Org. Chem. Front.* **2019**, *6*, 1022–1026. [CrossRef]
35. Zhou, N.; Wu, M.; Zhang, M.; Zhou, X. Visible-light-induced difluoroacetylation of O-(allyloxy) aryl-aldehydes: Access to difluoroacetylated chroman-4-ones. *Asian J. Org. Chem.* **2019**, *8*, 828–831. [CrossRef]
36. Huang, H.L.; Du, J.Y.; Li, Q.L.; Gao, F.; Ma, C.L. Visible-light-promoted cascade radical cyclization: Synthesis of chroman-4-ones and dihydroquinolin-4-ones. *J. Org. Chem.* **2020**, *85*, 3963–3972. [CrossRef]
37. Wang, P.; Du, P.; Sun, Q.; Zhang, J.; Deng, H.; Jiang, H. Silver-catalyzed decarboxylative radical allylation of α,α-difluoroarylacetic acids for the construction of CF_2-allyl bonds. *Org. Biomol. Chem.* **2021**, *19*, 2023–2029. [CrossRef]
38. Liu, X.; Wang, Z.; Cheng, X.; Li, C. Silver-Catalyzed decarboxylative alkynylation of aliphatic carboxylic acids in aqueous solution. *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333. [CrossRef] [PubMed]
39. Hu, F.; Shao, X.; Zhu, D.; Lu, L.; Shen, Q. Silver-Catalyzed decarboxylative trifluoromethylthiolation of aliphatic carboxylic acids in aqueous emulsion. *Angew. Chem. Int. Ed.* **2014**, *53*, 6105–6109. [CrossRef]
40. Zhu, Y.; Li, X.; Wang, X.; Huang, X.; Shen, T.; Zhang, Y.; Sun, X.; Zou, M.; Song, S.; Jiao, N. Silver-Catalyzed decarboxylative azidation of aliphatic carboxylic acids. *Org. Lett.* **2015**, *17*, 4702–4705. [CrossRef]
41. Du, P.; Sun, Q.; Li, H.; Zhang, J.; Deng, H.; Jiang, H. Silver-catalyzed radical cascade arylthiodifluoromethylation/cyclization of isonitriles for the synthesis of 6-phenanthridinyldifluoromethyl aryl thioethers. *Chem. Asian J.* **2022**, *17*, e202200088. [CrossRef] [PubMed]
42. Hu, H.; Chen, X.; Sun, K.; Wang, J.; Liu, Y.; Liu, H.; Yu, B.; Sun, Y.; Qu, L.; Zhao, Y. Silver-catalyzed decarboxylative cascade radical cyclization of tert-carboxylic acids and o-(allyloxy)arylaldehydes towards chroman-4-one derivatives. *Org. Chem. Front.* **2018**, *5*, 2925–2929. [CrossRef]
43. Cui, L.; Chen, H.; Liu, C.; Li, C. Silver-Catalyzed decarboxylative allylation of aliphatic carboxylic acids in aqueous solution. *Org. Lett.* **2016**, *18*, 2188–2191. [CrossRef] [PubMed]
44. Jagdale, A.R.; Park, J.H.; Youn, S.W. Cyclization Reaction for the Synthesis of Polysubstituted Naphthalenes in the Presence of Au (I) Precatalysts. *J. Org. Chem.* **2011**, *76*, 7204–7215. [CrossRef]
45. Mizuta, S.; Stenhagen, I.S.R.; O'Duill, M.; Wolstenhulme, J.; Kirjavainen, A.K.; Forsback, S.J.; Tredwell, M.; Sandford, G.; Moore, P.R.; Huiban, M.; et al. Catalytic decarboxylative fluorination for the synthesis of tri-and difluoromethyl arenes. *Org. Lett.* **2013**, *15*, 2648–2651. [CrossRef]
46. Chang, Y.; Tewari, A.; Adi, A.; Bae, C. Direct nucleophilic fluorination of carbonyl groups of benzophenones and benzils with Deoxofluor. *Tetrahedron* **2008**, *64*, 9837–9842. [CrossRef]