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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01635 • Publication Date (Web): 11 Oct 2017

Synthesis of 2,2-Difluorinated 4-Isoflavanols/4-Thioisoflavanols via a Base-Catalyzed [4+2] Annulation Reaction of *gem*-Difluoroolefins

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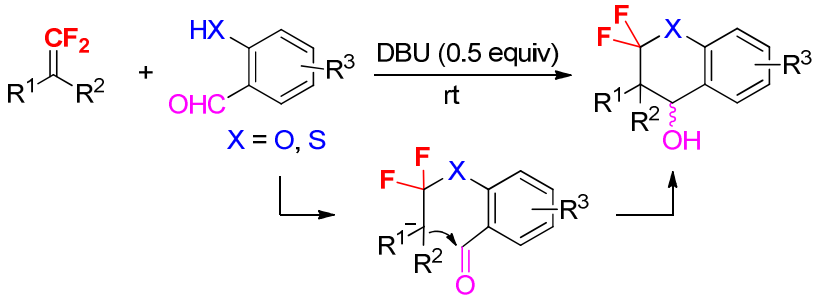


Abstract: DBU-catalyzed sequential intermolecular and intramolecular nucleophilic addition reactions between *gem*-difluoroolefins and *o*-hydroxy/mercapto benzaldehydes have been developed to provide a [4+2] annulation strategy for facile synthesis of *gem*-difluorinated isoflavanol derivatives. The competitive addition-elimination reaction of *gem*-difluoroolefins with nucleophiles was avoided under mild conditions, affording 2,2-difluorinated 4-isoflavanols or 2,2-difluoriated 4-thioisoflavanols in good to excellent yields.

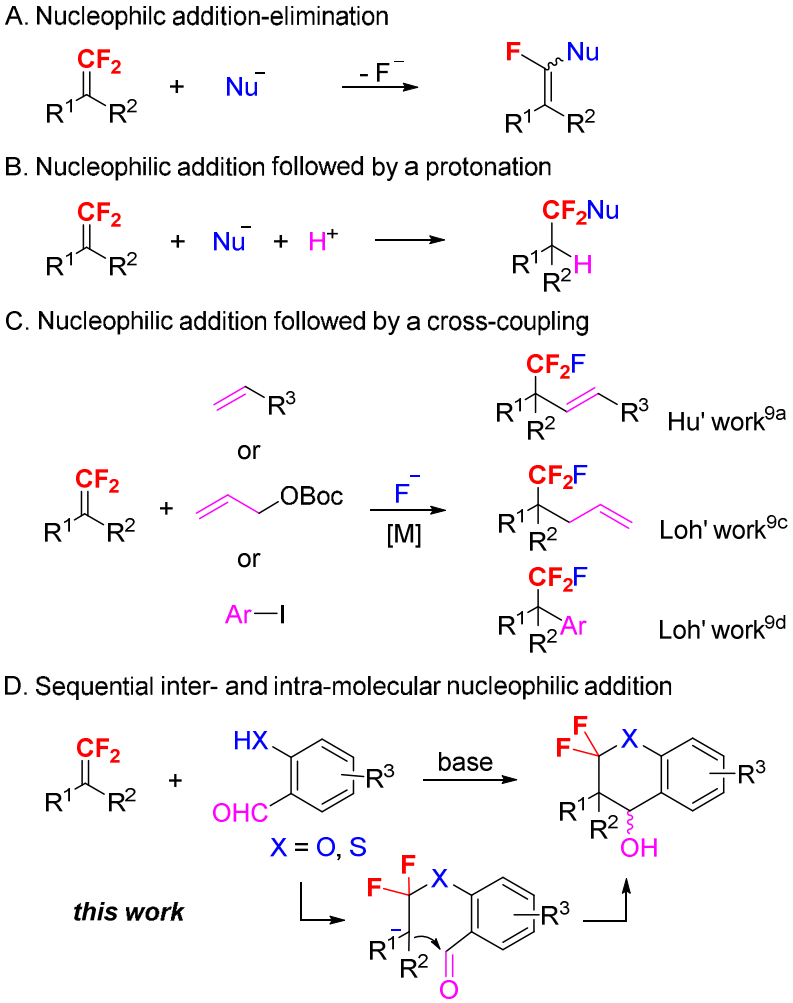
INTRODUCTION

Isoflavanols belong to the flavonoid family which is one of the most important natural products.[1] Their derivatives also play a role in medicinal chemistry.[1c] Organic molecules containing fluorine atom(s) generally display beneficial effects in either bioactivities or pharmaceutics.[2] Among them, CF_2-containing compounds are notable representatives.[3,4] Hence, reliable methods for the synthesis of *gem*-difluorinated isoflavanols are valuable for developing new drug candidates and biological probes.

gem-Difluoroolefins are useful fluorine-containing synthons.[5] The high electron-withdrawing property of two fluorine atoms along with thermodynamical instablility of fluoroalkenes endows their terminal CF_2 carbon with high reactivity to nucleophiles. As main reaction mode, nucleophilic vinylic substitution (S_NV) reactions of *gem*-difluoroolefins provide a useful approach for the synthesis of monofluoroalkenes (Scheme 1A).[5c,6] This addition-elimination process has proven to smoothly occur in the reactions of *gem*-difluoroolefins with various nucleophiles, including O-, S-, N-, Si-, P-, and C-based nucleophiles.[5c,6] Recently, *gem*-difluoroolefins have been found to be suitable coupling partners in metal-catalyzed cross-coupling reactions for achieving monofluoroalkenes.[5c,7] On the other hand, the nucleophilic addition to the difluorinated carbon of *gem*-difluoroolefins followed by an electrophilic trapping at the β-carbon is a competitive process which results in saturated *gem*-difluoromethyl adducts. Although it provides a facile route to synthesize CF_2-containing chemicals, the protocol has not yet been well applied in synthesis to date. To our knowledge, the direct quenching reaction at the β-C of *gem*-difluoroolefins is limited to protonation reaction by using a protonic solvent or a protonic reagent (Scheme 1B).[8] Hu's group reported in 2015 that the nucleophilic addition of fluorine anion to the *gem*-difluoroolefins could be evolved to a Ag-catalyzed cross-coupling with alkenes leading to trifluoromethyl-containing products (Scheme 1C).[9a] Loh and his co-workers recently

expended this F^- nucleophilic addition-induced cross-coupling to both allylic alkylation[9c] and arylation[9d] by using palladium catalyst (Scheme 1C). A cross-coupling-initiated process was also reported to deliver *gem*-difluorinated dihydroisoquinolin-1(2*H*)-ones *via* [4+2] cyclization between benzamides and 2,2-difluorovinyl tosylate.[10] Herein, we report a cascade process including a nucleophilic addition of ArO^-/ArS^- to *gem*-difluoroolefins followed by an intramolecular nucleophilic addition of the resulting anionic intermediate to the carbonyl group. It provides a new and catalytic [4+2] annulation method for the synthesis of *gem*-difluorinated heterocycles, including 2,2-difluorinated 4-isoflavanols and its thio-analogues.

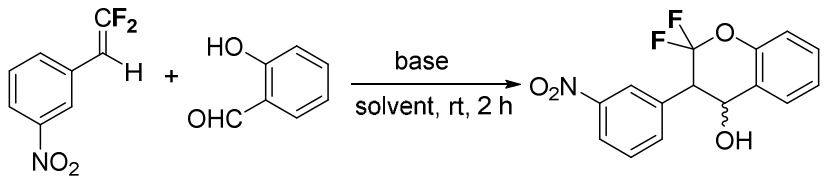
Scheme 1. Nucleophilic Addition Reactions of *gem*-Difluoroolefins and Transformations



RESULTS AND DISCUSSION

With our interest in the synthesis of difluorinated compounds[11] and heterocyclics,[12] we envisaged a strategy for the modular construction of 2,2-difluorinated 4-isoflavanol derivatives from *gem*-difluoroolefins and salicylaldehydes (Scheme 1D). Initially, we selected the reaction of 1-(2,2-difluorovinyl)-3-nitrobenzene **1a** with salicylaldehyde **2a** as the model reaction to identify reaction conditions. As described in Table 1, entry 1, the reaction indeed worked with the use of 2 equiv of K_2CO_3 in DMF at ambient temperature, affording the desired 2,2-difluorinated 4-isoflavanol **3a** in 62% yield. Trace amount of addition-elimination product was observed in the ^{1}H NMR spectrum of the crude product. When other bases were selected for the reaction, including carbonate, phosphate, hydroxide, alkoxide and hydride (entries 2-8), no increased yields were obtained. The reaction became messy in the case of using a strong base (entries 7 and 8). Among the tested organic bases, to our delight, DBU could give **3a** in quantitative yield in a shorter time (entries 9-14). Remarkably, a catalytic amount of DBU also furnished a high yield of **3a** (entries 15-17). Considering the importance of the base for this catalytic process, DABCO was also selected as the catalyst for the reaction. **3a** was obtained in 54% yield under identical conditions (entry 18). We proposed that both the pKa value and the solubility of the base should be the key factors for the catalytic transformations. A proper interaction between protonated DBU and phenolic anion might contribute to the annulation proceeding in a mild and catalytic manner. In addition, polar solvents gave better yields (entries 19-24). The compound **1a** was recovered quantitatively without a base even prolonging the reaction time to 12 h (entry 25).

Table 1. Optimization of the reaction conditions[a]



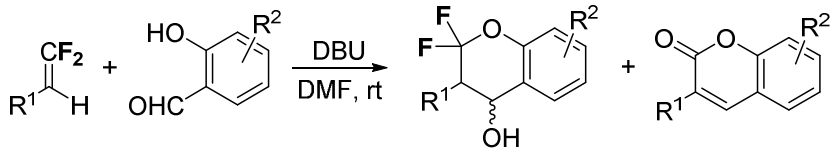
1a **2a** **3a**

entry	base/equiv	solvent	Yield[b]/% (trans:cis)[c]
1	K_2CO_3/2	DMF	62 (2:1)
2	Cs_2CO_3/2	DMF	67 (2:1)
3	Na_2CO_3/2	DMF	52 (2:1)
4	Li_2CO_3/2	DMF	22
5	K_3PO_4/2	DMF	68 (2:1)
6	KOH/2	DMF	25
7	*t*-BuOLi/2	DMF	23
8	NaH/2	DMF	ND[d]
9	piperidine/2	DMF	trace
10	Et_3N/2	DMF	33
11	*i*-Pr_2NEt/2	DMF	32
12	DMAP/2	DMF	30
13	DBU/2	DMF	100 (2:1)
14	DBU/1.1	DMF	100 (2:1), 93[e]
15	DBU/0.5	DMF	96 (2:1)
			92[e] (1.6:1)
16	DBU/0.3	DMF	88 (2:1)
17	DBU/0.1	DMF	80 (2:1)
18	DABCO/0.5	DMF	54 (2:1)
19	DBU/0.5	NMP	52 (2:1)
20	DBU/0.5	MeCN	54 (2:1)
21	DBU/0.5	DMSO	78 (2:1)
22	DBU/0.5	CH_2Cl_2	28
23	DBU/0.5	THF	34
24	DBU/0.5	diglyme	50
25[f]	-	DMF	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), solvent (1 mL), rt, 2 h. [b]^{1}H NMR yields standardized with 1,3,5-trimethoxybenzene. [c]The ratios of trans to cis were determined by ^{1}H NMR. [d]Not Determined. [e]isolated yields. [f]>12 h.

With the optimized conditions in hand, we explored the scope of *gem*-difluoroolefins **1** and salicylaldehydes **2**. As shown in Table 2, when **1** with R^1 bearing electron deficient group, including nitro, cyano, bromo, and alkoxycarbonyl, were selected as the substrates, **3a-e** could be obtained as a mixture of *trans* and *cis* isomers in good isolated yields (entries 1-5). Among these cases, **1e** also delivered 3-aryl coumarin **4e**, which should be formed by further dehydration and hydrolyzation of product **3e**, in 31% yield (entry 5).[13] Generally, the diastereoselectivities of the reactions were not satisfying, except that **3b** (Figure 1)[14] was isolated in a single isomer with hydroxyl group *cis* to R^1 likely due to the steric effect of *o*-NO_2 substituted R^1. In the cases of **1f** and **1g** with 2-naphthalenyl or cinnamyl substituent, **3f** and **3g** were isolated in 60% and 62% yield, respectively (entries 6 and 7). In comparison, **3h** along with **4h** were isolated in 28% and 65% yield, respectively with the use of **1h** as the substrate (entry 8). Moreover, electronic effect of the substrates **1** was proved to play a role in the transformations of 4-isoflavanols **3** into 3-aryl coumarins **4**. When *gem*-difluoroolefins **1i-k** having electron-rich R^1 substituents were used, **4i-k** were isolated as the final products (entries 9-11). In the next investigations, we examined the scope of salicylaldehydes **2**. It was found that all tested reactions could give **3** in high yields (entries 12-20).

Table 2. Synthesis of 2,2-Difluoro-4-isoflavanols[a]



1 **2** **3** **4**

entry	**1**, R^1	**2**, R^2	yield[b]/% (trans:cis)[c]
1	**1a**, 3-$NO_2C_6H_4$	**2a**, H	**3a**, 92 (1.6:1)
2	**1b**, 2-$NO_2C_6H_4$	**2a**, H	**3b**, 82[d]

3	**1c**, 3-CNC_6H_4	**2a**, H	**3c**, 88 (1.3:1)
4	**1d**, 4-BrC_6H_4	**2a**, H	**3d**, 79 (2:1)
5	**1e**, 4-$MeOCOC_6H_4$	**2a**, H	**3e**, 51 (2:1) **4e**, 31
6	**1f**, 2-naphthalenyl	**2a**, H	**3f**, 60 (3.8:1)[e]
7	**1g**, *E*-$PhCH_2$=CH	**2a**, H	**3g**, 62 (1.6:1)[e]
8	**1h**, 3-benzothiophenyl	**2a**, H	**3h**, 28 (3:1) **4h**, 65
9	**1i**, 4-$MeOC_6H_4$	**2a**, H	**4i**, 72
10	**1j**, 4-$BnOC_6H_4$	**2a**, H	**4j**, 68
11	**1k**, 3,4-$OCH_2OC_6H_3$	**2a**, H	**4k**, 69
12	**1a**, 3-$NO_2C_6H_4$	**2b**, 4-MeO	**3l**, 78 (1.7:1)
13	**1a,** 3-$NO_2C_6H_4$	**2c**, 5-MeO	**3m**, 86 (1.5:1)
14	**1a**, 3-$NO_2C_6H_4$	**2d**, 5-Me	**3n**, 79 (2:1)
15	**1a**, 3-$NO_2C_6H_4$	**2e**, 5-Cl	**3o**, 74 (1.5:1)
16	**1a**, 3-$NO_2C_6H_4$	**2f**, 3-F	**3p**, 80[f] (73[b], 1:1)
17	**1a**, 3-$NO_2C_6H_4$	**2g**, 5-F	**3q**, 71[f] (66[b], 1.3:1)
18	**1c**, 3-CNC_6H_4	**2g**, 5-F	**3r**, 78 (3.6:1)
19	**1a**, 3-$NO_2C_6H_4$	**2h**, 3,5-Br_2	**3s**, 83 (2.4:1)
20	**1a**, 3-$NO_2C_6H_4$	**2i**, 3-^{t}Bu	**3t**, 87[f] (73[b], 1:1.4)

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), DBU (0.5 equiv), DMF (3 mL), rt, 2 h. [b]Isolated yields. [c]The ratio of *trans*- to *cis*-isomers was determined by ^{1}H NMR. [d]*cis*-Isomer. [e]Coumarins **4** were detected. [f]The yield was determined by ^{1}H NMR using trimethoxybenzene as an internal standard.

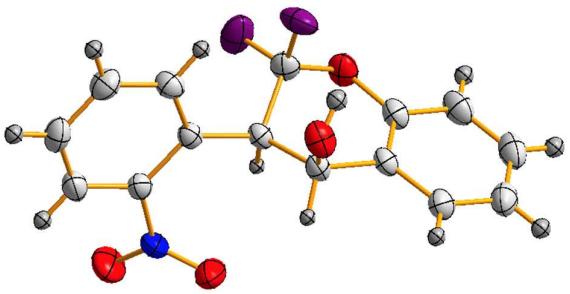
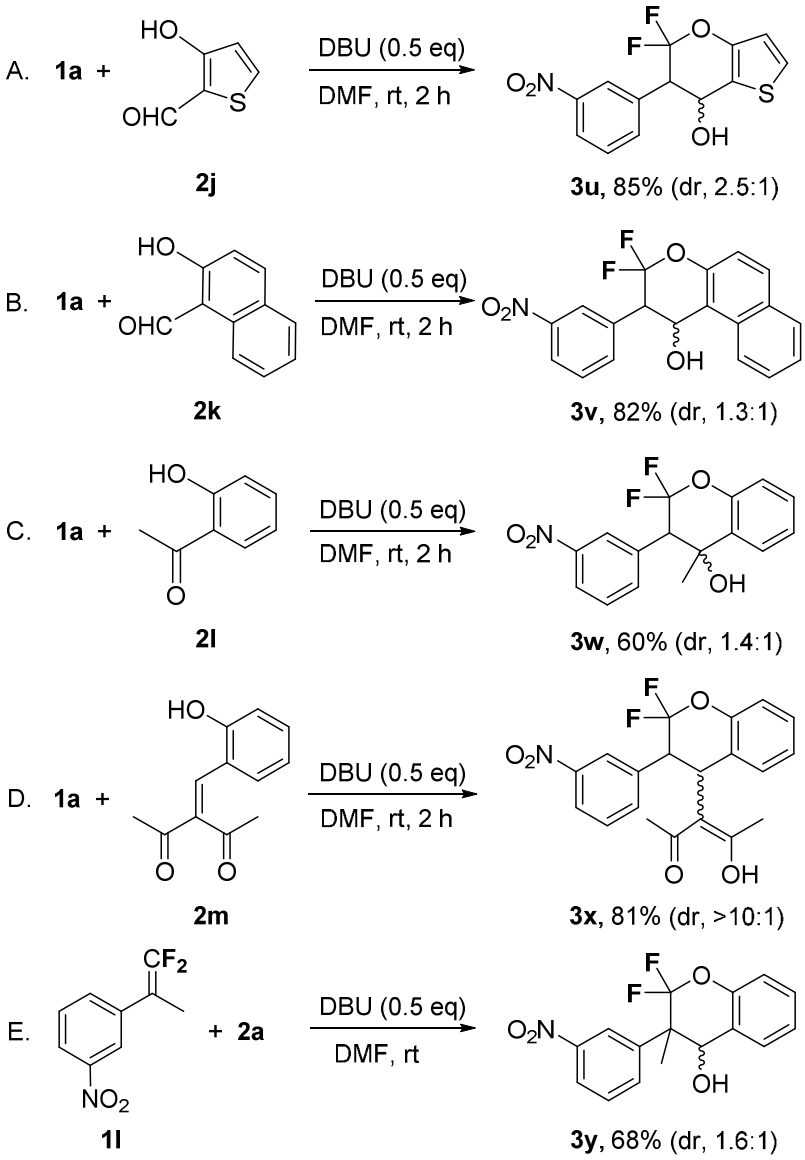


Figure 1. ORTEP representation of **3b** drawn with 50% probability thermal ellipsoids.

Encouraged by the above experimental results, we further expanded substrates **2** to those salicylaldehyde derivatives, including 3-hydroxythiophene-2-carbaldehyde **2j**, 2-hydroxy-1-naphthaldehyde **2k**, 1-(2-hydroxyphenyl)ethanone **2l**, and 3-(2-hydroxybenzylidene)pentane-

2,4-dione **2m**. It was found that the reactions of **2j**-**m** with **1a** could furnish the expected products **3u**-**x** in 60-85% yields under the standard reaction conditions (Scheme 2A-D). In addition, tetra-substituted *gem*-difluoroolefin **1l** also proved to be a suitable substrate toward this process. The reaction of **1l** and **2a** led to **3y** in 68% yield (Scheme 2E).

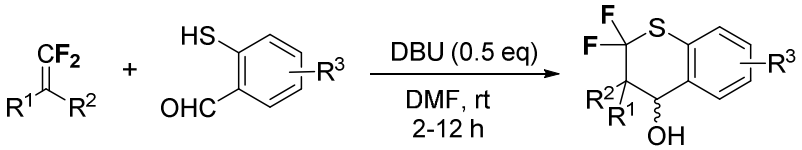
Scheme 2. Expanding Scope of Both **1** and **2**



Considering that thio-analogues of isoflavanols are also expected to have potential

bioactivity, we then carried out a set of reactions of **1** with 2-mercaptobenzaldehydes **5** using this [4+2] annulation strategy. As presented in Table 3, all tested *gem*-difluorolefins **1**, with electron-donating or electron-deficient substituent at different position (ortho, meta or para) of the phenyl ring, could smoothly react with **5a** or with **5b** to give 2,2-difluorinated 4-thioisoflavanols **6** in good yields. Among them, only **1b** gave **6b** in better diastereoselectivities (entries 2 and 11). Unlike salicylaldehydes **2** (Table 2, entries 5, 8-11), no corresponding thio-coumarin products were monitored even by reacting for longer time when 2-mercaptobenzaldehydes **5** were used as the substrates.

Table 3. Synthesis of 2,2-Difluoro-4-thioisoflavanols[a]



1 **5** **6**

entry	**1**, R^1, R^2	**5**, R^3	**6**	yield[b]/% (dr)[c]
1	**1a**, 3-$NO_2C_6H_4$, H	**5a**, H	6a	90 (1.7:1)
2	**1b**, 2-$NO_2C_6H_4$, H	**5a**, H	6b	81 (>20:1)
3	**1e**, 4-BrC_6H_4, H	**5a**, H	6c	86 (1:1)
4	**1n**, 1-naphthalenyl, H	**5a**, H	6d	83 (3.2:1)
5	**1g**, *E*-$PhCH_2$=CH, H	**5a**, H	6e	91 (1.8:1)
6	**1h**, 3-benzothiophenyl, H	**5a**, H	6f	82 (2.8:1)
7	**1i**, 4-$MeOC_6H_4$, H	**5a**, H	6g	76 (1:1)
8	**1j**, 4-$BnOC_6H_4$, H	**5a**, H	6h	71 (1.2:1)
9	**1k**, 3,4-$OCH_2OC_6H_3$, H	**5a**, H	6i	69 (1:1)
10	**1m**, 4-$MeSC_6H_4$, H	**5a**, H	6j	75 (1.2:1)
11	**1b**, 2-$NO_2C_6H_4$, H	**5b**, 4-MeO	6k	83 (>10:1)
12	**1l**, 3-$NO_2C_6H_4$, Me	**5b**, 4-MeO	6l	80 (2.8:1)

[a]Reaction conditions: **1** (0.3 mmol), **5** (0.3 mmol), DBU (0.5 equiv), DMF (3 mL), rt. [b]Isolated yields. [c]The dr values were determined by ^{1}H NMR.

CONCLUSION

In summary, we have successfully developed a facile approach for the synthesis of α,α-difluorinated isoflavanols and their thio-derivatives by using *gem*-difluoroolefins. Under the catalysis of a base, an intermolecular nucleophilic addition of ArO^-/ArS^- generated from *o*-hydroxy/mercaptobenzaldehydes affords an anionic intermediate for further intramolecular nucleophilic addition onto the *ortho*-carbonyl group of the aryl ring to complete a [4+2] annulation process. The competitive addition-elimination reaction of *gem*-difluoroolefins with nucleophiles is avoided under mild reaction conditions to afford 2,2-difluorinated 4-isoflavanols or 2,2-difluorinated 4-thioisoflavanols in good to excellent yields. The strategy broadened the synthetic utilization of *gem*-difluoroolefins and should facilitate access to libraries of fluorinated chemicals with potential bioactivities. Investigations on stereochemical control of the reaction are on-going in our laboratory.

EXPERIMENTAL SECTION

General: All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Solvents were distilled over CaH_2 or sodium/benzophenone before use, ultra anhydrous DMF was purchased from *J&K* Co. Ltd.. The products were isolated by silica gel column chromatography or preparative thin-layer chromatography (PTLC). ^1H NMR spectra were recorded at 25 ℃ on a Bruker 600 MHz or Varian (500 MHz, 400 MHz) and ^{13}C NMR were recorded at 25 ℃ on Bruker 151 MHz or Varian 126 MHz spectrometer by using TMS as internal standard, respectively. ^{19}F NMR were recorded at 25 ℃ on Bruker 565 MHz or Varian 470 MHz spectrometer by using $PhCF_3$ (δ = -63.7 ppm) as external standard. Coupling constants were reported in Hz and coupling patterns are described as s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dtd = doublet of triplet of doublets,

br = broad peak. High-resolution mass spectra (HRMS) were obtained using a Bruker micrOTOF Ⅱ spectrometer (ESI). Melting points were uncorrected. Compound **3b** with dimension 0.589 × 0.234 × 0.192 mm was glued on a glass fiber. Data were collected at 296 K using graphite-monochromated MoK\α radiation ($\lambda = 0.71073$ Å) and BrukerSmart Apex CCD detector in the range 2.41° <θ< 28.27°. *gem*-Difluorolefins **1**[15a], 2-hydroxybenzaldehydes **2j**[16a] and **2m**[16b], 2-mercaptobenzaldeydes **5a**[17] and **5b**[17] were prepared following the reported procedures. **1a**[15a], **1e**[15a], **1g**[15a], **1h**[15a], **1i**[15a], **1l**[15a], **1b**[15b], **1d**[15c], **1n**[15c], **1f**[15d], **1j**[15d], **1k**[15e], **1m**[15f] and products **4e**[18a], **4h**[18b], **4i**[18c], **4j**[18d], **4k**[18e] are known compounds.

General Procedure for the synthesis of 1c: To an oven-dried 25 mL flask with a magnetic stirrer, 3-formylbenzonitrile (656 mg, 5 mmol), (Triphenylphosphonio)difluoroacetate (PDFA, 3.56 g, 10 mmol) and NMP (8 mL) were added under N_2 (1 eq $B(OMe)_3$ was added for the preparation of **1b**). The reaction mixture was stirred at 80 ℃ for 4 h. Water was added to quench the reaction mixture after cooling to room temperature. The mixture was extracted with ethyl acetate (3× 15 mL) and then the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography (eluent: pure petroleum ether) to afford **1c** (677 mg, 82%).

General Procedure for the synthesis of 3 (**3a** was selected as an example): To a solution of **1a** (55.5 mg, 0.3 mmol) in DMF (3 mL) was added **2a** (32 μL, 0.3 mmol) and DBU (22 μL, 0.15 mmol) at ambient temperature, and the reaction was stirred under TLC monitoring until the starting material **1a** was consumed completely (2 h). Then, water was added to quench the reaction. After neutralization to pH = 7 using 1 M HCl, the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried over

anhydrous $MgSO_4$, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography (eluent: petroleum ether/EA = 24/1, V/V) to afford 2,2-difluorinated 4-isoflavanols **3a** as inseparable mixture of *trans*- and *cis*-diastereoisomers (84.8 mg, 92%, dr = 1.6 :1).

General Procedure for the synthesis of 6 (**6a** was selected as an example): To a solution of **1a** (55.5 mg, 0.3 mmol) in DMF (3 mL) was added **5a** (41.5 mg, 0.3 mmol) and DBU (22 μL, 0.15 mmol) at ambient temperature, and the reaction was stirred under TLC monitoring until the starting material **1a** was consumed completely (2 h). Then, water was added to quench the reaction. After neutralization to pH = 7 using 1 M HCl, the mixture was extracted with ethyl acetate (3 ×10 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacum. The crude product was purified by silica gel column chromatography (eluent: petroleum ether/EA = 20/1, V/V) to afford 2,2-difluorinated 4-thioisoflavanols **6a** as inseparable mixture of *trans*- and *cis*-diastereoisomers (87.3 mg, 90%, dr = 1.7 :1).

3-(2,2-difluorovinyl)benzonitrile (**1c**). White solid (677 mg, 82%). Mp: 55-56 ℃. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.58 – 7.48 (m, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 5.30 (dd, *J* = 24.4, 2.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.7 (dd, *J* = 300.4, 291.8 Hz), 131.8 (dd, *J* = 7.6, 6.3 Hz), 131.7 (dd, *J* = 6.3, 3.8 Hz), 130.8 (dd, *J* = 6.9, 3.7 Hz), 130.4, 129.5, 118.4, 113.0, 81.0 (dd, *J* = 30.6, 13.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -81.4 (t, *J* = 24.9 Hz), -82.9 (dd, *J* = 24.4, 2.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_9H_6F_2N$ $[M+H]^+$: 166.0468, found 166.0470.

trans-/cis-2,2-difluoro-3-(3-nitrophenyl)chroman-4-ol (**3a**). Light yellow semi-solid (84.8

mg, 92%, dr = 1.6∶1). *trans*-**3a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 8.0, 1H), 7.56 – 7.50 (m, 1H), 7.38 – 7.32 (m, 1H), 7.23 – 7.14 (m, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.33 – 5.19 (m, 1H), 3.61 (ddd, *J* = 19.2, 9.6, 2.4 Hz, 1H), 2.66 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.6 (d, *J* = 4.9 Hz), 148.3, 135.8, 134.9, 130.3, 129.8, 127.2, 124.3 (d, *J* = 1.5 Hz), 124.1, 123.5, 123.3, 122.5 (dd, *J* = 264.6, 258.3 Hz), 116.7, 68.3 (d, *J* = 5.5 Hz), 52.7 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.9 (d, *J* = 159.4 Hz), -76.0 (dd, *J* = 159.4, 19.2 Hz). *cis*-**3a**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.41 (t, *J* = 8.0, 1H), 7.38 – 7.32 (m, 1H), 7.23 – 7.14 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.17 – 5.06 (m, 1H), 3.88 (ddd, *J* = 17.6, 4.8, 2.0 Hz, 1H), 2.27 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0 (d, *J* = 1.6 Hz), 148.1, 136.13 (d, *J* = 1.1 Hz), 133.7, 130.9, 129.5, 128.8, 125.2 (d, *J* = 1.6 Hz), 124.3, 123.3, 122.6 (dd, *J* = 264.6, 258.3 Hz), 122.3, 117.0, 67.2 (d, *J* = 3.0 Hz), 49.5 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -69.3 (d, *J* = 159.7 Hz), -74.5 (dd, *J* = 159.7, 17.6 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{12}F_2NO_4$ $[M+H]^+$: 308.0729, found 308.0736.

cis-2,2-difluoro-3-(2-nitrophenyl)chroman-4-ol (**3b**). Light yellow solid (75.6 mg, 82%, dr = 100:0). Mp. 120-122 ℃. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.25 (dd, *J* = 12.7, 5.0 Hz, 1H), 4.53 (ddd, *J* = 19.1, 5.0, 1.9 Hz, 1H), 2.39 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 151.1, 149.0 (d, *J* = 3.5 Hz), 132.8, 131.2 (d, *J* = 6.2 Hz), 130.7, 129.4, 129.0, 126.1, 124.9, 124.2, 122.7 (dd, *J* = 267.1, 257.0 Hz), 122.3, 117.0, 67.0 (d, *J* = 3.5 Hz), 43.9 (t, *J* = 24.9 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -70.0 (d, *J* = 158.6 Hz), -73.7 (dd, *J* = 158.6, 19.1 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{11}F_2NNaO_4$ $[M+Na]^+$: 330.0548, found

330.0545.

trans-/cis-3-(2,2-difluoro-4-hydroxychroman-3-yl)benzonitrile (**3c**). Light yellow solid (75.8 mg, 88%, dr = 1.3∶1). *trans*-**3c**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.75 – 7.67 (m, 2H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz,1H), 7.48 – 7.39 (m, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.11 (dd, *J* = 8.0, 0.5 Hz, 1H), 5.30 – 5.24 (m, 1H), 3.63 (ddd, *J* = 19.5, 9.5, 2.0 Hz, 1H), 2.57 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.8 (d, *J* = 4.8 Hz), 134.6, 134.2, 132.9 (d, *J* = 1.8 Hz), 132.2, 130.3, 129.7, 127.3, 124.1, 123.4, 122.6 (dd, *J* = 265.2, 254.5 Hz), 118.3, 116.7, 113.0, 68.3 (d, *J* = 5.7 Hz), 52.7 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ 74.8 (d, *J* = 160.3 Hz), -76.0 (dd, *J* = 160.3, 19.5 Hz). *cis*-**3c**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.75 – 7.67 (m, 2H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.48 – 7.39 (m, 1 H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.14 (dd, *J* = 8.0, 0.5 Hz, 1H), 5.21 – 5.12 (m, 1H), 3.87 (ddd, *J* = 17.4, 5.0, 2.5 Hz, 1H), 2.16 (dd, *J* = 9.3, 1.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0, 134.5, 133.7 (d, *J* = 1.6 Hz), 133.3, 132.0, 130.9, 129.4, 128.8, 124.3, 122.6 (dd, *J* = 260.8, 257.0 Hz), 122.4, 118.4, 117.0, 112.7, 67.2 (d, *J* = 3.3 Hz), 49.6 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -69.0 (d, *J* = 161.0 Hz), -74.6 (dd, *J* = 161.0, 17.4 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{11}F_2NNaO_2$ $[M+Na]^+$: 310.0650, found 310.0644.

trans-/cis-3-(4-bromophenyl)-2,2-difluorochroman-4-ol (**3d**). Light yellow solid (80.9 mg, 79%, dr = 2∶1). *trans*-**3d**: **^{1}H** NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.10 – 5.04 (m, 1H), 3.42 – 3.34 (m, 1H), 2.60 (br, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9 (d, *J* = 4.7 Hz), 132.0 (2C), 131.6, 131.0 (2C), 130.1, 127.3, 123.8, 123.5, 122.8, 122.7 (dd, *J* = 260.3, 257.8 Hz), 116.6, 68.4 (d, *J* = 6.0 Hz), 52.5 (t, *J* =

25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -72.7 (d, *J* = 158.8 Hz), -74.2 (dd, *J* = 158.8, 19.8 Hz). *cis*-**3d**: **^{1}H** NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.01 (br, 1H), 3.74 – 3.67 (m, 1H), 2.15 – 2.06 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.1, 131.8 (2C), 131.6, 131.5 (2C), 130.5, 128.5, 124.1, 123.5, 122.9 (dd, *J* = 261.8, 258.2 Hz), 122.7, 116.8, 67.0 (t, *J* = 3.0 Hz), 49.3 (dd, *J* = 26.6, 24.5 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -66.2 (d, *J* = 159.3 Hz), -73.0 (dd, *J* = 159.3, 15.3 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{11}BrF_2NaO_2$ $[M+Na]^+$: 362.9803, found 362.9814.

trans-/cis-methyl 4-(2,2-difluoro-4-hydroxychroman-3-yl)benzoate (**3e**). White solid (49.0 mg, 51%, dr = 2∶1). *trans*-**3e**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 5.20 – 5.13 (m, 1H), 3.89 – 3.86 (m, 4H, CO_2Me, ArCH), 2.64 (d, *J* = 9.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6, 149.2, 136.5, 130.4 (2C), 130.0, 129.9, 129.8 (2C), 128.5, 124.0, 123.0, 122.9 (dd, *J* = 262.3, 258.7 Hz), 116.7, 67.0, 52.2, 49.9 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, d_6-DMSO) δ -61.4 (d, *J* = 156.5 Hz), -67.7 (dd, *J* = 156.5, 19.7 Hz). *cis*-**3e**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 5.27 – 5.20 (m, 1H), 3.92 (s, 3H), 3.60 (ddd, *J* = 20.0, 9.5, 2.0 Hz, 1H), 3.45 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6, 148.9 (d, *J* = 4.8 Hz), 138.1, 130.2, 130.0 (2C), 129.9, 129.6 (2C), 127.4, 123.8, 123.0, 122.8 (dd, *J* = 265.9, 254.1 Hz), 116.5, 68.2 (d, *J* = 5.9 Hz), 53.0 (t, *J* = 25.2 Hz), 52.2. **^{19}F NMR** (470 MHz, d_6-DMSO) δ -69.1 (d, *J* = 157.0 Hz), -69.9 (dd, *J* = 157.0, 23.5 Hz). **HRMS** (ESI, m/z): calcd. For $C_{17}H_{14}F_2NaO_4$ $[M+Na]^+$: 343.0752, found 343.0746.

trans-/cis-2,2-difluoro-3-(naphthalen-2-yl)chroman-4-ol (**3f**). Light yellow solid (56.2 mg, 60%, dr = 3.8∶1). *trans*-**3f**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88-7.73 (m, 4H), 7.53 – 7.45 (m, 3H), 7.45 – 7.36 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.30 – 5.21 (m, 1H), 3.67 – 3.55 (m, 1H), 2.39 – 2.30 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0 (d, *J* = 4.8 Hz), 133.2, 133.1, 130.1, 129.2, 128.7, 128.5 (d, *J* = 2.3 Hz), 127.9, 127.7, 127.3, 126.6, 126.5, 126.4, 123.7, 123.1 (dd, *J* = 265.9, 254.5 Hz, 2C), 116.6, 68.5 (d, *J* = 5.8 Hz), 53.1 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.8 (d, *J* = 159.8Hz), -75.9 (dd, *J* = 159.8, 19.8 Hz). *cis*-**3f**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88-7.73 (m, 4H), 7.53 – 7.45 (m, 3H), 7.45 – 7.36 (m, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.17 – 5.09 (m, 1H), 3.99 – 3.90 (m, 1H), 1.97 – 1.89 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.3, 133.1, 133.0, 130.4, 129.8, 129.4, 128.3 (d, *J* = 3.4 Hz), 128.0, 127.5, 127.0, 126.6 (2C), 126.4 (d, *J* = 1.9 Hz), 124.0, 123.6, 123.3 (dd, *J* = 262.1, 259.6 Hz), 116.7, 67.2 (t, *J* = 3.0 Hz), 49.9 (t, *J* = 25.2). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -67.6 (d, *J* = 159.8 Hz), -74.5 – -75.0 (m). **HRMS** (ESI, m/z): calcd. For $C_{19}H_{14}F_2NaO_2$ $[M+Na]^+$: 335.0854, found 335.0858.

trans-/cis-(E)-2,2-difluoro-3-styrylchroman-4-ol (**3g**). Light yellow solid (53.6 mg, 62%, dr = 1.6∶1). *trans*-**3g**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.25 (m, 6H), 7.18 – 7.11 (m, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 16.5 Hz, 1H), 6.12 (dd, *J* = 16.0, 9.0 Hz, 1H), 4.89 – 4.81 (m, 1H), 3.18 – 3.06 (m, 1H), 2.42 – 2.34 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.0 (d, *J* = 4.2 Hz), 137.8, 135.8, 130.0, 128.7 (2C), 128.4, 127.7, 126.6 (2C), 123.8, 123.1 (dd, *J* = 261.2, 255.7 Hz), 122.8, 120.1, 116.6, 67.9 (d, *J* = 5.0 Hz), 50.9 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.3 (d, *J* = 159.8 Hz), -75.9 (dd, *J* = 159.8, 14.1 Hz). *cis*-**3g**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.25 (m, 6H), 7.18 – 7.11 (m, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 16.5 Hz, 1H), 6.09 (dd, *J*

= 16.0, 9.0 Hz, 1H), 5.07 – 4.99 (m, 1H), 3.42 – 3.33 (m, 1H), 2.07 – 2.00 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.9 (d, *J* = 2.0 Hz), 138.7, 135.7, 130.2, 128.6 (2C), 128.2, 126.6 (2C), 123.9, 123.2 (dd, *J* = 261.7, 258.8 Hz), 123.1, 118.1 (d, *J* = 3.5 Hz), 118.1, 116.6, 66.7, 48.2 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -69.6 (d, *J* = 159.8 Hz), -76.2 (dd, *J* = 159.8, 11.3 Hz). **HRMS** (ESI, m/z): calcd. For $C_{17}H_{14}ClF_2O_2$ $[M+Cl]^-$: 323.0656, found 323.0648.

trans-/cis-3-(benzo[b]thiophen-3-yl)-2,2-difluorochroman-4-ol (**3h**). White solid (26.7 mg, 28%, dr = 3.2∶1). *trans*-**3h**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.46 (s, 1H), 7.44 – 7.30 (m, 4H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 5.18 – 5.10 (m, 1H), 4.10 (ddd, *J* = 14.5, 7.5, 1.0 Hz, 1H), 2.51 (d, *J* = 6.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.1 (d, *J* = 2.5 Hz), 139.9, 139.0, 130.3, 128.2, 127.4, 126.0, 124.8, 124.5, 124.5, 123.9, 122.9 (dd, *J* = 263.0, 257.4 Hz), 122.9, 121.5, 116.7, 69.3, 45.8 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -73.0 (d, *J* = 159.8 Hz), -75.4 (dd, *J* = 159.8, 14.5 Hz). *cis*-**3h**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.44 – 7.30 (m, 4H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 5.18 – 5.10 (m, 1H), 4.38 – 4.32 (m, 1H), 1.96 (d, *J* = 9.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.3, 139.7, 139.2, 130.5, 128.7, 127.4, 125.9, 124.8, 124.6, 124.5, 124.0, 123.0 (dd, *J* = 264.5, 257.3 Hz), 122.9, 121.2, 116.7, 66.6, 43.0 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -68.8 (d, *J* = 159.8 Hz), -75.0 – -75.7 (m). **HRMS** (ESI, m/z): calcd. For $C_{17}H_{12}ClF_2O_2S$ $[M+Cl]^-$: 353.0220, found 353.0213.

trans-/cis-2,2-difluoro-7-methoxy-3-(3-nitrophenyl)chroman-4-ol (**3l**). Light yellow solid (81.9 mg, 81%, dr = 1.7∶1). *trans*-**3l**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 1H),

6.74 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.56 (d, *J* = 2.1 Hz, 1H), 5.20 – 5.12 (m, 1H), 3.81 (s, 3H), 3.65 – 3.56 (m, 1H), 2.56 – 2.48 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.1, 149.7 (d, *J* = 4.7 Hz), 148.3, 135.7, 135.1, 129.8, 128.3, 125.2 (d, *J* = 1.8 Hz), 123.5, 122.6 (dd, *J* = 265.9, 255.8 Hz), 115.3, 110.9, 101.6, 68.4 (d, *J* = 5.2 Hz), 55.5, 52.9 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.3 (d, *J* = 159.8 Hz), -76.4 (dd, *J* = 159.8, 18.8 Hz). *cis*-**3l**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.72 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 5.06 – 4.99 (m, 1H), 3.87 – 3.81 (m, 1H), 3.82 (s, 3H), 2.16 – 2.07 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5, 150.1 (d, *J* = 2.9 Hz), 148.1, 136.1 (d, *J* = 1.4 Hz), 134.0, 129.5, 124.7, 124.3 (d, *J* = 1.3 Hz), 123.3, 122.6 (dd, *J* = 265.9, 255.8 Hz), 114.5, 111.1, 101.7, 67.0 (d, *J* = 4.0 Hz), 55.6, 49.7 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -70.2 (d, *J* = 159.8 Hz), -74.3 (dd, *J* = 159.8, 18.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{13}F_2NaNO_5$ $[M+Na]^+$: 360.0654, found 360.0659.

trans-/cis-2,2-difluoro-6-methoxy-3-(3-nitrophenyl)chroman-4-ol (**3m**). White solid (87.0 mg, 86%, dr = 1.5∶1). *trans*-**3m**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 1.5 Hz, 1H), 7.05 – 6.88 (m, 2H), 5.26 – 5.19 (m, 1H), 3.81 (s, 3H), 3.64 (ddd, *J* = 19.3, 9.5, 1.5 Hz, 1H), 2.41 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.0, 148.4, 142.6 (d, *J* = 5.0 Hz), 135.7, 135.0, 129.9, 124.4 (d, *J* = 1.5 Hz), 123.9, 123.6, 122.6 (dd, *J* = 265.6, 254.1 Hz), 117.7, 116.5, 111.3, 68.7 (d, *J* = 5.8 Hz), 55.8, 52.9 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.6 (d, *J* = 159.8 Hz), -76.1 (dd, *J* = 159.8, 19.3 Hz). *cis*-**3m**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.5 Hz), 7.54 (t, *J* = 8.0 Hz, 1H), 7.05 – 6.88 (m, 3H), 5.16 – 5.10 (m, 1H), 3.95 – 3.87 (m, 1H), 3.79 (s, 3H), 2.08 (d, *J* = 9.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.1, 148.2, 142.8, 136.0, 133.6, 129.6, 125.2, 123.4, 123.0,

122.8 (dd, *J* = 262.5, 258.6 Hz), 117.9, 117.0, 112.5, 67.4, 55.7, 49.6 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -68.9 (d, *J* = 159.8 Hz), -74.7 (dd, *J* = 159.8, 16.0 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{13}ClF_2NO_5$ $[M+Cl]^-$: 372.0456, found 372.0465.

trans-/cis-2,2-difluoro-6-methyl-3-(3-nitrophenyl)chroman-4-ol (**3n**). Light yellow solid (76.1 mg, 79%, dr = 2∶1). *trans*-**3n**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.22 (d, *J* =8.5 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 5.24 – 5.18 (m, 1H), 3.62 (ddd, *J* = 19.3, 8.7, 1.0 Hz, 1H), 2.46 (d, *J* = 8.5 Hz, 1H), 2.34 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.4, 146.6 (d, *J* = 4.8 Hz), 135.7, 135.1, 133.7, 131.0, 129.8, 127.4, 124.3 (d, *J* = 1.6 Hz), 123.5, 122.6 (dd, *J* = 265.9, 254.5 Hz), 122.8, 116.5, 68.5 (d, *J* = 5.2 Hz), 52.8 (t, *J* = 25.2 Hz), 20.7. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.5 (d, *J* = 159.8 Hz), -76.1 (dd, *J* = 159.8, 19.3 Hz). *cis*-**3n**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.23 (s, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 5.12 – 5.02 (m, 1H), 3.87 (ddd, *J* = 17.4, 4.8, 1.7 Hz, 1H), 2.33 (s, 3H), 2.10 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.2, 146.9 (d, *J* = 1.6 Hz), 136.1 (d, *J* = 1.5 Hz), 133.9, 133.8, 131.5, 129.5, 128.9, 125.2 (d, *J* = 1.5 Hz), 123.3, 122.7 (dd, *J* = 263.3, 257.0 Hz), 121.9, 116.8, 67.3 (d, *J* = 2.5 Hz), 49.7 (t, *J* = 25.2 Hz), 20.59. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -69.2 (d, *J* = 159.8 Hz), -74.5 (dd, *J* = 159.8, 17.4 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{13}F_2NaNO_4$ $[M+Na]^+$: 344.0705, found 344.0693.

trans-/cis-6-chloro-2,2-difluoro-3-(3-nitrophenyl)chroman-4-ol (**3o**). Yellow solid (71.8 mg, 70%, dr = 1.5∶1). *trans*-**3o**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 5.19 – 5.10 (m, 1H), 3.95 – 3.85 (m, 1H), 2.11 (d, *J* = 9.0 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.6, 135.9, 133.0, 130.9, 129.7, 129.5, 128.5, 125.2, 124.4, 123.6, 122.6 (dd, *J* = 263.3, 259.6 Hz), 118.5, 66.8, 49.3 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -68.9 (d, *J* = 160.7 Hz), -75.1 (dd, *J* = 159.8, 16.9 Hz). *cis*-**3o**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 5.31 – 5.22 (m, 1H), 3.69 – 3.58 (m, 1H), 2.42 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.5, 147.3, 135.8, 134.4, 130.4, 130.0, 129.4, 127.2, 125.0, 123.9, 123.8, 122.5 (dd, *J* = 264.6, `257.0 Hz), 118.2, 68.1 (d, *J* = 4.3 Hz), 52.6 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -75.5 (d, *J* = 159.8 Hz), -76.0 (dd, *J* = 159.8, 18.3 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{10}ClF_2NNaO_4$ $[M+Na]^+$: 364.0159, found 364.0150.

trans-/cis-2,2,8-trifluoro-3-(3-nitrophenyl)chroman-4-ol (**3p**). White solid (71.2 mg, 73%, dr = 1∶1). *trans*-**3p**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.21 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.22 – 7.09 (m, 2H), 5.24 – 5.09 (m, 1H), 3.67 (ddd, *J* = 14.7, 10.0, 8.1 Hz, 1H), 2.24 (d, *J* = 8.7 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 149.7 (d, *J* = 10.9 Hz), 148.3, 135.9, 134.5, 129.7, 125.3 (d, *J* = 2.1 Hz), 124.4, 124.3 (d, *J* = 6.9 Hz), 123.8, 123.6, 122.6 (dd, *J* = 264.1, 258.7 Hz), 122.1, 117.5 (d, *J* = 17.4 Hz), 68.3 – 68.2 (m), 49.5 (t, *J* = 25.1 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -74.0 – -74.1 (m), -133.7 (dd, *J* = 10.2, 4.6 Hz). *cis*-**3p**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.24 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.22 – 7.09 (m, 2H), 5.36 – 5.29 (m, 1H), 3.92 (ddd, *J* = 18.2, 5.0, 2.2 Hz, 1H), 2.55 (d, *J* = 7.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 151.4 (d, *J* = 11.6 Hz), 148.5, 136.1, 133.3, 130.0, 126.0, 124.9, 124.0 (d, *J* = 6.8 Hz), 123.8, 123.7, 122.6 (dd, *J* = 262.0, 258.5 Hz), 122.1, 117.0 (d, *J* = 17.4 Hz), 67.1 – 67.0 (m), 52.7 (t, *J* = 24.9 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -68.1 (d, *J* = 158.9 Hz), -72.8 (dd, *J*

= 158.9, 18.2 Hz), -134.3 (dd, *J* = 9.8, 5.1 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{10}F_3NNaO_4$ $[M+Na]^+$: 348.0454, found 348.0446.

trans-/cis-2,2,6-trifluoro-3-(3-nitrophenyl)chroman-4-ol (**3q**). Light yellow solid (64.4 mg, 66%, dr = 1.3∶1). *trans*-**3q**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 8.21 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.25 (dd, *J* = 7.8, 3.0 Hz, 1H), 7.11 – 6.97 (m, 2H), 5.28 – 5.23 (m, 1H), 3.61 (ddd, *J* = 19.2, 10.2, 3.4 Hz, 1H), 2.83 (br, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 158.1 (d, *J* = 2.1 Hz), 148.4, 144.7 (dd, *J* = 5.3, 2.5 Hz), 136.0, 134.7, 130.0, 125.2 (d, *J* = 7.6 Hz), 124.4 (d, *J* = 2.1 Hz), 123.7, 122.7 (dd, *J* = 265.0, 254.0 Hz), 118.13 (d, *J* = 8.3 Hz), 117.2 (d, *J* = 24.0 Hz), 113.7 (d, *J* = 24.8 Hz), 68.1 (d, *J* = 6.2 Hz), 52.5 (dd, *J* = 26.0, 24.9 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.5 (dd, *J* = 159.6, 3.4 Hz), -74.1 (dd, *J* = 159.6, 19.2 Hz), -118.4 (dd, *J* = 13.0, 7.9 Hz). *cis*-**3q**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 8.18 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 8.2, 2.9 Hz, 1H), 7.11 – 6.97 (m, 2H), 5.15 (t, *J* = 5.0 Hz, 1H), 3.92 (ddd, *J* = 15.2, 5.5, 2.5 Hz, 1H), 2.83 (br, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.8 (d, *J* = 2.5 Hz), 148.2, 145.1 – 145.0 (m), 136.1, 133.3, 129.7, 125.2 (d, *J* = 1.2 Hz), 124.0 (d, *J* = 7.1 Hz), 123.5, 122.7 (dd, *J* = 262.1, 258.4 Hz), 118.4 (d, *J* = 8.1 Hz), 117.8 (d, *J* = 23.7 Hz), 114.9 (d, *J* = 24.3 Hz), 66.8 (t, *J* = 3.1 Hz), 49.33 (dd, *J* = 26.8, 24.8 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -66.7 (d, *J* = 159.6 Hz), -73.2 (dd, *J* = 159.6, 15.0 Hz), -117.9 (dd, *J* = 13.0, 7.6 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{10}F_3NNaO_4$ $[M+Na]^+$: 348.0454, found 348.0442.

trans-/cis-3-(2,2,6-trifluoro-4-hydroxychroman-3-yl)benzonitrile (**3r**). Light yellow solid (71.4 mg, 78%, dr = 3.6∶1). *trans*-**3r**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.69 – 7.67 (m, 1H), 7.67 – 7.61 (m, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.28 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.12 – 7.04 (m, 1H), 7.03 – 6.99 (m, 1H), 5.25 – 5.17 (m, 1H), 3.55 (ddd, *J* = 18.5, 10.0, 4.0

Hz, 1H), 2.62 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 157.9, 144.7 – 144.6 (m), 134.3 (d, *J* = 21.4 Hz), 132.9, 132.3, 129.8, 125.0 (d, *J* = 7.4 Hz), 122.6 (dd, *J* = 264.6, 255.8 Hz), 118.3, 118.1 (d, *J* = 8.2 Hz), 117.2 (d, *J* = 23.9 Hz), 113.7 (d, *J* = 24.7 Hz), 113.0, 68.0 (d, *J* = 5.5 Hz), 52.5 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -75.5 (dd, *J* = 159.3, 4.0 Hz), -76.0 (dd, *J* = 159.3, 18.5 Hz), -120.3 – -120.4 (m). *cis*-**3r**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.69 (m, 2H), 7.67 – 7.61 (m, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.12 – 7.04 (m, 1H), 7.03 – 6.99 (m, 1H), 5.16 – 5.10 (m, 1H), 3.84 (ddd, *J* = 14.5, 5.5, 2.5 Hz, 1H), 2.17 (d, *J* = 9.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 157.9, 145.0 – 144.9 (m), 134.3 (d, *J* = 21.4 Hz), 133.6, 132.2, 129.6, 123.9 (d, *J* = 7.3 Hz), 122.7 (dd, *J* = 262.1, 259.6 Hz), 118.4 (d, *J* = 8.2 Hz), 118.3, 117.8 (d, *J* = 23.9 Hz), 114.9 (d, *J* = 24.2 Hz), 112.8, 66.8, 49.3 (dd, *J* = 27.1, 25.1 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -68.5 (d, *J* = 159.8 Hz), -75.2 (dd, *J* = 159.8, 14.5 Hz), -119.9 – -119.8 (m). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{10}F_3NNaO_2$ $[M+Na]^+$: 328.0556, found 328.0554.

trans-/cis-6,8-dibromo-2,2-difluoro-3-(3-nitrophenyl)chroman-4-ol (**3s**). Yellowish solid (115.8 mg, 83%, 2.4∶1). *trans*-**3s**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.24 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.78 (d, *J* = 2.4 Hz, 1H), 7.77 – 7.74 (m, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.56 – 7.54 (m, 1H), 5.21 – 5.11 (m, 1H), 3.91 (ddd, *J* = 16.4, 5.2, 2.4 Hz, 1H), 2.13 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.4, 145.5, 136.8, 135.8, 132.6, 130.8, 129.9, 125.6, 125.3 (d, *J* = 1.5 Hz), 123.8, 122.6 (dd, *J* = 265.2, 259.7 Hz), 116.8, 111.8, 67.0 (dd, *J* = 3.6, 1.8 Hz), 49.3 (dd, *J* = 25.7, 24.8 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -67.0 (d, *J* = 159.8 Hz), -73.0 (dd, *J* = 159.8, 16.4 Hz). *cis*-**3s**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.28 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.79 – 7.77 (m, 1H), 7.77 – 7.74 (m, 1H), 7.69 – 7.67 (m, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 5.35 – 5.29 (m, 1H), 3.65 (ddd, *J* = 20.2, 10.4, 2.4 Hz, 1H), 2.37 (d, *J* = 6.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.7, 145.2, 136.3, 133.9, 130.2, 129.3, 126.7, 125.6,

124.4 (d, *J* = 2.0 Hz), 124.0, 122.5 (dd, *J* = 265.6, 256.2 Hz), 116.7, 111.4, 68.0 (dd, *J* = 6.3, 1.8 Hz), 52.4 (t, *J* = 25.1 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.4 (dd, *J* = 159.8, 20.2 Hz), -74.1 (d, *J* = 159.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_9Br_2F_2NNaO_4$ $[M+Na]^+$: 485.8759, found 485.8802.

trans-/cis-8-(tert-butyl)-2,2-difluoro-3-(3-nitrophenyl)chroman-4-ol (**3t**). Colorless oil (69.8 mg, 64%, dr = 1.4∶1). *trans*-**3t**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.23 – 8.18 (m, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.44 – 7.36 (m, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.16 – 7.10 (m, 1H), 5.16 (m, 1H), 3.92 (ddd, *J* = 16.0, 5.2, 2.8 Hz, 1H), 1.99 (br, 1H), 1.46 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.4, 147.8, 138.3, 136.3 (d, *J* = 1.5 Hz), 133.9, 129.5, 128.3, 126.6, 125.1 (d, *J* = 1.5 Hz), 123.9, 123.4, 123.1, 122.7 (dd, *J* = 261.2, 258.9 Hz), 67.7 – 67.6 (m), 49.5 (dd, *J* = 26.4, 25.1 Hz), 35.0, 29.8 (3C). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -65.9 (d, *J* = 159.6 Hz), -72.3 (dd, *J* = 159.5, 16.0 Hz). *cis*-**3t**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.26 – 8.23 (m, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.16 – 7.10 (m, 1H), 5.24 – 5.20 (m, 1H), 3.71 (ddd, *J* = 17.6, 8.9, 2.4 Hz, 1H), 2.32 (br, 1H), 1.44 (s, 9H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.6, 147.6 (d, *J* = 4.5 Hz), 138.2, 135.6, 135.3, 129.9, 127.9, 125.5, 124.3 (d, *J* = 3.0 Hz), 123.8, 123.7, 123.5, 122.5 (dd, *J* = 263.0, 254.4 Hz), 69.0 (d, *J* = 4.7 Hz), 52.6 (t, *J* = 25.7 Hz), 35.0, 29.7 (3C). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -71.5 (d, *J* = 159.1 Hz), -73.8 (dd, *J* = 159.3, 17.6 Hz). **HRMS** (ESI, m/z): calcd. For $C_{19}H_{19}F_2NNaO_4$ $[M+Na]^+$: 386.1174, found 386.1173.

trans-/cis-5,5-difluoro-6-(3-nitrophenyl)-6,7-dihydro-5H-thieno[3,2-b]pyran-7-ol (**3u**). White solid (79.9 mg, 85%, dr = 2.5∶1). *trans*-**3u**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.24 – 8.20 (m, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 5.5 Hz, 1H), 6.79 (d, *J* = 5.5 Hz, 1H), 5.12 – 5.03 (m, 1H), 3.94 – 3.85 (m, 1H), 2.15 (br, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 147.1 (d, *J* = 4.7 Hz), 136.2 (d, *J* = 2.2 Hz), 133.7, 129.6, 127.0, 125.3 (d, *J* = 2.4 Hz), 123.5 (dd, *J* = 269.6, 257.0 Hz), 123.5, 117.5, 115.7, 64.5 (d, *J* = 4.2 Hz), 50.5 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -73.5 (d, *J* = 159.8 Hz), -76.3 (dd, *J* = 159.8, 21.2 Hz). *cis*-**3u**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.24 – 8.20 (m, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 5.5 Hz, 1H), 6.78 (d, *J* = 5.5 Hz, 1H), 5.23 – 5.17 (m, 1H), 3.73 (ddd, *J* = 17.5, 7.0, 2.0 Hz, 1H), 2.15 (br, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.4, 146.7 (d, *J* = 5.3 Hz), 135.5, 134.9 (d, *J* = 1.5 Hz), 129.9, 126.6, 124.3 (d, *J* = 1.3 Hz), 123.8 (dd, *J* = 267.1, 258.0 Hz), 123.6 (2C), 116.7, 67.4 (dd, *J* = 4.5, 1.4 Hz), 53.6 (t, *J* = 25.2 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -75.2 (d, *J* = 159.8 Hz), -78.0 (dd, *J* = 159.8, 17.5 Hz). **HRMS** (ESI, m/z): calcd. For $C_{13}H_9ClF_2NO_4S$ $[M+Cl]^-$: 347.9914, found 347.9908.

3,3-difluoro-2-(3-nitrophenyl)-2,3-dihydro-1H-benzo[f]chromen-1-ol (**3v**). White solid (87.9 mg, 82%, dr = 1.3∶1). *trans*-**3v**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.29 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.18 – 8.09 (m, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.94 – 7.83 (m, 2H), 7.54 – 7.40 (m, 2H), 7.29 – 7.17 (m, 1H), 5.55 – 5.47 (m, 1H), 3.92 – 3.79 (m, 1H), 2.66 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.3, 147.7 (d, *J* = 4.5 Hz), 136.4 (d, *J* = 2.9 Hz), 134.3, 132.4, 130.8, 129.9, 128.8, 128.0, 125.5, 125.4, 125.3, 123.5, 123.4, 122.5 (dd, *J* = 264.1, 258.9 Hz), 117.3, 113.9, 67.9 (d, *J* = 4.4 Hz), 52.0 (dd, *J* = 28.9, 23.1 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -69.9 (d, *J* = 160.3 Hz), -77.6 (d, *J* = 160.3 Hz). *cis*-**3v**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.18 – 8.09 (m, 2H), 7.94 – 7.83 (m, 2H), 7.68 – 7.55 (m, 2H), 7.54 – 7.40 (m, 2H), 7.29 – 7.17 (m, 1H), 5.47 – 5.37 (m, 1H), 4.15 – 4.05 (m, 1H), 2.25 (d, *J* = 9.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.3, 147.2 (d, *J* = 5.0 Hz), 135.4 (d, *J* = 7.7 Hz), 134.3, 132.1, 131.6, 131.4, 130.4, 129.5, 128.7, 128.0, 125.3, 123.9, 122.8, 122.5 (dd, *J* = 268.3, 253.6 Hz), 117.4, 114.5, 65.3 (d, *J* = 5.2 Hz), 49.7 (dd, *J* =

25.3, 23.1 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -74.6 (dd, *J* = 159.8, 8.9 Hz), -75.4 (dd, *J* = 159.8, 25.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{19}H_{13}F_2NNaO_4$ $[M+Na]^+$: 380.0705, found 380.0693.

trans-/cis-2,2-difluoro-4-methyl-3-(3-nitrophenyl)chroman-4-ol (**3w**). Colorless oil (57.8 mg, 60%, dr = 1.4∶1). *trans*-**3w**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.29 – 8.27 (m, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.39 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 3.92 (dd, *J* = 17.6, 2.8 Hz, 1H), 2.39 (d, *J* = 1.6 Hz, 1H), 1.45 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.2, 148.0 (d, *J* = 5.0 Hz), 136.1 (d, *J* = 3.2 Hz), 133.9, 130.4, 129.5, 127.5, 126.7, 125.3 (d, *J* = 3.2 Hz), 124.49, 123.30, 122.9 (dd, *J* = 263.8, 255.8 Hz), 117.2, 71.7 (d, *J* = 5.0 Hz), 56.4 (t, *J* = 25.2 Hz), 26.5 (d, *J* = 5.4 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -70.3 (d, *J* = 160.7 Hz), -71.5 (dd, *J* = 160.7, 17.6 Hz). *cis*-**3w**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.29 – 8.27 (m, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.41 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 3.70 (dd, *J* = 20.8, 2.8 Hz, 1H), 2.19 (d, *J* = 2.4 Hz, 1H), 1.58 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.3 (d, *J* = 4.2 Hz), 148.1, 137.0 (d, *J* = 1.8 Hz), 133.5, 130.7, 129.3, 126.9, 126.3, 126.1 (d, *J* = 2.0 Hz), 124.5, 123.5, 122.4 (dd, *J* = 265.5, 253.6 Hz), 117.5, 70.2 (d, *J* = 4.2 Hz), 55.1 (t, *J* = 25.2 Hz), 27.6 (d, *J* = 3.5 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -69.2 (d, *J* = 161.7 Hz), -75.9 (dd, *J* = 161.7, 20.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{13}F_2NaNO_4$ $[M+Na]^+$: 344.0705, found 344.0702.

trans-/cis-3-(2,2-difluoro-3-(3-nitrophenyl)chroman-4-yl)-4-hydroxypent-3-en-2-one (**3x**). Yellowish solid (94.6 mg, 81%, dr > 10∶1). *trans*-**3x**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 17.44 (s, 1H), 8.28 (s, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.04 (m, 3H), 4.62 (d, *J* = 12.9 Hz, 1H), 3.76 (dd, *J* = 21.0,

13.0 Hz, 1H), 2.03 (s, 3H), 1.83 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 194.3, 191.7, 149.8 (d, *J* = 5.9 Hz), 148.4, 135.9 (d, *J* = 1.8 Hz), 135.7, 129.9, 129.3, 127.3, 124.5, 123.8 (d, *J* = 3.6 Hz), 123.7, 123.6, 122.3 (dd, *J* = 270.0, 252.0 Hz), 117.6, 108.2 (d, *J* = 1.5 Hz), 49.6 (dd, *J* = 27.8, 23.7 Hz), 40.0 (d, *J* = 5.9 Hz), 25.3, 23.3. **^{19}F NMR** (565 MHz, $CDCl_3$) -75.1 (d, *J* = 154.2 Hz), -76.2 (dd, *J* = 154.2, 21.0 Hz). **HRMS** (ESI, m/z): calcd. For $C_{20}H_{17}F_2NNaO_5$ $[M+Na]^+$: 412.0967, found 412.0981.

trans-/cis-2,2-difluoro-3-methyl-3-(3-nitrophenyl)chroman-4-ol (**3y**). Pale yellow solid (65.5 mg, 68%, dr = 1.6∶1). *trans*-**3y**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 8.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 5.63 – 5.56 (m, 1H), 2.38 (d, *J* = 8.0 Hz, 1H), 1.60 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.3, 148.1, 139.6, 134.5, 130.1, 129.4, 127.5, 124.5 (t, *J* = 259.4 Hz), 124.1, 123.5 (d, *J* = 1.4 Hz), 122.9, 122.5, 116.4, 70.4 (d, *J* = 3.4 Hz), 47.7 (t, *J* = 23.4 Hz), 14.6 (d, *J* = 2.6 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -76.3 (d, *J* = 159.8 Hz), -83.5 (d, *J* = 159.8 Hz). *cis*-**3y**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.5 Hz, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 5.08 – 5.00 (m, 1H), 2.27 (d, *J* = 9.0 Hz, 1H), 1.68 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1, 148.0, 138.8, 134.4, 130.5, 129.2, 128.6, 124.8 (t, *J* = 265.4 Hz), 124.3, 123.5, 123.1, 122.7, 116.6, 72.7, 48.8 (t, *J* = 23.4 Hz), 21.4. **^{19}F NMR** (470 MHz, $CDCl_3$) δ -75.8 (d, *J* = 159.8 Hz), -78.8 (d, *J* = 159.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{13}ClF_2NO_4$ $[M+Cl]^-$: 356.0507, found 356.0490.

methyl 4-(2-oxo-2H-chromen-3-yl)benzoate (**4e**). White solid (26.1 mg, 31%). Mp. 208-209 ℃ (Lit.[18a] Mp. 209-210 ℃). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 2H),

7.90 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 3.95 (s, 3H).

3-(benzo[b]thiophen-3-yl)-2H-chromen-2-one (**4h**). Yellowish solid (54.3 mg, 65%). Mp. 190-191 ℃ (Lit.[18b] Mp. 181 ℃). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.60 – 7.52 m, 2H), 7.46 – 7.37 (m, 3H), 7.33 (t, *J* = 7.5 Hz, 1H). **^{13}C NMR** (500 MHz, $CDCl_3$) δ 160.4, 153.3, 140.5, 140.1, 137.4, 131.6, 129.6, 128.1, 127.9, 124.6, 124.6 (2C), 123.1, 123.0, 122.5, 119.3, 116.6.

3-(4-methoxyphenyl)-2H-chromen-2-one (**4i**). White solid (54.5 mg, 72%). Mp. 141-142 ℃ (Lit.[18a] Mp. 140-141 ℃).**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.56 – 7.49 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H).

3-(4-(benzyloxy)phenyl)-2H-chromen-2-one (**4j**). White solid (67.0 mg, 68%). Mp. 161-162 ℃ (Lit.[18c] Mp. 162-163 ℃). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 5.12 (s, 2H).

3-(benzo[d][1,3]dioxol-5-yl)-2H-chromen-2-one (**4k**). White solid (55.1 mg, 69%). Mp. 173-174 ℃ (Lit.[18d] Mp. 169-171 ℃). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 7.20 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.02 (s, 2H).

Compound **6** was not identified as *trans*- or *cis*-isomer.

trans-/cis-2,2-difluoro-3-(3-nitrophenyl)thiochroman-4-ol (**6a**). Light yellow solid (87.3 mg, 90%, dr = 1.7∶1). **6a**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.20 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.29 – 7.21 (m, 1H), 5.23 – 5.13 (m, 1H), 3.99 (ddd, *J* = 18.5, 8.5, 3.5 Hz, 1H), 2.35 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.1, 136.4, 134.7 (d, *J* = 3.4 Hz), 133.3, 129.5, 129.3, 128.8, 128.2 (dd, *J* = 277.2, 271.3 Hz), 127.6, 126.8, 126.4, 125.4, 123.3, 71.6 (d, *J* = 3.2 Hz), 54.5 (t, *J* = 21.4 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) δ -66.2 (dd, *J* = 227.0, 3.8 Hz), -74.0 (dd, *J* = 227.0, 18.5 Hz). **6a′**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.29 – 7.21 (m, 2H), 7.21 – 7.17 (m, 1H), 5.36 – 5.28 (m, 1H), 3.88 (ddd, *J* = 20.0, 10.0, 5.5 Hz, 1H), 2.30 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.3, 136.1, 135.2 (d, *J* = 3.0 Hz), 134.2, 129.7, 129.0, 128.6, 128.2 (dd, *J* = 270.3, 263.7 Hz), 127.6, 126.7, 126.3, 124.8 (d, *J* = 1.5 Hz), 123.5, 70.67 (d, *J* = 5.0 Hz), 57.8 (t, *J* = 21.4 Hz). **^{19}F NMR** (470 MHz, $CDCl_3$) -75.2 (dd, *J* = 228.4, 5.2 Hz), -76.3 (dd, *J* = 228.4, 20.0 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{11}ClF_2NO_3S$ $[M+Cl]^-$: 358.0122, found 358.0112.

trans-/cis-2,2-difluoro-3-(3-nitrophenyl)thiochroman-4-ol (**6b**). Yellowish solid (78.6 mg, 81%, dr > 20 ∶ 1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 5.27 (t, *J* = 9.8 Hz, 1H), 4.74 – 4.60 (m, 1H), 2.40 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 152.3, 134.7, 132.9, 129.8, 129.7, 129.2, 129.1, 127.7 (dd, *J* = 5.1 Hz), 127.6, 127.6 (dd, *J* = 286.9, 272.7 Hz), 126.7, 126.3, 125.0, 71.5, 51.2 (dd, *J* = 17.4, 12.2 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.2 (dd, *J* = 227.5, 21.2 Hz), -74.8 (d, *J* = 227.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{11}F_2NNaO_3S$ $[M+Na]^+$:

346.0320, found 346.0321.

trans-/cis-3-(4-bromophenyl)-2,2-difluorothiochroman-4-ol (**6c**). Light yellow solid (92.2 mg, 86%, dr = 1∶1). **6c**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.23 (m, 4H), 7.19 (dd, *J* = 7.8, 0.7 Hz, 1H), 5.18 – 5.09 (m, 1H), 3.86 (ddd, *J* = 16.8, 9.0, 3.8 Hz, 1H), 2.07 (d, *J* = 6.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 133.8, 132.2 (2C), 131.8 (3C), 129.2, 128.8, 127.9 (d, *J* = 3.9 Hz), 127.8 (dd, *J* = 277.1, 271.2 Hz), 126.8, 126.2 (t, *J* = 2.4 Hz), 122.9, 71.5 (t, *J* = 2.9 Hz), 57.7 (t, *J* = 20.2 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.1 (dd, *J* = 227.1, 16.8 Hz), -74.3 (dd, *J* = 227.1, 20.4 Hz). **6c′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 1H), 7.46 – 7.43 (m, 2H), 7.33 – 7.23 (m, 4H), 7.16 (dd, *J* = 7.2, 1.8 Hz, 1H), 5.22 (dd, *J* = 9.6, 6.0 Hz, 1H), 3.70 (ddd, *J* = 20.4, 9.6, 5.4 Hz, 1H), 2.09 (d, *J* = 10.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.4, 132.0 (2C), 131.6 (d, *J* = 1.5 Hz, 2C), 131.3 (d, *J* = 3.9 Hz), 128.9 (t, *J* = 2.4 Hz), 128.8, 128.5 (dd, *J* = 275.9, 271.8 Hz), 127.7, 126.6, 126.3 (t, *J* = 2.6 Hz), 123.0, 70.7 (dd, *J* = 5.0, 2.3 Hz), 54.5 (dd, *J* = 21.9, 19.0 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -63.0 (ddd, *J* = 226.0, 7.9, 2.3 Hz), -73.1 (dd, *J* = 226.0, 6.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{15}H_{11}BrF_2NaOS$ $[M+Na]^+$: 378.9574, found 378.9586.

trans-/cis-2,2-difluoro-3-(naphthalen-1-yl)thiochroman-4-ol (**6d**). Light yellow solid (81.8 mg, 83%, dr = 3.2∶1). **6d**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 1H), 7.90 – 7.80 (m, 3H), 7.55 – 7.46 (m, 3H), 7.46 – 7.42 (m, 1H), 7.33 – 7.28 (m, 1H), 7.24 – 7.18 (m, 2H), 5.32 – 5.18 (m, 1H), 4.93 (ddd, *J* = 18.6, 7.2, 4.2 Hz, 1H), 2.21 (d, *J* = 9.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 134.3, 134.1, 132.9, 129.4 (t, *J* = 245.1 Hz), 129.3, 129.2 (3C), 128.7, 128.3 (d, *J* = 3.2 Hz), 127.2 (d, *J* = 2.7 Hz), 126.8, 126.7, 126.4 (t, *J* = 2.3 Hz), 125.8, 125.4, 122.8, 71.9 (dd, *J* = 4.1, 1.8 Hz), 48.2 (dd, *J* = 21.0, 19.5 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ

-65.2 (d, *J* = 226.0 Hz), -71.6 (dd, *J* = 226.0, 18.6 Hz). **6d′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.07 – 8.01 (m, 1H), 7.90 – 7.80 (m, 2H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.42 – 7.37 (m, 3H), 7.33 – 7.28 (m, 1H), 7.28 – 7.24 (m, 2H), 5.44 – 5.36 (m, 1H), 4.73 (ddd, *J* = 19.8, 10.2, 6.0 Hz, 1H), 2.23 (d, *J* = 5.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.1, 134.2, 133.9, 129.4, 129.3, 129.1, 128.9 (d, *J* = 2.0 Hz), 128.8 (t, *J* = 213.3 Hz), 128.1 (d, *J* = 3.9 Hz), 127.3, 126.9, 126.6, 126.3 (t, *J* = 2.6 Hz), 126.1, 125.9 (d, *J* = 3.0 Hz), 125.3, 123.2, 71.1 (dd, *J* = 4.8, 2.0 Hz), 51.5 (t, *J* = 20.4 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -72.4 (dd, *J* = 227.1, 5.6 Hz), -73.2 (dd, *J* = 227.1, 19.8 Hz). **HRMS** (ESI, m/z): calcd. For $C_{19}H_{14}F_2NaOS$ $[M+Na]^+$: 351.0626, found 351.0625.

trans-/cis-(E)-2,2-difluoro-3-styrylthiochroman-4-ol (**6e**). Yellowish solid (83.1 mg, 91%, dr = 1.8∶1). **6e**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.30 – 7.20 (m, 4H), 7.14 – 7.11 (m, 1H), 6.76 (d, *J* = 15.6 Hz, 1H), 5.97 (dd, *J* = 15.6, 9.6 Hz, 1H), 5.10 – 5.05 (m, 1H), 3.44 (dtd, *J* = 13.3, 9.1, 4.4 Hz, 1H), 2.10 (d, *J* = 10.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.0, 135.8, 133.4, 128.9 (dd, *J* = 276.3, 270.3 Hz), 128.7, 128.6 (2C), 128.5, 127.9, 128.4, 126.7 (2C), 126.4, 125.7 (t, *J* = 2.5 Hz), 119.2 (d, *J* = 4.8 Hz), 70.0 (dd, *J* = 5.0, 2.1 Hz), 53.6 (dd, *J* = 23.3, 19.0 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -61.3 (ddd, *J* = 222.6, 8.5, 1.7 Hz), -77.5 (dd, *J* = 222.6, 11.3 Hz). **6e′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.30 – 7.20 (m, 5H), 7.15 – 7.13 (m, 1H), 6.72 (d, *J* = 15.6 Hz, 1H), 6.13 (dd, *J* = 15.6, 9.6 Hz, 1H), 4.92 – 4.83 (m, 1H), 3.31 (dtd, *J* = 14.7, 8.8, 5.9 Hz, 1H), 2.35 (dd, *J* = 6.0, 1.8 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 138.5, 135.9, 133.7, 128.7 (3C), 128.5 (2C), 128.3, 128.0 (t, *J* = 2.3 Hz), 126.7 (2C), 126.5, 126.2 (t, *J* = 2.4 Hz), 120.3 (t, *J* = 3.8 Hz), 70.6 (t, *J* = 3.0 Hz), 55.7 (t, *J* = 19.9 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -70.5 (dd, *J* = 226.6, 5.6 Hz), -74.9 (ddd, *J* = 226.6, 17.5, 2.3 Hz). **HRMS** (ESI, m/z): calcd. For $C_{17}H_{14}F_2NaOS$ $[M+Na]^+$: 327.0626, found 327.0626.

trans-/cis-3-(benzo[b]thiophen-3-yl)-2,2-difluorothiochroman-4-ol (**6f**). Yellowish solid (82.3 mg, 82%, dr = 2.8∶1). **6f**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 1H), 7.83 – 7.80 (m, 1H), 7.54 – 7.48 (m, 2H), 7.43 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 7.28 – 7.21 (m, 1H), 7.21 – 7.16 (m, 1H), 5.26 – 5.17 (m, 1H), 4.48 (ddd, *J* = 16.9, 7.8, 4.2 Hz, 1H), 2.17 (d, *J* = 9.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.7, 133.6, 129.2, 129.1, 128.8 (dd, *J* = 275.3, 272.6 Hz), 128.4, 126.6, 126.3, 126.0, 126.0 (t, *J* = 3.0 Hz), 125.9 (d, *J* = 4.4 Hz), 124.7, 124.5, 122.9, 121.4, 71.2 (t, *J* = 3.0 Hz), 47.6 (dd, *J* = 22.5, 19.3 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.9 (d, *J* = 226.0 Hz), -73.6 (dd, *J* = 226.0, 16.9 Hz). **6f′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 1H), 7.82 – 7.78 (m, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.44 (s, 1H), 7.43 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 7.28 – 7.21 (m, 1H), 7.21 – 7.16 (m, 1H), 5.32 – 5.26 (m, 1H), 4.30 (ddd, *J* = 18.6, 9.0, 6.0 Hz, 1H), 2.34 (d, *J* = 5.4 Hz, 1H). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -71.8 (d, *J* = 227.1 Hz), -73.1 (dd, *J* = 227.1, 18.6 Hz). **HRMS** (ESI, m/z): calcd. For $C_{17}H_{12}F_2NaOS_2$ $[M+Na]^+$: 357.0190, found 357.0203.

trans-/cis-2,2-difluoro-3-(4-methoxyphenyl)thiochroman-4-ol (**6g**). White solid (70.3 mg, 76%, dr = 1∶1). **6g**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.33 – 7.19 (m, 4H), 7.16 – 7.13 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.21 – 5.17 (m, 1H), 3.81 (s, 3H), 3.64 (ddd, *J* = 20.2, 10.2, 6.0 Hz, 1H), 2.14 (d, *J* = 4.0 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.0, 134.2, 131.4, 128.9, 128.6, 128.9 (dd, *J* = 275.4, 272.7 Hz), 127.6, 126.4 (2C), 126.1, 124.2 (d, *J* = 2.3 Hz), 114.6 (2C), 71.3 (t, *J* = 3.0 Hz), 57.4 (t, *J* = 20.1 Hz), 55.31. **^{19}F NMR** (565 MHz, CH_2Cl_2) δ -73.1 – -73.6 (m), -73.9 – -74.5 (m). **6g′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.19 (m, 4H), 7.19 – 7.15 (m, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.17 – 5.09 (m, 1H), 3.87 (ddd, *J* = 15.0, 9.6, 4.2 Hz, 1H), 3.76 (s, 3H), 2.09 (d, *J* = 9.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.8, 134.8, 131.2 (d, *J* = 1.2 Hz), 128.9, 128.5, 128.1

(dd, *J* = 276.3, 270.6 Hz), 127.6, 126.6 (2C), 126.1, 123.8 (d, *J* = 4.7 Hz), 114.1 (2C), 70.5 (dd, *J* = 5.0, 2.1 Hz), 55.2, 54.3 (dd, *J* = 22.3, 19.2 Hz). **^{19}F NMR** (565 MHz, CH_2Cl_2) δ -60.1 – -61.0 (m), -73.9 – -74.5 (m). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{14}F_2NaO_2S$ $[M+Na]^+$: 331.0575, found 331.0570.

trans-cis-3-(4-(benzyloxy)phenyl)-2,2-difluorothiochroman-4-ol (**6h**). Yellowish solid (81.9 mg, 71%, dr = 1.2∶1). **6h**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.36 – 7.31 (m, 1H), 7.30 – 7.20 (m, 4H), 7.15 – 7.12 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.21 – 5.16 (m, 1H), 5.06 (s, 2H), 3.64 (ddd, *J* = 20.2, 10.2, 6.8 Hz, 1H), 2.10 (d, *J* = 4.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.2, 136.7, 134.8, 131.5, 129.0 (2C), 128.7 (2C), 128.6, 128.2, 128.0 (dd, *J* = 290.4, 286.9 Hz), 127.6 (2C), 127.5, 126.4, 126.1 (2C), 124.1, 115.4, 71.4 (t, *J* = 3.0 Hz), 70.1, 57.4 (t, *J* = 20.0 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.3 (dd, *J* = 226.6, 6.8 Hz), -74.0 (dd, *J* = 240.1, 20.2 Hz). **6h′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.36 – 7.31 (m, 1H), 7.30 – 7.20 (m, 4H), 7.18 – 7.15 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.16 – 5.10 (m, 1H), 5.01 (s, 2H), 3.86 (ddd, *J* = 15.0, 10.2, 4.2 Hz, 1H), 2.06 (d, *J* = 10.2 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 159.0, 136.8, 134.2, 131.2, 129.0 (2C), 128.7 (2C), 128.5, 128.1 (d, *J* = 276.9, 269.2 Hz, 2C), 127.6, 127.5 (2C), 126.1 (2C), 124.4, 124.1, 115.0, 70.5 (dd, *J* = 4.7, 2.0 Hz), 70.0, 54.3 (dd, *J* = 22.5, 19.3 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.0 (d, *J* = 224.9), -74.0 (dd, *J* = 198.9, 15.0 Hz). **HRMS** (ESI, m/z): calcd. For $C_{22}H_{18}F_2NaO_2S$ $[M+Na]^+$: 407.0888, found 407.0905.

trans-/cis-3-(benzo[d][1,3]dioxol-5-yl)-2,2-difluorothiochroman-4-ol (**6i**). Light yellow solid (66.7 mg, 69%, dr = 1∶1). **6i**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 11.4 Hz, 2H), 6.75 – 6.72 (m, 1H), 5.98 – 5.96 (m, 2H), 5.14 – 5.08 (m, 1H), 3.66 – 3.57 (m, 1H), 2.15 (d, *J* = 9.6 Hz, 1H). **^{13}C**

NMR (151 MHz, $CDCl_3$) δ 148.3, 147.9, 134.1, 128.7 (dd, *J* = 275.1, 272.2 Hz), 128.7, 128.6, 127.6, 126.7, 126.1 (t, *J* = 2.3 Hz), 125.5 (d, *J* = 4.4 Hz), 124.2, 110.3, 108.8, 101.2, 71.5 (t, *J* = 2.9 Hz), 57.9 (t, *J* = 19.9 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.4 (dd, *J* = 224.9, 6.2 Hz), -74.0 (d, *J* = 18.6 Hz). **6i′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.20 (m, 2H), 7.15 – 7.13 (m, 1H), 6.85 – 6.78 (m, 3H), 5.93 – 5.91 (m, 2H), 5.18 – 5.14 (m, 1H), 3.82 (ddd, *J* = 16.2, 9.0, 4.2 Hz, 1H), 2.19 (d, *J* = 5.4 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 148.1, 147.8, 134.6, 129.0, 128.0 (dd, *J* = 276.0, 271.2 Hz), 127.9 (d, *J* = 3.5 Hz), 127.6, 126.4, 126.2 (t, *J* = 2.5 Hz), 125.8 (d, *J* = 2.0 Hz), 124.0, 109.7 (d, *J* = 1.8 Hz), 108.4, 101.4, 70.6 (dd, *J* = 4.5, 2.4 Hz), 54.6 (dd, *J* = 22.2, 19.2 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.8 (dd, *J* = 255.4, 16.2 Hz), -73.9 (d, *J* = 7.9 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{12}F_2NaO_3S$ $[M+Na]^+$: 345.0367, found 345.0378.

trans-/cis-2,2-difluoro-3-(4-(methylthio)phenyl)thiochroman-4-ol (**6j**). White solid (73.0 mg, 75%, dr = 1.2∶1). **6j**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.21 (m, 5H), 7.18 – 7.13 (m, 2H), 5.16 – 5.11 (m, 1H), 3.86 (ddd, *J* = 16.4, 9.6, 4.8 Hz, 1H), 2.43 (s, 3H), 2.13 (d, *J* = 9.6 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.3, 134.0, 130.7, 130.4, 128.5, 126.0 (dd, *J* = 280.7, 276.7 Hz), 127.7, 126.7 (2C), 126.4 (2C), 126.2, 126.1, 71.4, 57.7 (t, *J* = 20.1 Hz), 15.4. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -62.2 (dd, *J* = 226.0, 6.8 Hz), -73.7 (dd, *J* = 225.4, 16.4 Hz). **6j′**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.31 – 7.21 (m, 5H), 7.18 – 7.13 (m, 2H), 5.23 – 5.18 (m, 1H), 3.65 (ddd, *J* = 20.2, 10.2, 6.4 Hz, 1H), 2.48 (s, 3H), 2.17 (d, *J* = 5.3 Hz, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.6, 134.6, 130.4, 129.8, 129.0, 128.8 (dd, *J* = 275.1, 272.4 Hz), 128.7, 127.7, 126.7 (2C), 126.5 (2C), 126.1, 70.6, 54.6 (dd, *J* = 21.9, 19.2 Hz), 15.5. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -73.2 (d, *J* = 226.6 Hz), -74.0 (dd, *J* = 226.6, 20.2 Hz). **HRMS** (ESI, m/z): calcd. For $C_{16}H_{14}F_2NaOS_2$ $[M+Na]^+$: 347.0346, found 347.0356.

trans-/cis-2,2-difluoro-7-methoxy-3-(2-nitrophenyl)thiochroman-4-ol (**6k**). Light yellow solid (88.0 mg, 83%, dr > 10∶1). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.89 (t, *J* = 7.8 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.56 (s, 1H), 5.14 (s, 1H), 4.46 (dd, *J* = 19.8, 3.0 Hz, 1H), 3.80 (s, 3H), 2.37 (s, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.5, 151.2, 150.1 (d, *J* = 3.8 Hz), 132.7, 131.4 (d, *J* = 6.3 Hz), 130.3, 129.0, 126.3, 124.9, 122.8 (dd, *J* = 267.3, 256.7 Hz), 114.7, 111.1, 101.8, 66.7 (d, *J* = 4.1 Hz), 55.6, 44.1 (t, *J* = 24.5 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -68.7 (d, *J* = 158.2 Hz), -71.5 (dd, *J* = 158.2, 19.8 Hz). **HRMS** (ESI, *m/z*): calcd. For $C_{16}H_{13}F_2NNaO_4S$ $[M+Na]^+$: 376.0426, found 376.0433.

trans-/cis-2,2-difluoro-7-methoxy-3-methyl-3-(3-nitrophenyl)thiochroman-4-ol (**6l**). Yellowish solid (88.2 mg, 80%, dr = 2.8∶1). **6l**: **^{1}H NMR** (600 MHz, d_6-DMSO) δ 8.43 (s, 1H), 8.24 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.73 (t, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.15 (d, *J* = 7.2 Hz, 1H), 5.54 – 5.49 (m, 1H), 3.77 (s, 3H), 1.46 (s, 3H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 160.6, 148.6 (d, *J* = 6.3 Hz), 148.3, 140.3, 135.9, 130.2, 129.2, 125.5 (dd, *J* = 270.0, 254.3 Hz), 123.6, 123.1, 117.3, 110.9, 101.3, 68.1 (d, *J* = 5.4 Hz), 55.9, 47.8 (dd, *J* = 24.3, 21.0 Hz), 14.9 (d, *J* = 3.3 Hz). **^{19}F NMR** (565 MHz, d_6-DMSO) δ -72.5 (d, *J* = 157.1 Hz), -80.5 (d, *J* = 157.1 Hz). **6l′**: **^{1}H NMR** (600 MHz, d_6-DMSO) δ 8.35 (s, 1H), 8.09 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.78 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 5.06 – 4.93 (m, 1H), 3.73 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (151 MHz, d_6-DMSO) δ 160.7, 149.1 (d, *J* = 4.4 Hz), 147.7, 140.3, 135.9, 129.7, 129.1, 125.6 (dd, *J* = 267.0, 261.2 Hz), 124.0, 122.6, 117.4, 111.0, 101.4, 70.6, 55.9, 48.3 (dd, *J* = 24.3, 21.0 Hz), 21.0. **^{19}F NMR** (565 MHz, d_6-DMSO) δ -71.8 (d, *J* =

157.1 Hz), -78.0 (d, J = 157.1 Hz). **HRMS** (ESI, *m/z*): calcd. For $C_{17}H_{15}F_2NNaO_4S$ $[M+Na]^+$: 390.0582, found 390.0598.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

Crystallographic data for **3b** (CIF), and NMR (^1H, ^{13}C and ^{19}F) spectra for all new compounds (PDF).

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ACKNOWLEDGMENT

We thank National Natural Science Foundation of China (NNSFC-21372040 and 21672032), the State Key Laboratory of Fine Chemicals (KF1502), and Foundation of Jilin Educational Committee (JJKH20170907KJ) for funding support of this research.

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