Bull. Chem. Soc. Jpn., 74, 971—977 (2001)

Intramolecular Cyclizations of *o*-Substituted β,β-Difluorostyrenes: Synthesis of 3-Fluorinated Isochromenes and Isothiochromenes

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(Received November 7, 2000)

β,β-Difluorostyrenes bearing an oxygen (OH) or a sulfur (SH, $SCOCH_3$) nucleophile linked by a methylene unit to the *ortho* carbon are prepared from 2,2,2-trifluoroethyl *p*-toluenesulfonate via the in situ generation of 2,2-difluorovinylboranes and their palladium-catalyzed cross-coupling reaction with aryl iodides. These styrene derivatives readily undergo intramolecular nucleophilic substitution of the oxygen and sulfur with loss of fluorine under basic conditions, leading to 3-fluoroisochromenes and 3-fluoroisothiochromenes in high yields.

gem-Difluoroolefins are susceptible to nucleophilic attack, which occurs exclusively at the difluoromethylene carbon.[1] The orientation of attack is governed so that the fluorines are placed at the position β to the electron-rich carbon in the transition state to avoid electron-pair repulsion. In our recent publications,[2] we have reported the application of this unique reactivity to the nucleophilic 5-*endo*-trig cyclizations of *gem*-difluoroolefins bearing functional groups such as NHTs, OH, and SH, a cyclization process that is disfavored according to Baldwin's rules.[3] This 5-membered ring formation proceeds via intramolecular substitution of vinylic fluorine (addition–elimination processes)[1] to provide ring-fluorinated heterocycles such as indoles, benzo[*b*]furans, benzo[*b*]thiophenes, 2-pyrrolines, 2,3-dihydrofurans, and 2,3-dihydrothiophenes in high yields. The properties of *gem*-difluoroolefins: (i) the highly polarized C–C double bond which allows initial ring closure and (ii) the successive elimination of fluoride ion which suppresses the reverse ring opening, play an important role in this "anti-Baldwin" cyclization.

In continuation of our research on the cyclizations of *gem*-difluoroolefins,[2,4] we sought to apply the intramolecular substitution concept to the construction of 6-membered heterocyclic compounds. Our attention was focused on selectively ring-fluorinated isochromenes (1*H*-2-benzopyran derivatives)[5] and isothiochromenes (1*H*-2-benzothiopyran derivatives)[6] as synthetic targets, compounds which could be employed as intermediates in the synthesis of medicinal and agrochemical agents.[7–9] For that purpose β,β-difluorostyrene derivatives with an oxygen (OH) or a sulfur (SH) nucleophile linked by a methylene unit to the *ortho* carbon were designed and subjected to the ring-forming reaction under basic conditions. Herein we wish to report the results of our studies on the synthesis of 3-fluoroisochromenes and 3-fluoroisothiochromenes.

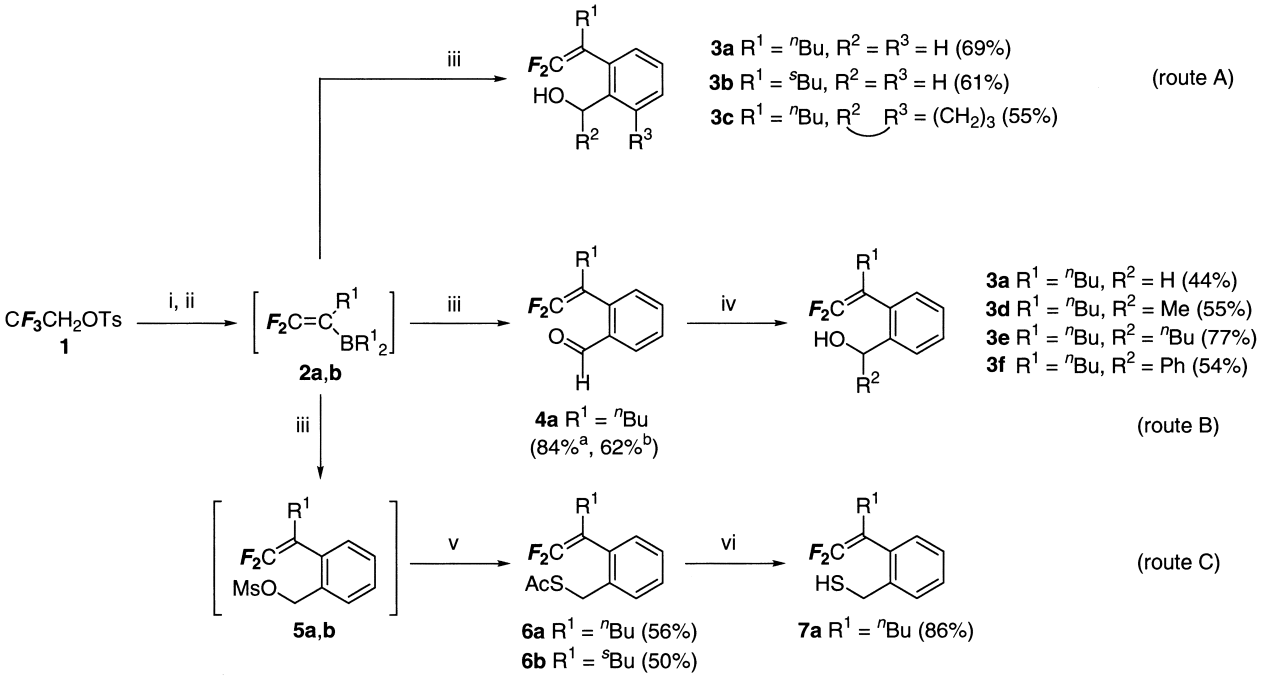
Results and Discussion

Preparation of β,β-Difluorostyrenes Bearing an Oxygen or a Sulfur Nucleophile. The starting materials, *o*-substituted β,β-difluorostyrenes, were easily prepared from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) using the one-pot method which we have previously established: the in situ generation of 2,2-difluorovinylboranes **2** and their palladium-catalyzed cross-coupling reaction with aryl iodides (Scheme 1).[10] Difluorostyrenes **3** bearing a hydroxymethyl group at the *ortho* position, precursors of 3-fluoroisochromenes, were successfully obtained by the direct coupling of **2** with the corresponding aryl iodides (Scheme 1, route A). Thus, *o*-iodobenzyl alcohols were pretreated with equimolar amounts of dibutylmagnesium or methylmagnesium iodide to generate the magnesium alkoxides, which in turn coupled with **2** in the presence of a palladium catalyst to afford the desired styrenes **3a–c** (55–69%) from **1**. The butylmagnesium alkoxides gave slightly better results, probably due to their solubility.

Alcohols **3** were also obtained via another route, which allows the introduction of a substituent (R^2) on the benzylic carbon (Scheme 1, route B). The coupling of **2a** with *o*-iodobenzaldehyde afforded difluorostyrene **4a** bearing an *o*-formyl group in an 84% yield determined by ^{19}F NMR, while the isolated yield was 62% because of its instability. The addition of nucleophiles such as Grignard reagents and diisobutylaluminum hydride to **4** regioselectively occurred at the formyl carbon in toluene to give **3a**,**d–f**.

As sulfur-containing substrates for the synthesis of 3-fluoroisothiochromenes, thioacetates **6** were readily prepared from **1** via mesylates **5** in a one-pot operation by (i) the coupling reaction of **2** with *o*-iodobenzyl methanesulfonate and (ii) the successive introduction of an acetylthio group at the benzylic position on treatment with sodium thioacetate (Scheme 1, route C). Thioacetate **6a** was transformed into thiol **7a** via transesterification with K_2CO_3 in methanol.

Cyclization of β,β-Difluorostyrenes Bearing an Oxygen or a Sulfur Nucleophile. We next attempted the cyclization of the difluorostyrenes obtained above under basic conditions.

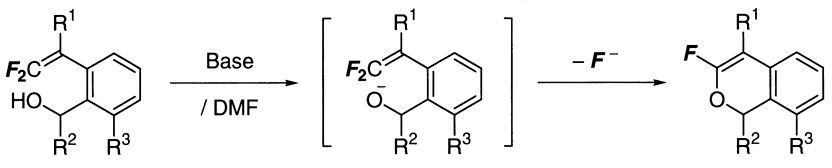


Scheme 1. Preparation of β,β-difluorostyrenes functionalized at the *ortho* position.
i, ^{n}BuLi (2.1 mol. amt.), THF, −78 °C, 0.5 h; ii, BR^1_3 (1.1 mol. amt.), THF, −78 °C, 1 h then r.t., 3 h; iii, ArI (0.9 mol. amt.), CuI (1.0–1.1 mol. amt.), $Pd_2(dba)_3$•$CHCl_3$ (0.02 mol. amt.), PPh_3 (0.08 mol. amt.), r.t., **3a**: 17 h; **3b**: 5 h; **3c**: 4 h; **4a**: 0.3 h; **5a**: 5 h; **5b**: 4 h; iv, **3a**: DIBAL (1.5 mol. amt.), toluene, 0 °C, 0.5 h; **3d**: MeMgI (1.5 mol. amt.), toluene, 0 °C, 0.3 h; **3e**: ^{n}BuMgBr (1.2 mol. amt.), toluene, 0 °C, 0.3 h; **3f**: PhMgBr (1.5 mol. amt.), toluene, −78 °C, 0.5 h; v, AcSNa (1.5 mol. amt.), THF, r.t., 10 h; vi, K_2CO_3 (2.4 mol. amt.), MeOH, r.t., 1.5 h.
a) Determined by ^{19}F NMR. b) Isolated yield.

Although treatment of **3a** with 1.0 molar amount of butyllithium in tetrahydrofuran (THF) resulted in a complex mixture of products, the expected intramolecular substitution was effected by the use of NaH (1.1 molar amount) or KH (1.2 molar amount) in dimethylformamide (DMF) at room temperature, where the cyclized product, 3-fluoroisochromene **8a**, was obtained in 78% or 72% yields, respectively (Table 1, Entries 1 and 2). Furthermore, adding 2 molar amounts of NaH improved the yield of **8a** to 84% (Entry 3). This cyclization in 6-*endo*-trig fashion smoothly proceeded under milder conditions, compared to the 5-*endo*-trig process, affording 2-fluorobenzo[*b*]furan at 60 °C.[2a]

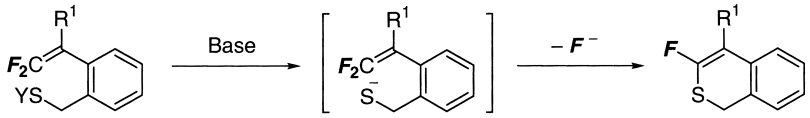
In a similar manner, several other 3-fluoroisochromenes **8** were synthesized from *o*-(hydroxymethyl)styrenes **3**. The ring closure of **3b** bearing a secondary alkyl group (R^1) at the vinylic position successfully proceeded to afford **8b** in an 84% yield (Entry 4). Even in the case of secondary alcohols **3c–f**, the cyclization of the corresponding alkoxides occurred under similar conditions, leading to **8c–f** including fused tricyclic compound **8c** in 50–71% yields, which are lower than those of

Table 1. Synthesis of 3-Fluoroisochromenes **8**



Entry	R^1	R^2	R^3	Substrate	Base (mol. amt.)	Conditions	Yield/%
1	^{n}Bu	H	H	**3a**	NaH (1.1)	r.t., 1.5 h	78 (**8a**)
2	^{n}Bu	H	H	**3a**	KH (1.2)	r.t., 2.0 h	72 (**8a**)
3	^{n}Bu	H	H	**3a**	NaH (2.0)	r.t., 1.2 h	84 (**8a**)
4	^{s}Bu	H	H	**3b**	NaH (2.0)	r.t., 1.7 h	84 (**8b**)
5	^{n}Bu	–$(CH_2)_3$–		**3c**	NaH (1.9)	r.t., 2.2 h	66 (**8c**)
6	^{n}Bu	Me	H	**3d**	NaH (2.0)	r.t., 2.0 h	60 (**8d**)
7	^{n}Bu	^{n}Bu	H	**3e**	NaH (2.0)	r.t., 2.0 h	71 (**8e**)
8	^{n}Bu	Ph	H	**3f**	NaH (2.0)	r.t., 2.0 h	50 (**8f**)

Table 2. Synthesis of 3-Fluoroisothiochromenes **9**



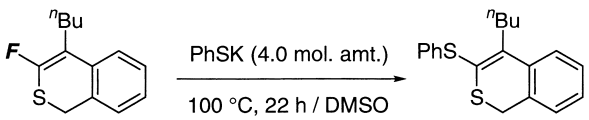
6.7 **9**

Entry	Y	R^1	Substrate	Base (mol. amt.)	Solvent	Conditions	Yield/%
1	H	^{n}Bu	**7a**	KH (1.2)	THF	r.t., 2.5 h	90 (**9a**)
2	Ac	^{n}Bu	**6a**	K_2CO_3 (1.2)	MeOH	60 °C, 8.5 h	61 (**9a**)
3	Ac	^{n}Bu	**6a**	NaOMe (2.0)	DMF	r.t., 0.3 h	94 (**9a**)
4	Ac	^{s}Bu	**6b**	NaOMe (2.0)	DMF	r.t., 0.3 h	90 (**9b**)

primary alcohols **8a**,**b**, probably due to their steric hindrance (Entries 5–8).

In addition, we tried this intramolecular substitution with sulfur nucleophiles. On treatment of thiol **7a** with KH (1.2 molar amount) in DMF, the corresponding 3-fluoroisothiochromene **9a** was obtained in a 90% yield (Table 2, Entry 1). Having found the cyclization of the potassium thiolate, we examined the combination of the two processes of deacetylation (**6** → **7**) and cyclization (**7** → **9**) into a one-pot operation, so as to refine the synthesis of **9** to make it more efficient. After the deacetylation of **6a** with K_2CO_3 (1.2 molar amount) in MeOH, the reaction mixture was heated at 60 °C to drive the in situ generated thiolate to undergo the cyclization, and **9a** was obtained in a 61% yield (Entry 2). Screening of the reaction conditions such as base and solvent revealed that treatment of **6a**,**b** with sodium methoxide (2.0 molar amount) in DMF successively promoted the two processes to proceed without heating, leading to **9a**,**b** in excellent yields (Entries 3 and 4).

The remaining fluorines in the cyclized products **9** were expected to be replaced by nucleophiles via similar addition–elimination processes.[1] On treatment of **9a** with potassium benzenethiolate as a nucleophile, the desired **10a** was obtained as shown in Scheme 2.



9a **10a** (71%)

Scheme 2. Introduction of substituent at the 3-position.

In conclusion, we have disclosed that our concept of intramolecular nucleophilic substitution of vinylic fluorines can be successfully applied to the construction of 6-membered rings as well as 5-membered rings. *o*-Substituted *β*,*β*-difluorostyrenes, prepared from CF_3CH_2OTs, trialkylboranes, and aryl iodides, readily undergo 6-membered ring closure, providing a facile method for the construction of a selectively ring-fluorinated benzo(thio)pyran framework.

Experimental

General. IR spectra were recorded on a Shimadzu IR-408 spectrometer or a JEOL JIR-WINSPEC50 spectrometer. NMR spectra were obtained on a JEOL JNM-A-500 spectrometer. Chemical shift values were given in ppm relative to internal Me_4Si (for ^{1}H and ^{13}C NMR: *δ*-value) or internal C_6F_6 (for ^{19}F NMR). Mass spectra were taken with a JEOL JMS-DX-300 or a JEOL JMS-SX-102A spectrometer. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus. THF was distilled from sodium diphenylketyl prior to use. Methanol was distilled from magnesium methoxide and stored over molecular sieves 3A. DMF was dried over P_2O_5, then distilled under reduced pressure from CaH_2 and stored over molecular sieves 4A. Commercial NaH and KH were used without further purification. Sodium methoxide was prepared from sodium and excess methanol, and then dried under vacuum at 100 °C.

***o*-(1-Butyl-2,2-difluorovinyl)benzyl Alcohol (3a):** Butyllithium (1.9 mL, 1.6 M in hexane (1 M = 1 mol dm^{-3}), 3.1 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (368 mg, 1.5 mmol) in THF (7.5 mL) at −78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at −78 °C, and then tributylborane (1.7 mL, 1.0 M in THF, 1.7 mmol) was added at −78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 1.5 mL), triphenylphosphine (30 mg, 0.12 mmol), and tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (30 mg, 0.029 mmol) and this mixture was stirred for 15 min. To the solution was added the magnesium salt (generated from *o*-iodobenzyl alcohol (307 mg, 1.3 mmol) and dibutylmagnesium (1.3 mL, 1.0 M in Et_2O, 1.3 mmol) in THF (3 mL) at 0 °C for 30 min) and copper(I) iodide (304 mg, 1.6 mmol). After the mixture had been stirred for 17 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 5:1) to give **3a** (205 mg, 69%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 0.86 (3H, t, *J* = 7.0 Hz), 1.25–1.35 (4H, m), 1.97 (1H, br s), 2.25–2.31 (2H, m), 4.62 (2H, s), 7.14 (1H, dd, *J* = 7.6, 1.4 Hz), 7.28 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.34 (1H, ddd, *J* = 7.6, 7.6, 1.4 Hz), 7.53 (1H, d, *J* = 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 13.8, 22.4, 29.1, 29.6 (d, J_{CF} = 2 Hz), 62.6 (d, J_{CF} = 2 Hz), 90.5 (dd, J_{CF} = 22, 17 Hz), 127.6, 127.9, 128.3, 129.9 (d, J_{CF} = 5 Hz), 132.2 (d, J_{CF} = 5 Hz), 139.5, 152.6 (dd, J_{CF} = 289, 284 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) 67.8 (1F, dt, J_{FF} = 47, J_{FH} = 3 Hz), 72.2 (1F, d, J_{FF} = 47 Hz) ppm. IR (neat) 3300, 2960, 2880, 1740, 1240, 1135, 1045, 790, 765, 735 cm^{-1}. MS (70 eV) *m/z* (rel inten-

sity) 226 (M^+; 38), 159 (87), 117 (100). HRMS Found: *m/z* 226.1176. Calcd for $C_{13}H_{16}OF_2$: M, 226.1170.

***o*-(1-*s*-Butyl-2,2-difluorovinyl)benzyl Alcohol (3b):** Compound **3b** was prepared by the method described for **3a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (254 mg, 1.0 mmol), butyllithium (1.4 mL, 1.5 M in hexane, 2.1 mmol), tri-*s*-butylborane (1.1 mL, 1.0 M in THF, 1.1 mmol), hexamethylphosphoric triamide (1.4 mL), triphenylphosphine (21 mg, 0.080 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (21 mg, 0.020 mmol), *o*-iodobenzyl alcohol (213 mg, 0.90 mmol) and methylmagnesium iodide (1.0 mL, 0.89 M in THF, 0.90 mmol), and copper(I) iodide (209 mg, 1.1 mmol) in THF (8 mL). Purification by thin layer chromatography on silica gel (chloroform–AcOEt 20:1) gave **3b** (123 mg, 61%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 °C) δ 0.92 (3H, t, J = 7.0 Hz), 1.02 (3H, d, J = 7.0 Hz), 1.26–1.40 (1H, m), 1.55 (1H, dqd, J = 14.0, 7.0, 7.0 Hz), 2.41 (1H, tq, J = 7.0, 7.0 Hz), 3.00 (1H, br s), 4.47 (2H, s), 7.08 (1H, d, J = 7.5 Hz), 7.23 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.32 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.56 (1H, d, J = 7.5 Hz). ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 11.1, 17.3, 27.0, 35.1, 60.1, 94.0 (dd, J_{CF} = 24, 16 Hz), 125.8, 127.0, 127.2, 129.0 (d, J_{CF} = 2 Hz), 130.3 (d, J_{CF} = 4 Hz), 140.7, 151.4 (dd, J_{CF} = 290, 284 Hz). ^{19}F NMR (470 MHz, $(CD_3)_2SO$, 100 °C) 70.2 (1F, br s), 74.9 (1F, d, J_{FF} = 47 Hz) ppm. IR (neat) 3330, 2990, 1735, 1460, 1290, 1235, 1200, 1065, 1020, 935, 760, 670 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 226 (M^+; 60), 159 (99), 129 (100). HRMS Found: *m/z* 226.1171. Calcd for $C_{13}H_{16}OF_2$: M, 226.1170.

8-(1-Butyl-2,2-difluorovinyl)-1,2,3,4-tetrahydro-1-naphthol (3c): Compound **3c** was prepared by the method described for **3a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (165 mg, 0.65 mmol), butyllithium (0.82 mL, 1.7 M in hexane, 1.4 mmol), tributylborane (0.71 mL, 1.0 M in THF, 0.71 mmol), hexamethylphosphoric triamide (1 mL), triphenylphosphine (14 mg, 0.053 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (13 mg, 0.013 mmol), 8-iodo-1,2,3,4-tetrahydro-1-naphthol (156 mg, 0.57 mmol) and dibutylmagnesium (1.1 mL, 0.51 M in Et_2O, 0.57 mmol) and copper(I) iodide (136 mg, 0.71 mmol) in THF (4 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 4:1) gave **3c** (84 mg, 55%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 120 °C) δ 0.85 (3H, t, J = 7.0 Hz), 1.24–1.37 (4H, m), 1.58–1.70 (2H, m), 1.90–2.07 (2H, m), 2.21–2.30 (1H, m), 2.37–2.45 (1H, m), 2.62–2.70 (1H, m), 2.80 (1H, t, J = 4.6 Hz), 4.18 (1H, br s), 4.66 (1H, br s), 6.91 (1H, d, J = 7.6 Hz), 7.04 (1H, d, J = 7.6 Hz), 7.14 (1H, dd, J = 7.6, 7.6 Hz). ^{13}C NMR (126 MHz, $(CD_3)_2SO$, 120 °C) δ 13.4, 16.8, 21.7, 28.8, 29.0, 29.1 (dd, J_{CF} = 3, 3 Hz), 32.0, 63.3, 91.9 (dd, J_{CF} = 21, 17 Hz), 126.8, 127.6 (d, J_{CF} = 2 Hz), 128.7, 134.1 (d, J_{CF} = 5 Hz), 137.8 (d, J_{CF} = 3 Hz), 138.0, 152.2 (dd, J_{CF} = 284, 281 Hz). ^{19}F NMR (470 MHz, $(CD_3)_2SO$, 120 °C) 67.2 (1F, br d, J_{FF} = 49 Hz), 73.0 (1F, br s) ppm. IR (neat) 3350, 2950, 1745, 1470, 1240, 1135, 1075, 1035, 1005, 785 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 266 (M^+; 6), 246 (43), 175 (54), 155 (100). HRMS Found: *m/z* 266.1461. Calcd for $C_{16}H_{20}OF_2$: M, 266.1483.

***o*-(1-Butyl-2,2-difluorovinyl)benzaldehyde (4a):** Butyllithium (5.0 mL, 1.7 M in hexane, 8.4 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (1.0 g, 4.0 mmol) in THF (20 mL) at −78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at −78 °C, and then tributylborane (4.4 mL, 1.0 M in THF, 4.4 mmol) was added at −78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (5 mL), triphenylphosphine (30 mg, 0.11 mmol), and tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (29 mg, 0.028 mmol) and this mixture was stirred for 15 min. To the solution was added *o*-iodobezaldehyde (738 mg, 3.2 mmol) and copper(I) iodide (757 mg, 4.0 mmol). After the mixture was stirred for 0.3 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (Et_2O–hexane 1:20) to give **4a** (441 mg, 62%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2 Hz), 1.29–1.35 (4H, m), 2.37–2.43 (2H, m), 7.31 (1H, dd, J = 7.6, 0.6 Hz), 7.47 (1H, dd, J = 7.6, 7.6 Hz), 7.61 (1H, ddd, J = 7.6, 7.6, 1.5 Hz), 7.96 (1H, dd, J = 7.6, 1.5 Hz), 10.16 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 22.2, 29.5 (d, J_{CF} = 3 Hz), 29.5, 89.1 (dd, J_{CF} = 24, 17 Hz), 128.3, 128.6, 130.6 (d, J_{CF} = 2 Hz), 133.9, 134.1, 137.3 (d, J_{CF} = 4 Hz), 152.7 (dd, J_{CF} = 290, 287 Hz), 191.1. ^{19}F NMR (470 MHz, $CDCl_3$) 70.0 (1F, dt, J_{FF} = 43, J_{FH} = 3 Hz), 72.8 (1F, dd, J_{FF} = 43, J_{FH} = 2 Hz) ppm. IR (neat) 2970, 2950, 2890, 1840, 1745, 1705, 1600, 1470, 1465, 1245 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 224 (M^+; 20), 205 (44), 131 (100), 91 (44). HRMS Found: *m/z* 224.1000. Calcd for $C_{13}H_{14}OF_2$: M, 224.1012.

***o*-(1-Butyl-2,2-difluorovinyl)benzyl Alcohol (3a):** To a solution of **4a** (204 mg, 0.91 mmol) in toluene (6 mL) was added DIBAL (1.4 mL, 0.95 M in hexane, 1.4 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred for 30 min, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 5:1) to give **3a** (90 mg, 44%) as a colorless liquid.

1-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]ethanol (3d): Compound **3d** was prepared by the method described for **3a** using **4a** (210 mg, 0.93 mmol) and methylmagnesium iodide (1.4 mL, 1.0 M in Et_2O, 1.4 mmol) in toluene (6 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **3d** (124 mg, 55%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz), 1.30–1.32 (4H, m), 1.44 (3H, d, J = 6.3 Hz), 1.89 (1H, br s), 2.16–2.36 (2H, m), 5.00 (1H, q, J = 6.3 Hz), 7.09 (1H, d, J = 7.7 Hz), 7.26 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.37 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.61 (1H, dd, J = 7.7, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 24.8, 29.4, 29.6, 66.8, 90.6 (dd, J_{CF} = 22, 17 Hz), 125.8, 127.5, 128.6, 129.9, 131.3, 144.5, 152.7 (dd, J_{CF} = 285, 285 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) 72.2 (1F, br s), 67.7 (1F, br s) ppm. IR (neat) 3369, 2960, 2861, 1741, 1456, 1232, 1132, 1076, 966, 762 cm^{-1}. MS (20 eV) *m/z* (rel intensity) 240 (M^+; 41), 220 (93). HRMS Found: *m/z* 249.1333. Calcd for $C_{14}H_{18}OF_2$: M, 240.1326.

1-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]pentan-1-ol (3e): Compound **3e** was prepared by the method described for **3a** using **4a** (141 mg, 0.63 mmol) and butylmagnesium bromide (0.69 mL, 1.1 M in THF, 0.76 mmol) in toluene (4 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **3e** (137 mg, 77%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 120 °C) δ 0.84 (3H, t, J = 7.2 Hz), 0.84 (3H, t, J = 7.0 Hz), 1.22–1.42 (8H, m), 1.46–1.55 (1H, m), 1.58–1.68 (1H, m), 2.21–2.32 (2H, m), 4.50 (1H, br d, J = 4.6 Hz), 4.54–4.60 (1H, m), 7.05 (1H, d, J = 7.6 Hz), 7.20 (1H, dd, J = 7.6, 7.6 Hz), 7.31 (1H, dd, J = 7.6, 7.6 Hz), 7.53 (1H, d, J = 7.6 Hz). ^{13}C NMR

(126 MHz, $(CD_3)_2SO$, 120 °C) δ 12.5, 12.8, 21.0, 21.2, 27.1, 28.0, 28.3 (dd, J_{CF} = 5, 3 Hz), 37.8, 68.6, 91.0 (dd, J_{CF} = 22, 17 Hz), 125.8, 125.8, 127.3, 128.9, 130.3 (d, J_{CF} = 5 Hz), 144.4, 151.6 (dd, J_{CF} = 287, 283 Hz). ^{19}F NMR (470 MHz, $(CD_3)_2SO$, 120 °C) 67.9 (1F, d, J_{FF} = 50 Hz), 73.1 (1F, d, J_{FF} = 50 Hz) ppm. IR (neat) 3379, 2958, 2862, 1741, 1468, 1234, 1132, 1045, 972, 760 cm^{-1}. MS (20 eV) *m/z* (rel intensity) 282 (M^+; 38), 145 (23), 88 (100). HRMS Found: *m/z* 282.1802. Calcd for $C_{17}H_{24}OF_2$: M, 282.1795.

1-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]-1-phenylmethanol (3f): Compound **3f** was prepared by the method described for **3a** using **4a** (114 mg, 0.51 mmol) and phenylmagnesium bromide (0.81 mL, 0.94 M in THF, 0.76 mmol) in toluene (3 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **3f** (83 mg, 54%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, br s), 1.28 (4H, br), 2.17–2.24 (2H, m), 2.30 (1H, br s), 5.92 (1H, s), 7.12 (1H, d, J = 7.3 Hz), 7.22–7.35 (7H, m), 7.49 (1H, dd, J = 7.9, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.3, 29.0, 29.5, 72.6, 90.7 (dd, J_{CF} = 23, 15 Hz), 126.6, 127.4, 127.5, 127.6, 128.3, 128.4, 130.2, 132.5 (d, J_{CF} = 4 Hz), 142.3, 143.3, 152.7 (dd, J_{CF} = 287, 287 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) 73.1 (1F, br s), 67.9 (1F, d, J_{FF} = 46 Hz) ppm. IR (neat) 3381, 2958, 1741, 1452, 1236, 1132, 1018, 764, 700 cm^{-1}. MS (20 eV) *m/z* (rel intensity) 302 (M^+; 21), 235 (94), 179 (100). HRMS Found: *m/z* 302.1469. Calcd for $C_{19}H_{20}OF_2$: M, 302.1482.

***S*-*o*-(1-Butyl-2,2-difluorovinyl)benzyl Thioacetate (6a):** Compound **6a** was prepared by the method described for **4a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (766 mg, 3.0 mmol), butyllithium (3.8 mL, 1.7 M in hexane, 6.3 mmol), tributylborane (3.3 mL, 1.0 M in THF, 3.3 mmol), hexamethylphosphoric triamide (3.5 mL), triphenylphosphine (189 mg, 0.72 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (62 mg, 0.060 mmol), *o*-iodobenzyl methanesulfonate (846 mg, 2.7 mmol), and copper(I) iodode (573 mg, 3.0 mmol) in THF (15 mL). To the resulting solution of **5a** was added a sodium thioacetate generated from thioacetic *S*-acid (0.32 mL, 4.5 mmol) and sodium hydride (175 mg, 62% dispersion in mineral oil, 4.5 mmol). After the mixture had been stirred for 10 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 50:1) to give **6a** (428 mg, 56%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $C_6D_5CD_3$, 90 °C) δ 0.81 (3H, t, J = 7.3 Hz), 1.22 (2H, tq, J = 7.3, 7.3 Hz), 1.31 (2H, tt, J = 7.3, 7.3 Hz), 1.93 (3H, s), 2.23 (2H, tdd, J = 7.3 Hz, J_{HF} = 2.3, 2.3 Hz), 4.12 (2H, s), 6.97–7.02 (3H, m), 7.23 (1H, d, J = 7.0 Hz). ^{13}C NMR (126 MHz, $C_6D_5CD_3$, 90 °C) δ 13.7, 22.7, 29.4, 29.6, 30.1 (dd, J_{CF} = 3, 3 Hz), 31.3, 91.5 (dd, J_{CF} = 39, 18 Hz), 127.6, 128.6, 130.6, 134.1 (d, J_{CF} = 4 Hz), 137.2, 137.6, 153.7 (dd, J_{CF} = 289, 286 Hz), 193.1. ^{19}F NMR (471 MHz, $C_6D_5CD_3$, 90 °C) 69.1 (1F, d, J_{FF} = 45 Hz), 74.7 (1F, d, J_{FF} = 45 Hz) ppm. IR (neat) 2950, 2925, 2850, 1740, 1690, 1240, 1130, 970, 760 cm^{-1}. Found: C, 63.21; H, 6.44%. Calcd for $C_{15}H_{18}OF_2S$: C, 63.36; H, 6.38%.

***S*-*o*-[1-*s*-Butyl-2,2-difluorovinyl]benzyl Thioacetate (6b):** Compound **6b** was prepared by the method described for **6a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (255 mg, 1.0 mmol), butyllithium (1.3 mL, 1.7 M in hexane, 2.1 mmol), tri-*s*-butylborane (1.1 mL, 1.0 M in THF, 1.1 mmol), hexamethylphosphoric triamide (1.5 mL), triphenylphosphine (21 mg, 0.080 mmol), tris(dibenzylideneacetone)dipalladium–chloroform (1/1) (21 mg, 0.020 mmol), 2-iodobenzyl methanesulfonate (282 mg, 0.90 mmol), copper(I) iodide (191 mg, 1.0 mmol), and thioacetic *S*-acid (0.11 mL, 1.5 mmol) and sodium hydride (58 mg, 62% dispersion in mineral oil, 1.5 mmol) in THF (5 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 50:1) gave **6b** (128 mg, 50%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 0.90–1.64 (8H, m), 2.33 (3H, s), 2.32–2.38 (1H, m), 4.16 (2H, s), 7.08 (1H, br s), 7.20 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.26 (1H, dd, J = 7.4, 7.4 Hz), 7.37 (1H, d, J = 7.4 Hz). IR (neat) 2970, 2940, 1735, 1695, 1235, 1135, 1105, 760, 670, 630 cm^{-1}. Found: C, 63.35; H, 6.44%. Calcd for $C_{15}H_{18}OF_2S$: C, 63.36; H, 6.38%.

***o*-(1-Butyl-2,2-difluorovinyl)phenylmethanethiol (7a):** K_2CO_3 (168 mg, 1.2 mmol) was added to a solution of **6a** (299 mg, 1.0 mmol) in methanol (3.5 mL) at 0 °C. After the reaction mixture was stirred for 2 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 20:1) to give **7a** (207 mg, 86%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.9 Hz), 1.28–1.37 (4H, m), 1.73 (1H, t, J = 7.5 Hz), 2.26–2.36 (2H, m), 3.70 (2H, d, J = 7.5 Hz), 7.11 (1H, d, J = 7.3 Hz), 7.22 (1H, ddd, J = 7.3, 7.3, 1.2 Hz), 7.30 (1H, ddd, J = 7.3, 7.3, 1.2 Hz), 7.45 (1H, d, J = 7.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 26.0, 29.0, 29.7, 90.7 (dd, J_{CF} = 22, 17 Hz), 127.1, 128.5, 129.5, 130.3 (dd, J_{CF} = 3, 3 Hz), 132.5 (d, J_{CF} = 5 Hz), 139.9, 152.8 (dd, J_{CF} = 289, 286 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) 67.9 (1F, d, J_{FF} = 45 Hz), 73.1 (1F, d, J_{FF} = 45 Hz) ppm. IR (neat) 2960, 2940, 1750, 1315, 1290, 1240, 1135, 970, 765, 670 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 242 (M^+; 51), 166 (100), 179 (44). HRMS Found: *m/z* 242.0912. Calcd for $C_{13}H_{16}F_2S$: M, 242.0941.

4-Butyl-3-fluoro-1*H*-2-benzopyran (8a): To a DMF suspension (0.5 mL) of sodium hydride (28 mg, 60% dispersion in mineral oil, 0.69 mmol) was added **3a** (78 mg, 0.35 mmol) in DMF (1 mL) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred at room temperature for 1.2 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 5:1) to give **8a** (60 mg, 84%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.40 (2H, tq, J = 7.4, 7.4 Hz), 1.46–1.56 (2H, m), 2.42 (2H, td, J = 7.4, J_{HF} = 1.4 Hz), 5.22 (2H, s), 7.00 (1H, d, J = 7.5 Hz), 7.08–7.14 (2H, m), 7.25 (1H, dd, J = 7.5, 0.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.4, 22.5, 30.7, 71.4, 89.0 (d, J_{CF} = 23 Hz), 120.9 (d, J_{CF} = 7 Hz), 123.7, 125.2, 126.6, 128.4, 133.3 (d, J_{CF} = 6 Hz), 158.0 (d, J_{CF} = 264 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 68.0 (1F, s) ppm. IR (neat) 2960, 2870, 1680, 1490, 1460, 1390, 1245, 1195, 760, 670 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 206 (M^+; 100), 164 (79), 135 (88), 115 (96). Found: C, 75.43; H, 7.45%. Calcd for $C_{13}H_{15}OF$: C, 75.70; H, 7.33%.

4-*s*-Butyl-3-fluoro-1*H*-2-benzopyran (8b): Compound **8b** was prepared by the method described for **8a** using sodium hydride (16 mg, 60% dispersion in mineral oil, 0.40 mmol) and **3b** (45 mg, 0.20 mmol) in DMF (1 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **8b** (35

mg, 84%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.28 (3H, dd, J = 7.4, J_{HF} = 1.2 Hz), 1.62 (1H, dqdd, J = 21.6, 7.4, 7.4, J_{HF} = 1.2 Hz), 1.73 (1H, dqdd, J = 21.6, 7.4, 7.4, J_{HF} = 1.5 Hz), 2.67 (1H, tq, J = 7.4, 7.4 Hz), 5.17 (2H, s), 7.02 (1H, d, J = 7.3 Hz), 7.07–7.13 (1H, m), 7.21–7.27 (2H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 19.3 (d, J_{CF} = 3 Hz), 28.3 (d, J_{CF} = 3 Hz), 32.0 (d, J_{CF} = 2 Hz), 71.4, 93.8 (d, J_{CF} = 28 Hz), 121.4 (d, J_{CF} = 6 Hz), 123.9, 125.1, 126.9, 128.3, 133.9 (d, J_{CF} = 7 Hz), 158.2 (d, J_{CF} = 268 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 72.2 (1F, s) ppm. IR (neat) 2860, 1660, 1605, 1450, 1385, 1240, 1190, 1060, 930, 760 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 206 (M^+; 9), 167 (37), 149 (100). Found: C, 75.63; H, 7.36%. Calcd for $C_{13}H_{15}OF$: C, 75.70; H, 7.33%.

3-Butyl-2-fluoro-7,8,9,9a-tetrahydro-1-oxaphenalene (8c): Compound **8c** was prepared by the method described for **8a** using sodium hydride (11 mg, 60% dispersion in mineral oil, 0.27 mmol) and **3c** (36 mg, 0.14 mmol) in DMF (1.7 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **8c** (22 mg, 66%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.33–1.57 (4H, m), 1.67–1.78 (1H, m), 1.93–2.10 (2H, m), 2.36–2.45 (3H, m), 2.69–2.84 (2H, m), 5.26 (1H, dd, J = 10.1, 6.1 Hz), 6.91 (1H, d, J = 7.6 Hz), 6.95 (1H, d, J = 7.6 Hz), 7.16 (1H, dd, J = 7.6, 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 20.8, 22.4, 22.5, 28.3, 28.6, 30.8, 78.1, 89.6 (d, J_{CF} = 23 Hz), 118.5 (d, J_{CF} = 7 Hz), 125.8 (d, J_{CF} = 2 Hz), 126.0, 128.0, 133.6 (d, J_{CF} = 6 Hz), 135.4, 158.0 (d, J_{CF} = 266 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 67.9 (1F, s) ppm. IR (neat) 2950, 2880, 1685, 1595, 1465, 1245, 1180, 1020, 810, 780, 755 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 246 (M^+; 78), 203 (58), 155 (100). HRMS Found: *m/z* 246.1418. Calcd for $C_{16}H_{19}OF$: M, 246.1421.

4-Butyl-3-fluoro-1-methyl-1*H*-2-benzopyran (8d): Compound **8d** was prepared by the method described for **8a** using sodium hydride (35 mg, 60% dispersion in mineral oil, 0.86 mmol) and **3d** (104 mg, 0.43 mmol) in DMF (3 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **8d** (57 mg, 60%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.39 (2H, tq, J = 7.3, 7.3 Hz), 1.50 (2H, tt, J = 7.3, 7.3 Hz), 1.63 (3H, d, J = 6.4 Hz), 2.42 (2H, td, J = 7.3 Hz, J_{HF} = 1.7 Hz), 5.42 (1H, q, J = 6.4 Hz), 7.00 (1H, dd, J = 7.6, 0.6 Hz), 7.12 (1H, ddd, J = 7.6, 7.6, 0.6 Hz), 7.13 (1H, d, J = 7.6 Hz), 7.25 (1H, ddd, J = 7.6, 7.6, 0.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 19.4, 22.3, 22.4, 30.7, 77.8, 88.0 (d, J_{CF} = 23 Hz), 121.1 (d, J_{CF} = 7 Hz), 123.2, 125.2 (d, J_{CF} = 2 Hz), 128.0, 131.2, 132.5 (d, J_{CF} = 7 Hz), 156.5 (d, J_{CF} = 264 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 68.2 (1F, s) ppm. IR (neat) 2960, 2930, 2860, 1685, 1560, 1490, 1460, 1375, 1360, 1240, 760 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 220 (M^+; 100), 163 (24), 149 (48), 129 (60). HRMS Found: *m/z* 220.1287. Calcd for $C_{14}H_{17}OF$: M, 220.1263.

1,4-Dibutyl-3-fluoro-1*H*-2-benzopyran (8e): Compound **8e** was prepared by the method described for **8a** using sodium hydride (48 mg, 60% dispersion in mineral oil, 1.2 mmol) and **3e** (171 mg, 0.61 mmol) in DMF (6 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **8e** (113 mg, 71%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 0.93 (3H, t, J = 7.3 Hz), 1.32–1.58 (8H, m), 1.69–1.77 (1H, m), 2.02–2.10 (1H, m), 2.36–2.46 (2H, m), 5.24 (1H, ddd, J = 8.2, 4.8, J_{HF} = 2.3 Hz), 6.96 (1H, d, J = 7.6 Hz), 7.09 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.12 (1H, dd, J = 7.5, 0.9 Hz), 7.23 (1H, dd, J = 7.5, 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 22.3, 22.5, 27.2, 30.7, 30.7, 33.5, 81.8, 87.7 (d, J_{CF} = 23 Hz), 121.2 (d, J_{CF} = 7 Hz), 123.8, 125.0, 128.0, 130.5, 132.4 (d, J_{CF} = 6 Hz), 156.2 (d, J_{CF} = 264 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 68.2 (1F, s) ppm. IR (neat) 2955, 2930, 2860, 1685, 1490, 1455, 1375, 1235, 1155, 965, 760 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 262 (M^+; 89), 205 (89), 88 (100). HRMS Found: *m/z* 262.1740. Calcd for $C_{17}H_{23}OF$: M, 262.1733.

4-Butyl-3-fluoro-1-phenyl-1*H*-2-benzopyran (8f): Compound **8f** was prepared by the method described for **8a** using sodium hydride (36 mg, 60% dispersion in mineral oil, 0.91 mmol) and **3f** (137 mg, 0.45 mmol) in DMF (4 mL). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **8f** (64 mg, 50%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.3 Hz), 1.23–1.52 (4H, m), 2.38–2.45 (2H, m), 6.28 (1H, s), 6.77 (1H, d, J = 7.3 Hz), 7.08 (1H, ddd, J = 8.5, 8.5, 1.2 Hz), 7.28–7.39 (7H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.3, 22.3, 30.5, 83.0, 89.2 (d, J_{CF} = 23 Hz), 121.2 (d, J_{CF} = 6 Hz), 125.2 (d, J_{CF} = 2 Hz), 125.5, 128.0, 128.4, 128.6 (d, J_{CF} = 3 Hz), 128.8, 129.3, 133.1 (d, J_{CF} = 6 Hz), 138.1, 156.5 (d, J_{CF} = 266 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 68.3 (1F, s) ppm. IR (neat) 2929, 2872, 1726, 1680, 1493, 1454, 1387, 1232, 1151, 1093 cm^{-1}. MS (20 eV) *m/z* (rel intensity) 282 (M^+; 41), 225 (100). HRMS Found: *m/z* 282.1429. Calcd for $C_{19}H_{19}OF$: M, 282.1420.

4-Butyl-3-fluoro-1*H*-2-benzothiopyran (9a): To a THF suspension (6.5 mL) of potassium hydride (KH, 41 mg, 35% dispersion in mineral oil, 0.36 mmol) was added **7a** (72 mg, 0.30 mmol) in THF (1.5 mL) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred at room temperature for 2.5 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 20:1) to give **9a** (61 mg, 90%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 1.38 (2H, tq, J = 7.3, 7.3 Hz), 1.45–1.53 (2H, m), 2.66 (2H, td, J = 7.6, J_{HF} = 3.4 Hz), 3.92 (2H, d, J_{HF} = 4.9 Hz), 7.13 (1H, d, J = 7.6 Hz), 7.17 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.25 (1H, dd, J = 7.5, 7.5 Hz), 7.28 (1H, d, J = 7.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.5, 24.8 (d, J_{CF} = 4 Hz), 30.8 (d, J_{CF} = 2 Hz), 33.6, 116.8 (d, J_{CF} = 14 Hz), 124.1 (d, J_{CF} = 6 Hz), 126.6, 126.9, 127.6, 128.6, 134.6 (d, J_{CF} = 4 Hz), 153.9 (d, J_{CF} = 282 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 64.7 (1F, tt, J_{FH} = 4, 4 Hz) ppm. IR (neat) 2960, 2890, 1620, 1570, 1490, 1450, 1155, 1100, 765 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 222 (M^+; 82), 179 (100), 146 (73), 135 (45). Found: C, 70.37; H, 6.85%. Calcd for $C_{13}H_{15}FS$: C, 70.23; H, 6.80%.

4-Butyl-3-fluoro-1*H*-2-benzothiopyran (9a): To a DMF suspension (4 mL) of sodium methoxide (33 mg, 0.61 mmol) was added **6a** (87 mg, 0.31 mmol) in DMF (1 mL). After the mixture was stirred at room temperature for 15 min, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 30:1) to give **9a** (64 mg, 94%) as a colorless liquid.

4-*s*-Butyl-3-fluoro-1*H*-2-benzothiopyran (9b): Compound **9b** was prepared by the method described for **9a** using sodium methoxide (28 mg, 0.52 mmol) and **6b** (70 mg, 0.25 mmol) in DMF (6 mL). Purification by column chromatography on silica gel (hexane–AcOEt 30:1) gave **9b** (49 mg, 90%) as a colorless

liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.34 (3H, dd, J = 7.3 Hz, J_{HF} = 1.2 Hz), 1.69 (1H, dqdd, J = 14.6, 7.3, 7.3 Hz, J_{HF} = 1.4 Hz), 1.83 (1H, dqdd, J = 14.6, 7.3, 7.3 Hz, J_{HF} = 1.4 Hz), 2.84 (1H, tq, J = 7.3, 7.3 Hz), 3.84 (1H, dd, J = 13.7, J_{HF} = 5.2 Hz), 3.93 (1H, dd, J = 13.7, J_{HF} = 4.6 Hz), 7.14 (1H, dd, J = 7.3, 1.3 Hz), 7.17 (1H, tq, J = 7.3, 1.3 Hz), 7.24 (1H, tq, J = 7.3, 1.3 Hz), 7.37 (1H, d, J = 7.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9, 19.6 (d, J_{CF} = 3 Hz), 28.5 (d, J_{CF} = 4 Hz), 34.1, 36.4, 121.3 (d, J_{CF} = 12 Hz), 124.4 (d, J_{CF} = 5 Hz), 126.4, 126.7, 127.4, 129.2, 136.0 (d, J_{CF} = 7 Hz), 155.3 (d, J_{CF} = 287 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) 68.3 (1F, br s) ppm. IR (neat) 2960, 2890, 1615, 1490, 1455, 1175, 1145, 1100, 890, 760 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 222 (M^+; 70), 193 (100), 160 (59). HRMS Found: *m/z* 222.0861. Calcd for $C_{13}H_{15}FS$: M, 222.0878.

4-Butyl-3-phenylthio-1*H*-2-benzothiopyran (10a): To a dimethyl sulfoxide (DMSO) suspension (3 mL) of potassium hydride (156 mg, 35% dispersion in mineral oil, 0.85 mmol) was added benzenethiol (0.14 mL, 1.4 mmol) at room temperature under a nitrogen atmosphere, and the mixture was stirred for 0.5 h. To the resulting solution was added **9a** (76 mg, 0.34 mmol) in DMSO (1 mL), and the mixture was stirred at 100 °C for 22 h. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 30:1) to give **10a** (76 mg, 71%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.5 Hz), 1.40 (2H, tq, J = 7.5, 7.5 Hz), 1.55 (2H, tt, J = 7.5, 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.70 (2H, s), 7.11–7.15 (1H, m), 7.19–7.32 (5H, m), 7.33–7.37 (2H, m), 7.40 (1H, d, J = 7.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.6, 30.9, 32.2, 33.9, 124.8, 126.2, 126.4, 126.5, 127.2, 128.1, 128.9, 128.9, 130.9, 134.8, 136.6, 141.0. IR (neat) 3050, 2950, 2930, 2860, 1580, 1470, 1440, 760, 740, 685 cm^{-1}. MS (70 eV) *m/z* (rel intensity) 312 (M^+; 45), 269 (32), 123 (100). Found: C, 72.92; H, 6.44%. Calcd for $C_{19}H_{20}S_2$: C, 73.03; H, 6.45%.

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