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Metal-Mediated Reformatsky Reaction of Bromodifluoromethyl Ketone and Imine

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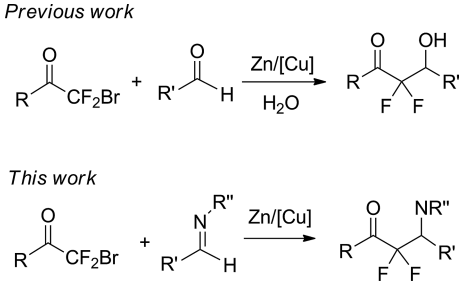
The Reformatsky reaction of bromodifluoromethyl ketones and imines took place readily in the presence of Zn/CuCl at room temperature to afford β-amino α,α-difluoro ketones in good yields. Using (*S*)-*tert*-butanesulfinyl as a chiral auxiliary, the asymmetric Reformatsky reaction was also achieved and found to proceed with excellent diastereoselectivities. A plausible model is proposed to account for the high stereoselectivity of the reaction.

Introduction

The incorporation of fluorine as a bioisosteric replacement for hydrogen has a profound influence on metabolic degradation, lipophilicity and reactivity of organic compounds, influencing their applications in both pharmaceutical and agrochemical areas.[1] Therefore, a large number of physiologically active fluorinated compounds are now widely used or under development.[2] In particular, β-amino α,α-difluoro ketones have received considerable attention due to their unique physical, chemical, and biological properties.[3] For example, the introduction of the β-amino α,α-difluoro ketone unit into a peptide has proven to be successful in the design of enzyme inhibitors such as protease inhibitors.[4] The β-amino α,α-difluoro ketones are also useful building blocks for the synthesis of more complex fluorinated molecules and biomolecules. Thus far, several methods have been developed for the preparation of β-amino α,α-difluoro ketones, including, but not limited to i) deoxydifluorination of β-keto carbonyl compounds with diethylaminosulfur trifluoride,[4c,5] ii) the Reformatsky reaction of α-bromo α,α-difluoroacetate with aldimines,[6] and iii) the Mannich-type reaction of difluorinated silyl enol ether with aldimines.[7]

The Reformatsky reaction is an efficient approach to C–C bond formation and has been used extensively for the synthesis of a wide range of different compounds.[8] Recently, our group reported the synthesis of α,α-difluorinated β-hydroxy carbonyl compounds using the Reformatsky reaction of bromodifluoromethyl ketones with aldehydes using water as an efficient and environmentally friendly solvent [Scheme 1, Equation (1)].[9] As an extension of our studies focused on Reformatsky reaction applications with bromodifluoromethyl ketones, we further investigated the reaction of bromodifluoromethyl ketones with imines as a means of constructing corresponding β-amino α,α-difluoro ketones [Scheme 1, Equation (2)]. The results are reported in this paper.



Scheme 1. Previous and current Reformatsky chemistries of interest.

Results and Discussion

Initially, *N*-benzylideneaniline (**2a**)[10] was used as the substrate to investigate the Reformatsky reaction of bromodifluoromethyl phenyl ketone (**1a**). When the reaction was carried out with 4.0 equiv. of imine **2a** and 4.0 equiv. of zinc powder in water at room temp., desired product **3a** was obtained in only 24% yield (Scheme 2). ^{19}F NMR monitoring revealed that α,α-difluorinated β-hydroxy carbonyl compound **4a** was formed as the major byproduct, indicating that the imine may decompose to its corresponding aldehyde in water.

Next, we used organic solvent to study the Reformatsky reaction of imine **2a**. Compound **3a** was still obtained in low yield (38%) when the reaction was carried out in acetonitrile (Table 1, Entry 1). The impact of various copper (I) species on reaction efficiency was tested; CuBr and CuI

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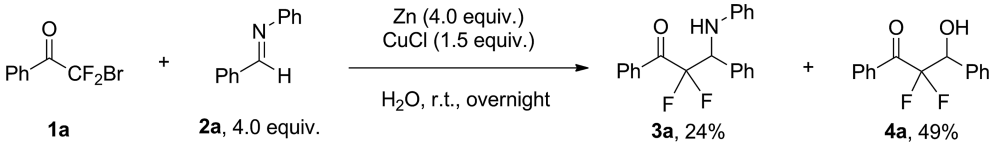
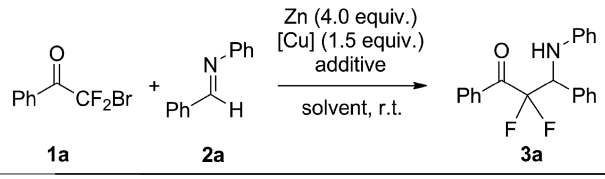


Scheme 2. Reformatsky reaction of bromodifluoromethyl phenyl ketone and *N*-benzylideneaniline in water.

were found to improve the yields of **3a** to 57% and 49%, respectively (Table 1, Entries 2, 3). The reaction did not occur in the absence of copper salt (Table 1, Entry 4). The use of $Ti(OEt)_4$ as an additive did not improve the yield of **3a** either (Table 1, Entry 5). However, when molecular sieves were added to the reaction mixture, **3a** was obtained in 82% yield (Table 1, Entry 6). Further examination of solvent effects revealed that tetrahydrofuran (THF), in the presence of molecular sieves, afforded a result similar to that noted when using acetonitrile as solvent (Table 1, Entries 6, 7). Despite inclusion of molecular sieves, no reaction was observed when using dichloroethane (DCE) or toluene as solvents (Table 1, Entries 8, 9). Consequently, the optimal reaction conditions were assigned to include 4.0 equiv. of imine, 4.0 equiv. of zinc and 1.5 equiv. of CuBr in the presence of molecule sieves in acetonitrile at room temp. It is worth noting that self-condensation and hydrogenation of **1a** were observed as competitive reactions along with the desired Reformatsky reaction (see Supporting Information).

Table 1. Screening of reaction conditions.

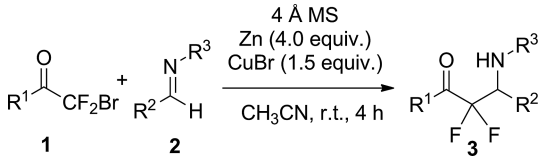


Entry[a]	[Cu]	Additive	Solvent	Time [h]	Yield [%][b]
1	CuCl	–	CH_3CN	4	38
2	CuBr	–	CH_3CN	4	57
3	CuI	–	CH_3CN	4	49
4	–	–	CH_3CN	9	trace
5	CuBr	$Ti(OEt)_4$ (0.4 equiv.)	CH_3CN	4	48
6	CuBr	4 Å MS (50 mg)	CH_3CN	4	82
7	CuBr	4 Å MS (50 mg)	THF	4	81
8	CuBr	4 Å MS (50 mg)	DCE	4	0
9	CuBr	4 Å MS (50 mg)	toluene	4	0

[a] Conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), Zn (0.8 mmol), [Cu] (0.3 mmol), additive (0.08 mmol or 50 mg) and 3 mL solvent at room temp. [b] Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Using the optimized conditions, a variety of imines were investigated to evaluate the scope of this reaction. The results are summarized in Table 2. It was found that the electronic effect of substituents influenced the reaction. Electron-rich imines bearing methyl or methoxy-substitution afforded the corresponding products in moderate yields (55–78%, Table 2, Entries 2, 5). Halogen-substituted imines reacted well with **1a** to give desired products **3c**, **3d** and **3f** in high yields (87–91%, Table 2, Entries 3, 4, 6); the use of bromo substitution is envisioned to enable further modification of the product (Table 2, Entry 4). The generality of the reaction was also surveyed with various bromodifluoro ketones **1** under the standard conditions. Unfortunately, both *p*-methoxy and *p*-chloro-substituted phenyl ketones (**1b** and **1c**) gave desired products **3g** and **3h** in low yields (Table 2, Entries 7, 8). The reaction of aliphatic ketone **1d** with imine **2a** took place readily to afford corresponding product **3i** in 81% yield (Table 2, Entry 9).

Table 2. Reformatsky reactions of bromodifluoromethyl ketones **1** and imines **2**.



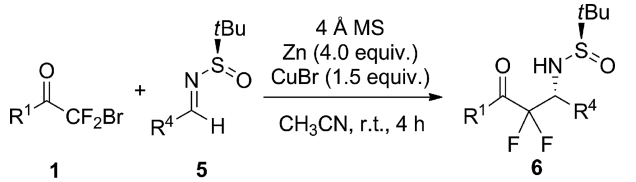
Entry[a]	**1**, R^1	**2**, R^2/R^3	Yield (**3**, %)[b]
1	**1a**, C_6H_5	**2a**, C_6H_5/C_6H_5	**3a**, 70
2	**1a**, C_6H_5	**2b**, C_6H_5/4-$MeOC_6H_4$	**3b**, 55
3	**1a**, C_6H_5	**2c**, C_6H_5/4-ClC_6H_4	**3c**, 87
4	**1a**, C_6H_5	**2d**, C_6H_5/4-BrC_6H_4	**3d**, 91
5	**1a**, C_6H_5	**2e**, 4-MeC_6H_4/C_6H_5	**3e**, 78
6	**1a**, C_6H_5	**2f**, 4-ClC_6H_4/C_6H_5	**3f**, 90
7	**1b**, 4-$MeOC_6H_4$	**2a**, C_6H_5/C_6H_5	**3g**, 57
8	**1c**, 4-ClC_6H_4	**2a**, C_6H_5/C_6H_5	**3h**, 28
9	**1d**, $C_6H_5(CH_2)_3$	**2a**, C_6H_5/C_6H_5	**3i**, 81

[a] Conditions: **1** (0.2 mmol), **2** (0.8 mmol), Zn (0.8 mmol), CuBr (0.3 mmol), 4 Å MS (50 mg) and 3 mL CH_3CN at room temp. for 4 h. [b] Isolated yield.

The diastereoselective addition of nucleophiles to chiral imines is a useful method for the preparation of optically active secondary amines.[11] Staas and Sorochinsky have independently reported the diastereoselective synthesis of α,α-difluoro β-amino acids via the Reformatsky reaction of ethyl bromodifluoroacetate and chiral sulfinylimines derived from optically pure *N*-*tert*-butanesulfinamide and *N*-*p*-toluenesulfinamide, respectively.[12] A group of α-fluoro β-amino acid derivatives have also been obtained with moderate diastereoselectivities from the reaction of chiral *N*-*tert*-butanesulfinylimines with ethyl bromofluoroacetate in the presence of activated Zn dust.[13] Motivated by the above results, we prepared a series of chiral ketimines **5** from (*R*)-*tert*-butanesulfinamide,[14] and studied their reactions with **1** under the optimized conditions.

The data in Table 3 indicates that the asymmetric reaction can tolerate a broad range of functional groups. The reactions of chiral ketimines **5** bearing methyl, methoxy, halide, and cyano substitution proceeded well to afford the corresponding products in moderate to good yields and with high diastereoselectivities (68–85%, 91:9–95:5 *dr*, Table 3, Entries 2–8). Imines derived from 4-biphenylcarbaldehyde or furfural also afforded the desired products with excellent diastereoselectivities (Table 3, Entries 9, 10). Slightly lower diastereoselectivities were obtained with naphthyl, alkyl or vinyl-substituted imines (86:14–89:11 *dr*, Table 3, Entries 11–13). The scope of these asymmetric reactions was also investigated using *p*-methoxy- and *p*-chloro-substituted phenyl ketones; moderate yields and excellent stereoselectivities were obtained (>95:5 *dr*, Table 3, Entries 14, 15). In the case of aliphatic ketone **1d**, desired product **6p** was obtained in 72% yield with 91:9 *dr* (Table 3, Entry 16).

Table 3. Asymmetric Reformatsky reaction of bromodifluoromethyl ketones **1** and chiral ketimines **5**.

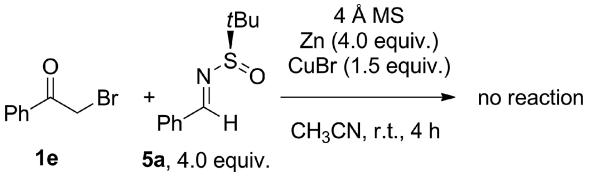


Entry[a]	**1**, R^1	**5**, R^4	Yield (**6**,%)[b]	*dr*[c]
1	**1a**, C_6H_5	**5a**, C_6H_5	**6a**, 60	>95:5
2	**1a**, C_6H_5	**5b**, 4-MeC_6H_4	**6b**, 72	>95:5
3	**1a**, C_6H_5	**5c**, 4-MeOC_6H_4	**6c**, 76	>95:5
4	**1a**, C_6H_5	**5d**, 4-ClC_6H_4	**6d**, 76	>95:5
5	**1a**, C_6H_5	**5e**, 4-BrC_6H_4	**6e**, 85	>95:5
6	**1a**, C_6H_5	**5f**, 4-CNC_6H_4	**6f**, 77	95:5
7	**1a**, C_6H_5	**5g**, 2-ClC_6H_4	**6g**, 73	>95:5
8	**1a**, C_6H_5	**5h**, 2-BrC_6H_4	**6h**, 68	91:9
9	**1a**, C_6H_5	**5i**, 4-PhC_6H_4	**6i**, 81	>95:5
10	**1a**, C_6H_5	**5j**, 2-furyl	**6j**, 68	95:5
11	**1a**, C_6H_5	**5k**, 2-naphthyl	**6k**, 56	89:11
12	**1a**, C_6H_5	**5l**, $C_6H_5(CH_2)_2$	**6l**, 63	86:14
13	**1a**, C_6H_5	**5m**, 4-ClC_6H_4CH=CH	**6m**, 64	88:12
14	**1b**, 4-MeOC_6H_4	**5d**, 4-ClC_6H_4	**6n**, 67	>95:5
15	**1c**, 4-ClC_6H_4	**5d**, 4-ClC_6H_4	**6o**, 60	>95:5
16	**1d**, $C_6H_5(CH_2)_3$	**5d**, 4-ClC_6H_4	**6p**, 72	91:9

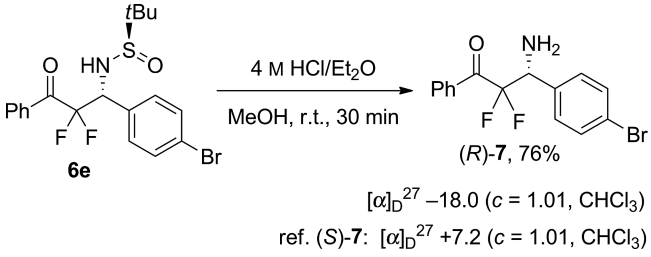
[a] Conditions: **1** (0.2 mmol), **5** (0.8 mmol), Zn (0.8 mmol), CuBr (0.3 mmol), 4 Å MS (50 mg) and 3 mL CH_3CN at room temp. for 4 h. [b] Isolated yield. [c] Determined by ^{19}F NMR spectra of the crude reaction mixture.

As a comparison, we further investigated the reactivity of bromomethyl phenyl ketone **1e**. Reformatsky chemistry with **1e** failed to proceed under our generally applied optimized reaction conditions and all starting materials were recovered (Scheme 3). Efforts to extend reaction time, increase reaction temperature, or to use additives failed to promote this reaction.

To determine the configuration of the products and to illustrate the synthetic utility of this reaction, we attempted the conversion of compound **6e** into optically pure amine (*R*)-**7**. Removal of the sulfinyl group with HCl in Et_2O/MeOH under mild conditions afforded amine **7** in 76% yield. Comparisons to optical data for previously reported (*R*)-**7**[15] revealed **7** generated herein to bear the *R*-configuration (Scheme 4). Consequently, the stereochemistry of products **6** (Table 3) is putatively assigned to be (*Rc*,*Rs*).



Scheme 3. Attempted Reformatsky reaction of bromomethyl phenyl ketone **1e**.



Scheme 4. Preparation of **7** by deprotection of **6e**.

These β-amino α,α-difluoro ketone derivatives could be used as potential synthons in organic synthesis. For example, enantiopure 3,3-difluoroazetidin-2-one, a pharmaceutically important target as well as a useful synthetic building block, was successfully synthesized from the corresponding β-amino α,α-difluoro ketone via a two-step route.[15]

Based on the above results and related literature,[12] the six-membered models **A** and **B** can be used to account for the high stereoselectivity of this reaction. As shown in Figure 1, transition state **B** is unfavored due to repulsive steric interactions between the chiral auxiliary and ketamine-born R′ group. Therefore, transition state **A** is believed to predominate during the course of reaction ultimately affording the *cis* adduct as the major Reformatsky product.

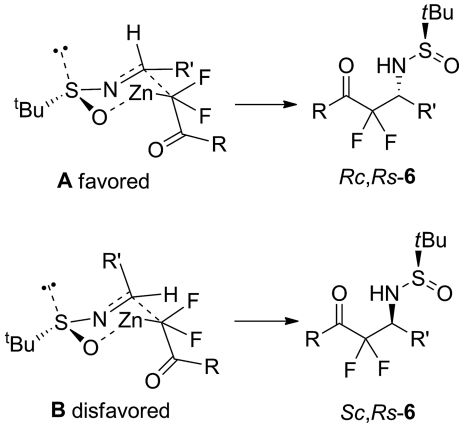


Figure 1. Proposed transition states for the Reformatsky reaction.

Conclusions

In summary, we have developed an efficient method for the synthesis of β-amino-α,α-difluoro ketones. In the presence of Zn/CuBr, the Reformatsky reaction of various imines and bromodifluoromethyl ketones took place readily under mild conditions to give the corresponding difluorinated products in good yields. Excellent diastereoselectivities were obtained in the asymmetric reaction of imines derived from (*R*)-*tert*-butanesulfinamide.

Experimental Section

General Experimental Details: Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. CH_3CN was freshly distilled by standard procedure prior to use. Melting points were measured with a Melt-Temp apparatus and uncorrected. IR spectra were recorded with an infrared spectrometer. ^1H NMR spectra were recorded with Bruker AM 300 (300 MHz) or Agilent 400 (400 MHz) spectrometers with TMS as the internal standard. ^{19}F NMR spectra were recorded using Bruker AM-300 (282 MHz) or Agilent 400 (376 MHz) spectrometers with $CFCl_3$ as the external standard. ^{13}C NMR spectra were recorded with DPX 400 (100 MHz) or Agilent 400 (100 MHz) spectrometers. HRMS spectra were obtained using a Waters Micromass GCT (EI) or Bruker APEXIII 7.0 TESLA FTMS (ESI) spectrometer.

Typical Procedure for the Reformatsky Reaction: To a flask containing imine **2** or **5** (0.8 mmol), bromodifluoromethyl ketone **1** (0.2 mmol), molecular sieves (4 Å, 50 mg) and acetonitrile (3 mL) were added zinc powder (0.8 mmol) and CuBr (0.3 mmol) with stirring. The mixture was stirred at room temp. for 4 h, and then quenched with saturated aqueous NH_4Cl solution. The resulting mixture was stirred for an additional 10 min, and then extracted with EtOAc (15 mL × 3). The combined organic layer was dried with sodium sulfate. After the removal of solvent under reduced pressure, the residue was subjected to column chromatography on silica gel using EtOAc and petroleum ether as eluent to afford corresponding product **3** or **6**.

Procedure for the Preparation of (*R*)-7: A suspension of (*Rc*,*Rs*)-**6a** (0.11 mmol) in MeOH (1 mL) was added the mixture of HCl/Et_2O (4 M, 0.5 mL) at room temp. After stirring for 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was stirred for an additional 10 min, and extracted with EtOAc (15 mL × 3). The combined organic layer was dried with sodium sulfate. After the removal of solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel (AcOEt/hexane, 1:5) to give (*R*)-**7**.

Compound 3a: 47 mg, yield 70%; yellow solid, m.p. 85–87 °C. IR (KBr): $\tilde{\nu}$ = 3382, 3057, 3026, 1685, 1606, 1510, 1498, 1303, 1288, 1214, 1123, 1075, 750, 700, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.0 Hz, 2 H), 7.61 (t, *J* = 7.1 Hz, 1 H), 7.46 (t, *J* = 7.9 Hz, 4 H), 7.40–7.28 (m, 3 H), 7.12 (t, *J* = 7.6 Hz, 2 H), 6.73 (t, *J* = 7.3 Hz, 1 H), 6.62 (d, *J* = 8.3 Hz, 2 H), 5.34 (dt, *J* = 17.7, 7.5 Hz, 1 H), 4.56 (d, *J* = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9 (dd, *J* = 29.6, 27.9 Hz), 145.5, 134.4, 134.3, 132.8, 129.8 (t, *J* = 3.4 Hz), 129.2, 128.9, 128.8, 128.7, 128.6, 119.3 (dd, *J* = 259.6, 257.8 Hz), 118.9, 114.2, 60.4 (dd, *J* = 25.9, 22.5 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –102.9 (dd, *J* = 272.9, 8.4 Hz, 1 F), –112.3 (dd, *J* = 272.9, 17.7 Hz, 1 F) ppm. MS (EI): *m*/*z* (%) = 337 (4.14), 183 (13.68), 182 (100.00), 180 (5.26), 140 (3.62), 105 (13.34), 104 (8.74), 77 (21.76). HRMS (EI): Calcd. for $C_{21}H_{17}F_2NO$ $[M]^+$: 337.1278, found 337.1277.

Compound 3b: 44 mg, yield 55%; yellow solid, m.p. 95–97 °C. IR (KBr): $\tilde{\nu}$ = 3363, 2930, 1696, 1677, 1516, 1451, 1287, 1234, 1121, 1075, 1034, 824, 708, 698, 611 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.8 Hz, 2 H), 7.60 (t, *J* = 7.4 Hz, 1 H), 7.52–7.39 (m, 4 H), 7.39–7.27 (m, 3 H), 6.65 (d, *J* = 8.9 Hz, 2 H), 6.54 (d, *J* = 8.9 Hz, 2 H), 5.21 (dd, *J* = 18.7, 7.1 Hz, 1 H), 4.24 (br., s, 1 H), 3.66 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2 (dd, *J* = 34.0, 28.0 Hz), 153.2, 139.5, 134.7, 134.1, 133.8 133.2, 129.8 (t, *J* = 3.3 Hz), 128.7, 128.6, 128.4, 117.5 (dd, *J* = 259.8, 256.8 Hz), 116.0, 114.8, 61.5 (dd, *J* = 23.0, 28.0 Hz), 55.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –102.0 (dd, *J* = 272.4, 7.8 Hz, 1 F), –113.1 (dd, *J* = 272.4, 18.7 Hz, 1 F) ppm. MS (EI): *m*/*z* (%) = 367 (6.91) $[M]^+$, 213 (17.39), 212 (100.00), 168 (8.25), 134 (6.16), 107 (4.74), 105 (16.00), 77 (21.69). HRMS (EI): Calcd. for $C_{22}H_{19}F_2NO_2$ $[M]^+$: 367.1384, found 367.1387.

Compound 3c: 64.5, yield 87%; pale yellow solid, m.p. 92–94 °C. IR (KBr): $\tilde{\nu}$ = 3379, 2916, 1679, 1598, 1506, 1403, 1287, 1122, 1074, 831, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.9 Hz, 2 H), 7.65–7.57 (m, 1 H), 7.44 (dd, *J* = 15.3, 7.5 Hz, 4 H), 7.38–7.28 (m, 3 H), 7.04 (d, *J* = 8.7 Hz, 2 H), 6.52 (d, *J* = 8.7 Hz, 2 H), 5.25 (dt, *J* = 17.3, 8.7 Hz, 1 H), 4.56 (d, *J* = 8.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8 (dd, *J* = 29.6, 28.1 Hz), 144.1, 134.3, 133.9, 132.7, 129.7 (t, *J* = 3.4 Hz), 129.1, 128.9, 128.7, 128.6, 128.5, 123.9, 117.1 (dd, *J* = 260.0, 259.0 Hz), 115.3, 60.5 (dd, *J* = 25.9, 22.7 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.0 (dd, *J* = 275.1, 8.3 Hz, 1 F), –111.9 (dd, *J* = 275.1, 17.3 Hz, 1 F) ppm. MS (EI): *m*/*z* (%) = 371 (6.10) $[M]^+$, 216 (100.00), 218 (34.42), 217 (16.28), 138 (7.57), 77 (6.15), 140 (5.24), 111 (5.13). HRMS (EI): Calcd. for $C_{21}H_{16}ClF_2NO$ $[M]^+$: 371.0888, found 371.0887.

Compound 3d: 75 mg, yield 91%; white solid, m.p. 104–106 °C. FT-IR (KBr): $\tilde{\nu}$ = 3378, 2923, 1696, 1676, 1596, 1286, 1135, 1071, 829, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.7 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.47–7.42 (m, 4 H), 7.38–7.32 (m, 3 H), 7.18 (d, *J* = 8.8 Hz, 2 H), 6.48 (d, *J* = 8.8 Hz, 2 H), 5.26 (dt, *J* = 17.0, 8.4 Hz, 1 H), 4.59 (d, *J* = 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7 (dd, *J* = 29.7, 28.2 Hz), 144.5, 134.4, 133.9, 132.7, 132.0, 129.8 (t, *J* = 3.3 Hz), 128.9, 128.8, 128.7, 128.5, 117.1 (dd, *J* = 259.6, 258.5 Hz), 115.8, 110.8, 60.3 (dd, *J* = 25.9, 22.7 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.0 (dd, *J* = 275.2, 8.4 Hz, 1 F), –111.8 (dd, *J* = 275.2, 17.2 Hz, 1 F) ppm. MS (EI): *m*/*z* (%) = 415 (2.68) $[M]^+$, 171 (100.00), 173 (94.57), 260 (52.44), 262 (42.57), 180 (37.57), 105 (25.03), 65 (23.62), 92 (21.83). HRMS (EI): Calcd. for $C_{21}H_{16}BrF_2NO$ $[M]^+$: 415.0383, found 415.0384.

Compound 3e: 55 mg, yield 78%; yellow solid; m.p. 108–110 °C. IR (KBr): $\tilde{\nu}$ = 3367, 1684, 1607, 1514, 1500, 1448, 1300, 1290, 1217, 1128, 1077, 840, 790, 751, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 7.8 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.7 Hz, 2 H), 7.36 (d, *J* = 7.8 Hz, 2 H), 7.17 (d, *J* = 7.8 Hz, 2 H), 7.11 (t, *J* = 7.8 Hz, 2 H), 6.72 (t, *J* = 7.3 Hz, 1 H), 6.62 (d, *J* = 7.9 Hz, 2 H), 5.32 (d, *J* = 14.5 Hz, 1 H), 4.54 (br., s, 1 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.0 (dd, *J* = 29.8, 28.0 Hz), 145.6, 138.6, 134.2, 132.9, 131.3, 129.8 (t, *J* = 3.4 Hz), 129.4, 129.2, 128.7, 128.4, 118.9, 117.4 (dd, *J* = 260.8, 258.7 Hz), 114.2, 60.2 (dd, *J* = 26.0, 22.5 Hz), 21.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.0 (dd, *J* = 272.1, 8.4 Hz, 1 F), –112.5 (dd, *J* = 272.1, 17.8 Hz, 1 F) ppm. MS (EI): *m*/*z* (%) = 351 (2.32) $[M]^+$, 197 (15.56), 196 (100.00), 194 (3.25), 105 (8.57), 104 (12.49),

91 (3.02), 77 (21.62), 51 (2.59). HRMS (EI): Calcd. for $C_{22}H_{19}F_2NO$ $[M]^+$: 351.1435, found 351.1433.

Compound 3f: 67 mg, yield 90%; pale yellow solid, m.p. 124–125 °C. IR (KBr): $\tilde{\nu}$ = 3353, 3053, 2919, 1698, 1604, 1498, 1180, 1070, 927, 756, 691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.7 Hz, 2 H), 7.63 (dd, J = 10.6, 4.2 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 2 H), 7.40 (d, J = 7.9 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.11 (t, J = 7.5 Hz, 2 H), 6.73 (t, J = 7.3 Hz, 1 H), 6.57 (d, J = 7.7 Hz, 2 H), 5.30 (dt, J = 17.6, 8.9 Hz, 1 H), 4.51 (d, J = 8.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5 (dd, J = 29.6, 27.9 Hz), 145.2, 134.7, 134.4, 133.0, 132.6, 129.9, 129.8 (t, J = 3.4 Hz), 129.3, 128.9, 128.7, 119.2, 117.0 (dd, J = 260.0, 257.9 Hz), 114.2, 59.8 (dd, J = 26.0, 22.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –102.5 (dd, J = 275.9, 8.0 Hz, 1 F), –112.3 (dd, J = 275.9, 17.6 Hz, 1 F) ppm. MS (EI): m/z (%) = 371 (3.57) $[M]^+$, 218 (31.64), 217 (43.25), 216 (100.00), 174 (5.06), 105 (15.21), 104 (14.06), 77 (43.25). HRMS (EI): Calcd. for $C_{21}H_{16}ClF_2NO$ $[M]^+$: 371.0888, found 371.0892.

Compound 3g: 42 mg, yield 57%; yellow solid; m.p. 127–129 °C. IR (KBr): $\tilde{\nu}$ = 3375, 1665, 1602, 1511, 1498, 1296, 1268, 1183, 1122, 1076, 749, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.7 Hz, 2 H), 7.48 (d, J = 7.2 Hz, 2 H), 7.38–7.28 (m, 3 H), 7.11 (t, J = 7.9 Hz, 2 H), 6.92 (d, J = 9.0 Hz, 2 H), 6.71 (t, J = 7.3 Hz, 1 H), 6.62 (d, J = 7.9 Hz, 2 H), 5.34–5.30 (m, 1 H), 4.65 (br., s, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.9 (dd, J = 29.1, 28.0 Hz), 164.6, 145.7, 134.7, 132.5 (t, J = 3.7 Hz), 129.2, 128.7, 128.6, 128.1, 125.6 (t, J = 1.8 Hz), 118.8, 117.5 (dd, J = 260.6, 259.0 Hz), 114.1, 114.0, 60.6 (dd, J = 25.8, 22.8 Hz), 55.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –102.7 (dd, J = 271.8, 8.7 Hz, 1 F), –111.0 (dd, J = 271.8, 17.1 Hz, 1 F) ppm. MS (EI): m/z (%) = 367 (1.70) $[M]^+$, 183 (14.33), 182 (100.00), 180 (7.85), 139 (4.20), 135 (13.51), 104 (9.34), 92 (4.39), 77 (22.51). HRMS (EI): Calcd. for $C_{22}H_{19}F_2NO_2$ $[M]^+$: 367.1384, found 367.1382.

Compound 3h: 21 mg, yield 28%; yellow solid; m.p. 100–102 °C. IR (KBr): $\tilde{\nu}$ = 3383, 1676, 1604, 1586, 1403, 1287, 1120, 1094, 1077, 1014, 933, 851, 808, 784, 717, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.5 Hz, 2 H), 7.45–7.36 (m, 4 H), 7.38–7.27 (m, 3 H), 7.10 (t, J = 7.9 Hz, 2 H), 6.71 (t, J = 7.3 Hz, 1 H), 6.60 (d, J = 7.9 Hz, 2 H), 5.27 (dd, J = 17.0, 8.2 Hz, 1 H), 4.49 (br., s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.9 (dd, J = 30.2, 28.3 Hz), 145.4, 140.9, 134.2, 133.2, 131.2 (t, J = 3.6 Hz), 129.3, 129.0, 128.8, 128.7, 128.5, 119.1, 117.3 (dd, J = 260.9, 259.2 Hz), 114.2, 60.4 (dd, J = 25.8, 22.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.0 (dd, J = 273.5, 8.2 Hz, 1 F), –112.1 (dd, J = 273.5, 17.6 Hz, 1 F) ppm. MS (EI): m/z (%) = 371 (1.66) $[M]^+$, 183 (14.82), 182 (100.00), 180 (4.11), 140 (3.43), 139 (5.66), 111 (5.85), 104 (9.28), 77 (13.65). HRMS (EI): Calcd. for $C_{21}H_{16}ClF_2NO$ $[M]^+$: 371.0888, found 371.0885.

Compound 3i: 60 mg, yield 81%; white solid; m.p. 100–102 °C. IR (KBr): $\tilde{\nu}$ = 3367, 1600, 1500, 1482, 1453, 1423, 1316, 1268, 1248, 1069, 752, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H), 7.25 (dd, J = 8.5, 6.0 Hz, 2 H), 7.18 (t, J = 7.3 Hz, 1 H), 7.12 (dd, J = 8.4, 7.5 Hz, 2 H), 7.08 (d, J = 6.9 Hz, 2 H), 6.74 (t, J = 7.3 Hz, 1 H), 6.61 (d, J = 7.8 Hz, 2 H), 5.06 (dd, J = 17.7, 8.5 Hz, 1 H), 4.40 (s, 1 H), 2.59–2.45 (m, 4 H), 1.89–1.82 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.5 (dd, J = 30.8, 27.2 Hz), 145.4, 141.1, 134.2, 129.3, 128.7, 128.6, 128.4 (d, J = 1.0 Hz), 128.3, 126.0, 119.2, 118.5, 115.9 (dd, J = 260.6, 258.9 Hz), 114.3, 59.5 (dd, J = 26.1, 22.6 Hz), 37.2, 34.5, 23.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –109.9 (dd, J = 260.7, 8.5 Hz, 1 F), –119.8 (dd, J = 260.7, 17.7 Hz, 1 F) ppm. MS (EI): m/z (%) = 379 (0.24) $[M]^+$, 183 (14.92), 182 (100.00), 180 (5.44), 104 (9.72), 91 (1.58), 78 (1.66), 77 (13.21), 51 (1.44). HRMS (EI): Calcd. for $C_{24}H_{23}F_2NO$ $[M]^+$: 371.1748, found 371.1745.

Compound (*Rc*,*Rs*)-6a: 44 mg, yield 60%; colorless oil. $[\alpha]_D^{26}$ = –76.1 (c = 1.01, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3206, 3066, 2960, 2926, 1701, 1597, 1474, 1449, 1183, 1060, 913, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.5 Hz, 2 H), 7.58 (t, J = 7.4 Hz, 1 H), 7.43–7.37 (m, 4 H), 7.33–7.31 (m, 3 H), 5.18 (td, J = 12.5, 4.3 Hz, 1 H), 4.36 (d, J = 4.3 Hz, 1 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3 (t, J = 29.6 Hz), 134.5, 132.8, 132.4, 130.1 (t, J = 3.3 Hz), 129.9, 129.2, 128.7, 128.6, 116.6 (t, J = 261.5 Hz), 61.1 (t, J = 23.5 Hz), 56.3, 22.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.5 (dd, J = 12.2, 7.1 Hz, 2 F) ppm. MS (MALDI): m/z (%) = 366 $[M + H]^+$, 388 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{19}H_{22}F_2NO_2S$ $[M + H]^+$: 366.1339, found 366.1334.

Compound (*Rc*,*Rs*)-6b: 55 mg, yield 72%; colorless oil. $[\alpha]_D^{27}$ = –49.7 (c = 0.93, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3205, 2975, 2959, 2924, 1701, 1597, 1449, 1183, 1087, 918, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.4 Hz, 1 H), 7.41 (t, J = 7.8 Hz, 2 H), 7.25 (d, J = 7.7 Hz, 2 H), 7.12 (d, J = 8.0 Hz, 2 H), 5.14 (td, J = 12.5, 4.2 Hz, 1 H), 4.33 (d, J = 4.2 Hz, 1 H), 2.30 (s, 3 H), 1.19 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.2 (t, J = 29.6 Hz), 139.1, 134.5, 132.3, 130.0 (t, J = 3.2 Hz), 129.7, 129.5, 129.3, 128.6, 116.5 (t, J = 261.2 Hz), 60.7 (t, J = 23.3 Hz), 56.1, 22.5, 21.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.2 (dd, J = 280.9, 12.5 Hz, 1 F), –107.2 (dd, J = 280.9, 12.5 Hz, 1 F) ppm. MS (ESI): m/z (%) = 380 $[M + H]^+$. HRMS (ESI): Calcd. for $C_{20}H_{24}F_2NO_2S$ $[M + H]^+$: 380.1496, found 380.1490.

Compound (*Rc*,*Rs*)-6c: 63 mg, yield 76%; colorless oil. $[\alpha]_D^{27}$ = –34.0 (c = 1.01, CH_3OH). IR (film): $\tilde{\nu}$ = 3073, 2961, 1701, 1612, 1598, 1515, 1449, 1252, 1028, 913, 838, 794, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 7.8 Hz, 2 H), 7.58 (t, J = 7.4 Hz, 1 H), 7.41 (t, J = 7.8 Hz, 2 H), 7.28 (d, J = 8.5 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.12 (td, J = 12.6, 3.8 Hz, 1 H), 4.31 (d, J = 3.8 Hz, 1 H), 3.76 (s, 3 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3 (t, J = 29.5 Hz), 160.2, 134.5, 132.3, 131.1, 129.9 (t, J = 3.3 Hz), 128.6, 124.2, 116.6 (t, J = 259.9 Hz), 113.9, 60.3 (t, J = 23.3 Hz), 56.1, 55.2, 22.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.2 (dd, J = 279.9, 12.2 Hz, 1 F), –107.8 (dd, J = 279.9, 12.8 Hz, 1 F) ppm. MS (ESI): m/z (%) = 396 $[M + H]^+$, 418 $[M + Na]^+$. HRMS (ESI): Calcd. for $C_{20}H_{23}F_2NNaO_3S$ $[M + Na]^+$: 418.1264, found 418.1269.

Compound (*Rc*,*Rs*)-6d: 64 mg, yield 76%; colorless oil. $[\alpha]_D^{27}$ = –41.9 (c = 1.05, CH_3OH). IR (film): $\tilde{\nu}$ = 3192, 2977, 2927, 2869, 1701, 1597, 1492, 1449, 1365, 1056, 1015, 904, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.43 (t, J = 7.9 Hz, 2 H), 7.33 (m, 4 H), 5.16 (td, J = 12.4, 4.1 Hz, 1 H), 4.39 (d, J = 4.1 Hz, 1 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8 (t, J = 29.9 Hz), 135.2, 134.8, 131.9, 131.2, 130.1, 130.0, 128.7, 116.2 (t, J = 260.6 Hz), 60.2 (t, J = 23.5 Hz), 56.3, 22.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.9 (dd, J = 286.2, 12.2 Hz, 1 F), –106.8 (dd, J = 286.2, 12.5 Hz, 1 F) ppm. MS (ESI): m/z (%) = 400 $[M + H]^+$, 422 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{19}H_{20}ClF_2NNaO_2S$ $[M + Na]^+$: 422.0769, found 422.0764.

Compound (*Rc*,*Rs*)-6e: 75 mg, yield 85%; colorless oil. $[\alpha]_D^{27}$ = –63.7 (c = 1.11, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3232, 2960, 2927, 2868, 1731, 1698, 1597, 1489, 1450, 1362, 1183, 1072, 1012, 773, 715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.5 Hz, 2 H), 7.59 (t, J = 7.5 Hz, 1 H), 7.48–7.39 (m, 4 H), 7.26 (d, J = 8.4 Hz, 2 H), 5.14 (td, J = 12.4, 4.2 Hz, 1 H), 4.39 (d, J = 4.2 Hz, 1 H), 1.19 (s, 9

H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8 (t, J = 29.9 Hz), 134.7, 131.9 (t, J = 2.4 Hz), 131.8, 131.7, 131.5, 130.1 (t, J = 3.3 Hz), 128.7, 123.5, 116.2 (t, J = 261.9 Hz), 60.3 (t, J = 23.4 Hz), 56.3, 22.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.8 (dd, J = 286.4, 12.2 Hz, 1 F), –106.8 (dd, J = 286.4, 12.6 Hz, 1 F) ppm. MS (MALDI): m/z (%) = 444 $[M + H]^+$, 467 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{19}H_{21}BrF_2NO_2S$ $[M + H]^+$: 444.0444, found 444.0439.

Compound (*Rc*,*Rs*)-6f: 64 mg, yield 77%; white solid; m.p. 50–52 °C. $[\alpha]_D^{28}$ = –70.3 (c = 1.03, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3383, 3209, 2975, 2961, 2230, 1700, 1597, 1449, 1186, 1065, 915, 716 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.5 Hz, 2 H), 7.63 (t, J = 8.2 Hz, 3 H), 7.55 (d, J = 8.2 Hz, 2 H), 7.45 (t, J = 7.9 Hz, 2 H), 5.23 (td, J = 12.6, 4.1 Hz, 1 H), 4.44 (d, J = 4.1 Hz, 1 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.5 (t, J = 30.1 Hz), 138.2, 135.0, 132.2, 131.6 (t, J = 2.7 Hz), 130.7, 130.1 (t, J = 3.3 Hz), 128.8, 118.2, 116.0 (t, J = 262.7 Hz), 113.2, 60.4 (dd, J = 24.9, 22.5 Hz), 56.4, 22.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –104.5 (dd, J = 291.7, 11.4 Hz, 1 F), –106.5 (dd, J = 291.7, 12.9 Hz, 1 F) ppm. MS (ESI): m/z (%) = 391 $[M + H]^+$, 413 $[M + Na]^+$. HRMS (ESI): Calcd. for $C_{20}H_{20}F_2N_2NaO_2S$ $[M + Na]^+$: 413.1111, found 413.1106.

Compound (*Rc*,*Rs*)-6g: 62 mg, yield 73%; colorless oil. $[\alpha]_D^{28}$ = –44.6 (c = 1.00, CH_3OH). IR (film): $\tilde{\nu}$ = 3199, 2958, 2923, 1701, 1598, 1474, 1449, 1182, 1066, 921, 756, 718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 7.4 Hz, 2 H), 7.62–7.58 (m, 1 H), 7.55–7.52 (m, 1 H), 7.46–7.42 (m, 2 H), 7.39–7.35 (m, 1 H), 7.28–7.27 (m, 2 H), 5.87–5.80 (m, 1 H), 4.34 (d, J = 5.6 Hz, 1 H), 1.15 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8 (t, J = 29.4 Hz), 135.1, 134.6, 132.0 (t, J = 2.1 Hz), 131.6 (d, J = 1.6 Hz), 130.4, 130.1, 130.0, 129.8, 128.7, 126.9, 116.6 (t, J = 261.7 Hz), 56.8 (dd, J = 25.3, 22.9 Hz), 56.4, 22.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.8 (dd, J = 284.3, 8.3 Hz, 1 F), –108.1 (dd, J = 284.3, 15.9 Hz, 1 F) ppm. MS (ESI): m/z (%) = 400 $[M + H]^+$, 422 $[M + Na]^+$. HRMS (ESI): Calcd. for $C_{19}H_{20}ClF_2NNaO_2S$ $[M + Na]^+$: 422.0769, found 422.0764.

Compound (*Rc*,*Rs*)-6h: 65 mg, yield 73%; white solid; m.p. 83–85 °C. $[\alpha]_D^{28}$ = –38.1 (c = 0.75, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3237, 2957, 2924, 2854, 1698, 1472, 1450, 1400, 1191, 1129, 1070, 1023, 755, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.9 Hz, 2 H), 7.62–7.52 (m, 3 H), 7.45 (t, J = 7.9 Hz, 2 H), 7.32 (t, J = 7.6 Hz, 1 H), 7.21–7.17 (m, 1 H), 5.87–5.79 (m, 1 H), 4.33 (d, J = 5.2 Hz, 1 H), 1.15 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7 (t, J = 29.3 Hz), 134.7, 133.3 (d, J = 1.6 Hz), 133.2, 132.0 (t, J = 2.1 Hz), 130.6, 130.4, 130.2 (t, J = 3.3 Hz), 128.7, 127.6, 125.6, 116.6 (t, J = 261.8 Hz), 59.4 (dd, J = 24.8, 23.5 Hz), 56.4, 22.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.6 (d, J = 285.4 Hz, 1 F), –107.9 (dd, J = 285.4, 13.9 Hz, 1 F) ppm. MS (ESI): m/z (%) = 444 $[M + H]^+$, 466 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{19}H_{21}BrF_2NO_2S$ $[M + H]^+$: 444.0444, found 444.0439.

Compound (*Rc*,*Rs*)-6i: 64 mg, yield 73%; white solid; m.p. 141–145 °C. $[\alpha]_D^{26}$ = –58.4 (c = 1.10, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3433, 3252, 2924, 1705, 1693, 1597, 1489, 1449, 1401, 1197, 1184, 1087, 1067, 1052, 756 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.62–7.50 (m, 5 H), 7.50–7.38 (m, 6 H), 7.34 (t, J = 7.3 Hz, 1 H), 5.24 (td, J = 12.4, 4.2 Hz, 1 H), 4.40 (d, J = 4.2 Hz, 1 H), 1.23 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.2 (t, J = 29.7 Hz), 142.0, 140.2, 134.6, 132.2, 131.5, 130.3, 130.1 (t, J = 3.2 Hz), 128.8, 128.7, 127.6, 127.2, 127.1, 116.5 (t, J = 260.3 Hz), 60.7 (t, J = 23.4 Hz), 56.3, 22.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.3 (d, J = 12.4 Hz, 2 F) ppm. MS (ESI): m/z (%) = 442 $[M + H]^+$, 464 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{25}H_{26}F_2NO_2S$ $[M + H]^+$: 442.1652, found 442.1647.

Compound (*Rc*,*Rs*)-6j: 50 mg, yield 68%; colorless oil. $[\alpha]_D^{28}$ = –33.1 (c = 0.53, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3201, 2956, 2866, 1701, 1598, 1449, 1279, 1215, 1066, 1014, 885, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 7.4 Hz, 2 H), 7.60 (d, J = 7.5 Hz, 1 H), 7.45 (t, J = 7.8 Hz, 2 H), 7.43–7.32 (m, 1 H), 6.40 (d, J = 3.2 Hz, 1 H), 6.33 (dd, J = 3.2, 1.8 Hz, 1 H), 5.41–5.21 (m, 1 H), 4.21 (d, J = 7.1 Hz, 1 H), 1.17 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8 (t, J = 29.5 Hz), 146.6, 143.4, 134.6, 132.0 (t, J = 2.3 Hz), 130.0 (t, J = 3.2 Hz) 128.7, 115.7 (t, J = 262.3 Hz), 111.2, 110.7, 56.6, 55.9 (t, J = 25.4 Hz), 22.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.7 (t, J = 13.0 Hz, 2 F) ppm. MS (ESI): m/z (%) = 356 $[M + H]^+$. HRMS (MALDI): Calcd. for $C_{17}H_{20}F_2NO_3S$ $[M + H]^+$: 356.1132, found 356.1126.

Compound (*Rc*,*Rs*)-6k: 46 mg, yield 56%; white solid, m.p. 64–66 °C. $[\alpha]_D^{27}$ = –45.3 (c = 0.98, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3240, 2924, 2853, 1599, 1450, 1399, 1070, 1011, 766, 703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (br., s, 1 H), 7.85 (t, J = 8.5 Hz, 4 H), 7.68 (d, J = 6.0 Hz, 1 H), 7.55–7.42 (m, 4 H), 7.35 (t, J = 7.9 Hz, 2 H), 6.13 (br., s, 1 H), 4.53 (d, J = 4.7 Hz, 1 H), 1.17 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5 (t, J = 29.8 Hz), 134.4, 133.7, 132.4, 132.0, 129.9 (t, J = 3.4 Hz), 129.8 (d, J = 3.1 Hz), 128.9, 128.6, 128.1, 127.5, 126.8, 125.8, 124.9, 122.9, 117.1 (t, J = 262.1 Hz), 56.3, 55.2, 22.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –103.3 (dd, J = 282.3, 6.5 Hz, 1 F), –106.4 (d, J = 282.3 Hz, 1 F) ppm. MS (ESI): m/z (%) = 416 $[M + H]^+$, 438 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{23}H_{24}F_2NO_2S$ $[M + H]^+$: 416.1496, found 416.1490.

Compound (*Rc*,*Rs*)-6l: 49 mg, yield 63%; colorless oil. $[\alpha]_D^{26}$ = –32.4 (c = 0.64, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3231, 3027, 2960, 2867, 1701, 1598, 1496, 1451, 1063, 718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 7.6 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.45 (t, J = 7.8 Hz, 2 H), 7.26 (t, J = 7.2 Hz, 2 H), 7.16 (dd, J = 6.2, 5.3 Hz, 3 H), 4.01–3.93 (m, 1 H), 3.91 (t, J = 8.6 Hz, 1 H), 3.02–2.93 (m, 1 H), 2.80–2.61 (m, 1 H), 2.17–1.93 (m, 2 H), 1.24 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3 (dd, J = 30.8, 30.2 Hz), 140.5, 134.5, 132.1 (t, J = 2.6 Hz), 130.1 (t, J = 3.2 Hz), 128.7, 128.5, 128.4, 126.2, 116.9 (t, J = 260.4 Hz), 58.7 (t, J = 23.9 Hz), 56.9, 31.9, 31.4 (t, J = 2.6 Hz), 22.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –104.2 (dd, J = 292.5, 11.9 Hz, 1 F), –106.1 (dd, J = 292.5, 11.3 Hz, 1 F) ppm. MS (ESI): m/z (%) = 394 $[M + H]^+$. HRMS (MALDI): Calcd. for $C_{21}H_{26}F_2NO_2S$ $[M + H]^+$: 394.1652, found 394.1647.

Compound (*Rc*,*Rs*)-6m: 54 mg, yield 64%; white solid; m.p. 110–112 °C. $[\alpha]_D^{27}$ = –52.1 (c = 0.98, CH_3OH). IR (KBr): $\tilde{\nu}$ = 3196, 2981, 2961, 1699, 1597, 1492, 1450, 1181, 1076, 721 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.6 Hz, 2 H), 7.61 (t, J = 7.4 Hz, 1 H), 7.46 (dd, J = 10.9, 4.6 Hz, 2 H), 7.29–7.24 (m, 4 H), 6.71 (d, J = 15.9 Hz, 1 H), 6.09 (dd, J = 15.9, 8.4 Hz, 1 H), 4.82–4.70 (m, 1 H), 4.14 (d, J = 4.8 Hz, 1 H), 1.20 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.7 (t, J = 29.3 Hz, 1 H), 134.7, 133.3 (d, J = 1.6 Hz), 133.2, 132.0 (t, J = 2.1 Hz), 130.6, 130.4, 130.2 (t, J = 3.3 Hz), 128.7, 127.6, 125.6, 116.6 (t, J = 261.8 Hz), 59.4 (dd, J = 24.8, 23.5 Hz), 56.4, 22.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.5 (dd, J = 288.8, 11.1 Hz, 1 F), –107.4 (dd, J = 288.8, 11.4 Hz, 1 F) ppm. MS (ESI): m/z (%) = 426 $[M + H]^+$. HRMS (MALDI): Calcd. for $C_{21}H_{23}ClF_2NO_2S$ $[M + H]^+$: 426.1106, found 426.1101.

Compound (*Rc*,*Rs*)-6n: 57 mg, yield 67%; colorless oil. $[\alpha]_D^{27}$ = –58.5 (c = 1.03, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3286, 2961, 1868, 2845, 1686, 1598, 1572, 1512, 1493, 1365, 1267, 1180, 1058, 1016, 911 cm^{-1}. ^{1}H

NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.8 Hz, 2 H), 7.41–7.29 (m, 4 H), 6.92 (d, J = 9.0 Hz, 2 H), 5.15 (td, J = 12.5, 3.9 Hz, 1 H), 4.46 (d, J = 3.9 Hz, 1 H), 3.87 (s, 3 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.0 (t, J = 29.5 Hz), 164.8, 135.1, 132.8 (t, J = 3.5 Hz), 131.4, 131.3, 128.7, 124.7 (t, J = 2.5 Hz), 116.4 (t, J = 261.9 Hz), 114.1, 60.3 (dd, J = 24.7, 22.9 Hz), 56.2, 55.6, 22.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –104.9 (dd, J = 284.9, 11.7 Hz, 1 F), –106.5 (dd, J = 284.9, 12.8 Hz, 1 F) ppm. MS (ESI): m/z (%) = 430 $[M + H]^+$. HRMS (MALDI): Calcd. for $C_{20}H_{23}ClF_2NO_3S$ $[M + H]^+$: 430.1055, found 430.1050.

Compound (*Rc*,*Rs*)-6o: 52 mg, yield 60%; colorless oil. $[\alpha]_D^{26}$ = –57.6 (c = 1.02, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3222, 2961, 2868, 1693, 1588, 1491, 1313, 1285, 1183, 1080, 1014, 731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 8.7 Hz, 2 H), 7.38–7.27 (m, 4 H), 5.17 (td, J = 12.5, 4.3 Hz, 1 H), 4.36 (d, J = 4.3 Hz, 1 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.8 (t, J = 30.4 Hz), 141.6, 135.3, 131.4 (t, J = 3.4 Hz), 131.2, 131.1, 130.2 (t, J = 2.6 Hz), 129.2, 128.8, 116.2 (t, J = 261.8 Hz), 60.1 (t, J = 22.8 Hz), 56.3, 22.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –105.5 (dd, J = 287.8, 12.0 Hz, 1 F), –106.9 (dd, J = 287.8, 12.8 Hz, 1 F) ppm. MS (ESI): m/z (%) = 434 $[M + H]^+$. HRMS (MALDI): Calcd. for $C_{19}H_{20}Cl_2F_2NO_2S$ $[M + H]^+$: 434.0560, found 434.0554.

Compound (*Rc*,*Rs*)-6p: 63 mg, yield 72%; pale yellow oil. $[\alpha]_D^{25}$ = –50.9 (c = 0.88, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3230, 3027, 2958, 2868, 1739, 1597, 1494, 1455, 1365, 1195, 1071, 1015, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.7 Hz, 2 H), 7.25 (dd, J = 9.9, 8.2 Hz, 4 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.06 (d, J = 6.9 Hz, 2 H), 4.94 (td, J = 12.5, 4.4 Hz, 1 H), 4.15 (d, J = 4.4 Hz, 1 H), 2.62–2.46 (m, 3 H), 2.44–2.30 (m, 1 H), 1.83–1.75 (m, 2 H), 1.19 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7 (dd, J = 30.6, 28.3 Hz), 140.8, 135.4, 131.2 (d, J = 3.5 Hz), 130.8, 128.9, 128.4, 128.3, 126.1, 114.8 (t, J = 260.0 Hz), 59.3 (t, J = 23.4 Hz), 56.3, 36.9, 34.5, 23.7, 22.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –112.5 (dd, J = 269.7, 12.0 Hz, 1 F), –115.2 (dd, J = 269.7, 13.0 Hz, 1 F) ppm. MS (ESI): m/z (%) = 442 $[M + H]^+$, 464 $[M + Na]^+$. HRMS (MALDI): Calcd. for $C_{22}H_{27}ClF_2NO_2S$ $[M + H]^+$: 442.1419, found 442.1414.

Compound (*R*)-7: 28 mg, yield 76%; this is a known compound.[15] Colorless oil. $[\alpha]_D^{27}$ = –18.0 (c = 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 7.7 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.51–7.40 (m, 4 H), 7.33–7.22 (m, 2 H), 4.68 (dd, J = 16.6, 8.8 Hz, 1 H), 1.79 (br., s, 2 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.1 (dd, J = 282.7, 8.2 Hz, 1 F), –112.8 (dd, J = 282.7, 16.9 Hz, 1 F) ppm.

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