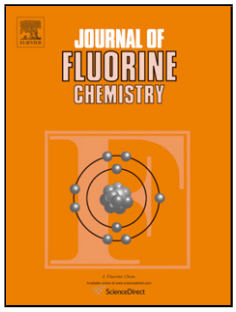


Title: One-pot Asymmetric Reductive Amination of Ketones Induced by Polyfluoroalkanesulfinamide

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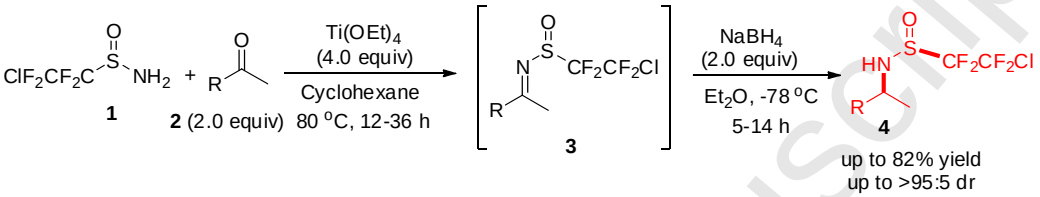
A highly diastereoselective reductive amination of ketones using 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide as auxiliary was developed. Both aromatic and aliphatic ketones reacted well under the reaction conditions, giving the corresponding amination products in good yields with excellent diastereoselectivities.



**Research highlights**:

The reductive amination of ketones using 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide as auxiliary was investigated.

The amination products were obtained in good yields with excellent diastereoselectivities.

2-Chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide afforded better diastereoselectivities for aliphatic and (*E*)-α,β-unsaturated ketones.

# One-pot Asymmetric Reductive Amination of Ketones Induced by Polyfluoroalkanesulfinamide

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**Abstract**

Using chiral 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide as the auxiliary, an efficient one-pot procedure for the asymmetric reductive amination of ketones was achieved in the presence of sodium borohydride. Both aromatic and aliphatic ketones reacted well to give the corresponding sulfinyl amides in good yields with excellent diastereoselectivities.

**Keywords:**

2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide/ ketimine/ ketone/ reductive amination/ diastereoselectivity

## 1. Introduction

α-Branched amines are key elements of many potent pharmaceuticals, asymmetric catalysts and materials such as unnatural biopolymers.[1] A large number of methods have been developed to prepare chiral α-branched amines via the addition of carbon nucleophiles to aldimines[2] and asymmetric reductions of ketimines.[3] Among them one-pot reductive amination of ketones is one of the most efficient methods towards the synthesis of α-branched amines, avoiding the isolation of imine intermediates. The reduction of *N*-sulfinyl imines was first reported by Cozzi[4] and later studied by Ellman[5]. Ellman's group also reported the first general one-pot method for the asymmetric synthesis of pre-protected α-branched amines from 2-methylpropane-2-sulfinamide[6] and the corresponding ketones. In 2004, Ellman and Kochi reported an isolated example of the stereoselective reduction of a *N*-*tert*-butylsulfinyl ketimines bearing a α-stereocenter to provide either amine diastereomer.[7] These conditions could also be applied to the reduction of ketimines with a β-stereocenter.[8] Encouragingly, Andersen and co-workers found that, with the choice of appropriate metal hydride reagent, either diastereomer could be obtained by the reduction of the corresponding *N*-*tert*-butylsulfinyl ketimines.[9] Since then, the reduction of *N*-*tert*-butylsulfinyl ketimines has attracted much attention[10] and has been applied to the synthesis of many drug candidates.[11] In addition, the scope of one-pot reduction method was expanded to include biologically relevant cyclic substrates. However, the achievement of high diastereoselectivities for the reductive amination of α,β-unsaturated ketones and aliphatic ketones is still a challenge.

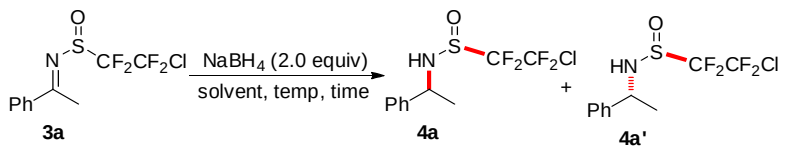
Recently, our group developed a novel fluorinated chiral auxiliary, polyfluoroalkanesulfinamide, which was applied successfully in many asymmetric reactions such as Strecker reaction,[12] three component aza Diels-Alder reaction[13], aminoallylation of aldehydes[14] and asymmetric vinylogous Mannich reaction.[15] Using this kind of fluorinated auxiliary, Ellman's group also developed an asymmetric intermolecular addition of non-acidic C-H bonds for the first time.[16] Among various polyfluoroalkanesulfinamides investigated in our previous work,

2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide (CTFSA, **1**) is a promising one due to its easy availability and high performance. In this paper, we report the one-pot reductive amination of ketones induced by CTFSA.

## 2. Results and Discussion

In our preliminary investigation, ketimine **3a** was prepared from 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide (**1**) and methylphenyl ketone **2a**. The reaction of **3a** and $NaBH_4$ was carried out at -78 $^oC$ in tetrahydrofuran (THF). Gratefully, the stereoisomers **4a** and **4a'** were obtained in a total yield of 75% with a ratio of >95:5 as shown by the $^{19}F$ NMR spectrum of the reaction mixture (Table 1, entry 1). Much lower yields were obtained in dichloromethane (DCM) or *n*-hexane (entries 2-3). Using methanol as solvent, the overall yield of isomers was improved to 95%, but the diastereoselectivity decreased to 90:10 (entry 4). When ethyl ether was used as solvent, 90% yield and excellent diastereoselectivity (>95:5) were achieved (entry 5). Considering the higher diastereoselectivity, $Et_2O$ was chosen as the solvent for this reduction reaction. When carrying out the reaction at -40 $^oC$, only 86% yield was obtained (entry 6). Adding $Ti(OEt)_4$ as additive, the yield could be improved to 94% in 6 h with excellent diastereoselectivity (entry 7). In our previous work,[12b] cyclohexane was the best solvent for the preparation of ketimine. However, cyclohexane could not be used at low temperature because its melting point is 6.5 $^oC$. Therefore, we tried to run the reductive reaction in a mixed solvent of cyclohexane and $Et_2O$ at -78 $^oC$, and gratefully the reaction worked well without any erosion in yield and stereoselectivity (entry 8).

**Table 1.** Reduction of sulfinyl ketimine **3a** under different conditions



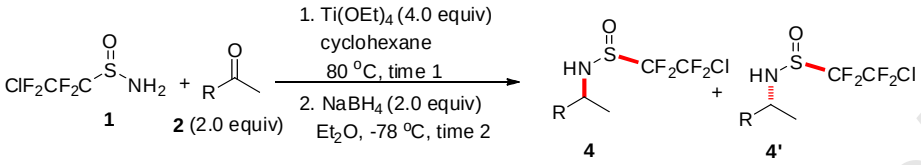

| Entry[a] | Solvent | Temp ($^oC$) | Time (h) | Yield (%)[b] | Dr (**4a**:**4a'**)[b] |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 1 | THF | -78 | 8 | 75% | >95:5 |
| 2 | DCM | -78 | 8 | 45% | >95:5 |
| 3 | *n*-Hexane | -78 | 8 | 13% | >95:5 |
| 4 | MeOH | -78 | 6 | 95% | 90:10 |
| 5 | $Et_2O$ | -78 | 7 | 90% | >95:5 |
| 6 | $Et_2O$ | -40 | 4 | 80% | >95:5 |
| 7[c] | $Et_2O$ | -78 | 6 | 94% | >95:5 |
| 8[c] | Cyclohexane/$Et_2O$(1:2) | -78 | 8 | 93% | >95:5 |

[a] Reactions were carried out with 2.0 equiv of $NaBH_4$ on a 0.25 mmol scale in 1.0 mL of solvent. [b] Determined by $^{19}F$ NMR spectra of the crude reaction mixtures with $PhCF_3$ as internal standard. [c] $Ti(OEt)_4$ (2.0 equiv) was added.

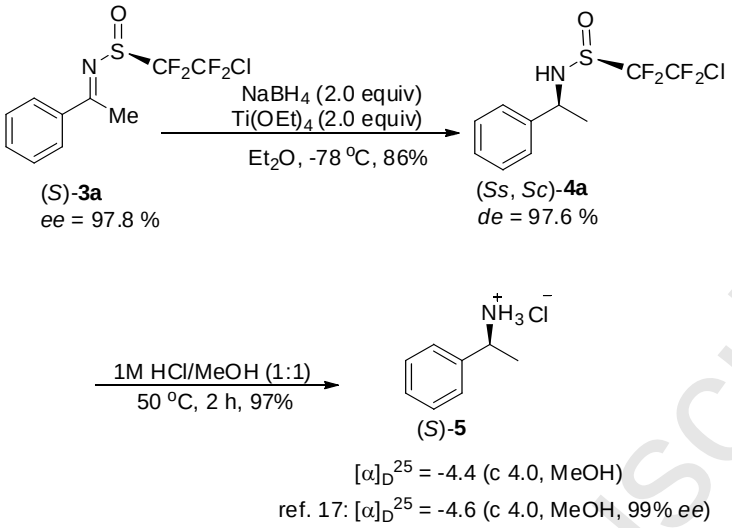
Based on the above results, the one-pot reductive amination of ketones was then investigated. Ketones (**2**, 2.0 equiv) was firstly treated with **1** in the presence of 4.0 equiv of $Ti(OEt)_4$ in cyclohexane at 80 $^oC$.[12b] After the reaction was completed, the reaction mixture was cooled to room temperature. Then anhydrous ether was added. After cooling the mixture to -78 $^oC$, $NaBH_4$ (2.0 equiv) was added in one portion under nitrogen atmosphere. As shown in Table 2, both electron-deficient and electron-rich aromatic ketones (**2a-h**) underwent this reductive amination to yield the desired products (**4a-h**) in moderate to good yields with excellent diastereoselectivities (65-80% yield, 94:6~>95:5 *dr*, entries 1-8). Good result was obtained with (*E*)-α,β-unsaturated ketone **2i**, giving only 1,2-adduct in 82% yield with >95:5 *dr* (entry 9). Moreover, aliphatic ketones (**2j-k**) also reacted well and gave the corresponding products (**4j-k**) in good yields with high diastereoselectivities (entries 10-11). It was reported that the asymmetric reductive amination reactions of **2i** and **2k** induced by 2-methylpropane-2-sulfinamide gave the corresponding products with 90:10 and 83:17 *dr*,[6] respectively, indicating that 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide was more effective for the amination reaction of aliphatic and α,β-unsaturated ketones.

**Table 2** One-pot reductive amination of ketones




| Entry[a] | **2**, R | Time 1/Time 2 (h) | Product | Yield (%)[b] | Dr[c] (**4**:**4'**) |
|---|---|---|---|---|---|
| 1 | **2a**, $C_6H_5$ | 24/9 | **4a**, **4a'** | 73 (85) | >95:5 |
| 2 | **2b**, *p*-$CF_3C_6H_4$ | 12/7 | **4b**, **4b'** | 75 (86) | >95:5 |
| 3 | **2c**, *p*-$FC_6H_4$ | 24/8 | **4c**, **4c'** | 77 (80) | 94:6 |
| 4 | **2d**, *p*-$ClC_6H_4$ | 24/8 | **4d**, **4d'** | 69 (87) | >95:5 |
| 5 | **2e**, *p*-$BrC_6H_4$ | 24/8 | **4e**, **4e'** | 71 (78) | >95:5 |
| 6 | **2f**, *m*-$CF_3C_6H_4$ | 12/7 | **4f**, **4f'** | 65 | >95:5 |
| 7 | **2g**, *p*-$MeC_6H_4$ | 24/9 | **4g**, **4g'** | 73 (77) | >95:5 |
| 8 | **2h**, *p*-$MeOC_6H_4$ | 36/9 | **4h**, **4h'** | 75 (81) | >95:5 |
| 9 | **2i**,$C_6H_5CH$=CH | 36/14 | **4i**, **4i'** | 82 (93) | >95:5 |
| 10 | **2j**,$(CH_3)_2CHCH_2$ | 12/9 | **4j**, **4j'** | 76 (80) | >95:5 |
| 11 | **2k**, *n*-Bu | 12/5 | **4k**, **4k'** | 78 (83) | 92:8 |

[a] Reaction conditions: 1) **1** (0.25 mmol), **2** (0.5 mmol), $Ti(OEt)_4$ (1.0 mmol), cyclohexane (1 mL), 80 °C; 2) $NaBH_4$ (0.5 mmol), $Et_2O$ (2.0 mL), -78 °C. [b] Isolated yield, yield in parentheses was determined by $^{19}F$ NMR spectroscopy using $PhCF_3$ as internal standard. [c] Determined by $^{19}F$ NMR spectra of the crude reaction mixture.




**Scheme 1**. The synthesis of (*S*)-**5**

To determine the configuration of major products, optically pure **4a** (97.6% de, determined by HPLC) was prepared from ketimine (*S*)-**3a** (97.8% ee). Treatment of **4a** with 1 M HCl in MeOH at 50°C afforded 1-phenylethylamine hydrochloride **5** in high yield (97% yield). Comparisons to optical data for previously reported *S*-**5** revealed compound **5** generated herein to bear the *S*-configuration (Scheme 1).[17] Therefore, the stereochemistry of **4a** was assigned to be (*Ss, Sc*), and accordingly, the major products in Table 2 are putatively assigned to be *syn*-confinguration.

## 3. Conclusion

In summary, we have presented a highly diastereoselective reductive amination of ketones using 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide as auxiliary. Both aromatic and aliphatic ketones reacted well under the reaction conditions, giving the corresponding amination products in good yields with excellent diastereoselectivities. Compared with *tert*-butylsulfinyl, this auxiliary afforded better diastereoselectivities for aliphatic and (*E*)-α,β-unsaturated ketones.

## 4. Experimental

### 4.1. General

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM-300 and AM-400 (100 MHz) spectrometer with TMS as internal standard. $^{19}F$ NMR spectra were taken on a Bruker AM-300 (282 MHz) spectrometer using $CFCl_3$ as external standard. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. The mass analyzer type was FTICR-MS used for the HRMS measurements.

### 4.2. Procedure for the synthesis of racemic 1[12a]

To a flask containing neat HMDS (0.075 mol) was added 2-chloro-1,1,2,2-tetrafluoroethanesulfinyl chloride (0.075 mol) dropwise at 0 $^{o}C$. After addition, stirring was continued for 2 h at room temperature. The mixture was concentrated under reduced pressure, followed by the addition of of saturated aqueous $NH_4Cl$ solution (50 mL) at room temperature. After stirring for 2 h, the resulting mixture was extracted with $Et_2O$ (30 mL × 4) and the extract was dried over anhydrous $Na_2SO_4$. After concentration, the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 1/5) to give **1**.

**Compound 1:** $^{1}H$ NMR (300 MHz, $CDCl_3$): δ 4.96 (s, 2H); $^{19}F$ NMR (282 MHz, $CDCl_3$): δ -67.27~-67.32 (m, 2F), -119.74 (d, $J_{FF}$ = 243.6 Hz, 1F), -122.47 (d, $J_{FF}$ = 243.6 Hz, 1F); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 122.4 (tt, $J$ = 298.4, 33.4 Hz), 116.3 (ddt, $J$ = 306.0, 302.0, 35.1 Hz); HRMS (EI) calcd for $C_2H_2ClF_4NOS$ ($M^+$) 198.9482, found 198.9480.

### 4.3. Procedure for the synthesis of (*S*)-1

*n*-BuLi (2.64 mL, 2.5 M in hexane) was added dropwise to the solution of (*S*)-4-phenyl-oxazolidin-2-one (6 mmol) in THF (30 mL) at -78 $^{o}C$ under nitrogen atmosphere. After addition, the mixture was stirred for 0.5 h. Then 2-chloro-1,1,2,2-tetrafluoroethanesulfinyl chloride (19.8 mmol) in 10 mL of THF was

added. After stirring for 3 h, the mixture was allowed to warm to room temperature. Solvent was removed, and the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 1/7). (*Rs, Sc*)-4-Phenyl-*N*-(2-chloro-1,1,2,2-tetrafluoroethanesulfinyl)oxazolidin-2-one was obtained as a white solid.

A solution of (*Rs, Sc*)-4-phenyl-*N*-(2-chlorotetrafluoroethanesulfinyl)oxazolidin -2-one (0.5 mmol) in $CH_2Cl_2$ (7 mL) was added slowly to a solution of LiHMDS (1.0 mmol) in $CH_2Cl_2$ (3 mL) in 3 h at -78 $^oC$ under nitrogen atmosphere. After addition, saturated $NH_4Cl$ (aq) (5 mL) was added. The resulting mixture was extracted with $CH_2Cl_2$ (10 mL × 3) and the extract was dried over anhydrous $Na_2SO_4$. After concentration, the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 1/5) to give (*S*)-**1**.

**Compound** (*S*)-**1**: yield 72%; white solid; $[\alpha]^{20}_D$ = -15.5 (*c* = 1.0, $CHCl_3$, 99% ee) [12].

### 4.4. Typical procedure for the reductive amination of ketones 2

To a solution of 2-chloro-1,1,2,2-tetrafluoroethane-1-sulfinamide **1** (0.25 mmol) and titanium (IV) ethoxide (1.0 mmol) in cyclohexane (1.0 mL) was added ketone **2** (0.5 mmol). The mixture was stirred at 80 $^oC$ under nitrogen atmosphere and monitored by TLC. After the reaction was completed, the mixture was cooled to room temperature. Then anhydrous ether (2.0 mL) was added, and the resulting mixture was cooled to -78 $^oC$. $NaBH_4$ (0.5 mmol) was added in one portion under nitrogen atmosphere. The mixture was stirred at -78 $^oC$ and monitored by TLC or $^{19}F$ NMR. After reaction, saturated aqueous $NH_4Cl$ solution (5.0 mL) was added slowly, and the resulting mixture was warmed to room temperature and filtered through celite. The filter cake was washed with EtOAc. The aqueous phase was extracted with EtOAc (5.0 mL×3), and the combined organic phase was dried over anhydrous $Na_2SO_4$. After concentration, the residue was subjected to flash column chromatography (silica gel, EtOAc/petroleum ether: 1/10). The desired products **4** and alcohol byproducts could be easily separated. Results are given in Table 2.

*4.4.1.* **Compound 4a**: 73%; Colorless oil. IR (film): 3242, 2976, 2929, 1650, 1603, 1453, 1261, 1115, 1017, 909, 803, 699 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.40-7.30 (m, 5H), 4.79-4.78 (m, 1H), 4.72-4.69 (m, 1H), 1.59 (d, $J$ = 6.4 Hz, 3H). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ -66.10 to -67.17 (m, 2F), -116.88 (dd, $J_{FF}$ = 233.8, 3.0 Hz ,1F), -120.35 (dd, $J_{FF}$ = 233.8, 6.0 Hz, 1F). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 142.1, 129.0, 128.3, 126.3, 122.2 (tt, $J_{C\text{-}F}$ = 298.6, 33.5 Hz), 116.4 (tt, $J_{C\text{-}F}$ = 306.9, 36.1 Hz), 54.8, 23.6. ESI-MS (m/z, %): 320.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{10}H_{11}ClF_4NOS$ $[M+H]^+$ requires 304.0181, found 304.0181.

(*Ss, Sc*)-**4a**: 97.6% *ee*; $[\alpha]^{25}_D$ = -33.5 (c = 1.0 in $CHCl_3$, λ = 589 nm).

*4.4.2.* **Compound 4b**: 75%; Colorless oil. IR (film): 3300, 2926, 1657, 1621, 1445, 1327, 1262, 1116, 1017, 804, 735, 697 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (d, $J$ = 8.0 Hz, 2H), 7.47-7.45 (d, $J$ = 8.4 Hz, 2H), 4.92-4.90 (d, $J$ = 5.2 Hz, 1H), 4.79-4.76 (m, 1H), 1.60 (d, $J$ = 6.8 Hz, 3H). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ -62.70 to -62.79 (m, 3F), -66.75 to -66.83 (m, 2F), -116.88 (dd, $J$ = 233.8, 3.0 Hz, 1F), -120.35 (dd, $J$ = 233.8, 5.6 Hz, 1F). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 146.0, 130.5 (t, $J$ = 33.2 Hz), 127.0, 126.8 (t, $J$ = 235.4 Hz), 126.0 (t, $J$ = 3.8 Hz), 122.1 (tt, $J_{C\text{-}F}$ = 298.6, 33.6 Hz), 116.4 (tt, $J_{C\text{-}F}$ = 305.6, 35.0 Hz), 54.1, 23.8. ESI-MS (m/z, %): 388.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_{10}ClF_7NOS$ $[M+H]^+$ requires 372.0054, found 372.0055.

*4.4.3.* **Compound 4c**: 77%; Colorless oil. IR (film): 3231, 2981, 1606, 1512, 1230, 1127, 1015, 908, 835, 798 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.32-7.29 (m, 2H), 7.07-7.02 (m, 2H), 4.86-4.84 (d, $J$ = 4.4 Hz, 1H), 4.70-4.67 (m, 1H), 1.56 (d, $J$ = 6.4 Hz, 3H). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ -66.18 to -67.23 (m, 2F), -113.71 to -113.78 (m, 1F), -117.65 (dd, $J$ = 232.3, 3.0 Hz, 1F), -119.54 (dd, $J$ = 232.3, 3.0 Hz, 1F). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 162.5 (d, $J$ = 245.4 Hz), 137.9 (d, $J$ = 2.7 Hz), 128.1 (d, $J$ = 8.8 Hz), 115.8 (d, $J$ = 21.3 Hz), 54.1, 23.7. ESI-MS (m/z, %): 338.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{10}H_{10}ClF_5NOS$ $[M+H]^+$ requires 322.0086, found 322.0085.

*4.4.4.* **Compound 4d**: 69%; Colorless oil. IR (film): 3223, 2978, 1449, 1377, 1261, 1179, 1080, 907, 748, 692 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.34-7.31 (d, *J* = 8.0 Hz, 2H), 7.27-7.25 (d, *J* = 7.2 Hz, 2H), 4.93-4.92 (m, 1H), 4.68-4.65 (m, 1H), 1.55 (d, *J* = 6.9 Hz, 3H). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ -66.68 to -66.75 (m, 2F), -117.15 (d, *J* = 232.8 Hz, 1F), -119.76 (d, *J* = 233.8 Hz, 1F). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 140.6, 134.1, 129.1, 127.7, 122.1 (tt, $J_{C\text{-}F}$ = 298.2, 33.2 Hz), 116.4 (tt, $J_{C\text{-}F}$ = 306.0, 35.4 Hz), 54.0, 23.7. ESI-MS (m/z, %): 354.8 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{10}H_{10}Cl_2F_4NOS$ $[M+H]^+$ requires 337.9791, found 337.9791.

*4.4.5.* **Compound 4e**: 71%; Colorless oil. IR (film): 3222, 2981, 2932, 1490, 1262, 1171, 1127, 1011, 908, 823, 799 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.5-7.49 (d, *J* = 8.0 Hz, 2H), 7.26-7.20 (d, *J* = 8.4 Hz, 2H), 4.68-4.65 (m, 2H), 1.58 (d, *J* = 6.9 Hz, 3H). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ -66.14 to -67.20 (m, 2F), -117.54 (dt, *J* = 231.6, 1.9 Hz, 1F), -119.43 (dt, *J* = 232.0, 1.9 Hz, 1F). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 141.0, 132.2, 128.0, 122.3, 54.1, 23.6. ESI-MS (m/z, %): 400.8 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{10}H_{10}BrClF_4NOS$ $[M+H]^+$ requires 381.9286, found 381.9283.

*4.4.6.* **Compound 4f**: 65%; Colorless oil. IR (film): 3224, 2983, 2935, 1453, 1380, 1329, 1266, 1179, 1079, 1016, 905, 802, 703 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 7.58-7.50 (m, 4H), 4.96-4.95 (d, *J* = 5.6 Hz, 1H), 4.80-4.77 (m, 1H), 1.61 (d, *J* = 6.9 Hz, 3H). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ -62.73 (s, 3F), -66.75 to -66.83 (m, 2F), -116.93 (dq, *J* = 233.6, 3.0 Hz, 1F), -119.85 (dq, *J* = 233.6, 1.9 Hz, 1F). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 143.2, 131.3 (t, *J* = 34.2 Hz), 129.7, 129.5, 125.1 (t, *J* = 3.7 Hz), 123.9 (t, *J* = 271.1 Hz), 123.1 (t, *J* = 3.8 Hz), 122.1 (tt, $J_{C\text{-}F}$ = 298.2, 33.2 Hz), 116.4 (tt, $J_{C\text{-}F}$ = 306.2, 35.3 Hz), 54.1, 23.7. ESI-MS (m/z, %): 388.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_{10}ClF_7NOS$ $[M+H]^+$ requires 372.0054, found 372.0054.

*4.4.7.* **Compound 4g**: 73%; Colorless oil, IR (film): 3230, 2979, 2928, 2872, 1516, 1452, 1377, 1261, 1179, 1016, 950, 908, 797, 603 $cm^{-1}$. $^{1}H$ NMR (400 MHz, $CDCl_3$):

δ 7.23 (d, *J* = 6.4 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.68-4.66 (m, 2H), 2.35 (s, 1H), 1.57 (d, *J* = 6.7 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -66.05 to -67.13 (m, 2F), -118.04 (dq, *J* = 233.8, 5.3 Hz, 1F), -119.37 (dq, *J* = 233.9, 3.4 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 139.0, 138.1, 129.7, 126.2, 54.7, 23.5, 21.1. ESI-MS (m/z, %): 350.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_{13}ClF_4NO_2S$ $[M+H]^+$ requires 334.0286, found 334.0282.

*4.4.8.* **Compound 4h**: 75%; Colorless oil. IR (film): 3239, 2977, 2838, 1613, 1514, 1460, 1249, 1179, 1028, 906, 813, 796, 687 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 4.73-4.72 (d, *J* = 3.6 Hz, 1H), 4.66-4.64 (m, 1H), 3.79 (s, 1H), 1.56 (d, *J* = 6.5 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -66.07 to -67.15 (m, 2F), -117.82 (dd, *J* = 230.8, 4.1 Hz, 1F), -119.37 (dd, *J* = 230.8, 4.5 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.5, 134.0, 127.6, 124.3, 122.2 (tt, $J_{C\text{-}F}$ = 298.2, 33.1 Hz), 116.4 (tt, $J_{C\text{-}F}$ = 305.0, 35.8 Hz), 55.3, 54.4, 23.5. ESI-MS (m/z, %): 350.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_{13}ClF_4NO_2S$ $[M+H]^+$ requires 334.0286, found 334.0282.

*4.4.9.* **Compound 4i**: 82%; Colorless oil. IR (film): 3300, 2928, 1666, 1494, 1454, 1166, 1124, 1014, 801 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.31-7.17 (m, 5H), 6.52 (d, *J* = 15.6 Hz, 1H), 6.14-6.08 (dd, *J* = 15.0, 6.4 Hz, 1H), 4.54-4.52 (m, 1H), 4.24-4.19 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -66.61 to -66.69 (m, 2F), -117.45 (d, *J* = 232.8 Hz, 1F), -119.83 (dd, *J* = 232.8, 4.5 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 135.9, 131.8, 130.2, 128.7, 128.2, 126.7, 53.5, 22.3. ESI-MS (m/z, %): 346.9 (100) $[M+NH_4]^+$; HRMS (ESI) Calcd for $C_{12}H_{13}ClF_4NOS$ $[M+H]^+$ requires 330.0337, found 330.0331.

*4.4.10.* **Compound 4j**: 76%; Colorless oil. IR (film): 3233, 2961, 2873, 1470, 1421, 1388, 1261, 1170, 1125, 1059, 1015, 908, 795, 598 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 1H), 3.64-3.57 (m, 1H), 1.75-1.68 (m, 1H), 1.52-1.47 (m, 1H), 1.38-1.31 (m, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 6.0 Hz, 6H). $^{19}$F NMR (376 MHz, $CDCl_3$): δ

-66.12 to -67.16 (m, 2F), -117.92 (d, $J$ = 232.6 Hz, 1F), -120.47 (d, $J$ = 232.6 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 50.8, 47.7, 24.6, 22.8, 22.4, 22.3. ESI-MS (m/z, %): 283.8 (100) $[M+H]^+$; HRMS (ESI) Calcd for $C_8H_{15}ClF_4NOS$ $[M+H]^+$ requires 284.0494, found 284.0492.

*4.4.11*. **Compound 4k**: 78%; Colorless oil. IR (film): 3237, 2963, 2862, 1461, 1417, 1261, 1125, 1013, 908, 801, 684 $cm^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ 4.23-4.14 (m, 1H), 3.57-3.50 (m, 1H), 1.61-1.50 (m, 2H), 1.33-1.31 (m, 4H), 1.24 (d, $J$ = 6.8 Hz, 3H), 0.90 (t, $J$ = 6.0 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$): δ -66.12 to -67.18 (m, 2F), -117.96 (dq, $J$ = 232.9, 3.0 Hz, 1F), -120.28(dd, $J$ = 232.9, 3.0 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 122.3 (tt, $J_{C\text{-}F}$ = 297.9, 33.6 Hz), 116.1 (tt, $J_{C\text{-}F}$ = 304.4, 34.9 Hz), 52.7, 38.1, 27.8, 22.4, 22.3, 13.9. ESI-MS (m/z, %): 283.8 (100) $[M+H]^+$; HRMS (ESI) Calcd for $C_8H_{15}ClF_4NOS$ $[M+H]^+$ requires 284.0494, found 284.0492.

*4.4.12*. **Compound 5a**: White solid, mp: 167-169 $^o$C. $^1$H NMR (400 MHz, $CD_3OD$): δ 7.35-7.47 (m, 5H), 4.43 (q, $J$ = 6.8 Hz, 1H), 1.63 (d, $J$ = 6.8 Hz, 3H). The data corresponded to that reported in the literature.[17]

### 4.5. Typical Procedure for the synthesis of (*S*)-5 from (*Ss, Sc*)-4a

To a 5.0 mL reaction tube equipped with a reflux condenser were added (*Ss*, *Sc*)-**4a** (60.4 mg), 1 M HCl (1 mL), and MeOH (1 mL). The mixture was stirred at 50 $^o$C for 2 h. After cooled to room temperature, the mixture was adjusted to pH = 10 with 1 M NaOH, and then extracted with EtOAc (2 mL × 5). Dry hydrogen chloride was bubbled through the combined organic solution for 5 min, and a white solid precipitated. Evaporation of the volatile solvent under reduced pressure afforded 30.6 mg (97% yield) of **(*S*)-5**: $[\alpha]_D^{25}$ = -4.4 (*c* 4.0, MeOH) [17].

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