Synthesis R. Gurbanov et al. Paper

# Synthesis of sp³-Enriched β-Fluoro Sulfonyl Chlorides

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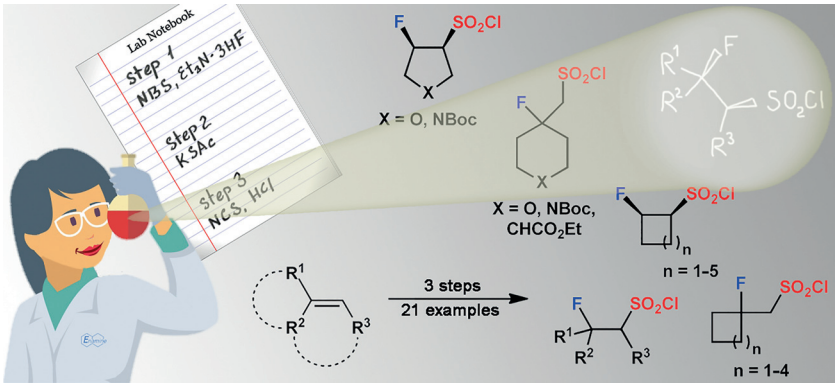


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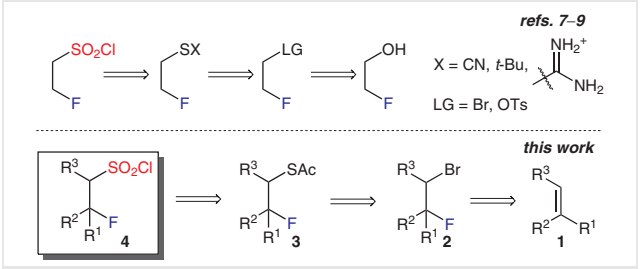
**Abstract** A three-step approach to the synthesis of sp³-enriched β-fluoro sulfonyl chlorides starting from alkenes is reported. The method was successfully applied to a wide range of acyclic and cyclic substrates, bearing either an exocyclic or an endocyclic double bond. The procedure worked with a wide range of substrates and tolerated a number of functional and protecting groups. Moreover, the target cyclic compounds were obtained as single cis diastereomers on a multigram scale. The title compounds are promising building blocks for drug discovery that can be used to obtain sp³-enriched β-fluoro and α,β-unsaturated sulfonamides.

**Key words** organosulfur compounds, organofluorine compounds, oxidation, sulfonyl chlorides, building blocks

Sulfonamides have taken an outstanding part in drug discovery for many years. First of all, the sulfonamide bond is considered as an amide bioisostere, although conformational properties of these structural units are rather different.[1] Another remarkable feature of the sulfonamide motif is its stability under physiological conditions: thus, only a few known enzymes are able to hydrolyze the $SO_2$–N bond.[2] It is not surprising therefore that sulfonamides were introduced into the pharmaceutical market as early as in the first half of the 20th century (the well-known 'sulfa drugs').[3] These antibacterial drugs earned their creator, Gerhard Domagk, a Nobel Prize in 1939.[4] Since then, more than a hundred sulfonamide-containing drugs have been approved and used over the world.[5]

Taking into account the importance of sulfonamides in drug discovery, as well as in line with ongoing trends towards the synthesis of advanced sulfonyl halide building blocks,[6] we have turned our attention to (hetero)aliphatic sulfonyl chlorides bearing a single fluorine atom at the β-position (**4**). Surprisingly, this compound class appeared to be largely underrepresented in the literature.[7,8] Thus, the parent 2-fluoroethanesulfonyl chloride has been described in several papers; the methods used for its preparation included $Cl_2$-mediated oxidation of β-fluoroethyl thiocyanate,[8a] thiouronium tosylate,[8b] and *tert*-butyl sulfide (Scheme 1).[8c] In turn, the latter substrates were prepared via nucleophilic substitution starting from 2-fluoroethanol. Additional to that, a few substituted β-fluoro sulfonyl chlorides,[9] as well as β-fluoro alkyl sulfides[10] considered as precursors to ones, are mentioned in the literature.




**Scheme 1** Synthesis of β-fluoro sulfonyl chlorides

In this work, we propose an alternative strategy for the preparation of sp³-enriched β-fluoro sulfonyl chlorides, which is similar to a three-step approach to aliphatic β-alkoxy sulfonyl chlorides described by us previously and based on alkoxybromination of the corresponding alkenes **1**.[6c] Similarly to the latter approach, the key step of the proposed method might include bromo*fluorination* of **1**, whereas to install the sulfonyl chloride moiety, nucleophilic substitution of the bromine atom by thioacetate anion and subsequent oxidative chlorination were envisaged. Twenty-three alkenes **1a**–**x**, significantly varied in structure, were studied as the substrates for the proposed reaction sequence to establish its scope and limitations (Figure 1).



First of all, acyclic substrates were studied, namely styrene (**1a**) and 3-methoxy-2-methylprop-1-ene (**1b**). The first step, i.e. bromofluorination, was carried out upon action of $Et_3N{\cdot}3HF$ and NBS in $CH_2Cl_2$ according to slightly modified literature procedures.[11] The reaction led to products **2a** and **2b** exclusively formed according to Markovnikov's rule.[11a] Further steps, i.e. KSAc-mediated preparation of β-fluoro ethanethioates **3a** and **3b**, as well as their oxidative chlorination upon action of *N*-chlorosuccinimide (NCS) and aqueous HCl, were performed following the well-established protocols.[6c] Thus, the corresponding β-fluoro sulfonyl chlorides **4a** and **4b** were isolated in 64% and 66% overall yield, respectively (Table 1, entries 1 and 2).

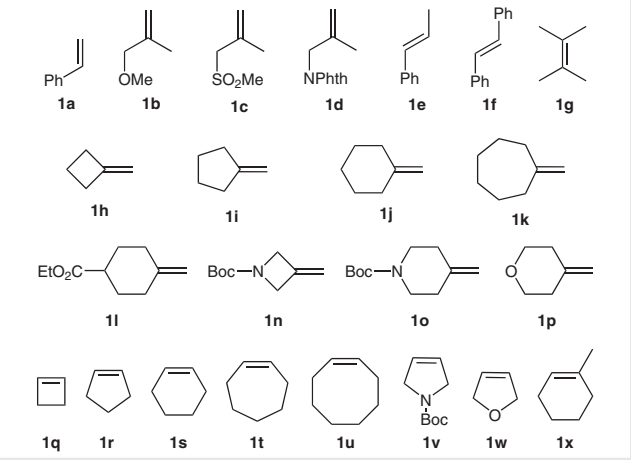



**Figure 1** Alkenes **1a–x** – starting materials for this study

These successful results prompted us to extend the substrate scope with other acyclic as well as carbo- and heterocyclic alkenes (Figure 1). Many of the starting materials shown in Figure 1 were available commercially; functionalized alkenes **1c** and **1d** were obtained from 3-chloro-2-methylprop-1-ene (**5**) (Scheme 2), whereas carbo- and heterocyclic alkenes **1h–l**,**n–p** were synthesized by Wittig olefination of the corresponding cyclic ketones **6** (Scheme 3).

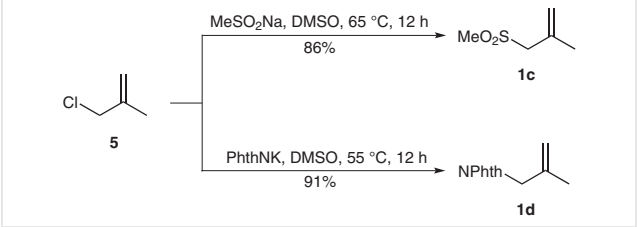
Analogously to the case of **1a** and **1b**, fluorobromination of alkenes **1c**,**d**,**h–l** and **1n–p** led to Markovnikov-type products **2c**,**d**,**h–p**, which were obtained in 38–99% yield (Table 1; entries 3, 4, and 8–16). In turn, alkene **1l** was converted into a ca. 1:1 mixture of diastereomeric products **2l** and **2m** that were separated by column chromatography (Table 1, entries 12 and 13).

Since the mechanism of the bromofluorination probably includes formation of bromonium ions, the reaction should occur as an *anti* addition.[11a] Indeed, under the aforementioned conditions, *trans*-β-methylstyrene (**1e**) and stilbene (**1f**) were converted into *anti*-β-fluoro bromides (**2e**,**f**), and cyclic substrates **1q–x** bearing an endocyclic double bond gave *trans*-β-fluoro bromides **2q–x** exclusively, in 59–94% yield (Table 1; entries 5, 6, and 17–24). Nevertheless, the developed procedure turned out to be inappropriate for the bromofluorination of cyclooctene (**1u**). The crude product contained a number of impurities (including some isomeric bromofluorocyclooctanes); possibly, transannular reactions (common in medium-sized rings[12]) were responsible for that. In this regard, cyclooctene (**1u**) was bromofluorinated at lowered temperature (–20 °C) with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and Py·HF as a source of the fluoride. This improvement allowed preparation of the target product **2u** in nearly quantitative yield (98%; Table 1, entry 21).

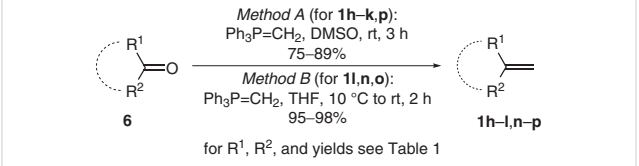
In general, bromofluorination of alkenes **1** proceeded smoothly and gave the desired products in moderate to good yields. The yields of the products correlated with their lipophilicity and (partially) volatility, obviously due to losses upon workup of the reaction mixture.

The next step, i.e. nucleophilic substitution of the bromine atom with thioacetate anion, was performed in DMF upon heating and provided the corresponding β-fluoro thioacetates **3** in up to 99% yield (Table 1). This method worked well with the substrates derived from mono- and disubstituted (vicinal and geminal) alkenes, and neither heteroatom position nor ring size had a tangible impact on its outcome. However, fine-tuning of the reaction temperature was necessary to attain optimal yield of the products. The reaction followed an $S_N2$ mechanism; thus, *syn*-**3e**,**f** and *cis*-**3q–w** products were obtained from the corresponding *anti*-**2e**,**f** and *trans*-**2q–w** isomeric substrates (Table 1; entries 5, 6, and 17–23). At the same time, tri- (**2x**) and tetrasubstituted (**2g**) β-fluoro bromides (Table 1, entries 7 and 24) did not participate in nucleophilic substitution, affording side elimination products instead.

Ultimately, the oxidative chlorination of **3** proceeded in a straightforward manner under typical conditions (NCS, aq HCl, MeCN, 0 °C to rt), and the target β-fluoro sulfonyl chlorides **4** were obtained in up to 97% yield (Table 1). Diminished yields were observed only for the products bearing




**Scheme 2** Synthesis of functionalized alkenes **1c** and **1d**



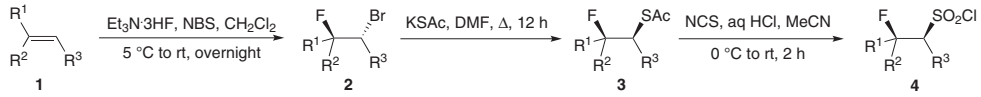

**Scheme 3** Synthesis of alkenes **1h–l** and **1n–p**

acid-labile groups [i.e., Boc-protected derivatives **4n** (13%), **4o** (39%), and **4v** (30%), as well as tetrahydrofuran **4w** (45%)]. Intriguingly, the stilbene-derived β-fluoro thioacetate **3f** failed to give the corresponding sulfonyl chloride, resulting in a complex mixture of side products.

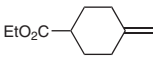
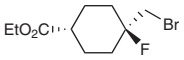
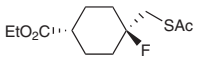
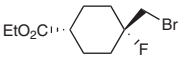
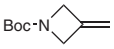
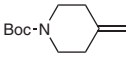
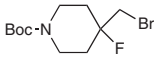
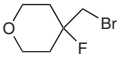
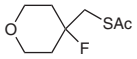
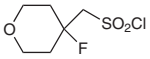
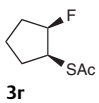
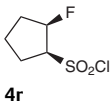
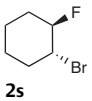
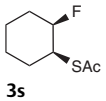
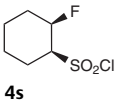
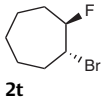
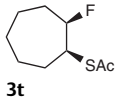
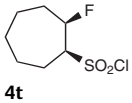
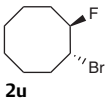
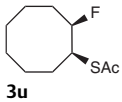
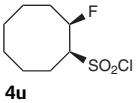
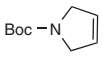
Notably, cyclic derivatives **4q–w** were obtained as pure *cis* diastereomers (Table 1, entries 17–23), which was confirmed by NOE experiments with products **4s** and **4v** (Figure 2). In addition, the configuration of sulfonyl chloride **4m** was also confirmed by NOE experiments.

**Table 1** Synthesis of β-Fluoro Sulfonyl Chlorides **4**[a]




| Entry | Alkene **1** | Yield (%)[b] | β-Fluoro bromides **2** | Yield (%) | β-Fluoro thioacetates **3** | Temp (°C) | Yield (%) | β-Fluoro sulfonyl chlorides **4** | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | – | **2a** | 85 | **3a** | 40 | 96 | **4a** | 78 |
| 2 | **1b** | – | **2b** | N/A[c] | **3b** | 50 | 79[d] | **4b** | 83 |
| 3 | **1c** | 86 | **2c** | 38 | **3c** | 50 | 25 | **4c** | 76 |
| 4 | **1d** | 91 | **2d** | 43 | **3d** | 55 | 95 | **4d** | 92 |
| 5 | **1e** | – | **2e** | 69 | **3e** | 45 | 76 | **4e** | 91 |
| 6 | **1f** | – | **2f** | 71 | **3f** | 45 | 78 | – | – |
| 7 | **1g** | – | **2g** | 68 | – | – | – | – | – |
| 8 | **1h** | 83 | **2h** | 68 | **3h** | 30 | 88 | **4h** | 90 |
| 9 | **1i** | 85 | **2i** | 82 | **3i** | 40 | 87 | **4i** | 79 |
| 10 | **1j** | 89 | **2j** | 73 | **3j** | 50 | 90 | **4j** | 95 |
| 11 | **1k** | 87 | **2k** | N/A[c] | **3k** | 50 | 71[d] | **4k** | 80 |

Table 1 (continued)

| Entry | Alkene **1** | Yield (%)[b] | β-Fluoro bromides **2** | Yield (%) | β-Fluoro thioacetates **3** | Temp (°C) | Yield (%) | β-Fluoro sulfonyl chlorides **4** | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 12 |  **1l** | 98 |  **2l** | 30 |  **3l** | 50 | 93 |  **4l** | 77 |
| 13 | | |  **2m** | 35 |  **3m** | 50 | 97 |  **4m** | 89 |
| 14 |  **1n** | 96 |  **2n** | 41 |  **3n** | 40 | 72 |  **4n** | 13 |
| 15 |  **1o** | 95 |  **2o** | 99 |  **3o** | 45 | 99 |  **4o** | 39 |
| 16 |  **1p** | 75 |  **2p** | 90 |  **3p** | 50 | 70 |  **4p** | 73 |
| 17 |  **1q** | – |  **2q** | 59 |  **3q** | 70 | N/A[c] |  **4q** | 92[d] |
| 18 |  **1r** | – |  **2r** | 82 |  **3r** | 70 | 82 |  **4r** | 97 |
| 19 |  **1s** | – |  **2s** | 91 |  **3s** | 75 | 92 |  **4s** | 63 |
| 20 |  **1t** | – |  **2t** | 94 |  **3t** | 85 | 97 |  **4t** | 83 |
| 21 |  **1u** | – |  **2u** | 98[e] |  **3u** | 90 | 53 |  **4u** | 56 |
| 22 |  **1v** | – |  **2v** | 40 |  **3v** | 70 | 64 |  **4v** | 30 |
| 23 |  **1w** | – |  **2w** | 46 |  **3w** | 65 | 82 |  **4w** | 45 |
| 24 |  **1x** | – |  **2x** | 71 | – | – | – | – | – |

[a] Relative configurations are shown.
[b] Compounds **1c** and **1d** were prepared according to Scheme 2. Compounds **1h–l** and **1n–p** were prepared according to Scheme 3 using Methods A and B.
[c] The product was used in the next step without purification.
[d] Yield over two steps.
[e] Reaction conditions: DBDMH, Py·HF, $CH_2Cl_2$, –20 °C to rt, overnight.

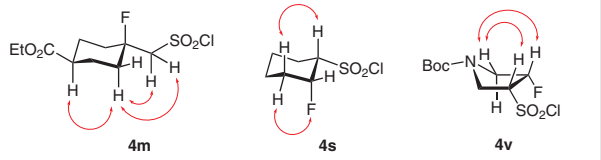
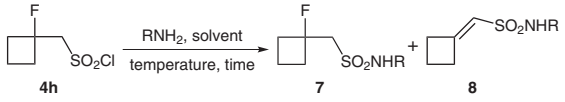



**Figure 2** Important NOE correlations observed for **4m**, **4s**, and **4v**

Next, we turned our attention to the preparation of the corresponding sulfonamides. For this purpose, **4h** was chosen as a model sulfonyl chloride, whereas ammonia and aniline were used as model nucleophiles. It was found that the sulfonylation with **4h** was accompanied with β-elimination to a great extent, so that the target β-fluoro sulfonamides **7** were formed together with the corresponding α,β-unsaturated sulfonamides **8**. Toward this end, a series of experiments were performed in order to find the favorable reaction conditions. Particularly, the effect of the solvent and the temperature were studied primarily (Table 2).

**Table 2** Optimization of the Sulfonylation Reaction Conditions




| Entry | R | Reaction conditions | Products (ratio)[a] |
|---|---|---|---|
| 1 | H | aq $NH_3$, rt, 20 min | **7a** + **8a** (1:6) |
| 2 | H | aq $NH_3$, 0 °C to rt, 20 min | **7a** + **8a** (1:10) |
| 3 | H | aq $NH_3$, 0 °C, 1 h | **7a** + **8a** (1:12)[b] |
| 4 | H | $NH_3$, THF, rt, 30 min[c] | **7a** + **8a** (1:3) |
| 5 | H | $NH_3$, THF, –30 °C, 30 min[c] | **7a** + **8a** (1:2.5) |
| 6 | Ph | $PhNH_2$ (1 equiv), *i*-$Pr_2NEt$ (1.1 equiv), THF, –30 °C, overnight | **7b** + **8b** (1:1) and by-products |
| 7 | Ph | $PhNH_2$ (1 equiv), AcONa (1 equiv), AcOH, rt, overnight | **7b** + **8b** (1.6:1) |
| 8 | Ph | $PhNH_2$ (1.2 equiv), AcONa (1.5 equiv), AcOH, rt, overnight | **7b** + **8b** (1.7:1)[d] |

[a] In the crude product, according to $^1H$ NMR spectra.
[b] Pure **8a** was isolated in 52% yield.
[c] A solution of $NH_3$ was added to a solution of **4h**.
[d] A mixture of **7b** and **8b** (1.7:1 ratio) was isolated in 73% total yield.

Upon sulfonylation of ammonia in aqueous media, lowering the temperature increased the content of α,β-unsaturated derivative **8a** up to 12:1 ratio (Table 2, entries 1–3). Contrary to that, THF media and reverse addition of the reagents (an ammonia solution was added to a solution of **4h**) facilitated the formation of β-fluoro sulfonamide **7a** and increased its content upon lowering the temperature, although **8a** still was the major product (up to 1:2.5 ratio of **7a** and **8a**; Table 2, entries 4 and 5). In its turn, the best results for the sulfonylation of aniline were obtained in AcOH media at room temperature using AcONa as a base. Although this also resulted in a mixture of β-fluoro (**7b**) and α,β-unsaturated (**8b**) sulfonamides, the former one was the major product (Table 2, entries 7 and 8). Importantly, no reaction occurred when an additional amount of the nucleophile was added to the obtained mixture of **7a** and **8a**, and the mixture left at room temperature overnight. Therefore, the elimination of HF occurred from the starting material **4h** and not from the product **7a**.

In conclusion, we have developed a general and efficient three-step approach to the preparation of $sp^3$-enriched β-fluoro sulfonyl chlorides starting from acyclic and carbo(hetero)cyclic alkenes. The method worked well with mono- and disubstituted alkenes (vicinal and geminal) except for diaryl-substituted ones; it was not fruitful with tri- and tetrasubstituted substrates. Owing to low molecular weight and $sp^3$-enrichment, as well as conformational restriction, β-fluoro sulfonyl chlorides meet the requirements for renowned criteria as building blocks for lead-oriented synthesis.[13] The obtained compounds can be used for the preparation of β-fluoro and (especially) α,β-unsaturated sulfonamides (that are not readily available by other methods), both being useful for early drug discovery programs.

Solvents were purified according to standard procedures.[14] All starting materials were obtained from Enamine Ltd. and UORSY. Melting points were measured on an MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Merck silica gel 60 (230–400 mesh) as the stationary phase. $^1H$, $^{19}F$, and $^{13}C$ NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (600 MHz for $^1H$ NMR and 151 MHz for $^{13}C$ NMR), a Bruker 170 Avance 500 spectrometer (at 500.1 MHz, 470.6 MHz, and 125.8 MHz for $^1H$, $^{19}F$, and $^{13}C$ nuclei, respectively) or Varian Unity Plus 400 spectrometer (at 400.4 MHz, 376.5 MHz, and 100.7 MHz for $^1H$, $^{19}F$, and $^{13}C$ nuclei, respectively). Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument [chemical ionization (APCI), electrospray ionization (ESI)] or Agilent 5890 Series II 5972 GCMS instrument [electron impact ionization (EI)]. HRMS analyses were conducted on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6200 Accurate Mass TOF mass spectrometer.

### 2-Methyl-3-(methylsulfonyl)prop-1-ene (1c)[15]

$MeSO_2Na$ (5.11 g, 50 mmol) and 3-chloro-2-methylprop-1-ene (**5**) (4.53 g, 50 mmol) were dissolved in anhydrous DMF (150 mL), and the resulting mixture was heated at 65 °C for 12 h. The volatiles were evaporated under reduced pressure; the remainder was diluted with water (200 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure, affording pure **1c**; yield: 5.77 g (86%).

### 2-(2-Methylallyl)isoindoline-1,3-dione (1d)[16]

Potassium phthalimide (9.26 g, 50 mmol) and 3-chloro-2-methylprop-1-ene (**5**) (4.53 g, 50 mmol) were dissolved in anhydrous DMF (150 mL), and the resulting mixture was heated at 55 °C for 12 h. The

volatiles were evaporated under reduced pressure, and the remainder was diluted with water (200 mL). The precipitate formed was filtered, washed with water, and dried, affording pure **1d**; yield: 9.16 g (91%).

### Alkenes 1h–k and 1p; Method A; General Procedure

NaH (60% dispersion in mineral oil; 2.40 g, 60 mmol) was washed with hexane under argon atmosphere and dissolved carefully in anhydrous DMSO (100 mL) at 60 °C. The resulting solution was cooled to 15 °C, $Ph_3PMeI$ (23.4 g, 58 mmol) was added under argon atmosphere, and the mixture was allowed to react for 20 min. The corresponding ketone **6** (50 mmol) was added dropwise at rt, and the resulting solution was stirred for 3 h at rt. The alkene formed was removed from the reaction mixture under reduced pressure and condensed in a liquid nitrogen cooled vacuum trap. The vacuum trap was sealed, removed, and allowed to equilibrate to rt. The product retrieved from the vacuum trap was pure enough so that no further purification was required.

### Methylenecyclobutane (1h)[17a]

Yield: 8.07 g (83%) from 10.0 g of cyclobutanone; colorless liquid.

### Methylenecyclopentane (1i)[17a]

Yield: 8.30 g (85%) from 10.0 g of cyclopentanone; colorless liquid.

### Methylenecyclohexane (1j)[17a,b]

Yield: 13.1 g (89%) from 15.0 g of cyclohexanone; colorless liquid.

### Methylenecycloheptane (1k)[17c]

Yield: 8.55 g (87%) from 10.0 g of cycloheptanone; colorless liquid.

### 4-Methylenetetrahydro-2*H*-pyran (1p)[17d]

Yield: 7.35 g (75%) from 10.0 g of dihydro-2*H*-pyran-4(3*H*)-one; yellowish liquid.

### Alkenes 1l, 1n, and 1o; Method B; General Procedure

*t*-BuOK (6.73 g, 60 mmol) was dissolved in anhydrous THF (100 mL), and the resulting solution was cooled to 0 °C. Then, $Ph_3PMeI$ (22.2 g, 55 mmol) was added under argon atmosphere, and the reaction mixture was stirred at 0 °C for 30 min. A solution of ketone **6** (50 mmol) in anhydrous THF (30 mL) was added dropwise maintaining the temperature below 10 °C. The mixture was allowed to react at rt for 2 h and then evaporated under reduced pressure. The residue was subjected to flash chromatography (hexane–*t*-BuOMe, 1:1), affording pure title product.

### Ethyl 4-Methylenecyclohexanecarboxylate (1l)[17e]

Yield: 14.5 g (98%) from 15.0 g of ethyl 4-oxocyclohexanecarboxylate; yellowish oil.

### *tert*-Butyl 3-Methyleneazetidine-1-carboxylate (1n)[17f]

Yield: 11.4 g (96%) from 12.0 g of *tert*-butyl 3-oxoazetidine-1-carboxylate; yellowish oil.

### *tert*-Butyl 4-Methylenepiperidine-1-carboxylate (1o)[17d]

Yield: 11.3 g (95%) from 12.0 g of *tert*-butyl 4-oxopiperidine-1-carboxylate; yellowish oil.

### β-Fluoro Bromides 2a–t and 2v–x; General Procedure

$Et_3N{\cdot}3HF$ (20.2 g, 125 mmol) was added to a solution of alkene **1a–l**,**n–t**,**v–x** (50 mmol) in $CH_2Cl_2$ (100 mL), and the resulting mixture was cooled to 5 °C. Then, NBS (10.7 g, 60 mmol) was added portionwise at 5 °C, and the reaction mixture was stirred at rt overnight. Then, it was poured onto an ice–water mixture (200 g). The organic layer was separated, washed with saturated aq $NaHCO_3$ (3 × 50 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure, affording pure product (**2a**,**g**,**i**,**o**,**p**,**r–t**), or crude product which was purified by distillation (**2e**,**h**,**j**,**q**,**w**,**x**), column chromatography (**2c**,**l–n**,**v**), recrystallization (**2d**,**f**), or used without purification (**2b**,**k**).

### (2-Bromo-1-fluoroethyl)benzene (2a)[11d]

Yield: 6.57 g (85%) from 4.00 g of styrene (**1a**); yellowish oil.

### 1-Bromo-2-fluoro-3-methoxy-2-methylpropane (2b)

The crude product was used in the subsequent step without further characterization; yield: 9.03 g from 5.00 g of **1b**; yellowish liquid.

### 1-Bromo-2-fluoro-2-methyl-3-(methylsulfonyl)propane (2c)

The product was purified by column chromatography (gradient $CHCl_3$ to EtOAc); yield: 3.76 g (38%) from 5.70 g of **1c**; yellowish oil.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 3.72 (t, *J* = 12.5 Hz, 1 H), 3.60 (t, *J* = 16.3 Hz, 2 H), 3.40 (t, *J* = 16.3 Hz, 1 H), 2.97 (s, 3 H), 1.71 (d, *J* = 22.0 Hz, 3 H).

$^{13}C$ NMR (101 MHz, $CDCl_3$): δ = 92.0 (d, *J* = 177.7 Hz), 60.0 (d, *J* = 24.0 Hz), 43.6 (d, *J* = 6.2 Hz), 36.9 (d, *J* = 28.5 Hz), 23.8 (d, *J* = 23.3 Hz).

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –143.3.

Anal. Calcd for $C_5H_{10}BrFO_2S$: C, 25.76; H, 4.32; S, 13.75. Found: C, 26.07; H, 4.45; S, 13.69.

### 2-(3-Bromo-2-fluoro-2-methylpropyl)isoindoline-1,3-dione (2d)

The product was purified by recrystallization (hexane–*t*-BuOMe, 1:1); yield: 3.21 g (43%) from 5.0 g of **1d**; yellowish powder; mp 70–72 °C.

$^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.99–7.84 (m, 2 H), 7.79–7.65 (m, 2 H), 4.03 (dt, *J* = 19.6, 3.3 Hz, 2 H), 3.63–3.46 (m, 2 H), 1.54 (dd, *J* = 19.6, 3.3 Hz, 3 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 167.6, 133.9, 131.4, 123.2, 93.5 (d, *J* = 180.9 Hz), 43.3 (d, *J* = 25.7 Hz), 36.3 (d, *J* = 27.3 Hz), 21.9 (d, *J* = 23.3 Hz).

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –148.9.

Anal. Calcd for $C_{12}H_{11}BrFNO_2$: C, 48.02; H, 3.69; N, 4.67. Found: C, 48.03; H, 3.97; N, 4.37.

### *anti*-(2-Bromo-1-fluoropropyl)benzene (2e)[11f]

The product was purified by distillation; bp 37 °C/0.1 mmHg; yield: 20.3 g (69%) from 16.0 g of **1e**; yellowish liquid.

### *anti*-(1-Bromo-2-fluoroethane-1,2-diyl)dibenzene (2f)

The product was purified by recrystallization (hexane); yield: 3.30 g (71%) from 3.00 g of **1f**; white powder; mp 123–124 °C.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.46–7.19 (m, 10 H), 5.84 (dd, *J* = 46.0, 6.7 Hz, 1 H), 5.12 (dd, *J* = 14.8, 6.7 Hz, 1 H).

$^{13}C$ NMR (126 MHz, $CDCl_3$): δ = 136.8, 136.5 (d, *J* = 20.5 Hz), 129.2, 128.9, 128.8, 128.4, 128.3, 126.8 (d, *J* = 6.2 Hz), 95.5 (d, *J* = 181.7 Hz), 54.6 (d, *J* = 28.2 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –170.1.

Anal. Calcd for $C_{14}H_{12}BrF$: C, 60.24; H, 4.33. Found: C, 60.00; H, 4.63.

**2-Bromo-3-fluoro-2,3-dimethylbutane (2g)**[11g]

Yield: 12.4 g (68%) from 8.42 g of **1g**; yellowish crystals.

**1-(Bromomethyl)-1-fluorocyclobutane (2h)**[11b]

The product was purified by distillation; bp 64 °C/38 mmHg; yield: 13.3 g (68%) from 8.00 g of **1h**; yellowish liquid.

**1-(Bromomethyl)-1-fluorocyclopentane (2i)**[11b]

Yield: 14.9 g (82%) from 8.25 g of **1i**; yellowish liquid.

**1-(Bromomethyl)-1-fluorocyclohexane (2j)**[11b]

The product was purified by distillation; bp 60 °C/7 mmHg; yield: 19.2 g (73%) from 13.00 g of **1j**; yellowish liquid.

**1-(Bromomethyl)-1-fluorocycloheptane (2k)**

The crude product was used in the subsequent step without further purification; yield: 7.62 g from 5.00 g of **1k**; yellowish liquid.

**Ethyl (1*r*,4*r*)-4-(Bromomethyl)-4-fluorocyclohexanecarboxylate (2l)**

The product was purified by column chromatography (hexane–EtOAc, 10:1; $R_f$ = 0.4); yield: 4.77 g (30%) from 10.0 g of **1l**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.09 (q, *J* = 7.1 Hz, 2 H), 3.40 (d, *J* = 17.3 Hz, 2 H), 2.21 (t, *J* = 11.9 Hz, 1 H), 2.11–2.00 (m, 2 H), 1.91–1.82 (m, 2 H), 1.82–1.67 (m, 2 H), 1.52 (td, *J* = 13.8, 4.5 Hz, 1 H), 1.42 (td, *J* = 13.8, 4.5 Hz, 1 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 174.8, 92.0 (d, *J* = 177.2 Hz), 60.4, 42.0, 39.3 (d, *J* = 27.6 Hz), 32.7 (d, *J* = 22.5 Hz), 23.9, 14.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –160.2.

Anal. Calcd for $C_{10}H_{16}BrFO_2$: C, 44.96; H, 6.04. Found: C, 45.34; H, 6.39.

**Ethyl (1*s*,4*s*)-4-(Bromomethyl)-4-fluorocyclohexanecarboxylate (2m)**

The product was purified by column chromatography (hexane–EtOAc, 10:1; $R_f$ = 0.2); yield: 5.33 g (35%) from 10.0 g of **1l**; yellowish liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.11 (q, *J* = 7.1 Hz, 2 H), 3.47 (d, *J* = 20.0 Hz, 2 H), 2.53 (t, *J* = 5.2 Hz, 1 H), 1.93–1.75 (m, 8 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 174.6, 92.8 (d, *J* = 177.2 Hz), 60.4, 39.2, 38.7 (d, *J* = 26.3 Hz), 31.3 (d, *J* = 21.9 Hz), 23.7 (d, *J* = 4.9 Hz), 14.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –154.3.

Anal. Calcd for $C_{10}H_{16}BrFO_2$: C, 44.96; H, 6.04; Br, 29.91. Found: C, 45.01; H, 6.10; Br, 29.79.

***tert*-Butyl 3-(Bromomethyl)-3-fluoroazetidine-1-carboxylate (2n)**

The product was purified by column chromatography (gradient hexane to *t*-BuOMe); yield: 6.50 g (41%) from 10.0 g of **1n**; yellowish oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.08 (dd, *J* = 20.6, 10.3 Hz, 2 H), 3.98 (dd, *J* = 16.5, 10.3 Hz, 2 H), 3.66 (d, *J* = 20.6 Hz, 2 H), 1.43 (s, 9 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 155.5, 89.0 (d, *J* = 212.2 Hz), 80.0, 58.4 (2 C), 33.7 (d, *J* = 27.1 Hz), 27.9.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –152.2.

Anal. Calcd for $C_9H_{15}BrFNO_2$: C, 40.32; H, 5.64; N, 5.22. Found: C, 40.41; H, 5.91; N, 5.45.

***tert*-Butyl 4-(Bromomethyl)-4-fluoropiperidine-1-carboxylate (2o)**[11c]

Yield: 15.00 g (99%) from 10.0 g of **1o**; yellowish oil.

**4-(Bromomethyl)-4-fluorotetrahydro-2*H*-pyran (2p)**

Yield: 12.7 g (90%) from 7.0 g of **1p**; yellowish liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.83 (dd, *J* = 11.4, 3.7 Hz, 2 H), 3.68 (td, *J* = 11.4, 3.7 Hz, 2 H), 3.44 (d, *J* = 18.5 Hz, 2 H), 1.92–1.83 (m, 2 H), 1.83–1.67 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 90.6 (d, *J* = 178.0 Hz), 63.5, 39.0 (d, *J* = 26.4 Hz), 34.1 (d, *J* = 21.4 Hz).

$^{19}$F NMR (470 MHz, $CDCl_3$): δ = –160.9.

Anal. Calcd for $C_6H_{10}BrFO$: C, 36.57; H, 5.12. Found: C, 36.47; H, 5.19.

***trans*-1-Bromo-2-fluorocyclobutane (2q)**

The product was purified by distillation; bp 116 °C/760 mmHg; yield: 16.7 g (59%) from 10.0 g of **1q**; colorless liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.93 (dq, *J* = 54.9, 7.6 Hz, 1 H), 4.40–4.21 (m, 1 H), 2.51–2.38 (m, 2 H), 2.07–1.95 (m, 1 H), 1.85–1.76 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 92.0 (d, *J* = 227.2 Hz), 43.1 (d, *J* = 22.2 Hz), 27.2 (d, *J* = 19.4 Hz), 22.3 (d, *J* = 18.7 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –162.5.

Anal. Calcd for $C_4H_6BrF$: C, 31.40; H, 3.95; Br, 52.23. Found: C, 31.65; H, 3.67; Br, 52.09.

***trans*-1-Bromo-2-fluorocyclopentane (2r)**[11e]

Yield: 20.1 g (82%) from 10.0 g of **1r**; colorless liquid.

***trans*-1-Bromo-2-fluorocyclohexane (2s)**[11d,e]

Yield: 20.1 g (91%) from 10.0 g of **1s**; brown oil.

***trans*-1-Bromo-2-fluorocycloheptane (2t)**[11e]

Yield: 22.9 g (94%) from 12.0 g of **1t**; brown oil.

***tert*-Butyl *trans*-3-Bromo-4-fluoropyrrolidine-1-carboxylate (2v)**

The product was purified by column chromatography (gradient hexane to *t*-BuOMe); yield: 3.17 g (40%) from 5.0 g of **1v**; yellowish oil; ca. 1:1 mixture of rotamers.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.17 (dd, *J* = 51.6, 4.0 Hz, 1 H), 4.34 (dd, *J* = 11.6, 4.0 Hz, 1 H), 4.00–3.81 (m, 3 H), 3.77–3.57 (m, 1 H), 1.47 (s, 9 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 153.8, 95.6 (d, *J* = 184.7 Hz) and 94.8 (d, *J* = 184.5 Hz), 79.8, 52.5 and 52.1, 49.5 (d, *J* = 22.0 Hz) and 49.1 (d, *J* = 22.4 Hz), 46.3 (d, *J* = 26.4 Hz) and 45.6 (d, *J* = 26.9 Hz), 28.0.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –165.5.

Anal. Calcd for $C_9H_{15}BrFNO_2$: C, 40.32; H, 5.64; N, 5.22. Found: C, 40.18; H, 5.56; N, 5.13.

***trans*-3-Bromo-4-fluorotetrahydrofuran (2w)**

The product was purified by distillation; bp 84 °C/76 mmHg; yield: 11.1 g (46%) from 10.0 g of **1w**; colorless liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.29 (dd, *J* = 53.2, 3.5 Hz, 1 H), 4.43–4.34 (m, 2 H), 4.34–4.23 (m, 1 H), 4.14–4.00 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 97.2 (d, *J* = 185.8 Hz), 73.8, 71.1 (d, *J* = 22.9 Hz), 47.2 (d, *J* = 25.9 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –164.7.

Anal. Calcd for $C_4H_6BrFO$: C, 28.43; H, 3.58. Found: C, 28.31; H, 3.64.

### *trans*-2-Bromo-1-fluoro-1-methylcyclohexane (2x)[11h]

The product was purified by distillation; bp 52 °C/20 mmHg; yield: 37.4 g (71%) from 26.0 g of **1x**; colorless liquid.

### *trans*-1-Bromo-2-fluorocyclooctane (2u)[11d]

Cyclooctene (**1u**) (4.30 g, 39 mmol) and Py·HF (7.73 g, 78 mmol) were dissolved in $CH_2Cl_2$ (80 mL) and the resulting solution was cooled to –20 °C. Then, DBDMH (11.2 g, 39 mmol) was added portionwise at –20 °C, and the reaction mixture was allowed to stir at rt overnight. Then, it was poured onto an ice–water mixture (200 g), and the organic layer was separated, washed with saturated aq $NaHCO_3$ (3 × 40 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure, affording pure **2u** as a brown oil; yield: 8.00 g (98%).

### β-Fluoro Ethanethioates 3a–f and 3h–w; General Procedure

KSAc (17.1 g, 150 mmol) was added to a solution of fluoro bromide **2a–f**,**h–w** (50 mmol) in anhydrous DMF (150 mL), and the resulting mixture was stirred at the temperature given below for the preparation of each ethanethioate for 12 h. Then, it was cooled to rt, poured onto an ice–water mixture (200 g), and extracted with *t*-BuOMe (3 × 100 mL). The combined organic layer was washed with brine (2 × 100 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure, affording pure title product, which was used in the subsequent step without further purification (**3a–d**,**h–w**), or crude product which was purified by either distillation (**3e**) or column chromatography (**3f**).

### *S*-(2-Fluoro-2-phenylethyl) Ethanethioate (3a)

The reaction mixture was stirred at 40 °C.

Yield: 4.92 g (96%) from 5.25 g of **2a**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.34 (m, 5 H), 5.49 (dd, *J* = 47.3, 8.3 Hz, 1 H), 3.51–3.39 (m, 1 H), 3.33–3.22 (m, 1 H), 2.37 (s, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.4, 138.0 (d, *J* = 20.1 Hz), 128.4 (d, *J* = 1.8 Hz), 128.2, 125.1 (d, *J* = 6.7 Hz), 92.2 (d, *J* = 175.0 Hz), 35.0 (d, *J* = 26.2 Hz), 30.1.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –175.1.

Anal. Calcd for $C_{10}H_{11}FOS$: C, 60.58; H, 5.59; S, 16.17. Found: C, 60.50; H, 5.58; S, 16.49.

### *S*-(2-Fluoro-3-methoxy-2-methylpropyl) Ethanethioate (3b)

The reaction mixture was stirred at 50 °C.

Yield: 8.24 g (79%) from 5.0 g of **1b**; brown liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.42 (d, *J* = 20.0 Hz, 2 H), 3.37 (s, 3 H), 3.29–3.13 (m, 2 H), 2.34 (s, 3 H), 1.32 (d, *J* = 20.0 Hz, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 194.5, 95.4 (d, *J* = 174.4 Hz), 76.4, 59.6, 34.6 (d, *J* = 25.3 Hz), 30.4, 21.0 (d, *J* = 23.5 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –150.5.

Anal. Calcd for $C_7H_{13}FO_2S$: C, 46.65; H, 7.27; S, 17.79. Found: C, 46.83; H, 7.63; S, 18.09.

### *S*-(2-Fluoro-2-methyl-3-(methylsulfonyl)propyl) Ethanethioate (3c)

The reaction mixture was stirred at 50 °C.

Yield: 0.92 g (25%) from 3.75 g of **2c**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 3.56–3.38 (m, 2 H), 3.29 (ddd, *J* = 38.1, 21.2, 14.9 Hz, 2 H), 2.99 (s, 3 H), 2.39 (s, 3 H), 1.65 (d, *J* = 21.2 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 193.3, 93.1 (d, *J* = 176.1 Hz), 60.6 (d, *J* = 24.1 Hz), 43.1 (d, *J* = 6.6 Hz), 39.0 (d, *J* = 25.8 Hz), 30.0, 23.2 (d, *J* = 23.6 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –143.4.

Anal. Calcd for $C_7H_{13}FO_3S_2$: C, 36.83; H, 5.74; S, 28.09. Found: C, 36.87; H, 5.74; S, 28.45.

### *S*-(3-(1,3-Dioxoisoindolin-2-yl)-2-fluoro-2-methylpropyl) Ethanethioate (3d)

The reaction mixture was stirred at 55 °C.

Yield: 3.41 g (95%) from 3.65 g of **2d**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2 H), 7.77–7.71 (m, 2 H), 4.02–3.82 (m, 2 H), 3.33–3.20 (m, 2 H), 2.38 (s, 3 H), 1.37 (s, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 193.9, 167.7, 133.8, 131.4, 123.1, 94.8 (d, *J* = 178.8 Hz), 44.0 (d, *J* = 25.4 Hz), 35.5 (d, *J* = 24.8 Hz), 30.0, 21.6 (d, *J* = 23.6 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –147.1.

Anal. Calcd for $C_{14}H_{14}FNO_3S$: C, 56.94; H, 4.78; N, 4.74; S, 10.86. Found: C, 57.11; H, 5.10; N, 4.52; S, 10.90.

### *syn*-(1-Fluoro-1-phenylpropan-2-yl) Ethanethioate (3e)

The reaction mixture was stirred at 45 °C.

The product was purified by distillation; bp 61 °C/0.5 mmHg; yield: 6.70 g (76%) from 9.0 g of **2e**; yellowish oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.31 (m, 5 H), 5.47 (dd, *J* = 46.3, 6.8 Hz, 1 H), 4.06 (dquint, *J* = 20.5, 6.8 Hz, 1 H), 2.29 (s, 3 H), 1.32 (dd, *J* = 6.8, 2.5 Hz, 3 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 194.3, 137.3 (d, *J* = 20.9 Hz), 128.6 (d, *J* = 2.5 Hz), 128.2, 126.1 (d, *J* = 7.4 Hz), 95.3 (d, *J* = 178.3 Hz), 43.8 (d, *J* = 24.2 Hz), 30.6, 17.5 (d, *J* = 2.5 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –178.1.

Anal. Calcd for $C_{11}H_{13}FOS$: C, 62.24; H, 6.17; S, 15.10. Found: C, 62.49; H, 6.52; S, 15.32.

### *syn*-(2-Fluoro-1,2-diphenylethyl) Ethanethioate (3f)

The reaction mixture was stirred at 45 °C.

The product was purified by column chromatography [gradient hexane (100) to EtOAc (30:70)]; yield: 2.30 g (78%) from 3.00 g of **2f**; yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.11 (m, 10 H), 5.74 (dd, *J* = 46.2, 5.7 Hz, 1 H), 5.07 (dd, *J* = 21.0, 5.7 Hz, 1 H), 2.27 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 193.2, 138.2, 137.2 (d, *J* = 20.9 Hz), 128.8, 128.6, 128.5, 128.1, 127.8, 126.1 (d, *J* = 7.0 Hz), 95.0 (d, *J* = 181.7 Hz), 53.4 (d, *J* = 23.1 Hz), 30.4.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –176.7.

Anal. Calcd for $C_{16}H_{15}FOS$: C, 70.05; H, 5.51; S, 11.69. Found: C, 69.93; H, 5.64; S, 11.64.

**S-((1-Fluorocyclobutyl)methyl) Ethanethioate (3h)**

The reaction mixture was stirred at 30 °C.

Yield: 4.27 g (88%) from 5.00 g of **2h**; brown liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.29 (d, *J* = 24.3 Hz, 2 H), 2.34 (s, 3 H), 2.33–2.20 (m, 2 H), 2.12–2.00 (m, 2 H), 1.85–1.73 (m, 1 H), 1.60–1.49 (m, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 195.2, 95.2 (d, *J* = 214.9 Hz), 35.6 (d, *J* = 23.9 Hz), 33.0 (d, *J* = 21.2 Hz), 30.5, 11.2 (d, *J* = 13.4 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –128.1.

Anal. Calcd for $C_7H_{11}FOS$: C, 51.83; H, 6.84; S, 19.76. Found: C, 52.07; H, 7.14; S, 19.56.

**S-((1-Fluorocyclopentyl)methyl) Ethanethioate (3i)**

The reaction mixture was stirred at 40 °C.

Yield: 12.3 g (87%) from 14.5 g of **2i**; brown liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 3.30 (d, *J* = 20.6 Hz, 2 H), 2.36 (s, 3 H), 2.03–1.88 (m, 2 H), 1.88–1.75 (m, 2 H), 1.74–1.55 (m, 4 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 195.0, 105.3 (d, *J* = 176.3 Hz), 37.1 (d, *J* = 23.3 Hz), 36.4 (d, *J* = 26.6 Hz), 30.4, 24.0.

$^{19}$F NMR (470 MHz, $CDCl_3$): δ = –138.6.

Anal. Calcd for $C_8H_{13}FOS$: C, 54.52; H, 7.43; S, 18.19. Found: C, 54.58; H, 7.71; S, 17.99.

**S-((1-Fluorocyclohexyl)methyl) Ethanethioate (3j)**

The reaction mixture was stirred at 50 °C.

Yield: 4.61 g (90%) from 5.25 g of **2j**; brown liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 3.17 (d, *J* = 20.4 Hz, 2 H), 2.36 (s, 3 H), 1.90–1.80 (m, 2 H), 1.64–1.52 (m, 5 H), 1.50–1.37 (m, 2 H), 1.28–1.18 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.6, 94.2 (d, *J* = 173.7 Hz), 37.8 (d, *J* = 24.5 Hz), 33.9 (d, *J* = 21.8 Hz), 30.1, 24.6, 21.4 (d, *J* = 2.8 Hz).

$^{19}$F NMR (470 MHz, $CDCl_3$): δ = –153.4.

Anal. Calcd for $C_9H_{15}FOS$: C, 56.81; H, 7.95; S, 16.85. Found: C, 57.13; H, 7.95; S, 16.78.

**S-((1-Fluorocycloheptyl)methyl) Ethanethioate (3k)**

The reaction mixture was stirred at 50 °C.

Yield: 6.55 g (71%) from 5.0 g of **1k**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 3.20 (d, *J* = 20.6 Hz, 2 H), 2.37 (s, 3 H), 2.00–1.91 (m, 2 H), 1.78–1.59 (m, 6 H), 1.55–1.48 (m, 2 H), 1.46–1.38 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.7, 98.4 (d, *J* = 172.7 Hz), 38.8 (d, *J* = 24.9 Hz), 37.6 (d, *J* = 23.5 Hz), 30.1, 29.1, 21.7 (d, *J* = 5.5 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –152.5.

Anal. Calcd for $C_{10}H_{17}FOS$: C, 58.79; H, 8.39; S, 15.69. Found: C, 58.65; H, 8.25; S, 15.83.

**Ethyl (1*r*,4*r*)-4-((Acetylthio)methyl)-4-fluorocyclohexanecarboxylate (3l)**

The reaction mixture was stirred at 50 °C.

Yield: 1.19 g (93%) from 1.30 g of **2l**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.11 (q, *J* = 7.1 Hz, 2 H), 3.15 (d, *J* = 19.6 Hz, 2 H), 2.36 (s, 3 H), 2.23 (tt, *J* = 12.0, 3.5 Hz, 1 H), 2.03–1.95 (m, 2 H), 1.86 (d, *J* = 13.6 Hz, 2 H), 1.75 (qd, *J* = 13.6, 3.5 Hz, 2 H), 1.46 (td, *J* = 13.6, 4.6 Hz, 1 H), 1.38 (td, *J* = 13.6, 4.6 Hz, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.7, 175.0, 93.3 (d, *J* = 174.9 Hz), 60.3, 42.0, 38.2 (d, *J* = 24.6 Hz), 33.1 (d, *J* = 22.3 Hz), 30.4, 23.9, 14.2.

$^{19}$F NMR (470 MHz, $CDCl_3$): δ = –157.5.

Anal. Calcd for $C_{12}H_{19}FO_3S$: C, 54.94; H, 7.30; S, 12.22. Found: C, 54.90; H, 6.95; S, 12.08.

**Ethyl (1*s*,4*s*)-4-((Acetylthio)methyl)-4-fluorocyclohexanecarboxylate (3m)**

The reaction mixture was stirred at 50 °C.

Yield: 2.05 g (97%) from 2.15 g of **2m**; brown oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.06 (qt, *J* = 7.2, 1.8 Hz, 2 H), 3.13 (d, *J* = 21.2 Hz, 2 H), 2.45 (t, *J* = 5.2 Hz, 1 H), 2.28 (s, 3 H), 1.79 (q, *J* = 5.2 Hz, 4 H), 1.72–1.60 (m, 4 H), 1.17 (tt, *J* = 7.2, 1.8 Hz, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 194.5, 174.4, 94.2 (d, *J* = 174.2 Hz), 60.3, 39.2, 37.1 (d, *J* = 24.2 Hz), 31.8 (d, *J* = 21.9 Hz), 30.4, 23.6 (d, *J* = 5.1 Hz), 14.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –151.3.

Anal. Calcd for $C_{12}H_{19}FO_3S$: C, 54.94; H, 7.30; S, 12.22. Found: C, 54.75; H, 7.03; S, 12.26.

***tert*-Butyl 3-((Acetylthio)methyl)-3-fluoroazetidine-1-carboxylate (3n)**

The reaction mixture was stirred at 40 °C.

Yield: 2.47 g (72%) from 3.50 g of **2n**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.03 (dd, *J* = 19.4, 10.5 Hz, 2 H), 3.88 (dd, *J* = 19.4, 10.5 Hz, 2 H), 3.40 (d, *J* = 19.4 Hz, 2 H), 2.39 (s, 3 H), 1.43 (s, 9 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 193.6, 155.6, 90.2 (d, *J* = 209.1 Hz), 79.8, 58.8 (2 C), 33.5 (d, *J* = 25.4 Hz), 30.1, 27.9.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –147.8.

Anal. Calcd for $C_{11}H_{18}FNO_3S$: C, 50.17; H, 6.89; N, 5.32; S, 12.17. Found: C, 49.88; H, 6.63; N, 4.95; S, 11.91.

***tert*-Butyl 4-((Acetylthio)methyl)-4-fluoropiperidine-1-carboxylate (3o)**

The reaction mixture was stirred at 45 °C.

Yield: 14.7 g (99%) from 15.0 g of **2o**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.03–3.75 (m, 2 H), 3.14 (d, *J* = 19.9 Hz, 2 H), 2.98 (t, *J* = 13.1 Hz, 2 H), 2.33 (s, 3 H), 1.81 (t, *J* = 10.9 Hz, 2 H), 1.62–1.48 (m, 2 H), 1.41 (s, 9 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.0, 154.1, 92.6 (d, *J* = 174.9 Hz), 79.3, 39.0 (2 C), 37.8 (d, *J* = 24.2 Hz), 33.3 (d, *J* = 21.4 Hz), 30.0, 28.0.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –159.9.

Anal. Calcd for $C_{13}H_{22}FNO_3S$: C, 53.59; H, 7.61; N, 4.81; S, 11.00. Found: C, 53.58; H, 7.78; N, 4.52; S, 11.33.

**S-((4-Fluorotetrahydro-2*H*-pyran-4-yl)methyl) Ethanethioate (3p)**

The reaction mixture was stirred at 50 °C.

Yield: 5.12 g (70%) from 7.50 g of **2p**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 3.84–3.76 (m, 2 H), 3.67 (td, *J* = 11.5, 2.6 Hz, 2 H), 3.19 (d, *J* = 20.2 Hz, 2 H), 2.37 (s, 3 H), 1.82–1.75 (m, 3 H), 1.70 (td, *J* = 13.0, 5.3 Hz, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.2, 91.7 (d, *J* = 175.0 Hz), 63.1, 37.5 (d, *J* = 24.2 Hz), 34.0 (d, *J* = 21.4 Hz), 30.1.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –158.0.

Anal. Calcd for $C_8H_{13}FO_2S$: C, 49.98; H, 6.82; S, 16.68. Found: C, 49.87; H, 7.21; S, 16.28.

### *S*-(*cis*-2-Fluorocyclobutyl) Ethanethioate (3q)

The reaction mixture was stirred at 70 °C.

The crude product was used in the subsequent step without further purification; yield: 15.5 g from 16.7 g of **2q**; brown liquid.

### *S*-(*cis*-2-Fluorocyclopentyl) Ethanethioate (3r)

The reaction mixture was stirred at 70 °C.

Yield: 7.96 g (82%) from 10.0 g of **2r**; brown liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.00 (dt, *J* = 54.1, 3.7 Hz, 1 H), 3.78–3.41 (m, 1 H), 2.34 (s, 3 H), 2.14–1.88 (m, 4 H), 1.73 (d, *J* = 10.8 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 195.2, 144.2, 95.5 (d, *J* = 176.5 Hz), 46.2 (d, *J* = 18.3 Hz), 31.5 (d, *J* = 21.8 Hz), 28.7, 21.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –180.5.

Anal. Calcd for $C_7H_{11}FOS$: C, 51.83; H, 6.84; S, 19.76. Found: C, 51.52; H, 6.59; S, 19.38.

### *S*-(*cis*-2-Fluorocyclohexyl) Ethanethioate (3s)

The reaction mixture was stirred at 75 °C.

Yield: 8.96 g (92%) from 10.0 g of **2s**; brown liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.74 (ddd, *J* = 48.7, 4.6, 2.3 Hz, 1 H), 3.66 (ddt, *J* = 29.6, 10.2, 2.3 Hz, 1 H), 2.33 (s, 3 H), 2.08–1.98 (m, 1 H), 1.81–1.69 (m, 3 H), 1.68–1.54 (m, 2 H), 1.53–1.39 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.8, 90.5 (d, *J* = 173.3 Hz), 45.1 (d, *J* = 18.9 Hz), 30.6 (d, *J* = 21.0 Hz), 30.2, 27.4, 24.9, 19.1.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –190.0.

Anal. Calcd for $C_8H_{13}FOS$: C, 54.52; H, 7.43; S, 18.19. Found: C, 54.90; H, 7.39; S, 18.32.

### *S*-(*cis*-2-Fluorocycloheptyl) Ethanethioate (3t)

The reaction mixture was stirred at 85 °C.

Yield: 20.3 g (97%) from 21.5 g of **2t**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.83 (ddd, *J* = 47.5, 6.6, 2.3 Hz, 1 H), 3.81 (ddt, *J* = 29.6, 10.2, 2.3 Hz, 1 H), 2.33 (s, 3 H), 2.00–1.84 (m, 3 H), 1.79–1.68 (m, 3 H), 1.64–1.56 (m, 3 H), 1.53–1.47 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.9, 94.1 (d, *J* = 173.9 Hz), 47.8 (d, *J* = 19.9 Hz), 32.4 (d, *J* = 21.6 Hz), 30.2, 28.3 (d, *J* = 4.7 Hz), 26.5, 25.8, 20.6 (d, *J* = 7.1 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –180.7.

Anal. Calcd for $C_9H_{15}FOS$: C, 56.81; H, 7.95; S, 16.85. Found: C, 56.86; H, 7.89; S, 16.99.

### *S*-(*cis*-2-Fluorocyclooctyl) Ethanethioate (3u)

The reaction mixture was stirred at 90 °C.

Yield: 4.14 g (53%) from 8.0 g of **2u**; brown oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 4.67 (dtt, *J* = 45.7, 8.1, 3.7 Hz, 1 H), 3.69 (tt, *J* = 8.1, 4.4 Hz, 1 H), 2.28 (s, 3 H), 2.19–2.11 (m, 1 H), 2.05–1.94 (m, 2 H), 1.91–1.75 (m, 4 H), 1.67–1.52 (m, 4 H), 1.47–1.40 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 194.9, 144.2, 93.3 (d, *J* = 165.2 Hz), 43.4, 31.0 (d, *J* = 22.3 Hz), 30.4, 30.2 (d, *J* = 4.8 Hz), 27.0 (d, *J* = 9.1 Hz), 24.5, 21.8 (d, *J* = 10.0 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –161.2.

Anal. Calcd for $C_{10}H_{17}FOS$: C, 58.79; H, 8.39; S, 15.69. Found: C, 58.77; H, 8.16; S, 15.54.

### *tert*-Butyl *cis*-3-(Acetylthio)-4-fluoropyrrolidine-1-carboxylate (3v)

The reaction mixture was stirred at 70 °C.

Yield: 1.04 g (64%) from 1.65 g of **2v**; brown oil; ca. 1:0.9 mixture of rotamers.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.08 (dd, *J* = 53.0, 4.0 Hz, 1 H), 4.00 (d, *J* = 33.0 Hz, 1 H), 3.92–3.66 (m, 2 H), 3.61 (d, *J* = 39.9 Hz, 1 H), 3.27 (q, *J* = 10.4 Hz, 1 H), 2.37 (s, 3 H), 1.45 (s, 9 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 193.9, 153.5 and 153.4, 92.3 (d, *J* = 180.4 Hz) and 91.8 (d, *J* = 181.1 Hz), 79.7, 51.9 (d, *J* = 23.0 Hz) and 51.4 (d, *J* = 23.0 Hz), 47.7 and 47.0, 43.6 (d, *J* = 18.5 Hz) and 43.1 (d, *J* = 18.5 Hz), 30.1, 28.0.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –184.4.

Anal. Calcd for $C_{11}H_{18}FNO_3S$: C, 50.17; H, 6.89; N, 5.32; S, 12.17. Found: C, 49.84; H, 7.04; N, 5.32; S, 12.18.

### *S*-(*cis*-4-Fluorotetrahydrofuran-3-yl) Ethanethioate (3w)

The reaction mixture was stirred at 65 °C.

Yield: 2.87 g (82%) from 3.60 g of **2w**; brown liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 5.15 (dt, *J* = 45.7, 8.1 Hz, 1 H), 4.17 (t, *J* = 8.1 Hz, 1 H), 4.10 (d, *J* = 3.1 Hz, 1 H), 4.07–4.02 (m, 1 H), 3.96 (s, 1 H), 3.64 (ddt, *J* = 10.6, 8.1, 3.1 Hz, 1 H), 2.36 (s, 3 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 194.4, 92.8 (d, *J* = 181.8 Hz), 73.3 (d, *J* = 23.6 Hz), 69.8, 44.7 (d, *J* = 17.4 Hz), 30.4.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –182.6.

Anal. Calcd for $C_6H_9FO_2S$: C, 43.89; H, 5.53; S, 19.53. Found: C, 44.06; H, 5.71; S, 19.17.

### β-Fluoro Sulfonyl Chlorides 4a–e and 4h–w; General Procedure

A solution of fluoro ethanethioate **3a–e**,**h–w** (50 mmol) in MeCN (45 mL) was added dropwise a cold (0 °C) stirred solution of NCS (20.0 g, 150 mmol) and concd HCl (7.5 mL, 75 mmol) in MeCN (150 mL), maintaining the temperature below 5 °C. After the addition was finished and no more exothermic reaction was observed, the solution was stirred at rt for an additional 1 h. The resulting mixture was diluted with water (200 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layer was washed with brine (2 × 100 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure, affording pure product **4a–e**,**h**,**i**,**k–m**,**o–s**,**w**, or crude product **4j**,**n**,**t–v** which was purified by column chromatography.

### 2-Fluoro-2-phenylethanesulfonyl Chloride (4a)

Yield: 4.12 g (78%) from 4.70 g of **3a**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.42 (m, 3 H), 7.42–7.30 (m, 2 H), 6.13 (ddd, *J* = 47.3, 9.3, 2.3 Hz, 1 H), 4.42–4.28 (m, 1 H), 3.99 (ddd, *J* = 28.9, 14.9, 2.3 Hz, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 135.4 (d, *J* = 20.1 Hz), 130.1 (d, *J* = 1.9 Hz), 129.3, 125.6 (d, *J* = 6.4 Hz), 88.1 (d, *J* = 182.1 Hz), 70.4 (d, *J* = 27.1 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –175.6.

MS (APCI): *m*/*z* = 203 $[M - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_8H_8ClFO_2S$: C, 43.15; H, 3.62; S, 14.40. Found: C, 43.49; H, 3.23; S, 14.57.

**2-Fluoro-3-methoxy-2-methylpropane-1-sulfonyl Chloride (4b)**

Yield: 7.73 g (83%) from 8.20 g of **3b**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.26–4.11 (m, 2 H), 3.61 (dd, *J* = 12.4, 10.5 Hz, 1 H), 3.50 (dd, *J* = 21.7, 10.5 Hz, 1 H), 3.41 (s, 3 H), 1.63 (d, *J* = 21.7 Hz, 3 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 93.1 (d, *J* = 180.5 Hz), 76.0 (d, *J* = 25.4 Hz), 69.8 (d, *J* = 26.6 Hz), 59.6, 21.9 (d, *J* = 22.7 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –149.8.

MS (APCI): *m*/*z* = 185 $[M - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_5H_{10}ClFO_3S$: C, 29.35; H, 4.93; S, 15.67. Found: C, 29.64; H, 4.88; S, 15.33.

**2-Fluoro-2-methyl-3-(methylsulfonyl)propane-1-sulfonyl Chloride (4c)**

Yield: 0.76 g (76%) from 0.90 g of **3c**; yellow crystals; mp 60–62 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.59–4.45 (m, 2 H), 3.77–3.55 (m, 2 H), 3.04 (s, 3 H), 1.87 (d, *J* = 22.8 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 90.96 (d, *J* = 182.2 Hz), 70.37 (d, *J* = 25.6 Hz), 60.31 (d, *J* = 24.0 Hz), 43.97 (d, *J* = 5.3 Hz), 25.72 (d, *J* = 23.2 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –139.5.

MS (EI): *m*/*z* = 133 $[M - SO_2Cl - HF]^+$.

Anal. Calcd for $C_5H_{10}ClFO_4S_2$: C, 23.77; H, 3.99; S, 25.37. Found: C, 23.77; H, 3.87; S, 25.24.

**3-(1,3-Dioxoisoindolin-2-yl)-2-fluoro-2-methylpropane-1-sulfonyl Chloride (4d)**

Yield: 3.19 g (92%) from 3.20 g of **3d**; white crystals; mp 161–163 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 5.5, 3.1 Hz, 2 H), 7.77 (dd, *J* = 5.5, 3.1 Hz, 2 H), 4.28–4.13 (m, 2 H), 4.11–3.95 (m, 2 H), 1.76 (d, *J* = 21.6 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 168.0, 134.6, 131.6, 123.9, 92.9 (d, *J* = 185.5 Hz), 71.4 (d, *J* = 25.1 Hz), 45.3 (d, *J* = 26.9 Hz), 22.4 (d, *J* = 23.2 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –147.5.

MS (APCI): *m*/*z* = 280 $[M - HF - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_{12}H_{11}ClFNO_4S$: C, 45.08; H, 3.47; N, 4.38; S, 10.03. Found: C, 44.96; H, 3.42; N, 4.77; S, 10.34.

***syn*-1-Fluoro-1-phenylpropane-2-sulfonyl Chloride (4e)**

Yield: 552 mg (91%) from 540 mg of **3e**; yellow crystals; mp 42–43 °C.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.41 (m, 3 H), 7.41–7.32 (m, 2 H), 5.79 (dd, *J* = 46.2, 7.3 Hz, 1 H), 4.19 (dquint, *J* = 9.6, 7.3 Hz, 1 H), 1.36 (d, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 134.6 (d, *J* = 20.4 Hz), 130.2 (d, *J* = 2.5 Hz), 129.1, 126.9 (d, *J* = 5.8 Hz), 92.2 (d, *J* = 183.2 Hz), 75.0 (d, *J* = 24.6 Hz), 13.1 (d, *J* = 2.5 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –167.9.

MS (APCI): *m*/*z* = 217 $[M - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_9H_{10}ClFO_2S$: C, 45.67; H, 4.26; S, 13.55. Found: C, 45.49; H, 4.37; S, 13.62.

**(1-Fluorocyclobutyl)methanesulfonyl Chloride (4h)**

Yield: 4.45 g (90%) from 4.30 g of **3h**; colorless oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.16 (d, *J* = 19.7 Hz, 2 H), 2.60–2.40 (m, 4 H), 2.07–1.92 (m, 1 H), 1.75–1.62 (m, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 93.3 (d, *J* = 218.6 Hz), 70.7 (d, *J* = 24.5 Hz), 33.4 (d, *J* = 21.5 Hz), 12.0 (d, *J* = 10.5 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –134.6.

MS (EI): *m*/*z* = 131 $[M - HF - Cl]^+$, 67 $[M - SO_2Cl - HF]^+$.

Anal. Calcd for $C_5H_8ClFO_2S$: C, 32.18; H, 4.32; S, 17.18. Found: C, 32.12; H, 4.15; S, 17.36.

**(1-Fluorocyclopentyl)methanesulfonyl Chloride (4i)**

Yield: 11.0 g (79%) from 12.2 g of **3i**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.18 (d, *J* = 17.9 Hz, 2 H), 2.30–2.17 (m, 2 H), 1.93–1.72 (m, 6 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 101.6 (d, *J* = 183.3 Hz), 72.3 (d, *J* = 26.2 Hz), 37.7 (d, *J* = 23.0 Hz), 23.3.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –142.8.

MS (APCI): *m*/*z* = 181 $[M - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_6H_{10}ClFO_2S$: C, 35.92; H, 5.02; S, 15.98. Found: C, 35.99; H, 4.82; S, 15.67.

**(1-Fluorocyclohexyl)methanesulfonyl Chloride (4j)**

The product was purified by column chromatography (gradient hexane to EtOAc); yield: 4.82 g (95%) from 4.50 g of **3j**; yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.03 (d, *J* = 16.6 Hz, 2 H), 2.16–2.02 (m, 2 H), 1.72–1.45 (m, 7 H), 1.34–1.19 (m, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 93.2 (d, *J* = 181.9 Hz), 73.9 (d, *J* = 25.9 Hz), 34.9 (d, *J* = 22.0 Hz), 24.4, 21.5 (d, *J* = 2.9 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –153.7.

MS (APCI): *m*/*z* = 195 $[M - H]^-$, 175 $[M - HF - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_7H_{12}ClFO_2S$: C, 39.16; H, 5.63; S, 14.93. Found: C, 39.23; H, 5.59; S, 14.72.

**(1-Fluorocycloheptyl)methanesulfonyl Chloride (4k)**

Yield: 3.40 g (80%) from 3.80 g of **3k**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.07 (d, *J* = 15.9 Hz, 2 H), 2.25–2.12 (m, 2 H), 2.00 (ddd, *J* = 25.4, 15.9, 10.0 Hz, 2 H), 1.81–1.62 (m, 4 H), 1.60–1.41 (m, 4 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 97.3 (d, *J* = 180.5 Hz), 74.6 (d, *J* = 26.6 Hz), 38.4 (d, *J* = 23.2 Hz), 29.1, 21.7 (d, *J* = 5.3 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –138.5.

MS (APCI): *m*/*z* = 209 $[M - H]^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_8H_{14}ClFO_2S$: C, 42.01; H, 6.17; S, 14.02. Found: C, 42.02; H, 5.81; S, 13.64.

**Ethyl (1*r*,4*r*)-4-((Chlorosulfonyl)methyl)-4-fluorocyclohexanecarboxylate (4l)**

Yield: 1.05 g (77%) from 1.25 g of **3l**; yellow crystals; mp 54–55 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.12 (q, *J* = 7.1 Hz, 2 H), 4.03 (d, *J* = 15.9 Hz, 2 H), 2.33–2.20 (m, 3 H), 1.99–1.90 (m, 2 H), 1.84 (qd, *J* = 12.5, 3.0 Hz, 2 H), 1.71 (td, *J* = 13.6, 4.5 Hz, 1 H), 1.61 (td, *J* = 13.6, 4.5 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 174.4, 91.9 (d, *J* = 182.4 Hz), 73.8 (d, *J* = 26.2 Hz), 60.6, 41.3, 33.8 (d, *J* = 22.3 Hz), 23.5, 14.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –156.7.

MS (APCI): *m*/*z* = 167 [M – $SO_2Cl$ – HF]$^+$.

Anal. Calcd for $C_{10}H_{16}ClFO_4S$: C, 41.89; H, 5.62; S, 11.18. Found: C, 42.20; H, 5.29; S, 11.36.

**Ethyl (1*s*,4*s*)-4-((Chlorosulfonyl)methyl)-4-fluorocyclohexanecarboxylate (4m)**

Yield: 1.07 g (89%) from 1.10 g of **3m**; yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.1 Hz, 2 H), 4.05 (d, *J* = 17.8 Hz, 2 H), 2.60 (t, *J* = 4.8 Hz, 1 H), 2.05–1.86 (m, 8 H), 1.25 (t, *J* = 7.1 Hz, 3 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 174.2, 92.9 (d, *J* = 182.3 Hz), 72.9 (d, *J* = 25.1 Hz), 60.6, 38.4, 32.1 (d, *J* = 21.8 Hz), 23.2 (d, *J* = 4.2 Hz), 14.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –153.7.

MS (APCI): *m*/*z* = 267 [M – H]$^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_{10}H_{16}ClFO_4S$: C, 41.89; H, 5.62; S, 11.18. Found: C, 42.13; H, 5.51; S, 11.34.

***tert*-Butyl 3-((Chlorosulfonyl)methyl)-3-fluoroazetidine-1-carboxylate (4n)**

The product was purified by column chromatography (hexane–*t*-BuOMe, 1:1; $R_f$ = 0.3); yield: 0.33 g (13%) from 2.30 g of **3n**; yellow oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.28 (d, *J* = 19.2 Hz, 2 H), 4.29–4.15 (m, 4 H), 1.43 (s, 9 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 155.7, 87.6 (d, *J* = 215.4 Hz), 81.0, 68.9 (d, *J* = 24.5 Hz), 59.6, 59.4, 28.3.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –151.9.

MS (APCI): *m*/*z* = 170 [M – $C_4H_8$ – $CO_2$ + H]$^+$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_9H_{15}ClFNO_4S$: C, 37.57; H, 5.25; N, 4.87; S, 11.14. Found: C, 37.60; H, 5.38; N, 4.48; S, 10.76.

***tert*-Butyl 4-((Chlorosulfonyl)methyl)-4-fluoropiperidine-1-carboxylate (4o)**

Yield: 5.92 g (39%) from 14.0 g of **3o**; yellow crystals; mp 99–100 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.04 (d, *J* = 17.0 Hz, 2 H), 4.09–3.96 (m, 2 H), 3.09 (td, *J* = 12.2, 11.6 Hz, 2 H), 2.12 (t, *J* = 11.6 Hz, 2 H), 1.88–1.71 (m, 2 H), 1.44 (d, *J* = 2.0 Hz, 9 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 154.4, 91.4 (d, *J* = 182.5 Hz), 80.2, 73.1 (d, *J* = 24.9 Hz), 38.9 (2 C), 34.2 (d, *J* = 21.4 Hz), 28.3.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –160.3.

MS (APCI): *m*/*z* = 296 [M – H]$^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_{11}H_{19}ClFNO_4S$: C, 41.84; H, 6.06; N, 4.44; S, 10.15. Found: C, 41.66; H, 5.72; N, 4.04; S, 10.18.

**(4-Fluorotetrahydro-2*H*-pyran-4-yl)methanesulfonyl Chloride (4p)**

Yield: 3.95 g (73%) from 4.80 g of **3p**; yellow crystals; mp 72–73 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.05 (d, *J* = 17.9 Hz, 2 H), 3.86 (dd, *J* = 11.5, 5.0 Hz, 2 H), 3.75 (t, *J* = 11.5 Hz, 2 H), 2.12–1.98 (m, 3 H), 1.93 (ddt, *J* = 17.9, 13.8, 5.0 Hz, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 90.6 (d, *J* = 182.8 Hz), 73.5 (d, *J* = 24.9 Hz), 62.9, 34.9 (d, *J* = 21.4 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –158.8.

MS (APCI): *m*/*z* = 197 [M – H]$^-$, 177 [M – HF – H]$^-$ (for the corresponding sulfonic acid).

Anal. Calcd for $C_6H_{10}ClFO_3S$: C, 33.26; H, 4.65; S, 14.80. Found: C, 33.53; H, 4.62; S, 14.91.

***cis*-2-Fluorocyclobutane-1-sulfonyl Chloride (4q)**

Yield: 17.3 g (92%) from 16.7 g of **2q**; yellowish oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.35 (dq, *J* = 52.2, 7.1 Hz, 1 H), 4.70–4.47 (m, 1 H), 2.93–2.76 (m, 1 H), 2.75–2.62 (m, 1 H), 2.62–2.44 (m, 1 H), 2.40–2.21 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 84.6 (d, *J* = 227.7 Hz), 72.9 (d, *J* = 19.0 Hz), 28.9 (d, *J* = 22.1 Hz), 18.3 (d, *J* = 9.0 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –175.8.

MS (APCI): *m*/*z* = 117 [M – HCl – F]$^+$.

Anal. Calcd for $C_4H_6ClFO_2S$: C, 27.84; H, 3.50; S, 18.57. Found: C, 27.77; H, 3.81; S, 18.20.

***cis*-2-Fluorocyclopentane-1-sulfonyl Chloride (4r)**

Yield: 42.4 g (97%) from 38.0 g of **3r**; yellowish oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.47 (dt, *J* = 52.5, 3.8 Hz, 1 H), 4.08 (dtd, *J* = 27.2, 9.4, 3.8 Hz, 1 H), 2.64–2.48 (m, 1 H), 2.44–2.31 (m, 1 H), 2.29–2.12 (m, 2 H), 2.04–1.81 (m, 2 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 93.3 (d, *J* = 185.4 Hz), 78.1 (d, *J* = 17.7 Hz), 32.4 (d, *J* = 21.4 Hz), 25.7, 21.4.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –186.7.

MS (EI): *m*/*z* = 87 [M – $SO_2Cl$]$^+$, 67 [M – $SO_2Cl$ – HF]$^+$.

Anal. Calcd for $C_5H_8ClFO_2S$: C, 32.18; H, 4.32; S, 17.18. Found: C, 32.53; H, 4.08; S, 17.58.

***cis*-2-Fluorocyclohexane-1-sulfonyl Chloride (4s)**

Yield: 6.38 g (63%) from 8.90 g of **3s**; yellow crystals; mp 44–48 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.44 (dd, *J* = 49.5, 3.9 Hz, 1 H), 3.63 (ddd, *J* = 29.6, 12.7, 4.2 Hz, 1 H), 2.39–2.30 (m, 1 H), 2.30–2.15 (m, 2 H), 2.08–1.98 (m, 1 H), 1.73–1.58 (m, 2 H), 1.58–1.34 (m, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 85.5 (d, *J* = 180.4 Hz), 77.3 (d, *J* = 10.2 Hz), 30.9 (d, *J* = 21.0 Hz), 24.4, 22.4, 18.6.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –134.6.

MS (EI): *m*/*z* = 101 [M – $SO_2Cl$]$^+$, 81 [M – $SO_2Cl$ – HF]$^+$.

Anal. Calcd for $C_6H_{10}ClFO_2S$: C, 35.92; H, 5.02; S, 15.98. Found: C, 35.74; H, 5.40; S, 16.23.

***cis*-2-Fluorocycloheptane-1-sulfonyl Chloride (4t)**

The product was purified by column chromatography (hexane–*t*-BuOMe, 1:1; $R_f$ = 0.5); yield: 18.7 g (83%) from 20.0 g of **3t**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.61 (dd, *J* = 48.7, 3.4 Hz, 1 H), 3.60 (ddd, *J* = 26.2, 10.7, 3.4 Hz, 1 H), 2.47–2.38 (m, 1 H), 2.38–2.17 (m, 2 H), 2.03–1.89 (m, 1 H), 1.86–1.70 (m, 3 H), 1.69–1.61 (m, 1 H), 1.60–1.49 (m, 2 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 88.0 (d, *J* = 182.3 Hz), 78.8 (d, *J* = 21.8 Hz), 33.1 (d, *J* = 21.5 Hz), 26.1, 25.5, 22.5 (d, *J* = 4.7 Hz), 21.5 (d, *J* = 3.0 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –188.7.

MS (EI): *m*/*z* = 95 [M – $SO_2Cl$ – HF]$^+$.

Anal. Calcd for $C_7H_{12}ClFO_2S$: C, 39.16; H, 5.63; S, 14.93. Found: C, 39.28; H, 5.38; S, 14.70.

### *cis*-2-Fluorocyclooctane-1-sulfonyl Chloride (4u)

The product was purified by column chromatography (gradient hexane to *t*-BuOMe); yield: 2.50 g (56%) from 4.0 g of **3u**; yellow liquid.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.76 (ddt, *J* = 45.1, 8.4, 4.1 Hz, 1 H), 3.69 (dd, *J* = 8.4, 4.1 Hz, 1 H), 2.62–2.43 (m, 2 H), 2.25–2.10 (m, 1 H), 2.09–1.95 (m, 3 H), 1.92–1.72 (m, 4 H), 1.68–1.58 (m, 1 H), 1.55–1.46 (m, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 91.6 (d, *J* = 168.0 Hz), 75.5, 31.5 (d, *J* = 22.8 Hz), 29.1 (d, *J* = 23.2 Hz), 25.8, 25.4, 22.3 (d, *J* = 7.6 Hz), 20.7 (d, *J* = 9.7 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –167.3.

MS (EI): *m*/*z* = 109 [M – $SO_2Cl$ – HF]$^+$.

Anal. Calcd for $C_8H_{14}ClFO_2S$: C, 42.01; H, 6.17; S, 14.02. Found: C, 42.33; H, 6.49; S, 13.63.

### *tert*-Butyl *cis*-3-(Chlorosulfonyl)-4-fluoropyrrolidine-1-carboxylate (4v)

The product was purified by column chromatography (hexane–*t*-BuOMe, 1:1; $R_f$ = 0.3); yield: 0.33 g (30%) from 1.0 g of **3v**; yellow liquid; ca. 1:0.8 mixture of rotamers.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.55 (dt, *J* = 52.3, 3.5 Hz, 1 H), 4.42–4.27 (m, 1 H), 4.22–4.03 (m, 2 H), 3.99–3.82 (m, 1 H), 3.69–3.54 (m, 1 H), 1.48 (s, 9 H).

$^{13}$C NMR (151 MHz, $CDCl_3$): δ = 153.5, 90.1 (d, *J* = 189.4 Hz) and 89.3 (d, *J* = 189.9 Hz), 81.3 and 81.2, 74.2 (d, *J* = 18.4 Hz) and 73.7 (d, *J* = 16.7 Hz), 52.2 (d, *J* = 23.2 Hz) and 51.9 (d, *J* = 22.4 Hz), 44.7, 28.3.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –189.5 and –189.9.

MS (EI): *m*/*z* = 195 [M – $C_4H_8$ – HCl]$^+$.

Anal. Calcd for $C_9H_{15}ClFNO_4S$: C, 37.57; H, 5.25; N, 4.87; S, 11.14. Found: C, 37.76; H, 5.36; N, 4.61; S, 10.76.

### *cis*-4-Fluorotetrahydrofuran-3-sulfonyl Chloride (4w)

Yield: 1.45 g (45%) from 2.80 g of **3w**; yellowish oil.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.60 (ddd, *J* = 53.6, 4.9, 3.5 Hz, 1 H), 4.59–4.54 (m, 1 H), 4.53–4.43 (m, 1 H), 4.43–4.35 (m, 1 H), 4.29 (dd, *J* = 24.9, 11.5 Hz, 1 H), 4.05 (ddd, *J* = 33.5, 11.5, 3.5 Hz, 1 H).

$^{13}$C NMR (101 MHz, $CDCl_3$): δ = 90.6 (d, *J* = 191.8 Hz), 75.4 (d, *J* = 16.7 Hz), 73.7 (d, *J* = 23.5 Hz), 67.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –189.9.

MS (APCI): *m*/*z* = 89 [M – $SO_2Cl$]$^+$.

Anal. Calcd for $C_4H_6ClFO_3S$: C, 25.47; H, 3.21; S, 17.00. Found: C, 25.68; H, 3.38; S, 17.03.

### 1-Cyclobutylidenemethanesulfonamide (8a)

β-Fluoro sulfonyl chloride **4h** (200 mg, 1.07 mmol) was added to ice-cold 25% aq ammonia (10 mL), and the reaction mixture was stirred at 0 °C for 1 h. Then, it was extracted with $CH_2Cl_2$ (6 × 10 mL), and the combined organic layer was dried ($Na_2SO_4$) and evaporated to dryness under reduced pressure. The residue was dispersed in hexane (10 mL), stirred at reflux for 5 min, and filtered. This operation was repeated twice more, affording **8a** as a colorless solid; yield: 81 mg (52%); mp 94–96 °C.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.12 (s, 1 H), 4.67 (s, 2 H), 3.13 (t, *J* = 8.2 Hz, 2 H), 2.86 (t, *J* = 8.2 Hz, 2 H), 2.10 (quint, *J* = 8.2 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 161.5, 121.1, 32.2, 31.8, 17.5.

MS (EI): *m*/*z* = 147 [M]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{10}NO_2S$: 148.0432; found: 148.0427.

Anal. Calcd for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52; S, 21.78. Found: C, 40.68; H, 6.31; N, 9.71; S, 21.42.

### 1-(1-Fluorocyclobutyl)-*N*-phenylmethanesulfonamide (7b) and 1-Cyclobutylidene-*N*-phenylmethanesulfonamide (8b)

Sulfonyl chloride **4h** (200 mg, 1.07 mmol) was dissolved in AcOH (2 mL), then $PhNH_2$ (120 mg, 1.29 mmol) and AcONa (132 mg, 1.61 mmol) were added, and the resulting mixture was stirred at rt overnight. Then, it was diluted with water (5 mL) and extracted with $CHCl_3$ (3 × 2 mL). The combined organic layer was washed with water (3 × 1 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure, affording the crude product, which was subjected to HPLC purification [Chromatorex 18 SMB100-5T 100 × 19 mm, 5 μm column; linear gradient water–MeCN, 70:30 (0 min) to 45:55 (5 min); 30 mL/min flow] followed by recrystallization (hexane) to give a 1.7:1 mixture of **7b** and **8b** as a colorless solid; yield: 184 mg (73%); mp 61–62 °C. Further separation of the obtained mixture was not successful.

#### Spectroscopic Data for 7b

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.12 (m, 5 H), 6.58 (s, 1 H), 3.42 (d, *J* = 20.3 Hz, 2 H), 2.56–2.35 (m, 4 H), 1.97–1.88 (m, 1 H), 1.64–1.55 (m, 1 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 129.5, 125.8, 121.9, 94.5 (d, *J* = 212.3 Hz), 54.7 (d, *J* = 22.3 Hz), 33.7 (d, *J* = 22.5 Hz), 11.9 (d, *J* = 11.7 Hz).

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –137.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}FNO_2S$: 244.0808; found: 244.0806.

#### Spectroscopic Data for 8b

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.12 (m, 5 H), 6.73 (s, 1 H), 5.99 (q, *J* = 2.3 Hz, 1 H), 3.07–2.92 (m, 2 H), 2.86–2.74 (m, 2 H), 2.00 (quint, *J* = 8.1 Hz, 2 H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 136.5, 129.3, 125.1, 121.1, 118.1, 32.6, 32.0, 29.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{14}NO_2S$: 224.0745; found: 224.0742.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706101.

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