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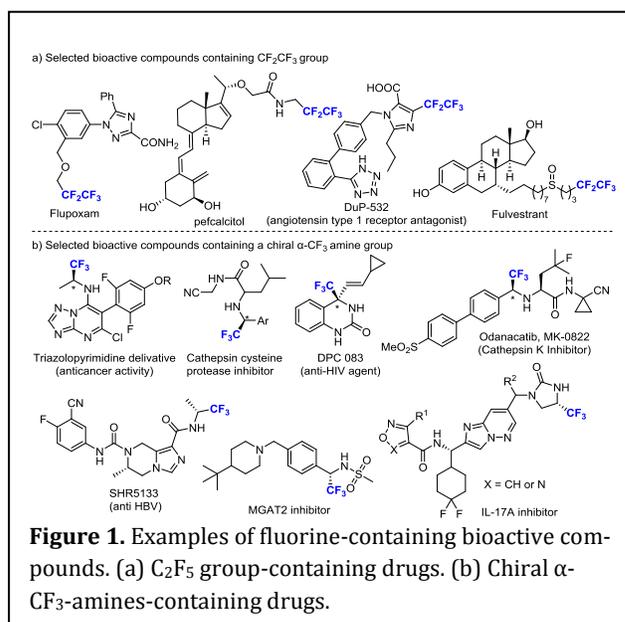
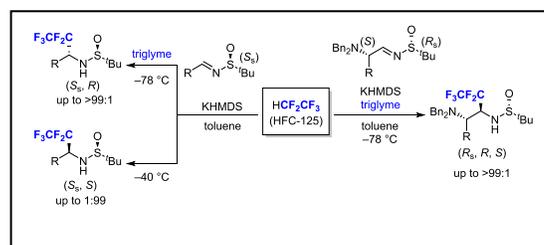
KHMDS/Triglyme Cryptate as an Alternative to Phosphazene Base in Stereodivergent Pentafluoroethylation of *N*-Sulfinylimines Using HFC-125

Yuji Sumii, Hiroto Iwasaki, Yamato Fujihira, Elsayed M. Mahmoud, Hiroaki Adachi, Takumi Kagawa, Dominique Cahard and Norio Shibata*

AUTHOR ADDRESS

Supporting Information Placeholder

ABSTRACT: A protocol for the stereodivergent pentafluoroethylation of *N*-sulfinylimines using HFC-125 with KHMDS/triglyme is demonstrated. Both diastereomers of the pentafluoroethylated amines can be selectively synthesized based on the presence or absence of triglyme. This KHMDS/triglyme protocol is a practical alternative to the more expensive P_4 -*t*Bu/KHMDS protocol used in the previously reported



stereodivergent fluoroalkylations.

Fluorofunctionalization influences the physicochemical and biological properties of organic compounds and has become a prevalent strategy in drug discovery and materials science.¹ Monofluoro and CF_3 motifs are constitutive of more than 80% of the fluorine-containing bioactive compounds in marketed pharmaceuticals and agrochemi-

cal.¹ Recently, the pentafluoroethyl (C_2F_5) group has also received considerable attention as an attractive alternative to CF_3 in drug design.^{1,2} Indeed, C_2F_5 is larger than CF_3 and has a higher electron-withdrawing effect. It also exhibits high metabolic stability, lower susceptibility to cytochrome oxidation, and significant lipophilicity; thus, its

incorporation in drug candidates can significantly alter the bioactivity. Figure 1a shows some representative examples of C₂F₅-bearing drugs (Figure 1a).³

The asymmetric synthesis of α -fluoroalkylated amines and diamines is of considerable interest due to their ubiquity in the design of medicinal agents as well as their potential applications in the synthesis of fluorinated peptidomimetics (Figure 1b).⁴ Despite the significant advances in the asymmetric synthesis of α -CF₃-amines,^{5,6} stereoselective synthetic methods for α -C₂F₅-amines remain underexplored.⁷ Direct stereoselective pentafluoroethylation of imines is an ideal strategy to access chiral α -C₂F₅-amines and diamines from non-fluorinated precursors, but there are few examples of this approach. Prakash *et al.* developed a pentafluoroethylating reagent, namely pentafluoroethyl phenyl sulfone (C₂F₅SO₂Ph), and demonstrated an example of the stereoselective pentafluoroethylation of Ellman's *N*-(*tert*-butanesulfinyl)imine (Scheme 1a).^{7a} Fustero *et al.* reported a highly stereoselective pentafluoroethylation of imines using pentafluoroethyl trimethylsilane (C₂F₅SiMe₃) and demonstrated a tandem reaction with the pentafluoroethylation of imines followed by an intramolecular aza-Michael reaction (Scheme 1b).^{7b,c} The asymmetric synthesis of fluoroalkyl-substituted diamines is even more rare.^{6a,e} In 2020, Hu *et al.* developed a synthesis of enantioenriched fluoroalkyl-substituted *syn*-diamines using fluoroalkylated diazoalkanes; the polyfluoro ylide species were generated under Fe(III) catalysis and the asymmetric induction was achieved by means of a chiral phosphoric acid (PPA).^{7d} In this study, one example of

asymmetric synthesis of a pentafluoroethylated diamine was demonstrated. We can see from this literature survey that the asymmetric synthesis of α -C₂F₅-amines and diamines is only fragmentarily reported essentially as an extension of studies toward α -CF₃-amines.^{6a,e,7} Therefore, efficient and general methods are strongly required for the stereoselective synthesis of α -C₂F₅-amines and diamines.

During the last decades, the greenhouse gas HFC-125, also known as pentafluoroethane (HC₂F₅), has emerged as a source of C₂F₅ for organic synthesis.⁸ HFC-125 is widely used as a refrigerant and fire suppression agent and does not contribute to ozone layer depletion.⁹ However, due to the negative influence of HFC-125 on climate change and global warming, the use of HFC-125 is being phased out.^{10a} Thus, alternative uses of HFC-125 such as its chemical transformation to high-value chiral fluoro-organics are essential.^{10b,11} Even though several pentafluoroethylations using HFC-125 have been reported, stereoselective pentafluoroethylation of amines using HFC-125 has not been reported to date. Recently, we reported the stereodivergent trifluoromethylation of imines using the greenhouse gas, HFC-23 (fluoroform, HCF₃).^{11d} We observed that depending on the base used, either potassium hexamethyldisilazide (KHMDS) or phosphazene super base, P₄-*t*Bu, opposite diastereomeric pentafluoroethylated amines were selectively obtained via a chelated or non-chelated transition state, respectively. This method was then extended to the diastereoselective synthesis of enantioenriched trifluoromethylated ethylenediamines.^{6e} Although excellent stereodivergent diastereoselectivities can be achieved by this protocol, P₄-*t*Bu is expensive, hindering the extension of this methodology. In the continuation of our efforts in using HFCs for organic chemical transformations,^{6e,8f,g,11} we now disclose a new protocol for the stereodivergent penta-

Scheme 1. Synthesis of α -C₂F₅-Amines and Diamines.

a) Prakash (2010)

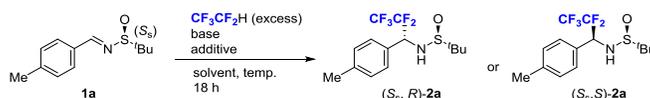


Table 1. Optimization of the Nucleophilic Addition of HFC-125 to *N*-Sulfinylimines 1a

entry	base (equiv)	additive (equiv)	solvent	temp. (°C)	yield (%) ^a	(S _s , R): (S _s , S) ^a
1	KHMDS (2.0)	–	toluene	–78	55	12:88
2	KHMDS (2.0)	–	THF	–78	39	50:50
3	KHMDS (4.0)	–	toluene	–78	88	11:89
4	<i>t</i> BuOK (2.0)	–	toluene	–78	0	–
5	KHMDS (2.0)	–	toluene	–40	97(91) ^b	7:93
6 ^c	KHMDS (2.0)	–	toluene	–40	74	25:75
7	KHMDS (2.0)	triglyme (4.0)	toluene	–78	69	>99:1
8	KHMDS (2.0)	triglyme (8.0)	toluene	–78	>99(98) ^b	>99:1
9	KHMDS (2.0)	triglyme (8.0)	THF	–78	>99	>99:1
10	<i>t</i> BuOK (2.0)	triglyme (8.0)	toluene	–78	13	>99:1
11	KHMDS (2.0)	triglyme (8.0)	toluene	–40	85	>99:1
12 ^c	KHMDS (2.0)	triglyme (8.0)	toluene	–78	40	67:33
13 ^d	KHMDS (2.0)	triglyme (8.0)	toluene	–78	92	97:3

fluoroethylation of *N*-sulfinylimines using HFC-125 that affords highly enantioenriched pentafluoroethylated amines. Classic batch conditions but also micro-flow pentafluoroethylation were investigated.

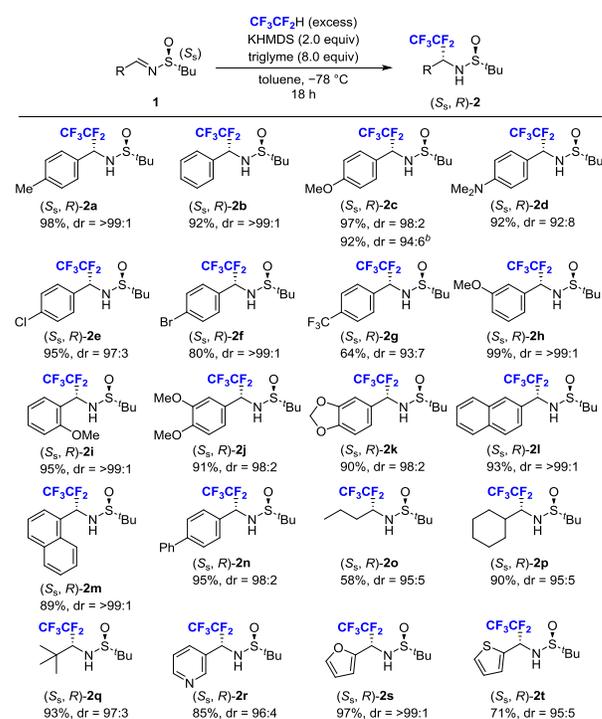
Based on our previous studies,^{11d} we first tested the pentafluoroethylation reaction of *N*-sulfinylimine (**1a**) by an excess amount of gaseous HFC-125 (about 20 equiv) using 2.0 equiv of KHMDS as the base in toluene at $-78\text{ }^{\circ}\text{C}$ for 18 h. The desired product (*S,S*)-**2a** was obtained in 55% yield and 12:88 diastereomeric ratio (dr, Table 1, entry 1). When THF, a polar solvent, was used in the pentafluoroethylation reaction, a decreased yield of 39% was obtained and the diastereoselectivity was extremely low (entry 2). When more equivalents of KHMDS were used, the product was obtained in 88% yield, and the diastereoselectivity was 11:89 (entry 3). ^tBuOK was not effective in this transformation (entry 4). Performing the reaction at $-40\text{ }^{\circ}\text{C}$ with KHMDS in toluene greatly improved the reaction yield to 97% and the selectivity toward the (*S,S*) diastereomer in a 7:93 dr ratio (entry 5). When HFC-125 loading was reduced to 1.1 equiv, an unfavorable result was obtained; both the yield and diastereoselectivity decreased (entry 6).

In recent years, we have reported that the encapsulation of potassium cation (K^+) by glymes efficiently promotes perfluoroalkylations using HFC-23 and HFC-125 by increasing the nucleophilicity and stability of the $^-\text{CF}_3$ and $^-\text{C}_2\text{F}_5$ anions.^{8f,11g} We envisaged that the use of K-bases and glymes would be an efficient and inexpensive alternative protocol to the $\text{P}_4\text{-}^t\text{Bu}$ method. To our great satisfaction, the addition of 4.0 equiv of triglyme along with 2.0 equiv of KHMDS afforded a highly diastereoselective reaction $>99:1$ in favor of the (*S,R*) diastereomer of **2a** (opposite to the one previously obtained as major diastereomer) in 69% yield (entry 7) and 98% isolated yield when 8.0 equiv of triglyme were employed with retention of the $>99:1$ dr ratio (entry 8). Under these new conditions, both THF and toluene performed equally well (entries 8 and 9); however, ^tBuOK gave a poor yield albeit in a $>99:1$ dr ratio (entry 10). Increasing the temperature from $-78\text{ }^{\circ}\text{C}$ to $-40\text{ }^{\circ}\text{C}$ resulted in 85% yield with $>99:1$ dr (entry 11). Although the reaction under the best conditions (entry 8) using 1.1 equiv of HFC-125 afforded low yield with low selectivity (entry 12), the yield and selectivity were almost restored (92% yield, 97:3) by using 5.0 equiv of HFC-125. It is worthy of note that the yield and diastereoselectivity outperform (entry 8) that obtained with $\text{P}_4\text{-}^t\text{Bu}$ ^{11d} when using HFC-125 (entry 14). Our new conditions clearly offer an opportunity to improve previous results using $\text{P}_4\text{-}^t\text{Bu}$.

Using the optimized conditions of KHMDS/triglyme (Table 1, entry 8), we explored the substrate scope of (*S,S*)-*N*-sulfinylimines **1** to generate (*S,R*) diastereomers of **2** (Table 2). A wide range of substrates with different electronic properties tolerated the reaction conditions well to

furnish the desired (*S,R*) products in good to high yields and with high to excellent diastereoselectivities. Non-substituted benzylimine and benzylimines bearing electron-donating groups afforded the corresponding trifluoro-

Table 2. Substrate Scope of *N*-Sulfinylimines **1 for Pentafluoroethylation Using HFC-125 and Triglyme^a**



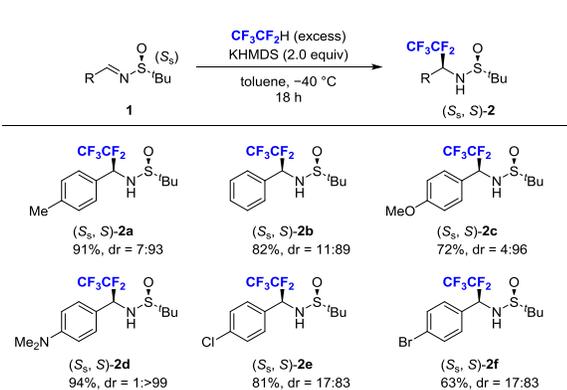
^aReaction conditions: **1** (0.2 mmol), HFC-125 (excess),

roethylation products **2b**, **2c**, and **2d** in excellent yields (92–97%) with high to excellent diastereoselectivities ($>99:1$, 98:2, and 92:8 dr, respectively). Halogen (Cl and Br)- and electron-withdrawing group (CF_3)-substituted (*S*)-*N*-sulfinylimines **1e–g** furnished the corresponding sulfinamides **2e–g** in good yields (64–95%) and high diastereoselectivities (97:3, $>99:1$, and 93:7 dr, respectively). Pentafluoroethylated derivatives **2h**, **2i**, and **2j** bearing *m*-, *o*-, and disubstituted methoxy groups were obtained in excellent yields (91–99%) and high to excellent diastereoselectivities ($>99:1$, $>99:1$, and 98:2, respectively). Sulfinylimines bearing a dioxole ring, a naphthyl moiety, and a 4-phenyl substituent tolerated the reaction well and furnished the corresponding C_2F_5 -sulfinamides in high yields (**2k**: 98:2, **2l**: $>99:1$, **2m**: $>99:1$, and **2n**: 98:2 dr). Moreover, substrates with aliphatic side chains such as *n*-propyl, cyclohexyl, and *tert*-butyl afforded the desired products in 58, 90, and 93% yields, respectively, together with diastereomeric ratios in the range 95:5–97:3. Furthermore, heterocycle-based sulfinylimines **1r–t** exhibited good reactivity

and the expected products were obtained in high yields (**2r**: 85%, **2s**: 97%, and **2t**: 71%) and high to excellent diastereoselectivities (**2r**: 96:4, **2s**: >99:1, and **2t**: 95:5 dr). A gram-scale reaction was also carried out using **1c** to furnish **2c** in 92% yield with 94:6 dr.

Next, we investigated the generality of the pentafluoroethylation reaction of (*S*)-*N*-sulfinylimines **1** for the synthesis of (*S_s*, *S*) diastereomers of **2** under triglyme-free conditions (entry 5, Table 1). The reaction proceeded well with all of the screened substrates and generated the desired (*S_s*, *S*)-sulfinamides **2** (Table 3) in good to excellent yields. Substrate **1** bearing diverse electron-donating groups and halogen afforded the corresponding C₂F₅-sulfinamides in 63–94% yields with good to high diastereoselectivities

Table 3. Scope of Pentafluoroethylation of *N*-Sulfinylimines **1 Using HFC-125 in the Absence of Triglyme^a**



^aReaction conditions: **1** (0.2 mmol), HFC-125 (excess),

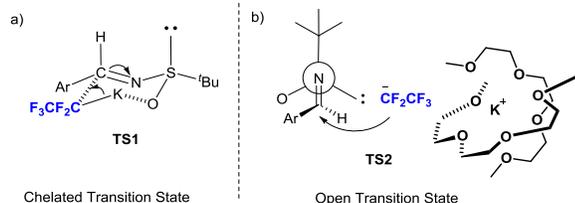


Figure 2. Proposed transition state models. (a) A six-membered chelated transition state. (b) An open transition state.

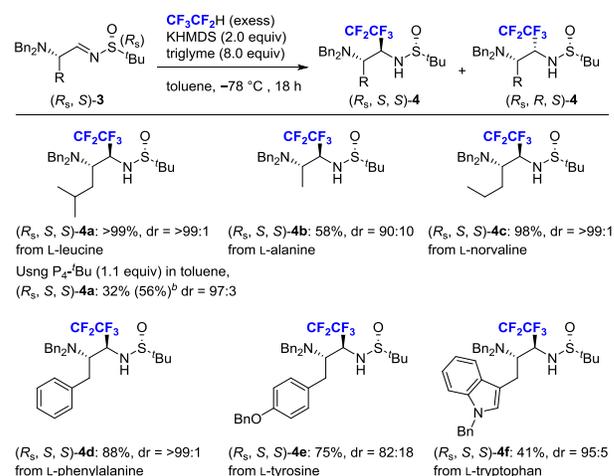
ranging from 17:83 to 1:>99.

The stereodivergence in the two solvent systems is explained by the chelated and open transition states.^{11d,e} In the absence of triglyme, the diastereoselectivity is explained by the formation of a six-membered chelated transition state **TS1** with (*S*)-**1** and K-C₂F₅ where C₂F₅ anion attacks a “*Re*” face to furnish the (*S_s*, *S*)-**2** (Figure 2a). On the other hand, in the presence of triglyme, the formation of K-cryptate by triglyme affords a naked C₂F₅ anion that

approaches (*S*)-**1** via the open transition state **TS2** in a less hindered “*Si*” face to give the (*S_s*,*R*)-**2** (Figure 2b).

Encouraged by these results, we investigated the scope of this KHMDS/triglyme protocol in the synthesis of biologically-relevant enantioenriched pentafluoroethylated vicinal diamines. Pentafluoroethylation of the L-leucine-derivative (*R_s*, *S*)-*N*-sulfinylimine **3a** under the optimized conditions (entry 8, Table 1) afforded the desired (*R_s*, *S_s*, *S*)-product **4a** in >99 % yield and >99:1 dr (Table 4). When we attempted the reaction under previously reported conditions using P₄-*t*Bu (1.1 equiv) in toluene^{6e} instead of KHMDS/triglyme, the isolated yield significantly decreased (32%, 97:3 dr). Thus the new protocol clearly outperforms the P₄-*t*Bu method.^{6e,11d} Subsequently, we explored

Table 4. Substrate Scope in the Synthesis of Pentafluoroethylated Vicinal Diamines **4^a**



^aReaction conditions: **4** (0.2 mmol), HFC-125 (excess),

substrate generality using a variety of imines **3** derived from L-amino acids. Aliphatic amino acid derivatives (**3b** from L-alanine and **3c** from L-norvaline) afforded the corresponding pentafluoroethylated products in good to excellent yields and diastereoselectivities (90:10 and 99:1 dr for **4b** and **4c**, respectively).

Scheme 2. Continuous-flow Pentafluoroethylation of *N*-Sulfinylimine **1d with HFC-125**

vely). The unsubstituted phenyl-containing imine **3d** derived from L-phenylalanine afforded a high yield (88%) and diastereoselectivity (>99:1 dr) of the product **4d**. However, the 4-benzyloxy derivative **3e** prepared from L-tyrosine afforded a good yield of **4e** (75%) but a relatively low stereoselectivity (82:18 dr). The L-tryptophan derivative imine **3f** afforded the corresponding product **4f** in 41% yield and high dr (95:5). Because the stereoselective synthesis of CF₃-variant of (*R*, *S*, *S*)-products requires expensive P₄-^tBu,^{6e} the KHMDS/triglyme protocol does indeed provide a practical alternative to the use of phosphazene super bases.

Continuous flow strategies for using HFCs in fluoroalkylations have received increasing attention in academic and industrial research.¹² In 2019, we reported the stereoselective micro-flow trifluoromethylation of *N*-sulfinylimines using HFC-23 and KHMDS.^{11f} However, the stereodivergent process could not be realized because the P₄-^tBu base is unsuitable for the continuous flow process. Conversely, our KHMDS/triglyme protocol was deemed suitable for the continuous-flow pentafluoroethylation of *N*-sulfinylimines. After a brief optimization of reaction conditions for micro-flow reaction (Table S1, in the supporting information (SI)), *N*-sulfinylimine **1d** underwent the flow-reaction at -30 °C to afford the corresponding pentafluoroethylated product **2d** in good yield (75%) with high diastereoselectivity ((*S*, *R*) diastereomer of **2d**, 92:8). As expected, when we attempted the reaction using HFC-125, KHMDS with toluene under triglyme-free conditions, opposite, (*S*, *S*) diastereomer of **2d** was exclusively obtained in high yield (81%) with high diastereoselectivity (1:>99) (Scheme 2).

In conclusion, we have developed a novel protocol exploiting KHMDS/triglyme cryptate for the stereodivergent pentafluoroethylation of chiral *N*-sulfinylimines using the HFC-125 greenhouse gas. Both diastereomers of the pentafluoroethylated amines can be selectively synthesized based on the presence or absence of triglyme. In the presence of triglyme and at -78 °C, (*S*, *R*)-pentafluoroethylated sulfinamides were obtained in high yields and up to >99:1 dr. By contrast, in the absence of triglyme and at -40 °C, (*S*, *S*)-pentafluoroethylated sulfinamides were generated in up to >99:1 dr. The new method is more practical and inexpensive compared to the previously reported stereodivergent protocol in which P₄-^tBu base was required. Therefore, the KHMDS/triglyme system is a useful alternative in a variety of chemical transformations that include stereoselective synthesis of medically attractive pentafluoroethylated ethylenediamines. Stereodivergent micro-flow perfluoroalkylation of imines was also achieved for the first time by the KHMDS/triglyme protocol.

EXPERIMENTAL SECTION

General Information. The batch reactions were performed in frame-dried flask under N₂ atmosphere. The solvents were transferred via syringe. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60-F₂₅₄, Merck). The TLC plates were visualized under UV light and stained with 7% phosphomolybdic acid or KMnO₄ in water, followed by heating. Column chromatography was performed on silica gel 60N spherical neutral size, 64–210 μm (FUJIFILM Wako). NMR spectra were recorded on a Varian Mercury 300 spectrometer for ¹H NMR (300 MHz) and ¹⁹F NMR (282 MHz), and a Bruker Avance 500 for ¹H NMR (500 MHz) and ¹³C{¹H} NMR (125 MHz). The chemical shifts (δ) were measured in parts per million with respect to solvent (¹H: TMS, δ = 0.00 ppm, ¹⁹F: CDCl₃, δ = -162.2 ppm with C₆F₆ as internal standard; ¹³C{¹H}: CDCl₃, δ = 77.16 ppm), and coupling constants (J) are given in hertz. The following abbreviations denoted the corresponding multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; td, triplet of doublets; dt, doublet of triplets; m, multiplet; br, broad. Mass spectra were recorded using an LCMS-2020EV (ESI-MS) system. High-resolution mass spectrometry (HR-MS) was performed on a Waters Synapt G2 HDMS (ESI-TOF-MS) instrument. Infrared spectra were recorded using a JASCO FT/IR-4100 spectrometer. Melting points were determined using a BUCHI M-565 apparatus. The diastereomeric ratio was determined by ¹⁹F NMR spectroscopic analysis of the crude product. *N*-Sulfinylimines **1** and **3** were prepared according to the reported methods.^{6e,11d} The commercial grade of triglyme was used without further drying.

Components of Flow System: A syringe pump (YMC) was used for the addition of the solutions of substrate and base. A mass flow controller (Fujikin, FCST1005MLC) was used to control the flow rate of gaseous HFC-125. The pressure of HFC-125 was regulated by the regulator connected to the HFC-125 cylinder. A three-inlet mixer (4-direction swirl mixer, Sugiyama Shoji, SUS316, internal volume = 60 μL, 16YSM-0.8-0.5-S) was used for the mixing of the solutions and HFC-125. All flow apparatus (syringes, three inlets mixer, reaction coil, tubes) were dried and filled with N₂ gas prior to use. The residence tube (SUS316, ID = 0.8 mm; residence volume V = 0.81 mL) was used for the reaction coil.

General procedure 1: Pentafluoroethylation of *N*-sulfinylimines using HFC-125 and Triglyme. A test tube containing the corresponding *N*-sulfinylimine **1** (0.2 mmol) in dry toluene (0.2 mL) was charged with CF₃CF₂H (excess) by cooling with liquid N₂ bath under vacuum. To this mixture, KHMDS in toluene (0.5 M, 0.8 mL, 2.0 equiv) and triglyme (0.29 mL, 8.0 equiv) were added to the mixture at -78 °C, and the mixture was stirred at -78 °C for 18 h. Saturated NH₄Cl aq (1.0 mL) was added to the mixture, and

the aqueous layer was extracted with Et₂O (1.0 mL × 3). The combined organic layer was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure, and purified by column chromatography on silica gel to give (*S_s, R*)-**2**.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(p-tolyl)propyl)propane-2-sulfonamide ((S_s, R)-2a). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2a** (67.3 mg, 98%, dr = >99:1) as a white solid. [α]_D²⁵ = +63.4 (c 0.60, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.28–7.19 (m, 4H), 4.87–4.75 (m, 1H), 3.61 (d, *J* = 7.6 Hz, 1H), 2.35 (s, 3H), 1.24 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 139.6, 130.6, 129.8, 128.1, 119.0 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.1, 35.5 Hz), 113.8 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 258.4, 35.5 Hz), 60.2 (t, ²*J*_{C-F} = 22.7 Hz), 57.0, 22.3, 21.2 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.2 (s, 3F), -122.00 (d, *J* = 5.0 Hz, 1F), -122.05 (d, *J* = 5.0 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3321, 2968, 2388, 2130, 1925, 1473, 1363, 1179, 1069, 880, 733, 538 cm⁻¹. m.p.: 98.1–99.0 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₄H₁₈F₅NOS; 366.0927 Found 366.0921.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-phenylpropyl)propane-2-sulfonamide ((S_s, R)-2b). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2b** (60.6 mg, 92% dr = >99:1) as a white solid. [α]_D²⁵ = +68.3 (c 0.60, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.40 (br s, 5H), 4.92–4.80 (m, 1H), 3.66 (d, *J* = 7.0 Hz, 1H), 1.25 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 133.6, 129.8, 129.3, 128.3, 119.0 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.0, 35.9 Hz), 113.8 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 258.5, 35.6 Hz), 60.5 (t, ²*J*_{C-F} = 22.7 Hz), 57.2, 22.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.2 (s, 3F), -122.0 (d, *J* = 7.9 Hz, 1F), -122.1 (d, *J* = 6.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3327, 3069, 2965, 2344, 1475, 1366, 1176, 1066, 880, 722, 600 cm⁻¹. m.p.: 106.3–106.9 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₃H₁₆F₅NOS; 352.0770 Found 352.0771.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(4-methoxyphenyl)propyl)propane-2-sulfonamide ((S_s, R)-2c). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2c** (69.7 mg, 97%, dr = 98:2) as a white solid. [α]_D²⁵ = +60.4 (c 0.62, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.29 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.87–4.75 (m, 1H), 3.81 (s, 3H), 3.57 (d, *J* = 7.6 Hz, 1H), 1.24 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 160.5, 129.5, 125.6, 119.0 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.1, 35.6 Hz), 114.6, 116.3–111.4 (m), 60.0 (t, ²*J*_{C-F} = 22.7 Hz), 57.1, 55.4, 22.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.2 (s, 3F), -122.0 (d, *J* = 13.9 Hz, 1F), -122.3 (d, *J* =

12.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3327, 2966, 2496, 1902, 1615, 1521, 1175, 1063, 822, 544 cm⁻¹. m.p.: 116.8–117.5 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₄H₁₈F₅N₂O₂S; 382.0876 Found 382.0879.

Gram-scale: Followed by the general procedure 1 with **1c** (1.0 g, 4.18 mmol), the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2c** (1.38 g, 92%, dr = 94:6) as a white solid.

N-((R)-1-(4-(Dimethylamino)phenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((S_s, R)-2d). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2d** (68.4 mg, 92% dr = 92:8) as a white solid. [α]_D²⁵ = +49.4 (c 0.61, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.22 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 4.81–4.70 (m, 1H), 3.52 (d, *J* = 7.0 Hz, 1H), 2.96 (s, 6H), 1.24 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 151.1, 129.0, 120.5 (d-like, ³*J*_{C-F} = 3.6 Hz), 119.1 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.2, 35.8 Hz), 112.4, 116.5–111.8 (m), 60.0 (dd, ²*J*_{C-F}, ²*J*_{C-F} = 23.6, 20.9 Hz), 59.8, 56.9, 40.3, 22.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.2 (s, 3F), -120.9 (dd, *J* = 273.0, 14.4 Hz, 1F), -123.2 (dd, *J* = 272.5, 13.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3335, 2926, 2129, 1895, 1618, 1532, 1363, 1179, 820, 541 cm⁻¹. m.p.: 136.0–137.0 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₅H₂₁F₅N₂O₂S; 395.1192 Found 395.1187.

N-((R)-1-(4-Chlorophenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((S_s, R)-2e). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S_s, R*)-**2e** (69.1 mg, 95%, dr = 97:3) as a white solid. [α]_D²⁵ = +54.6 (c 0.63, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.41–7.37 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 4.90–4.78 (m, 1H), 3.64 (d, *J* = 8.5 Hz, 1H), 1.24 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 135.9, 132.0, 129.7, 129.5, 120.0 (tt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.0, 35.4 Hz), 113.6 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 258.6, 35.9 Hz), 60.0 (dd, ²*J*_{C-F}, ²*J*_{C-F} = 25.0, 21.3 Hz), 57.3, 22.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.1 (s, 3F), -121.0 (dd, *J* = 274.5, 11.9 Hz, 1F), -123.0 (dd, *J* = 274.5, 15.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3329, 3033, 2971, 2130, 1955, 1599, 1497, 1174, 1068, 809, 536 cm⁻¹. m.p.: 70.7–71.7 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₃H₁₅ClF₅NOS; 386.0381 Found 386.0381.

N-((R)-1-(4-Bromophenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((S_s, R)-2f). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S_s, R*)-**2f** (65.3 mg, 80%, dr = >99:1) as a white solid. [α]_D²⁵ = +45.6 (c 0.65, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.55 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 6.4 Hz,

2H), 4.88–4.77 (m, 1H), 3.64 (d, $J = 8.5$ Hz, 1H), 1.24 (s, 9H) ppm. ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ : 132.55, 132.47, 129.9, 124.2, 118.9 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.4 Hz), 113.5 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 258.7$, 35.9 Hz), 60.1 (dd, $^2J_{\text{C-F}}$, $^2J_{\text{C-F}} = 24.5$, 20.9 Hz), 57.3, 22.4 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.1 (s, 3F), -121.0 (dd, $J = 274.5$, 11.9 Hz, 1F), -123.1 (dd, $J = 274.5$, 15.9 Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3328$, 2970, 2122, 1595, 1493, 1322, 1174, 1125, 1064, 876, 808, 741, 537 cm^{-1} . m.p.: 107.7–108.6 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{13}\text{H}_{15}\text{BrF}_5\text{NOS}$; 429.9876 Found 429.9877.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(4-(trifluoromethyl)phenyl)propyl)propane-2-sulfinamide ((S_s, R)-2g). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S_s, R*)-**2g** (50.9 mg, 64%, dr = 93:7) as a yellow solid. $[\alpha]_{\text{D}}^{25} = +51.0$ (c 0.63, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.69 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 8.2$ Hz, 2H), 4.99–4.87 (m, 1H), 3.73 (d, $J = 8.8$ Hz, 1H), 1.25 (s, 9H) ppm. ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ : 137.4, 132.0 (q, $^2J_{\text{C-F}} = 32.7$ Hz), 128.9, 126.2 (d-like, $^3J_{\text{C-F}} = 3.6$ Hz), 123.8 (q, $^1J_{\text{C-F}} = 272.5$ Hz), 118.9 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.4 Hz), 113.5 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 258.9$, 36.1 Hz), 60.3 (dd, $^2J_{\text{C-F}}$, $^2J_{\text{C-F}} = 25.4$, 20.9 Hz), 57.4, 22.4 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -63.5 (s, 3F), -81.1 (s, 3F), -120.1 (dd, $J = 275.5$, 9.9 Hz, 1F), -123.5 (dd, $J = 275.5$, 15.9 Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3146$, 2990, 2874, 1933, 1624, 1425, 1330, 1130, 1067, 906, 726, 602 cm^{-1} . m.p.: 68.3–69.3 °C. HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{15}\text{F}_8\text{NOS}$; 420.0644 Found 420.0651.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(3-methoxyphenyl)propyl)propane-2-sulfinamide ((S_s, R)-2h). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2h** (71.1 mg, 99%, dr = >99:1) as a white solid. $[\alpha]_{\text{D}}^{25} = +71.7$ (c 0.66, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.35–7.26 (m, 2 H), 6.98–6.91 (m, 2H), 4.87–4.76 (m, 1H), 3.82 (s, 3H), 3.64 (d, $J = 7.0$ Hz, 1H), 1.25 (s, 9H) ppm. ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ : 160.0, 135.0, 130.4, 120.4, 122.7–115.3 (m), 114.8, 114.4, 116.2–111.3 (m), 60.4 (t, $^2J_{\text{C-F}} = 22.7$ Hz), 57.2, 55.4, 22.4 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.2 (s, 3F), -122.0 (d, $J = 13.9$ Hz, 1F), -122.1 (d, $J = 12.9$ Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3342$, 2982, 1958, 1587, 1464, 1325, 1183, 1066, 876, 787, 735 cm^{-1} . m.p.: 121.2–121.8 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{18}\text{F}_5\text{NO}_2\text{S}$; 382.0876 Found 382.0878.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(2-methoxyphenyl)propyl)propane-2-sulfinamide ((S_s, R)-2i). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-

hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2i** (70.9 mg, 95 %, dr = >99:1) as a white solid. $[\alpha]_{\text{D}}^{25} = +93.0$ (c 0.61, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.38–7.33 (m, 3H), 7.01–6.93 (m, 2H), 5.21 (br, 1H), 4.50 (br, 1H), 3.89 (s, 3H), 1.24 (s, 9H) ppm. ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ : 157.4, 130.8, 129.6, 121.8, 121.2, 119.1 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.9 Hz), 113.9 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 258.4$, 35.5 Hz), 111.8, 56.9, 55.8, 22.5 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.7 (s, 3F), -120.3 (br d, $J = 267.5$ Hz, 1F), -122.1 (dd, $J = 270.5$, 16.8 Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3337$, 3172, 2979, 2512, 1934, 1602, 1496, 1182, 1067, 1182, 830, 762 cm^{-1} . m.p.: 119.4–120.4 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{18}\text{F}_5\text{NO}_2\text{S}$; 382.0876 Found 382.0879.

N-((R)-1-(3,4-Dimethoxyphenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfinamide ((S_s, R)-2j). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 4/6) to give (*S_s, R*)-**2j** (67.3 mg, 91 %, dr = 98:2) as a white solid. $[\alpha]_{\text{D}}^{25} = +59.4$ (c 0.68, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 6.97 (d, $J = 7.6$ Hz, 1H), 6.89–6.86 (m, 2H), 4.86–4.74 (m, 1H), 3.89 (d, $J = 2.6$ Hz, 6H), 3.85 (d, $J = 7.6$ Hz, 1H), 1.25 (s, 9H) ppm. ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ : 150.1, 149.3, 125.9, 120.8, 119.0 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.4 Hz), 116.3–111.4 (m), 111.4, 111.2, 60.2 (t, $^2J_{\text{C-F}} = 22.3$ Hz), 57.1, 56.0, 55.9, 22.4 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.2 (s, 3F), -121.9 (d, $J = 13.9$ Hz, 1F), -122.1 (d, $J = 13.9$ Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3320$, 2964, 2594, 2025, 1593, 1524, 1180, 1067, 858, 1067, 858, 721, 579 cm^{-1} . m.p.: 107.2–107.8 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{20}\text{F}_5\text{NO}_3\text{S}$; 412.0982 Found 412.0988.

N-((R)-1-(Benzo[d][1,3]dioxol-5-yl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfinamide ((S_s, R)-2k). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2k** (67.0 mg, 90%, dr = 98:2) as a white solid. $[\alpha]_{\text{D}}^{25} = +46.1$ (c 0.65, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 6.88–6.80 (m, 3H), 6.00 (s, 2H), 4.82–4.70 (m, 1H), 3.56 (d, $J = 7.3$ Hz, 1H), 1.24 (s, 9H) ppm. ^{13}C { ^1H } NMR (126 MHz, CDCl_3) δ : 148.8, 148.4, 127.2, 122.5, 119.0 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.9 Hz), 113.7 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 258.4$, 35.5 Hz), 108.8, 108.1, 101.6, 60.3 (t, $^2J_{\text{C-F}} = 22.7$ Hz), 57.2, 22.4 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.2 (s, 3F), -122.1 (d, $J = 13.9$ Hz, 1F), -122.3 (d, $J = 12.9$ Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3321$, 2910, 1837, 1507, 1323, 1176, 1037, 926, 794, 740, 561 cm^{-1} . m.p.: 97.5–98.4 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{F}_5\text{NO}_3\text{S}$; 396.0669 Found 396.0666.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(naphthalen-2-yl)propyl)propane-2-sulfinamide ((S_s, R)-2l). Followed by the general procedure 1, the crude product was purified by

silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S*, *R*)-**2l** (70.2 mg, 93%, dr = >99:1) as a white solid. $[\alpha]_{\text{D}}^{25} = +80.9$ (*c* 0.60, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.91–7.84 (m, 4H), 7.55–7.46 (m, 3H), 5.09–4.97 (m, 1H), 3.77 (d, *J* = 6.7 Hz, 1H), 1.26 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 133.7, 133.2, 130.9, 129.4, 128.5, 128.4, 127.8, 127.2, 126.9, 124.7, 119.0 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.0, 35.4 Hz), 113.9 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 258.6, 35.6 Hz), 60.7 (t, ²*J*_{C-F} = 22.7 Hz), 57.2, 22.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.2 (s, 3F), -121.7 (d, *J* = 13.9 Hz, 2F) ppm. ATR-FTIR (KBr): ν = 3324, 2982, 2382, 1947, 1600, 1469, 1366, 1186, 1072, 868, 748, 563 cm⁻¹. m.p.: 142.4–142.8 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₇H₁₈F₅NOS; 402.0927 Found 402.0936.

N-((*R*)-1-(2,2,3,3,3-pentafluoro-1-(naphthalen-1-yl)propyl)propane-2-sulfinamide ((*S*, *R*)-**2m**). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S*, *R*)-**2m** (67.5 mg, 89%, dr = >99:1) as a white solid. $[\alpha]_{\text{D}}^{25} = +173.5$ (*c* 0.66, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 8.07 (d, *J* = 8.8 Hz, 1H), 7.94–7.90 (m, 2H), 7.66–7.50 (m, 4H), 5.81 (br, 1H), 3.85 (d, *J* = 5.9 Hz, 1H), 1.25 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 134.0, 131.0, 130.5, 129.9, 129.4, 127.4, 126.3, 125.2, 122.2, 119.1 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.0, 35.9 Hz), 116.6–111.6 (m), 57.2, 54.1 (br d), 22.8, 22.4 (br d, *J* = 4.5 Hz) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.3 (s, 3F), -121.0 (br s, 2F) ppm. ATR-FTIR (KBr): ν = 3339, 3048, 2967, 2132, 1920, 1601, 1471, 1367, 1181, 1069, 860, 797 cm⁻¹. m.p.: 125.4–126.2 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₇H₁₈F₅NOS; 402.0935 Found 402.0927.

N-((*R*)-1-([1,1'-Biphenyl]-4-yl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfinamide ((*S*, *R*)-**2n**). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S*, *R*)-**2n** (77.0 mg, 95%, dr = 98:2) as a white solid. $[\alpha]_{\text{D}}^{25} = +44.6$ (*c* 0.68, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 7.64–7.57 (m, 4H), 7.47–7.42 (m, 4H), 7.39–7.34 (m, 1H), 4.96–4.85 (m, 1H), 3.70 (d, *J* = 8.2 Hz, 1H), 1.27 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 142.6, 140.2, 132.4, 128.9, 128.7, 127.9, 127.8, 127.3, 119.0 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.0, 35.9 Hz), 113.8 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 258.4, 35.7 Hz), 60.4 (dd, ²*J*_{C-F}, ²*J*_{C-F} = 24.5, 20.9 Hz), 57.2, 22.4 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.1 (s, 3F), -121.7 (d, *J* = 12.9 Hz, 1F), -122.0 (d, *J* = 14.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3325, 2962, 1921, 1709, 1596, 1473, 1364, 1208, 1070, 823, 764, 560 cm⁻¹. m.p.: 158.0–158.8 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₉H₂₀F₅NOS; 428.1083 Found 428.1085.

N-((*R*)-1-(1,1,1,2,2-pentafluorohexan-3-yl)propane-2-sulfinamide ((*S*, *R*)-**2o**). Followed by the general procedure 1, the crude product was purified by

silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S*, *R*)-**2o** (34.3 mg, 58%, dr = 95:5) as a white solid. $[\alpha]_{\text{D}}^{25} = +74.5$ (*c* 0.62, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 3.79–3.73 (m, 1H), 3.08 (d, *J* = 8.5 Hz, 1H), 1.87–1.56 (m, 4H), 1.24 (s, 9H), 0.98 (t, *J* = 7.0 Hz, 3H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 119.2 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 287.0, 35.9 Hz), 114.3 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 256.8, 35.7 Hz), 58.0 (t, ²*J*_{C-F} = 23.6 Hz), 57.1, 31.8, 22.6, 18.6, 13.7 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -80.8 (s, 3F), -120.9 (dd, *J* = 273.5, 10.9 Hz, 1F), -122.8 (dd, *J* = 273.5, 13.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3202, 2971, 2102, 1475, 1334, 1188, 1056, 895, 732, 596 cm⁻¹. m.p.: 118.5–119.5 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₀H₁₈F₅NOS; 318.0927 Found 318.0926.

N-((*R*)-1-Cyclohexyl-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfinamide ((*S*, *R*)-**2p**). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S*, *R*)-**2p** (60.4 mg, 90%, dr = 95:5) as a white solid. $[\alpha]_{\text{D}}^{25} = +75.1$ (*c* 0.66, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 3.69–3.56 (m, 1H), 3.47 (d-like, *J* = 9.1 Hz, 1H), 1.92–1.80 (m, 4H), 1.66–1.57 (m, 3H), 1.38–1.08 (m, 4H), 1.25 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 119.1 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 286.9, 36.2 Hz), 114.9 (tq, ¹*J*_{C-F}, ²*J*_{C-F} = 258.0, 35.7 Hz), 62.2 (dd, ²*J*_{C-F}, ²*J*_{C-F} = 23.6, 20.9 Hz), 57.2, 37.6, 30.7, 27.3, 26.4, 26.0, 25.7, 22.6 ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.6 (s, 3F), -119.3 (d, *J* = 11.9 Hz, 1F), -120.0 (d, *J* = 17.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3277, 2934, 2675, 2131, 1454, 1305, 1203, 1057, 850, 683 cm⁻¹. m.p.: 75.3–76.3 °C (*n*-hexane). HRMS (ESI) *m/z*: [M+Na]⁺ calcd. for C₁₃H₂₂F₅NOS; 358.1240 Found 358.1244.

N-((*R*)-1-(1,1,1,2,2-pentafluoro-4,4-dimethylpentan-3-yl)propane-2-sulfinamide ((*S*, *R*)-**2q**). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S*, *R*)-**2q** (57.3 mg, 93%, dr = 97:3) as a white solid. $[\alpha]_{\text{D}}^{25} = +80.5$ (*c* 0.61, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 3.65–3.56 (m, 2H), 1.26 (s, 9H), 1.16 (s, 9H) ppm. ¹⁹F NMR (282 MHz, CDCl₃) δ: -81.3 (s, 3F), -111.4 (d, *J* = 273.5 Hz, 1F), -123.1 (dd, *J* = 273.0, 20.3 Hz, 1F) ppm. MS (ESI) *m/z*: [M + H]⁺ 310.00. Analytical data are consistent with reported values.¹³

N-((*R*)-1-(2,2,3,3,3-pentafluoro-1-(pyridin-3-yl)propyl)propane-2-sulfinamide ((*S*, *R*)-**2r**). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (ethyl acetate) to give (*S*, *R*)-**2r** (56.2 mg, 85%, dr = 96:4) as a brown solid. $[\alpha]_{\text{D}}^{25} = +57.3$ (*c* 0.65, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ: 8.67 (br s, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.98–4.86 (m, 1H), 3.75 (d, *J* = 8.5 Hz, 1H), 1.25 (s, 9H) ppm. ¹³C {¹H} NMR (126 MHz, CDCl₃) δ: 151.1, 149.6, 135.9, 129.6, 124.0, 118.9 (qt, ¹*J*_{C-F}, ²*J*_{C-F} = 286.9, 35.8 Hz), 113.5

(tq, $^1J_{C-F}$, $^2J_{C-F}$ = 258.7, 36.0 Hz), 58.8 (dd, $^2J_{C-F}$, $^2J_{C-F}$ = 25.9, 21.3 Hz), 57.5, 22.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ : -81.0 (s, 3F), -120.0 (dd, J = 275.5, 10.9 Hz, 1F), -123.4 (dd, J = 275.5, 15.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3090, 2867, 1972, 1591, 1435, 1366, 1203, 1132, 1027, 837, 737 cm^{-1} . m.p.: 96.1–96.8 °C (*n*-hexane). HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{12}H_{15}F_5N_2OS$; 353.0723 Found 353.0731.

2-Methyl-N-((R)-2,2,3,3,3-pentafluoro-1-(furan-2-yl)propyl)propane-2-sulfonamide ((S_S, R)-2s). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_S, R*)-**2s** (61.9 mg, 97%, dr = >99:1) as a colorless oil. $[\alpha]_D^{25}$ = +52.0 (*c* 0.56, $CHCl_3$). 1H NMR (300 MHz, $CDCl_3$) δ : 7.47 (d, J = 1.2 Hz, 1H), 6.50–6.40 (m, 2H), 5.02–4.90 (m, 1H), 3.89 (d, J = 9.4 Hz, 1H), 1.26 (s, 9H) ppm. ^{13}C { 1H } NMR (126 MHz, $CDCl_3$) δ : 145.6, 144.1, 118.8 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.1, 35.5 Hz), 112.9 (tq, $^1J_{C-F}$, $^2J_{C-F}$ = 259.5, 35.9 Hz), 111.0, 110.9, 57.4, 55.2 (t, $^2J_{C-F}$ = 24.5 Hz), 22.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ : -81.7 (s, 3F), -120.9 (dd, J = 272.5, 11.9 Hz, 1F), -122.4 (dd, J = 272.5, 13.9 Hz, 1F) ppm. ATR-FTIR (NaCl): ν = 3601, 3296, 3033, 2816, 2238, 1471, 1363, 1011, 732, 593 cm^{-1} . HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{11}H_{14}F_5NO_2S$; 342.0563 Found 342.0563.

2-Methyl-N-((S)-2,2,3,3,3-pentafluoro-1-(thiophen-2-yl)propyl)propane-2-sulfonamide ((S_S, R)-2t). Followed by the general procedure 1, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_S, R*)-**2t** (47.6 mg, 71%, dr = 95:5) as a yellow solid. $[\alpha]_D^{25}$ = +51.3 (*c* 0.67, $CHCl_3$). 1H NMR (300 MHz, $CDCl_3$) δ : 7.39 (d, J = 5.3 Hz, 1H), 7.21 (br s, 1H), 7.04 (t-like, J = 4.0 Hz, 1H), 5.24–5.13 (m, 1H), 3.53 (d, J = 7.3 Hz, 1H), 1.25 (s, 9H) ppm. ^{13}C { 1H } NMR (126 MHz, $CDCl_3$) δ : 134.9, 128.7, 127.6, 127.4, 118.9 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.7, 35.9 Hz), 113.3 (tq, $^1J_{C-F}$, $^2J_{C-F}$ = 259.1, 35.8 Hz), 57.3, 56.5 (dd, $^2J_{C-F}$, $^2J_{C-F}$ = 25.4, 22.7 Hz), 22.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ : -81.0 (s, 3F), -121.1 (dd, J = 271.5, 11.9 Hz, 1F), -122.9 (dd, J = 272.5, 13.9 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3317, 3112, 2970, 2125, 1837, 1462, 1363, 1184, 1065, 878, 718 cm^{-1} . m.p.: 52.3–53.3 °C (*n*-hexane). HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{11}H_{14}F_5NOS_2$; 358.0335 Found 358.0334.

General procedure 2: Pentafluoroethylation of *N*-Sulfinyl Imines by KHMDS/HFC-125 system. A test tube containing corresponding *N*-sulfinylimine **1** (0.2 mmol) in dry toluene (0.2 mL) was charged with CF_3CF_2H (excess) by cooling with liquid N_2 bath under vacuum. KHMDS in toluene (0.5 M, 0.8 mL, 2.0 equiv) was added to the mixture at -40 °C, and the mixture was stirred at -40 °C for 18 h. Saturated NH_4Cl aq (1.0 mL) was added to the mixture, and the aqueous layer was extracted with Et_2O (1.0 mL \times

3). The combined organic layer was washed with brine, dried over Na_2SO_4 , concentrated under reduced pressure, and purified by column chromatography on silica gel to give (*S_S, S*)-**2**.

*2-Methyl-N-((S)-2,2,3,3,3-pentafluoro-1-(*p*-tolyl)propyl)propane-2-sulfonamide ((S_S, S)-2a)*. Followed by the general procedure 2, the crude product was purified by silica gel column chromatography (toluene/acetone/dichloromethane = 9/0.5/0.5) to give (*S_S, S*)-**2a** (31.2 mg, 91%, dr = 7:93) as a colorless oil. $[\alpha]_D^{25}$ = +105.9 (*c* 0.59, $CHCl_3$). 1H NMR (300 MHz, $CDCl_3$) δ : 7.29 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 4.95–4.86 (m, 1H), 3.90 (s, 1H), 2.37 (s, 3H), 1.21 (s, 9H) ppm. ^{13}C { 1H } NMR (126 MHz, $CDCl_3$) δ : 140.0, 129.7, 129.6, 128.1 (d-like, $^3J_{C-F}$ = 3.6 Hz), 118.8 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.0, 35.4 Hz), 116.4–111.4 (m), 58.6 (t, $^2J_{C-F}$ = 20.9 Hz), 56.4, 22.5, 21.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ : -81.3 (s, 3F), -120.1 (dd, J = 268.0, 8.4 Hz, 1F), -126.1 (dd, J = 268.5, 16.8 Hz, 1F) ppm. ATR-FTIR (NaCl): ν = 3758, 3173, 2966, 2866, 1911, 1611, 1462, 1362, 1207, 1073, 888, 731 cm^{-1} . HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{14}H_{18}F_5NOS$; 366.0927 Found 366.0922.

2-Methyl-N-((S)-2,2,3,3,3-pentafluoro-1-phenylpropyl)propane-2-sulfonamide ((S_S, S)-2b). Followed by the general procedure 2, the crude product was purified by silica gel column chromatography (*n*-hexane/diethyl ether/dichloromethane = 7/2/1) to give (*S_S, S*)-**2b** (54.3 mg, 82%, dr = 11:89) as a white solid. $[\alpha]_D^{25}$ = +108.8 (*c* 0.61, $CHCl_3$). 1H NMR (300 MHz, $CDCl_3$) δ : 7.41 (br s, 5H), 4.99–4.90 (m, 1H), 3.92 (br s, 1H), 1.22 (s, 9H) ppm. ^{13}C { 1H } NMR (126 MHz, $CDCl_3$) δ : 131.3 (d, $^3J_{C-F}$ = 3.6 Hz), 130.0, 129.8, 128.9, 118.8 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.0, 35.4 Hz), 116.4–111.4 (m), 58.9 (t, $^2J_{C-F}$ = 21.3 Hz), 56.5, 22.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ : -81.3 (s, 3F), -120.1 (dd, J = 268.5, 8.9 Hz, 1F), -125.9 (dd, J = 269.5, 16.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3164, 2958, 2380, 1966, 1726, 1461, 1184, 1066, 896, 701 cm^{-1} . m.p.: 42.9–43.9 °C (*n*-hexane). HRMS (ESI) m/z : $[M+Na]^+$ calcd. for $C_{13}H_{16}F_5NOS$; 352.0770 Found 352.0772.

2-Methyl-N-((S)-2,2,3,3,3-pentafluoro-1-(4-methoxyphenyl)propyl)propane-2-sulfonamide ((S_S, S)-2c). Followed by the general procedure 2, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_S, S*)-**2c** (51.7 mg, 72%, dr = 4:96) as a white solid. $[\alpha]_D^{25}$ = +110.5 (*c* 0.56, $CHCl_3$). 1H NMR (300 MHz, $CDCl_3$) δ : 7.33 (d, J = 8.2 Hz, 2H), 6.94–6.89 (m, 2H), 4.95–4.85 (m, 1H), 3.89 (br s, 1H), 3.83 (s, 3H), 1.22 (s, 9H) ppm. ^{13}C { 1H } NMR (126 MHz, $CDCl_3$) δ : 160.8, 131.1, 122.8 (d, $^3J_{C-F}$ = 4.5 Hz), 118.8 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.0, 35.4 Hz), 114.3, 116.4–111.5 (m), 58.2 (t, $^2J_{C-F}$ = 20.9 Hz), 56.3, 55.3, 22.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ :

-81.3 (s, 3F), -120.1 (dd, $J = 268.0$, 8.4 Hz, 1F), -126.5 (dd, $J = 268.0$, 17.3 Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3227$, 2961, 2258, 2239, 1742, 1611, 1516, 1362, 1185, 1081, 839, 735 cm^{-1} . m.p.: 54.5–55.5 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{14}\text{H}_{18}\text{F}_5\text{NO}_2\text{S}$; 382.0876 Found 382.0867.

N-((*S*)-1-(4-(Dimethylamino)phenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((*S*_s, *S*)-**2d**). Followed by the general procedure 2, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S*_s, *S*)-**2d** (70.0 mg, 94%, dr = 1:>99) as a yellow solid. $[\alpha]_{\text{D}}^{25} = +115.8$ (*c* 0.50, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.24 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 8.8$ Hz, 2H), 4.89–4.80 (m, 1H), 3.86 (br s, 1H), 2.99 (s, 6H), 1.22 (s, 9H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 151.2, 130.7, 118.9 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.4 Hz), 117.4 (d, $^3J_{\text{C-F}} = 3.6$ Hz), 116.6–111.6 (m), 111.9, 58.3 (t, $^2J_{\text{C-F}} = 20.9$ Hz), 56.1, 40.2, 22.5 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.3 (s, 3F), -119.9 (dd, $J = 267.0$, 8.4 Hz, 1F), -126.7 (dd, $J = 267.0$, 17.3 Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3554$, 3201, 2957, 2106, 1891, 1530, 1363, 1181, 1063, 810, 632 cm^{-1} . m.p.: 98.1–99.0 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{15}\text{H}_{21}\text{F}_5\text{N}_2\text{OS}$; 395.1192 Found 395.1198.

N-((*S*)-1-(4-Chlorophenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((*S*_s, *S*)-**2e**). Followed by the general procedure 2, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 8/2) to give (*S*_s, *S*)-**2e** (58.9 mg, 81%, dr = 17:83) as a colorless oil. $[\alpha]_{\text{D}}^{25} = +105.8$ (*c* 0.90, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.41–7.34 (m, 4H), 4.98–4.89 (m, 1H), 3.91 (s, 1H), 1.22 (s, 9H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 136.2, 131.2, 129.8 (d, $^3J_{\text{C-F}} = 4.5$ Hz), 129.2, 118.7 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.4 Hz), 116.2–111.2 (m), 58.2 (t, $^2J_{\text{C-F}} = 21.3$ Hz), 56.5, 22.4 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.2 (s, 3F), -120.4 (dd, $J = 268.5$, 8.9 Hz, 1F), -125.8 (dd, $J = 269.5$, 15.9 Hz, 1F) ppm. ATR-FTIR (NaCl): $\nu = 3183$, 2957, 2358, 1601, 1496, 1365, 1186, 1057, 894, 741 cm^{-1} . HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{13}\text{H}_{15}\text{ClF}_5\text{NOS}$; 386.0381 Found 386.0380.

N-((*S*)-1-(4-Bromophenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((*S*_s, *S*)-**2f**). Followed by the general procedure 2, the crude product was purified by silica gel column chromatography (*n*-hexane/diethyl ether/dichloromethane = 7/2.5/0.5) to give (*S*_s, *S*)-**2f** (51.4 mg, 63%, dr = 17:83) as a white solid. $[\alpha]_{\text{D}}^{25} = +101.1$ (*c* 0.53, CHCl_3). ^1H NMR (300 MHz, CHCl_3) δ : 7.55 (d, $J = 8.2$ Hz, 2H), 7.31–7.26 (m, 2H), 4.96–4.88 (m, 1H), 3.91 (br s, 1H), 1.23 (s, 9H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CHCl_3) δ : 132.2, 131.4, 130.3 (d, $^3J_{\text{C-F}} = 3.6$ Hz), 124.4, 118.7 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.0$, 35.4 Hz), 113.6 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 260.0$, 36.0 Hz), 58.2 (t, $^2J_{\text{C-F}} = 21.3$ Hz), 56.6, 22.5 ppm. ^{19}F NMR (282 MHz,

CHCl_3) δ : -81.2 (s, 3F), -120.5 (dd, $J = 269.5$, 8.9 Hz, 1F), -125.7 (dd, $J = 269.0$, 16.3 Hz, 1F) ppm. ATR-FTIR (KBr): $\nu = 3199$, 2959, 2745, 2379, 1947, 1595, 1495, 1357, 1178, 1076, 893, 740 cm^{-1} . m.p.: 98.2–99.1 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{13}\text{H}_{15}\text{BrF}_5\text{NOS}$; 429.9876 Found 429.9883.

General procedure 3: pentafluoroethylation of amino acid derivative *N*-Sulfinyl Imines by

KHMDS/triglyme/HFC-125 system. A test tube containing corresponding *N*-sulfinylimine **3** (0.2 mmol) in dry toluene (0.2 mL) was charged with $\text{CF}_3\text{CF}_2\text{H}$ (excess) by cooling with liquid N_2 bath under vacuum. KHMDS in toluene (0.5 M, 0.8 mL, 2.0 equiv) containing triglyme (0.29 mL, 8.0 equiv) was added to the mixture at -78 °C, and the mixture was stirred at -78 °C for 16 h. Saturated NH_4Cl aq (1.0 mL) was added to the mixture, and the aqueous layer was extracted with Et_2O (1.0 mL \times 3). The combined organic layer was washed with brine, dried over Na_2SO_4 , concentrated under reduced pressure, and purified by column chromatography on silica gel to give (*R*_s, *S*, *S*)-**4**.

N-((3*S*,4*S*)-4-(dibenzylamino)-1,1,1,2,2-pentafluoro-6-methylheptan-3-yl)-2-methylpropane-2-sulfonamide ((*R*_s, *S*, *S*)-**4a**). Followed by the general procedure 3, the crude product was purified by silica gel column chromatography (*n*-hexane/diethyl ether = 7/3) to give (*R*_s, *S*, *S*)-**4a** (59.4 mg, >99%, dr = >99:1) as a yellow oil. $[\alpha]_{\text{D}}^{25} = -57.7$ (*c* 0.57, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.33–7.26 (m, 10H), 4.32 (d, $J = 8.8$ Hz, 1H), 4.19–4.08 (m, 1H), 3.84 (d, $J = 13.8$ Hz, 2H), 3.70 (d, $J = 13.8$ Hz, 2H), 3.49–3.45 (m, 2H), 1.82–1.68 (m, 1H), 1.29–1.27 (m, 2H), 1.27 (s, 9H), 0.90 (d, $J = 6.7$ Hz, 3H), 0.60 (d, $J = 6.4$ Hz, 3H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 138.8, 129.4, 128.4, 127.2, 119.1 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.6$, 36.6 Hz), 115.3 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 258.9$, 35.1 Hz), 57.8, 57.1, 55.7 (t, $^2J_{\text{C-F}} = 24.1$ Hz), 53.6, 36.6 (d, $^3J_{\text{C-F}} = 3.6$ Hz), 24.8, 22.6, 22.5 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.0 (s, 3F), -116.5 (d, $J = 276.4$ Hz, 1F), -123.4 (dd, $J = 272.5$, 22.8 Hz, 1F) ppm. ATR-FTIR (NaCl): $\nu = 3752$, 3373, 3214, 3033, 2958, 2726, 2242, 1952, 1604, 1460, 1208, 910, 741 cm^{-1} . HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{26}\text{H}_{35}\text{F}_5\text{N}_2\text{OS}$; 541.2288 Found 541.2289.

N-((3*S*,4*S*)-4-(dibenzylamino)-1,1,1,2,2-pentafluoropentan-3-yl)-2-methylpropane-2-sulfonamide ((*R*_s, *S*, *S*)-**4b**). Followed by the general procedure 3, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 85/15) to give (*R*_s, *S*, *S*)-**4b** (55.6 mg, 58%, dr = 90:10) as a white solid. $[\alpha]_{\text{D}}^{25} = -38.6$ (*c* 0.53, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.34–7.30 (m, 10H), 4.39 (d, $J = 9.1$ Hz, 1H), 3.96–3.88 (m, 1H), 3.86 (d, $J = 14.1$ Hz, 2H), 3.67–3.57 (m, 3H), 1.26 (s, 9H), 1.09 (dd, $J = 7.0$, 2.3 Hz, 3H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 138.7, 129.2, 128.5, 127.3, 119.1 (qt, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 287.9$, 36.3 Hz), 115.3 (tq, $^1J_{\text{C-F}}$, $^2J_{\text{C-F}} = 259.4$, 35.1 Hz),

59.1 (dd, $^2J_{C-F}$, $^2J_{C-F}$ = 25.4, 21.8 Hz), 57.0, 56.0, 53.6, 22.7, 12.7 (d, $^3J_{C-F}$ = 4.5 Hz) ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.1 (s, 3F), -115.5 (d, J = 269.5 Hz, 1F), -124.2 (dd, J = 272.5, 22.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3215, 3031, 2961, 1947, 1603, 1455, 1366, 1185, 1062, 889, 698, 603 cm^{-1} . m.p.: 76.9–77.8 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{23}\text{H}_{29}\text{F}_5\text{N}_2\text{O}_5$; 499.1818 Found 499.1826.

N-((3*S*,4*S*)-4-(dibenzylamino)-1,1,1,2,2-pentafluoroheptan-3-yl)-2-methylpropane-2-sulfonamide ((*R*_s, *S*, *S*)-**4c**). Followed by the general procedure 3, the crude product was purified by silica gel column chromatography (*n*-hexane/dichloromethane/diethyl ether = 8/2/0.5) to give (*R*_s, *S*, *S*)-**4c** (98.6 mg, 98%, dr = >99:1) as a white solid. $[\alpha]_{\text{D}}^{25}$ = -72.3 (*c* 0.65, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.33–7.24 (m, 10H), 4.40 (d, J = 8.8 Hz, 1H), 4.18–4.09 (m, 1H), 3.83 (d, J = 14.1 Hz, 2H), 3.72 (d, J = 14.1 Hz, 2H), 3.46–3.39 (m, 1H), 1.47–1.31 (m, 4H), 1.26 (s, 9H), 0.80–0.76 (m, 3H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 138.8, 129.3, 128.4, 127.2, 119.1 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.6, 36.8 Hz), 115.3 (tq, $^1J_{C-F}$, $^2J_{C-F}$ = 259.1, 35.0 Hz), 60.1, 57.1, 55.7 (t, $^2J_{C-F}$ = 24.1 Hz), 53.4, 29.8 (d, $^3J_{C-F}$ = 4.5 Hz), 22.6, 20.0, 13.9 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.1 (s, 3F), -116.3 (d, J = 276.4 Hz, 1F), -123.7 (dd, J = 272.5, 21.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3195, 3033, 2963, 1951, 1603, 1457, 1364, 1181, 1060, 874, 700 cm^{-1} . m.p.: 80.7–81.7 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{25}\text{H}_{33}\text{F}_5\text{N}_2\text{O}_5$; 527.2131 Found 527.2148.

N-((3*S*,4*S*)-4-(dibenzylamino)-1,1,1,2,2-pentafluoro-5-phenylpentan-3-yl)-2-methylpropane-2-sulfonamide ((*R*_s, *S*, *S*)-**4d**). Followed by the general procedure 3, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate/dichloromethane = 9/0.8/0.2) to give (*R*_s, *S*, *S*)-**4d** (96.8 mg, 88%, dr = >99:1) as a white solid. $[\alpha]_{\text{D}}^{25}$ = -91.9 (*c* 0.66, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.35–7.26 (m, 13H), 7.13 (d, J = 7.0 Hz, 2H), 4.31 (d, J = 10.0 Hz, 1H), 3.97–3.80 (m, 6H), 2.98–2.91 (m, 1H), 2.73–2.66 (m, 1H), 1.20 (s, 9H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 138.3, 138.0, 129.4, 129.2, 128.8, 128.5, 127.4, 126.7, 118.9 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.6, 36.6 Hz), 117.8–112.9 (m), 62.5, 57.0, 57.0–56.7 (m), 53.8, 33.1 (d, $^3J_{C-F}$ = 3.6 Hz), 22.6 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.6 (s, 3F), -115.2 (d, J = 272.5 Hz, 1F), -124.5 (dd, J = 271.5, 24.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3253, 3033, 2867, 2342, 1950, 1602, 1454, 1295, 1212, 1074, 904, 702 cm^{-1} . m.p.: 103.4–104.7 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{29}\text{H}_{33}\text{F}_5\text{N}_2\text{O}_5$; 575.2131 Found 575.2128.

N-((3*S*,4*S*)-5-(4-(benzyloxy)phenyl)-4-(dibenzylamino)-1,1,1,2,2-pentafluoropentan-3-yl)-2-methylpropane-2-sulfonamide ((*R*_s, *S*, *S*)-**4e**). Followed by the general procedure 3, the crude product was purified by silica gel column

chromatography (*n*-hexane/dichloromethane/diethyl ether = 6/3.6/0.4) to give (*R*_s, *S*, *S*)-**4e** (98.5 mg, 75%, dr = 82:18) as a colorless oil. $[\alpha]_{\text{D}}^{25}$ = -78.5 (*c* 0.63, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.47–7.37 (m, 3H), 7.34–7.26 (m, 12H), 7.04 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.06 (s, 2H), 4.32 (d, J = 9.7 Hz, 1H), 3.97–3.79 (m, 6H), 2.94–2.83 (m, 1H), 2.67–2.57 (m, 1H), 1.20 (s, 9H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 157.5, 138.3, 137.1, 130.3, 130.2, 129.2, 128.7, 128.5, 128.1, 127.6, 127.3, 118.9 (qt, $^1J_{C-F}$, $^2J_{C-F}$ = 287.6, 36.6 Hz), 117.8–112.9 (m), 115.2, 70.1, 62.6, 56.9 (dd, $^2J_{C-F}$, $^2J_{C-F}$ = 26.3, 20.9 Hz), 53.7, 32.2 (d, $^3J_{C-F}$ = 3.6 Hz), 22.6 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.5 (s, 3F), -115.2 (d, J = 272.5 Hz, 1F), -124.3 (dd, J = 271.5, 24.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3243, 3031, 2959, 1953, 1609, 1512, 1211, 1076, 849, 741 cm^{-1} . HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{36}\text{H}_{39}\text{F}_5\text{N}_2\text{O}_2\text{S}$; 681.2550 Found 681.2563.

N-((3*S*,4*S*)-5-(1-benzyl-1*H*-indol-3-yl)-4-(dibenzylamino)-1,1,1,2,2-pentafluoropentan-3-yl)-2-methylpropane-2-sulfonamide ((*R*_s, *S*, *S*)-**4f**). Followed by the general procedure 3, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 9/1) to give (*R*_s, *S*, *S*)-**4f** (55.6 mg, 41%, dr = 95:5) as a brown solid. $[\alpha]_{\text{D}}^{25}$ = -72.7 (*c* 0.58, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 7.45 (d, J = 8.2 Hz, 1H), 7.26–7.05 (m, 19H), 5.40 (s, 2H), 4.26 (t-like, J = 8.2 Hz, 1H), 4.19–4.06 (m, 2H), 3.97 (d, J = 14.4 Hz, 2H), 3.85 (d, J = 14.1 Hz, 2H), 3.11 (d, J = 7.9 Hz, 2H), 1.21 (s, 9H) ppm. ^{13}C $\{^1\text{H}\}$ NMR (126 MHz, CDCl_3) δ : 138.8, 137.2, 135.5, 129.1, 128.9, 128.2, 127.6, 127.1, 126.8, 126.4, 124.6, 122.7–116.8 (m), 122.3, 120.4, 119.1, 117.7–112.7 (m), 59.3, 57.3, 57.0 (dd, $^2J_{C-F}$, $^2J_{C-F}$ = 27.7, 21.3 Hz), 54.0, 47.0, 24.0 (d, $^3J_{C-F}$ = 2.7 Hz), 22.7 ppm. ^{19}F NMR (282 MHz, CDCl_3) δ : -81.3 (s, 3F), -115.2 (d, J = 274.5 Hz, 1F), -124.7 (dd, J = 272.5, 22.8 Hz, 1F) ppm. ATR-FTIR (KBr): ν = 3312, 3031, 2929, 1950, 1604, 1457, 1363, 1211, 1078, 816, 740 cm^{-1} . m.p.: 57.3–58.3 °C (*n*-hexane). HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{38}\text{H}_{40}\text{F}_5\text{N}_3\text{O}_5$; 704.2710 Found 704.2726.

General procedure 4: Micro-flow pentafluoroethylation of *N*-sulfinylimines using HFC-125. A solution of (*S*)- or (*R*)-*N*-sulfinylimine **1d** (0.6 mmol, 1.0 equiv) in toluene or triglyme (2.0 mL) was fed into a three-inlet mixer (0.33 mL/min) using a syringe pump; simultaneously, a mixture of KHMDs (solid, 1.2 mmol, 2.0 equiv) in toluene or triglyme (4.0 mL) was fed into the mixer (0.50 mL/min) using another syringe pump. HFC-125 (5.2 equiv) was introduced into the mixer under a pressure of 0.1 MPa and at a flow rate of 25 mL/min controlled by a mass flow controller. The combined mixture was passed through residence tubing (residence volume V = 0.81 mL) at -30 °C.

After the gas flow rate stabilized (about 2 min), the product was collected for 2 min. The product stream was quenched with saturated NH₄Cl aq. The aqueous layer was extracted with Et₂O, and the combined organic layer was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure, and purified by column chromatography on a silica gel to give (*S_s, R*)- or (*S_s, S*)-**2d**.

N-((*R*)-1-(4-(Dimethylamino)phenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((*S_s, R*)-**2d**). Followed by the general procedure 4 with triglyme as a solvent, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, R*)-**2d** (55.4 mg, 75%, dr = 92:8) as a white solid.

N-((*S*)-1-(4-(Dimethylamino)phenyl)-2,2,3,3,3-pentafluoropropyl)-2-methylpropane-2-sulfonamide ((*S_s, S*)-**2d**). Followed by the general procedure 4 with toluene as a solvent, the crude product was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 7/3) to give (*S_s, S*)-**2d** (59.5 mg, 81%, dr = 1:>99) as a white solid.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Table S1, photos of continuous-flow system and copies of ¹H, ¹⁹F, and ¹³C{¹H} NMR spectra of compounds **2**, **4** (PDF).

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Author Contributions

H.I. and Y.F. performed the experiments and analyzed the data. E.M.M. prepared a couple of starting materials. N.S. wrote the manuscript. Y.S. and E.M.M. helped with the preparation of the manuscript. N.S. supervised the project, and Y.S. co-supervised. H.A. T.K. and D.C. contributed to an important discussion. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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