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SUBSTITUENT EFFECTS IN REGIO- AND STEREOSELECTIVE RING-OPENING REACTION OF AZIRIDINES WITH $Et_3N{\cdot}3HF$ FOR *β*-FLUOROAMINE SYNTHESIS

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Abstract – This paper discusses the reactivity of various 2-substituted aziridine derivatives. The reaction of chiral 2-aryl-substituted aziridines with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) afforded chiral *β*-fluoroamines with high stereoselectivity. In contrast, the reaction of chiral 2-aliphatic-substituted aziridines with benzyl bromide, followed by treatment with $Et_3N{\cdot}3HF$, gave chiral *β*-fluoroamines with high stereoselectivity.

INTRODUCTION

Organofluorine compounds often show bioactivities and behavior that are distinctive from those of their non-fluorinated counterparts.[1] Currently, 20–30% of the agrochemicals and pharmaceuticals in use owe their effectiveness to the presence of one or more fluorine atoms in their structure. Therefore, numerous research groups have developed methods for the efficient syntheses of organofluorine compounds.[2]

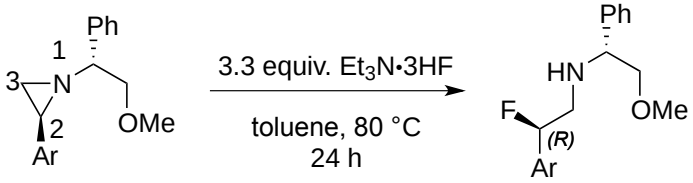
Aziridines comprise an attractive class of compounds because of their large ring strain, which is the driving force of their reactivity.[3] Therefore, considerable research has been focused on the regio- and stereo-selective ring-opening reaction of aziridines with a variety of nucleophiles to enable easy access to diverse optically active compounds.[4] In 1980, Wade reported the reaction of aziridine derivatives with hydrogen fluoride to yield *β*-fluoroamines.[5] Furthermore, the ring-opening reaction of aziridines with fluorinating reagents has been demonstrated to yield optically active organofluorine compounds.[6]

In a previous work, we described the asymmetric synthesis of chiral 2-substituted aziridines **1** from (*R*)-*O*-methyl-2-phenylglycinol with high stereoselectivity.[7] Herein, we report the asymmetric synthesis of chiral *β*-fluoroamines from a chiral aziridine using $Et_3N{\cdot}3HF$.

RESULTS AND DISCUSSION

We initially examined ring-opening reaction of chiral 2-aryl-substituted aziridines **1a–n**, which were readily obtained from our previous methodology.[7] The reaction of **1a–m** with 3.3 equiv. of $Et_3N{\cdot}3HF$ proceeded smoothly in toluene at 80 °C to afford the corresponding ring-opening products **2a–m** in 33–97% yields (Table 1).

Table 1. Ring-opening reaction of 2-aryl-substituted aziridines with $Et_3N{\cdot}3HF$



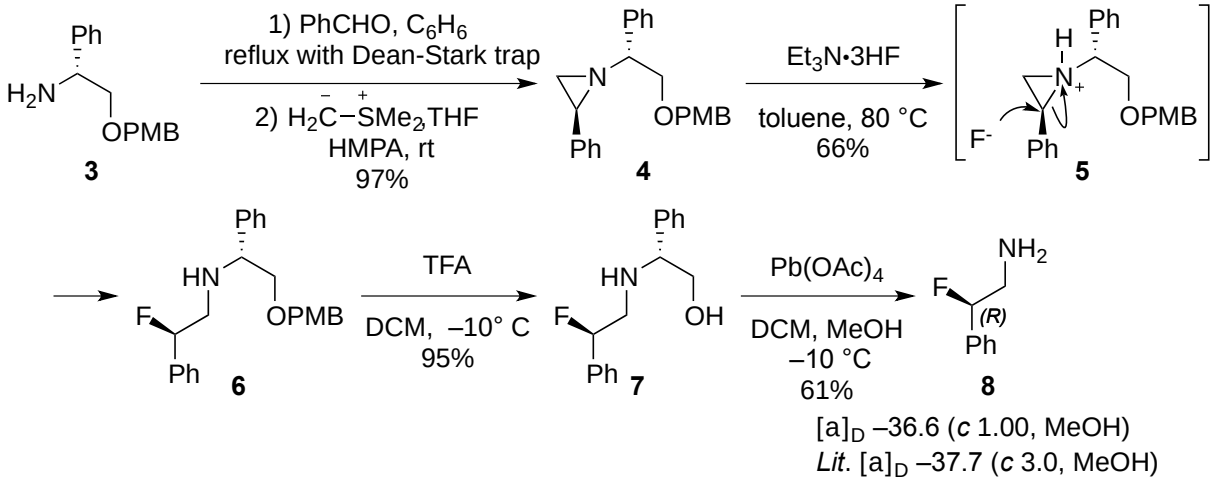
1a-n **2a-n**

	Aziridine (Ar)	Yield of **2** (%)[a]	Diastereomeric ratio of **2**[b]
a	Ph	79	>99 : 1
b	*o*-Cl-C_6H_4	70	>99 : 1
c	*m*-Cl-C_6H_4	63	>99 : 1
d	*p*-Cl-C_6H_4	78	>99 : 1
e	*o*-Br-C_6H_4	58	>99 : 1
f	*m*-Br-C_6H_4	72	>99 : 1
g	*p*-Br-C_6H_4	73	>99 : 1
h	*p*-NO_2-C_6H_4	44	>99 : 1
i	*o*-Me-C_6H_4	97	>99 : 1
j	*m*-Me-C_6H_4	67	>99 : 1
k	*p*-Me-C_6H_4	91	>99 : 1
l	*o*-MeO-C_6H_4	33	71 : 29
m	*m*-MeO-C_6H_4	79	>99 : 1
n	*p*-MeO-C_6H_4	not detected	-

a) Isolated yield. b) Estimated from the ^1H NMR spectrum.

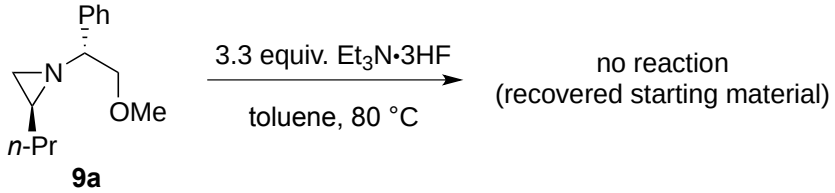
Most of these reactions proceeded with excellent stereoselectivity. However, aziridines with *o*- and *p*-methoxyphenyl groups (**1l**,**n**) gave lower yields and regioselectivities because of their instability under acidic conditions, which was due to the strong electron-donating effect of the methoxy group on the aromatic ring.[8] To estimate the absolute stereochemistry, a known *β*-fluoroamine **8** was prepared from (*R*)-*O*-PMB-2-phenylglycinol **3**[9] *via* aziridine **4** synthesized as per our previous methodology[7] (Scheme 1). Condensation of benzaldehyde with **3** gave an imine, which was reacted with dimethylsulfonium methylide (prepared from trimethylsulfonium iodide in THF) to furnish the desired aziridine **4** in good yield with high diastereoselectivity (dr = >99:1). Next, the regio- and stereoselective ring-opening

reaction of **4** with 3.3 equiv. of $Et_3N{\cdot}3HF$ in toluene at 80 °C gave the desired *β*-fluoroamine **6** in moderate yield as a single isomer. Treatment of **6** with trifluoroacetic acid (TFA) in CH_2Cl_2 (DCM) at –10 °C gave **7** in 95% yield. Oxidative cleavage of the amino alcohol moiety[10] from **7** with $Pb(OAc)_4$ gave **8**. The stereochemistry of **8** was assigned as *R*-configuration by comparing the optical rotation of this compound with literature data.[11] These results led us to believe that the reaction proceeds *via* the formation of an intermediate aziridinium salt **5** with protonation by hydrogen fluoride, and subsequent regioselective ring-opening reaction by F^- at the active benzylic *C*(2) position.



Scheme 1. Estimation of stereochemistry of *β*-fluoroamine **8**

Next, we attempted the ring-opening reaction of chiral 2-aliphatic-substituted aziridine derivative **9a** with $Et_3N{\cdot}3HF$; however, the reaction did not proceed at all, and the starting material was recovered (Scheme 2).



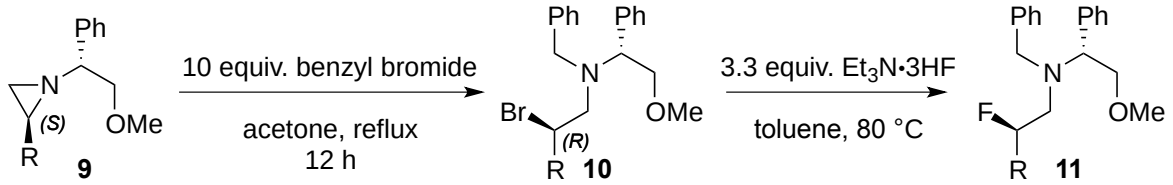
Scheme 2. Reaction of 2-*n*-propylaziridine derivative **9a** with $Et_3N{\cdot}3HF$

The reactivity of 2-aryl-substituted aziridines **1** increases due to the resonance possibilities provided by benzylic system in the transition state.[12] However, aziridine **9a** has an aliphatic moiety which has no active property in the case.

In our previous work,[13] we reported that 2-aliphatic-substituted chiral aziridine derivative **9** could be converted into a *β*-amino alcohol through *β*-bromoamine **10**. Accordingly, **9** was reacted with benzyl

bromide to afford **10**, which was then treated with $Et_3N{\cdot}3HF$ to give **11** (Table 2). The ring-opening reaction of aziridines **9a–g** using 10 equiv. benzyl bromide in acetone under reflux gave *β*-bromoamines **10a–g** with an *R*-chiral center as single isomers. Next, fluorination of **10a–g** with 3.3 equiv. $Et_3N{\cdot}3HF$ in toluene at 80 °C yielded the desired fluorinated products **11a–g** with excellent diastereoselectivity. With an increase in the size of the alkyl chain (R: *i*-Pr, *c*-C_5H_9 and *c*-C_6H_{11}), a longer time was required for reaction completion. The presence of a very bulky group (R: *t*-Bu) in the substrate significantly decreased the yield of the fluorinated product **11g**.

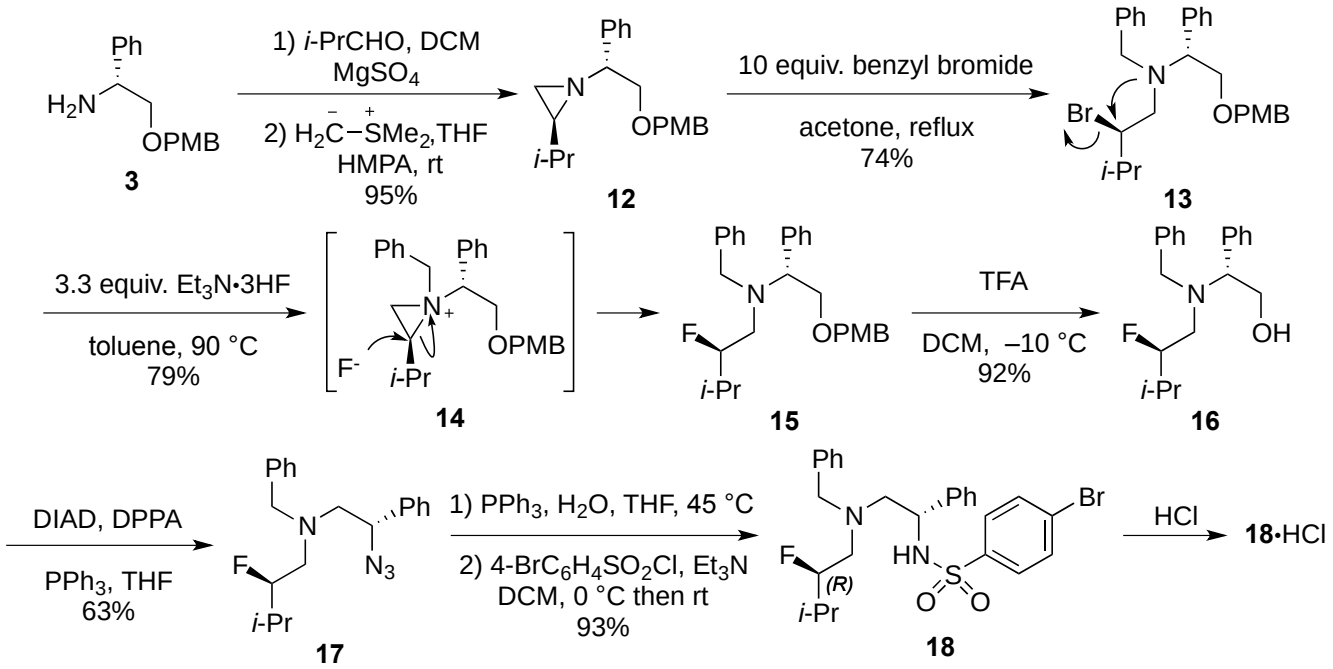
Table 2. Ring-opening reaction of 2-aliphatic-substituted aziridine derivatives **9**



	Aziridine (R)	Yield of **10** (%)[a]	Reaction time of fluorination (h)	Yield of **11** (%)[a]	Diastereomeric ratio of **11**[d]
a	*n*-Pr	92	24	91	>99 : 1
b	*i*-Pr	92	96	93	>99 : 1
c	*i*-Bu	53	72	78	>99 : 1
d	*n*-C_7H_{15}	72	24	72	>99 : 1
e	*c*-C_5H_9	96	96	54	>99 : 1
f	*c*-C_6H_{11}	69	96	73	>99 : 1
g	*t*-Bu	81[b]	168[c]	23	>99 : 1

a) Isolated yield. b) The reaction was performed with 3-pentanone as solvent at 90 °C.
c) The reaction was carried out at 90 °C. d) Estimated from the ^{1}H-NMR spectrum.

We next proceeded to determine the stereochemistry of aliphatic *β*-fluoroamine **11** based on the X-ray crystallographic analysis of **18**·HCl (Scheme 3). The ring-opening reaction of aziridine **12** (prepared from (*R*)-*O*-PMB-2-phenylglycinol **3**) with benzyl bromide, followed by fluorination with $Et_3N{\cdot}3HF$, produced the expected *β*-fluoroamine **15** as a single isomer. Removal of the PMB group with TFA and subsequent azidation using a modified Tomioka's method[14] with diisopropyl azodicarboxylate (DIAD) and diphenylphosphoryl azide (DPPA) gave azide **17** as a single isomer. Staudinger reduction of **17** with PPh_3, followed by sulfonylation with 4-bromobenzenesulfonyl chloride, afforded sulfonamide **18** (Scheme 3). Single-crystal X-ray analysis of the HCl salt of **18** confirmed the absolute configuration at the *β*-position to be *R* (see ORTEP diagram in the Figure 1).



Scheme 3. Estimation of stereochemistry of *β*-fluoroamine **18**

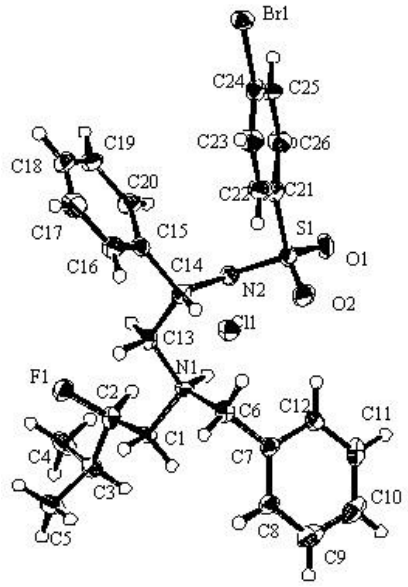


Figure 1. ORTEP drawing of **18**·HCl

In this reaction, the *R*-configuration at the *β*-position of *β*-bromoamine **10** is completely retained in **11a–g** (see the reaction in Table 2). The high regio- and stereocontrol of this reaction can be explained by neighboring group participation of the nitrogen atom, which gives *N*-benzylaziridinium salt **14** as an active species upon heating. Subsequent ring-opening reaction induced by the attack of F^- at the *C*(2) position of the aziridinium ion gives the desired product **11**.

In conclusion, we developed an efficient method for the fluorination of chiral aziridine derivatives to afford chiral *β*-fluoroamines. 2-Aryl-substituted aziridines underwent ring-opening reaction with

$Et_3N·3HF$ in a regio- and stereocontrolled manner. Moreover, stereocontrolled syntheses of chiral *β*-fluoroamines from less reactive chiral 2-aliphatic-substituted aziridines were accomplished *via* conversion to *β*-bromoamines using benzyl bromide, followed by treatment with $Et_3N·3HF$. The proposed methodology is particularly well suited for the stereocontrolled introduction of a fluorine atom at the *β*-position of amines and would be useful for obtaining fluorine-containing biologically active compounds.

EXPERIMENTAL

General: All reactions were carried out under a nitrogen atmosphere. Aldehydes were distilled prior to use. Other reagents were obtained from commercial sources, and used as received. Anhydrous toluene and CH_2Cl_2 were purchased form Kanto Chemical Co. Inc. Anhydrous THF was purchased form Wako Pure Chemical Industries, Ltd. ^1H, ^{13}C, and ^{19}F NMR spectra were measured on a BRUKER BioSpin AVANCE-III-400 spectrometer at 400, 100, and 376 MHz, respectively. All NMR spectra were measured in $CDCl_3$. Chemical shifts were reported downfield from TMS (0 ppm) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported relative to $CDCl_3$ (77.0 ppm). For ^{19}F NMR, chemical shifts were reported relative to $CF_3C_6H_5$ (–63.72 ppm). Mass spectra were recorded on a JEOL JMS-T100LP mass spectrometer by electrospray ionization (ESI). For chemical ionization (CI), a JEOL JMS 600 mass spectrometer was used. Optical rotation were taken with a JASCO-DIP-1000 polarimeter at rt. Infrared spectra were measured on a Perkin-Elmer Spectrum Two. Purification was by column chromatography using 63–210 mm silica gel 60N (Kanto Chemical Co. Inc.)

1. General procedure for ring-opening reaction of 2-aryl-substituted aziridine derivatives **1**.

To a stirred solution of the aziridine **1** (0.2 mmol) in dry toluene (1 mL) was added $Et_3N·3HF$ (0.66 mmol, 108 mL) in Teflon® vessel at rt. The reaction mixture was then heated, and stirred for 24 h (no attempt was made to monitor these reactions due to the hazardous nature of HF). After cooling, the reaction mixture was slowly poured into 1M NaOH aqueous solution (10 mL) and the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (10 mL × 3 times), and the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. Finally, the residue was purified by silica gel chromatography.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-phenylethylamine (2a) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 6 : 1) to afford product as a yellow oil (79%). ^1H NMR: δ 1.26 (br s, 1H), 2.83 (ddd, *J* = 3.4, 13.6, 29.6 Hz, 1H), 2.96 (ddd, *J* = 8.4, 13.6, 18.1 Hz, 1H), 3.36 (s, 3H), 3.42 (dd, *J* = 8.6, 9.4 Hz, 1H), 3.48 (dd, *J* = 4.1, 9.4 Hz, 1H), 4.01 (dd, *J* = 4.1, 8.6 Hz, 1H), 5.59 (ddd, *J* = 3.4, 8.4, 48.7 Hz, 1H), 7.24–7.37 (m, 10H). ^{13}C NMR: δ 52.6 (d, *J* = 24.2 Hz), 58.7, 61.7,

77.6, 92.9 (d, *J* = 171.3 Hz), 125.4 (d, *J* = 7.0 Hz), 127.4, 127.4, 128.1 (d, *J* = 1.8 Hz), 128.2, 128.4, 138.3 (d, *J* = 19.4 Hz), 140.1. ^{19}F NMR: δ −183.7 (ddd, *J* = 17.7, 30.0, 48.4 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{21}FNO$ $(M+H)^+$: 274.1607, Found: 274.1606. $[\alpha]_D$ −63.3 (*c* 1.00, $CHCl_3$). IR (film): 2926, 1454, 1109 cm^{-1}.

(*R*)-2-(2-Chlorophenyl)-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (2b) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) to afford product as a yellow oil (70%). ^{1}H NMR: δ 2.43 (br s, 1H), 2.77–2.99 (m, 2H), 3.39 (s, 1H), 3.41–3.52 (m, 2H), 4.10 (dd, *J* = 4.0, 8.8 Hz, 1H), 5.98 (ddd, *J* = 2.5, 8.2, 48.2 Hz, 1H), 7.19–7.35 (m, 8H), 7.45–7.49 (m, 1H). ^{13}C NMR: δ 51.0 (d, *J* = 23.5 Hz), 58.8, 61.1, 77.8, 89.9 (d, *J* = 172.4 Hz), 126.8, 126.9 (d, *J* = 9.9 Hz), 127.5, 127.6, 128.4, 129.1 (d, *J* = 1.1 Hz), 129.2 (d, *J* = 0.7 Hz), 130.8 (d, *J* = 5.9 Hz), 136.2 (d, *J* = 21.6 Hz), 140.0. ^{19}F NMR: δ −190.8 (ddd, *J* = 21.1, 32.7, 48.4 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}ClFNO$ $(M+H)^+$: 308.1217, Found: 308.1220. $[\alpha]_D$ −93.4 (*c* 0.50, $CHCl_3$). IR (film): 3350, 2924, 1575, 1453, 1109, 701 cm^{-1}.

(*R*)-2-(3-Chlorophenyl)-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (2c) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford product as a yellow oil (63%). ^{1}H NMR: δ 1.58 (br s, 1H), 2.79–2.97 (m, 1H), 3.36 (s, 3H), 3.37–3.43 (m, 1H), 3.46 (dd, *J* = 4.0, 9.5 Hz, 1H), 3.99 (dd, *J* = 4.0, 8.9 Hz, 1H), 5.54 (ddd, *J* = 4.0, 7.3, 48.3 Hz, 1H), 7.10–7.16 (m, 1H), 7.24–7.36 (m, 8H). ^{13}C NMR: δ 52.4 (d, *J* = 23.5 Hz), 58.8, 61.8, 77.7, 92.3 (d, *J* = 173.1 Hz), 123.6 (d, *J* = 7.3 Hz), 125.7 (d, *J* = 7.7 Hz), 127.5, 127.6, 128.3 (d, *J* = 1.8 Hz), 128.5, 129.6, 134.3, 140.0, 140.5 (d, *J* = 20.1 Hz). ^{19}F NMR: δ −185.4 (ddd, *J* = 20.8, 27.2, 48.0 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}ClFNO$ $(M+H)^+$: 308.1217, Found: 308.1224. $[\alpha]_D$ −5.1 (*c* 1.00, $CHCl_3$). IR (film): 2925, 1454, 1109 cm^{-1}.

(*R*)-2-(4-Chlorophenyl)-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (2d) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford product as a yellow oil (78%). ^{1}H NMR: δ 2.25 (br s, 1H), 2.77–2.97 (m, 2H), 3.36 (s, 3H), 3.36–3.43 (m, 1H), 3.46 (d, *J* = 3.9, 9.4 Hz, 1H), 3.98 (dd, *J* = 3.9, 9.4 Hz, 1H), 5.54 (ddd, *J* = 3.8, 7.5, 48.1 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.27–7.36 (m, 7H). ^{13}C NMR: δ 52.5 (d, *J* = 23.8 Hz), 58.8, 61.8, 77.6, 92.4 (d, *J* = 172.4 Hz), 126.9 (d, *J* = 7.0 Hz), 127.5, 127.6, 128.4, 128.5, 134.0 (d, *J* = 1.8 Hz), 136.9 (d, *J* = 20.2 Hz), 140.0. ^{19}F NMR: δ −184.0 (ddd, *J* = 19.8, 27.8, 47.9 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}ClFNO$ $(M+H)^+$: 308.1217, Found: 308.1191. $[\alpha]_D$ −6.3 (*c* 1.00, $CHCl_3$). IR (film): 2889, 1454, 1109 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(2-bromophenyl)ethylamine (2e) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford product as a yellow oil (58%). ^{1}H NMR: δ 2.44 (br s, 1H), 2.75–3.01 (m, 2H), 3.39 (s, 3H), 3.39–3.46 (m, 1H), 3.49 (dd, *J* = 3.9, 9.4 Hz, 1H), 4.12 (dd, *J* = 3.9, 8.9 Hz, 1H), 5.92 (ddd, *J* = 2.3, 8.4, 43.1 Hz, 1H), 7.12–7.18 (m, 1H),

7.22–7.36 (m, 6H), 7.43–7.48 (m, 2H). ^{13}C NMR: δ 51.1 (d, *J* = 23.5 Hz), 58.8, 61.1, 77.8, 91.9 (d, *J* = 173.1 Hz), 120.5 (d, *J* = 5.9 Hz), 127.2 (d, *J* = 10.3 Hz), 127.4, 127.5, 127.3, 128.4, 129.5 (d, *J* = 1.5 Hz), 132.5, 137.8 (d, *J* = 21.3 Hz), 140.1. ^{19}F NMR: δ −189.5 (ddd, *J* = 20.8, 33.4, 48.0 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}{}^{79}BrFNO$ $(M+H)^+$: 352.0712, Found: 352.0736. $[\alpha]_D$ −88.2 (*c* 1.00, $CHCl_3$). IR (film): 2888, 1470, 1109 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(3-bromophenyl)ethylamine (2f) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) to afford product as a yellow oil (72%). ^{1}H NMR: δ 1.59 (br s, 1H), 2.79–2.97 (m, 2H), 3.36 (s, 3H), 3.37–3.43 (m, 1H), 3.46 (dd, *J* = 3.9, 9.4 Hz, 1H), 3.98 (dd, *J* = 3.9, 8.8 Hz, 1H), 5.54 (ddd, *J* = 4.1, 7.3, 48.2 Hz, 1H), 7.15–7.44 (m, 9H). ^{13}C NMR: δ 52.4 (d, *J* = 23.5 Hz), 58.8, 61.8, 77.6, 92.2 (d, *J* = 173.5 Hz), 122.4, 124.1 (d, *J* = 7.3 Hz), 127.5, 127.6, 128.5, 128.6 (d, *J* = 7.7 Hz), 129.9, 131.2 (d, *J* = 1.5 Hz), 140.0, 140.7 (d, *J* = 19.8 Hz). ^{19}F NMR: δ −185.3 (ddd, *J* = 20.8, 27.2, 48.0 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}{}^{79}BrFNO$ $(M+H)^+$: 352.0712, Found: 352.0730. $[\alpha]_D$ −51.8 (*c* 1.00, $CHCl_3$). IR (film): 3342, 2924, 1573, 1453 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(4-bromophenyl)ethylamine (2g) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) to afford product as a yellow oil (73%). ^{1}H NMR: δ 2.23 (br s, 1H), 2.75–2.99 (m, 2H), 3.36 (s, 3H), 3.37–3.43 (m, 1H), 3.46 (dd, *J* = 4.0, 9.5 Hz, 1H), 3.98 (dd, *J* = 4.0, 8.9 Hz, 1H), 5.53 (ddd, *J* = 3.8, 7.5, 48.1 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.24–7.35 (m, 5H), 7.46 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR: δ 52.4 (d, *J* = 23.8 Hz), 58.8, 61.9, 77.6, 92.4 (d, *J* = 172.4 Hz), 122.2 (d, *J* = 2.2 Hz), 127.2 (d, *J* = 7.0 Hz), 127.5, 127.6, 128.5, 131.4, 137.5 (d, *J* = 20.2 Hz), 140.0. ^{19}F NMR: δ −184.5 (ddd, *J* = 19.8, 27.6, 48.0 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}{}^{79}BrFNO$ $(M+H)^+$: 352.0712, Found: 352.0695. $[\alpha]_D$ −6.6 (*c* 1.00, $CHCl_3$). IR (film): 2925, 1454, 1111 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(4-nitrophenyl)ethylamine (2h) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 1 : 1) to afford product as a yellow oil (44%). ^{1}H NMR: δ 1.58 (br s, 1H), 2.81–3.04 (m, 2H), 3.37 (s, 3H), 3.33–3.41 (m, 1H), 3.44 (dd, *J* = 3.8, 9.4 Hz, 1H), 3.98 (dd, *J* = 3.8, 9.1 Hz, 1H), 5.67 (ddd, *J* = 3.4, 6.6, 47.6 Hz, 1H), 7.19–7.38 (m, 5H), 7.42 (d, *J* = 8.6 Hz, 2H), 8.21 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR: δ 52.2 (d, *J* = 22.7 Hz), 58.8, 61.9, 77.6, 92.0 (d, *J* = 175.0 Hz), 123.5, 126.2 (d, *J* = 7.7 Hz), 127.5, 127.8, 128.5, 139.8, 145.8 (d, *J* = 20.5 Hz), 147.6. ^{19}F NMR: δ −188.7 (ddd, *J* = 22.5, 25.5, 48.0 Hz). HRMS (ESI+) Calcd. for $C_{17}H_{20}FN_2O_3$ $(M+H)^+$: 319.1458, Found: 319.1442. $[\alpha]_D$ −6.3 (*c* 1.00, $CHCl_3$). IR (film): 2922, 1454, 1108 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(2-methylphenyl)ethylamine (2i) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford product as a yellow oil (97%). ^{1}H NMR: δ 1.63 (br s, 1H), 2.17 (s, 3H), 2.77 (ddd, *J* = 2.8, 14.1, 32.9 Hz, 1H), 2.93 (ddd, *J* = 8.9, 14.1, 17.4 Hz, 1H), 3.38 (s, 3H), 3.41–3.47 (m, 1H), 3.50 (dd, *J* = 4.0, 9.4 Hz, 1H), 4.08 (dd, *J* = 4.0, 8.5

Hz, 1H), 5.82 (ddd, *J* = 2.8, 8.9, 48.5 Hz, 1H), 7.03–7.24 (m, 3H), 7.24–7.39 (m, 6H). ^{13}C NMR: δ 18.7, 51.5 (d, *J* = 24.6 Hz), 58.8, 61.2, 77.8, 90.0 (d, *J* = 170.2 Hz), 125.2 (d, *J* = 8.8 Hz), 126.0, 127.5, 128.0 (d, *J* = 1.8 Hz), 128.4, 130.2, 134.1 (d, *J* = 5.1 Hz), 136.5 (d, *J* = 18.7 Hz), 140.0. ^{19}F NMR: δ −186.3 (ddd, *J* = 17.7, 32.7, 49.0 Hz). HRMS (ESI+) Calcd. for $C_{18}H_{23}FNO$ $(M+H)^+$: 288.1764, Found: 288.1769. $[\alpha]_D$ −71.3 (*c* 1.00, EtOH). IR (film): 3028, 2924, 1455, 1110 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(3-methylphenyl)ethylamine (2j) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford product as a yellow oil (67%). ^{1}H NMR: δ 1.63 (br s, 1H), 2.33 (s, 3H), 2.82 (ddd, *J* = 3.4, 13.6, 30.0 Hz, 1H), 2.96 (ddd, *J* = 8.4, 13.6, 17.7 Hz, 1H), 3.36 (s, 3H), 3.43 (dd, *J* = 8.7, 9.5 Hz, 1H), 3.48 (dd, *J* = 4.1, 9.5 Hz, 1H), 4.00 (dd, *J* = 4.1, 8.7 Hz, 1H), 5.55 (ddd, *J* = 3.4, 8.4, 48.7 Hz, 1H), 7.03–7.12 (m, 4H), 7.20–7.35 (m, 5H). ^{13}C NMR: δ 21.4, 52.7 (d, *J* = 24.2 Hz), 58.8, 61.8, 77.7, 93.1, 122.6 (d, *J* = 7.0 Hz), 126.2 (d, *J* = 7.0 Hz), 127.5 (C × 2), 128.2, 128.5, 129.1 (d, *J* = 1.8 Hz), 138.0, 138.3 (d, *J* = 19.4 Hz), 140.2. ^{19}F NMR: δ −183.2 (ddd, *J* = 17.7, 30.1, 48.2 Hz). HRMS (ESI+) Calcd. for $C_{18}H_{23}FNO$ $(M+H)^+$: 288.1764, Found: 288.1769. $[\alpha]_D$ −2.5 (*c* 1.00, EtOH). IR (film): 2923, 1454, 1110 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(4-methylphenyl)ethylamine (2k) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford product as a yellow oil (91%). ^{1}H NMR: δ 1.73 (br s, 1H), 2.33 (s, 3H), 2.80 (ddd, *J* = 3.4, 13.4, 29.6 Hz, 1H), 2.96 (ddd, *J* = 8.4, 13.4, 17.2 Hz, 1H), 3.36 (s, 3H), 3.42 (dd, *J* = 8.6, 9.4 Hz, 1H), 3.47 (dd, *J* = 4.1, 9.4 Hz, 1H), 4.00 (dd, *J* = 8.6, 4.0 Hz, 1H), 5.55 (ddd, *J* = 3.4, 8.4, 48.6 Hz, 1H), 7.12–7.18 (m, 4H), 7.24–7.36 (m, 5H). ^{13}C NMR: δ 21.1, 52.7 (d, *J* = 24.6 Hz), 58.8, 61.8, 77.7, 93.0 (d, *J* = 170.6 Hz), 125.6 (d, *J* = 6.6 Hz), 127.5, 128.4, 129.0, 135.4 (d, *J* = 19.4 Hz), 138.1 (d, *J* = 1.8 Hz), 140.2. ^{19}F NMR: δ −181.6 (ddd, *J* = 17.7, 30.0, 48.4 Hz). HRMS (ESI+) Calcd. for $C_{18}H_{23}FNO$ $(M+H)^+$: 288.1764, Found: 288.1770. $[\alpha]_D$ −12.0 (*c* 1.00, $CHCl_3$). IR (film): 2924, 1454, 1110 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-2-(2-methoxylphenyl)ethylamine (2l: major isomer) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 5 : 1) to afford product as a yellow oil (33%, inseparable diastereomeric mixture). ^{1}H NMR: δ 2.07 (br s, 1H), 2.78–2.91 (m, 2H), 3.38 (s, 3H), 3.41–3.52 (m, 2H), 3.68 (s, 3H), 4.08 (dd, *J* = 4.1, 8.5 Hz, 1H), 5.62 (ddd, *J* = 3.9, 7.0, 48.7 Hz, 1H), 6.77–6.81 (m, 1H), 6.92–6.97 (m, 1H), 7.21–7.27 (m, 2H), 7.28–7.41 (m, 5H). ^{13}C NMR: δ 51.3 (d, *J* = 23.1Hz), 55.0, 58.8, 61.2, 77.8, 88.5 (d, *J* = 169.5 Hz), 110.0, 120.5, 126.0 (d, *J* = 9.5 Hz), 127.1 (d, *J* = 20.2 Hz), 127.4, 127.7, 128.3, 128.9 (d, *J* = 1.5 Hz), 140.4, 155.4 (d, *J* = 5.9 Hz). ^{19}F NMR: δ −192.6– −192.3 (m, major isomer), −190.7 (ddd, *J* = 18.4, 36.1, 48.4 Hz, minor isomer). HRMS (CI) Calcd. for $C_{18}H_{23}FNO_2$ $(M+H)^+$: 304.1713, Found: 304.1695. IR (film): 2920, 1494, 1248 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-Methoxy-1-phenylethyl)-2-(3-methoxyphenyl)ethylamine (2m) The compound

was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) to afford product as a yellow oil (79%). ^{1}H NMR: δ 1.63 (br s, 1H), 2.74–3.01 (m, 2H), 3.36 (s, 3H), 3.39–3.50 (m, 2H), 3.79 (s, 3H), 4.00 (dd, *J* = 3.9, 8.4 Hz, 1H), 5.56 (ddd, *J* = 2.8, 8.0, 48.5 Hz, 1H), 6.76–6.89 (m, 3H), 7.20–7.33 (m, 6H). ^{13}C NMR: δ 52.6 (d, *J* = 23.8 Hz), 55.0, 58.7, 61.7, 77.6, 92.8 (d, *J* = 172.4 Hz), 110.9 (d, *J* = 7.7 Hz), 113.7 (d, *J* = 1.1 Hz), 117.6 (d, *J* = 7.0 Hz), 127.4, 127.5, 128.4, 129.3, 139.9 (d, *J* = 19.4 Hz), 140.1, 159.5. ^{19}F NMR: δ −184.0 (ddd, *J* = 18.4, 30, 48.4 Hz) HRMS (ESI+) Calcd. for $C_{18}H_{23}FNO_2$ $(M+H)^+$: 304.1713, Found: 304.1715. $[\alpha]_D$ −65.2 (*c* 1.00, $CHCl_3$). IR (film): 2924, 1454, 1107, 699 cm^{-1}.

2. Synthesis of **8**.

(*S*)-*N*-((*R*)-2-(4-Methoxybenzyloxy)-1-phenylethyl)-2-phenylaziridine (4) A solution of *n*-butyllithium (1.2 mL, 1.6 M in hexane, 1.9 mmol) was added dropwise over several minutes to a stirred solution of powdered trimethylsulfonium iodide (0.4 g, 1.9 mmol) and HMPA (0.3 mL, 1.9 mmol) in 3 mL of dry THF under nitrogen at 0 °C. After stirring for 20 min, a solution of imine in 0.6 mL of dry THF, which was prepared from **3** (200 mg, 0.78 mmol) and benzaldehyde (83 mg, 0.78 mmol), was added. After stirring for 12 h at rt, the resulting mixture was diluted with 10 mL of water and extracted with AcOEt (15 mL × 3 times). The combined organic layer was washed with brine (20 mL × 2 times), dried over Na_2SO_4, and evaporated to give the residue, which was purified by silica gel chromatography (*n*-hexane : AcOEt = 5 : 1) to afford **4** as a yellow oil (271 mg, 0.75 mmol, 97%). ^{1}H NMR: δ 2.13 (d, *J* = 6.5 Hz, 1H), 2.15 (d, *J* = 3.6 Hz, 1H), 2.35 (dd, *J* = 3.6, 6.5 Hz, 1H), 2.91 (dd, *J* = 4.9, 7.4 Hz, 1H), 3.68 (dd, *J* = 4.9, 9.8 Hz, 1H), 3.81 (s, 3H), 3.86 (dd, *J* = 7.4, 9.8 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.15–7.20 (m, 3H), 7.20–7.28 (m, 6H), 7.34–7.42 (m, 3H). ^{13}C NMR: δ 38.8, 39.1, 55.2, 73.0, 74.4, 75.6, 113.7, 126.4, 126.6, 127.3, 127.6, 128.1, 128.2, 129.0, 130.5, 140.1, 140.7, 159.0. HRMS (ESI+) Calcd. for $C_{24}H_{25}NNaO_2$ $(M+Na)^+$: 382.1783, Found: 382.1823. $[\alpha]_D$ −24.2 (*c* 1.00, $CHCl_3$). IR (film): 3030, 2855, 1513, 1247 cm^{-1}.

(*R*)-2-Fluoro-*N*-((*R*)-2-(4-methoxybenzyloxy)-1-phenylethyl)-2-phenylethylamine (6) To a stirred solution of **4** (271 mg, 0.753 mmol) in dry toluene (3.8 mL) was added $Et_3N{\cdot}3HF$ (3.3 equiv., 0.41 mL, 2.51 mmol) in Teflon® vessel at rt. The reaction mixture was then heated, and stirred for 24 h (no attempt was made monitor these reactions due to the hazardous nature of HF). After cooling, the reaction mixture was slowly poured into 1M NaOH aqueous solution (20 mL) and the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (20 mL × 3 times), and the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford **6** as a yellow oil (188 mg, 0.49 mmol, 66%). ^{1}H NMR: δ 1.61 (br s, 1H), 2.82 (ddd, *J* = 3.8, 13.4, 28.2 Hz, 1H), 2.96 (ddd, *J* = 8.1, 13.4,

17.8 Hz, 1H), 3.46 (t, *J* = 9.2 Hz, 1H), 3.54 (dd, *J* = 3.8, 9.2 Hz, 1H), 3.81 (s, 3H), 4.01 (dd, *J* = 3.8, 9.2 Hz, 1H), 4.41–4.49 (m, 1H), 5.56 (ddd, *J* = 3.8, 8.1, 48.3 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.27–7.37 (m, 10H). ^{13}C NMR: δ 52.6 (d, *J* = 24.6 Hz), 55.3, 62.0, 72.8, 75.1, 93.1 (d, *J* = 171.7 Hz), 113.8, 125.6 (d, *J* = 7.0 Hz), 127.6, 127.6, 128.4, 128.5, 129.3, 130.1, 138.5 (d, *J* = 19.4 Hz), 140.2, 159.2, 162.0. ^{19}F NMR: δ −183.1 (ddd, *J* = 17.7, 28.6, 47.0 Hz). HRMS (ESI+) Calcd. for $C_{24}H_{26}FNNaO_2$ $(M+Na)^+$: 402.1845, Found: 402.1866. $[\alpha]_D$ −72.7 (*c* 1.00, $CHCl_3$). IR (film): 2928, 2837, 1493, 1248, 1111, 756 cm^{-1}.

(*R*)-2-((*R*)-2-Fluoro-2-phenylethylamino)-2-phenylethanol (7) To a stirred solution of **6** (30 mg, 79 μmol) in DCM (0.79 mL) was added TFA (0.79 mL) at −10 °C and stirred for 26 h. The reaction mixture was quenched with 1N NaOH aqueous solution (20 mL), and extracted with $CHCl_3$ (15 mL × 3 times). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 1 : 1) to afford **7** as a yellow oil (19.5 mg, 0.075 mmol, 95%). ^{1}H NMR: δ 1.72 (br s, 2H), 2.80 (ddd, *J* = 3.0, 13.3, 32.7 Hz, 1H), 3.06 (ddd, *J* = 8.8, 13.3, 16.9 Hz, 1H), 3.57 (dd, *J* = 8.7, 10.9 Hz ,1H), 3.73 (dd, *J* = 4.4, 10.9 Hz, 1H), 3.84 (dd, *J* = 4.4, 8.7 Hz, 1H), 5.63 (ddd, *J* = 3.0, 8.8, 48.9 Hz, 1H), 7.24–7.41 (m, 10H). ^{13}C NMR: δ 53.1 (d, *J* = 23.5 Hz), 64.3, 66.7, 93.9 (d, *J* = 171.3 Hz), 125.5 (d, *J* = 7.0 Hz), 127.0, 127.8, 128.4, 128.51 (d, *J* = 1.8 Hz), 128.8, 138.1 (d, *J* = 1.4 Hz), 140.0. ^{19}F NMR: δ −183.8 (ddd, *J* = 17.0, 31.3, 49.7 Hz). HRMS (ESI+) Calcd. for $C_{16}H_{19}FNO$ $(M+H)^+$: 260.1451, Found: 260.1448. $[\alpha]_D$ −36.3 (*c* 1.00, $CHCl_3$). IR (film): 2926, 1454, 1028 cm^{-1}.

(*R*)-2-Fluoro-2-phenylethylamine (8) To a stirred solution of **7** (50 mg, 0.193 mmol) in DCM/MeOH (1 : 1, 3.9 mL) was added $Pb(OAc)_4$ (1 equiv. 90 mg, 0.193 mmol) at −10 °C. After stirring for 30 min, another $Pb(OAc)_4$ (1 equiv. 90 mg, 0.193 mmol) was added to the reaction mixture, stirred for additional 2.5 h. The reaction was quenched with hydroxyammonium chloride, alkalized with 1M NaOH aqueous solution and extracted with $CHCl_3$ (5 mL × 3 times). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The residue was purified by silica gel chromatography ($CHCl_3$: MeOH : NH_4OH = 110 : 9 : 1) to afford **8** as yellow oil (16.3 mg, 0.117 mmol, 61%). ^{1}H NMR: δ 1.49 (br s, 2H), 2.99–3.19 (m, 2H), 5.45 (ddd, *J* = 3.8, 7.1, 48.2 Hz, 1H), 7.3–7.44 (m, 5H). The ^{1}H NMR spectrum matched that reported in the literature.[5]

3. General procedure for the ring-opening reaction of aziridine **9** with benzyl bromide.

A mixture of **9** (1.5 mmol) and benzyl bromide (10 equiv., 1.8 mL, 15.0 mmol) in acetone (4.5 mL) was refluxed for 12 h under nitrogen atmosphere. After cooling, the reaction mixture was evaporated to give the crude product, which was purified by silica gel chromatography (*n*-hexane : AcOEt = 16 : 1). The

β-bromoamine **10** was immediately used in the next step.

(*R*)-*N*-Benzyl-2-bromo-*N*-((*R*)-2-methoxy-1-phenylethyl)pentylamine (10a) Yellow oil, 92% yield.[13]

(*R*)-*N*-Benzyl-2-bromo-*N*-((*R*)-2-methoxy-1-phenylethyl)-3-methylbutylamine (10b) Yellow oil, 92% yield.[13]

(*R*)-*N*-Benzyl-2-bromo-*N*-((*R*)-2-methoxy-1-phenylethyl)-4-methylpentylamine (10c) Yellow oil, 53% yield. ^{1}H NMR: δ 0.70 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H), 1.34 (ddd, *J* = 4.1, 10.5, 14.4 Hz, 1H), 1.46–1.54 (m, 1H), 1.70–1.83 (m, 1H), 2.78 (dd, *J* = 7.0, 14.2 Hz, 1H), 3.12 (dd, *J* = 6.9, 14.2 Hz, 1H), 3.36 (s, 3H), 3.63 (d, *J* = 13.7 Hz, 1H), 3.77 (d, *J* = 13.7 Hz, 1H), 3.77–3.82 (m, 1H), 3.84 (dd, *J* = 7.2, 9.8 Hz, 1H), 3.91 (dd, *J* = 6.0, 9.8 Hz, 1H), 4.04 (dd, *J* = 6.0, 7.2 Hz, 1H), 7.21–7.39 (m, 10H). ^{13}C NMR: δ 20.7, 23.3, 26.1, 45.3, 55.2, 56.5, 28.9, 60.0, 63.3, 72.5, 120.8, 127.4, 128.2, 128.5, 130.5, 131.3, 138.8, 139.1. HRMS (ESI+) Calcd. for $C_{22}H_{31}BrNO$ $(M+H)^+$: 404.1589, Found: 404.1567. $[\alpha]_D$ −147.1 (*c* 1.00, $CHCl_3$). IR (film): 2956, 1486, 1451, 1115, 700 cm^{-1}.

(*R*)-*N*-Benzyl-2-bromo-*N*-((*R*)-2-methoxy-1-phenylethyl)octylamine (10d) Yellow oil, 72% yield. ^{1}H NMR: δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.11–1.55 (m, 9H), 1.76–1.84 (m, 1H), 2.79 (dd, *J* = 7.3, 14.0 Hz, 1H), 3.10 (dd, *J* = 6.6, 14.0 Hz, 1H), 3.36 (s, 3H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.76–3.81 (m, 2H), 3.84 (dd, *J* = 7.3, 9.9 Hz, 1H), 3.90 (dd, *J* = 6.0, 9.9 Hz, 1H), 4.02 (dd, *J* = 6.0, 7.3 Hz, 1H), 7.22–7.37 (m, 10H). ^{13}C NMR: δ 13.7, 22.1, 26.8, 28.5, 31.2, 32.6, 35.2, 36.6, 58.8, 74.0, 77.4, 127.0, 127.5, 127.8, 140.8. HRMS (ESI+) Calcd. for $C_{24}H_{35}{}^{79}BrNO$ $(M+H)^+$: 432.1902, Found: 432.1881. $[\alpha]_D$ −31.7 (*c* 1.12, $CHCl_3$). IR (film): 2958, 2927, 2856, 1602 cm^{-1}.

(*R*)-*N*-Benzyl-2-bromo-2-cyclopentyl-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (10e) Yellow oil, 96% yield. ^{1}H NMR: δ 1.17–1.30 (m, 8H), 2.04–2.13 (m, 1H), 2.79 (dd, *J* = 6.2, 14.1 Hz, 1H), 3.07 (dd, *J* = 7.5, 14.1 Hz, 1H), 3.35 (s, 3H), 3.69 (dd, *J* = 13.9, 46.2 Hz, 2H), 3.84–3.92 (m, 2H), 3.98–4.04 (m, 2H), 7.29–7.39 (m, 10H). ^{13}C NMR: δ 25.3, 25.6, 28.9, 31.2, 43.4, 56.0, 58.1, 58.9, 62.3, 63.0, 72.3, 127.0, 127.2, 128.1, 128.2, 128.6, 128.9, 139.0, 140.0. HRMS (ESI+) Calcd. for $C_{23}H_{31}BrNO$ $(M+H)^+$: 416.1589, Found: 416.1570. $[\alpha]_D$ −49.6 (*c* 1.00, $CHCl_3$). IR (film): 2952, 2868, 1602 cm^{-1}.

(*R*)-*N*-Benzyl-2-bromo-2-cyclohexyl-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (10f) Yellow oil, 69% yield. ^{1}H NMR: δ 0.94–1.59 (m, 10H), 1.67–1.68 (m, 1H), 2.89 (dd, *J* = 7.5, 13.9 Hz, 1H), 3.06 (dd, *J* = 6.7, 13.9 Hz, 1H), 3.36 (s, 3H), 3.65 (d, *J* = 13.9 Hz, 1H), 3.75 (d, *J* = 13.9 Hz, 1H), 3.84–3.93 (m, 3H), 4.01 (dd, *J* = 5.8, 7.2Hz, 1H), 7.22–7.37 (m, 10H). ^{13}C NMR: δ 25.9, 26.2, 26.3, 27.4, 31.7, 40.2, 56.1 (C × 2), 58.9, 62.6, 63.6, 71.9, 127.0, 127.2, 128.1, 128.2, 128.5, 128.8, 139.3, 140.0. HRMS (ESI+) Calcd. for $C_{24}H_{33}{}^{79}BrNO$ $(M+H)^+$: 430.1746, Found: 430.1725. $[\alpha]_D$ −36.8 (*c* 1.00, $CHCl_3$). IR (film): 2926, 2853, 1602 cm^{-1}.

(*R*)-*N*-Benzyl-2-bromo-*N*-((*R*)-2-methoxy-1-phenylethyl)-3,3-dimethylbutylamine (10g) Yellow oil,

81% yield. ^{1}H NMR: δ 0.91 (s, 9H), 2.82 (dd, *J* = 1.7, 14.8 Hz, 1H), 3.06 (dd, *J* = 10.2, 14,8 Hz, 1H), 3.32 (s, 3H), 3.63 (s, 2H), 3.78 (dd, *J* = 1.7, 10.2 Hz, 1H), 3.89 (d, *J* = 6.7 Hz, 2H), 4.07 (t, *J* = 6.7 Hz, 1H), 7.21–7.38 (m, 10H). ^{13}C NMR: δ 27.5, 35.1, 55.6, 55.7, 58.9, 62.6, 70.9, 72.8, 126.9, 127.2, 128.0, 128.2, 128.7, 128.8, 138.6, 139.9. HRMS (ESI+) Calcd. for $C_{22}H_{31}{}^{79}BrNO$ $(M+H)^+$: 404.1589, Found: 404.1599. $[\alpha]_D$ −104.1 (*c* 0.62 $CHCl_3$). IR (film): 2962, 2915, 2863, 1601 cm^{-1}.

4. General procedure for the fluorination reaction of *β*-bromoamine **10** with $Et_3N{\cdot}3HF$.

To a stirred solution of fleshly prepared *β*-bromoamine **10** (0.2 mmol) in dry toluene (1 mL) was added $Et_3N{\cdot}3HF$ (3.3 equiv., 0.66 mmol, 108 μL) in Teflon® vessel at rt. The reaction mixture was then heated, and stirred for shown time in Table 2. After cooling, the reaction mixture was slowly poured into 1M NaOH aqueous solution (10 mL) and the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (10 mL × 3 times), and the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The residue was purified by silica gel chromatography.

(*R*)-*N*-Benzyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)pentylamine (11a) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) to afford product as a colorless oil (91%). ^{1}H NMR: δ 0.83 (t, *J* = 7.2 Hz, 3H), 1.15–1.54 (m, 4H), 2.56 (ddd, *J* = 3.6, 14.6, 28.0 Hz, 1H), 2.87 (ddd, *J* = 7.4, 14.6, 18.8 Hz, 1H), 3.34 (s, 3H), 3.63 (d, *J* = 14.1 Hz, 1H), 3.75–3.89 (m, 2H), 3.80 (d, *J* = 14.1 Hz, 1H), 4.07 (dd, *J* = 5.9, 7.0 Hz, 1H), 4.46 (ttd, *J* = 3.6, 7.4, 49.9 Hz, 1H), 7.17–7.41 (m, 10H). ^{13}C NMR: δ 13.8, 18.2 (d, *J* = 4.8 Hz), 35.1 (d, *J* = 20.5 Hz), 54.6 (d, *J* = 22.0 Hz), 56.0 (d, *J* = 1.1 Hz), 58.9, 62.9 (d, *J* = 1.1 Hz), 72.8, 93.7 (d, *J* = 168.7 Hz), 126.9, 127.1, 128.1, 128.2, 128.5, 128.7, 139.3, 140.2. ^{19}F NMR: δ −183.3–−182.8 (m). HRMS (ESI+) Calcd. for $C_{21}H_{29}FNO$ $(M+H)^+$: 330.2233, Found: 330.2238. $[\alpha]_D$ −42.2 (*c* 1.26, $CHCl_3$). IR (film) : 2959, 1493, 1452, 1116 cm^{-1}.

(*R*)-*N*-Benzyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-3-methylbutylamine (11b) The compound was purified by silica gel chromatography (toluene) to afford product as a colorless oil (93%). ^{1}H NMR: δ 0.77 (d, *J* = 6.8 Hz, 6H), 1.64–1.81 (m, 1H), 2.60 (ddd, *J* = 2.8, 14.7, 32.1 Hz, 1H), 2.87 (ddd, *J* = 7.6, 14.7, 19.3 Hz, 1H), 3.34 (s, 3H), 3.67 (d, *J* = 13.9 Hz, 1H), 3.77 (d, *J* = 13.9 Hz, 1H), 3.81–3.90 (m, 2H), 4.07 (dd, *J* = 5.8, 7.0 Hz, 1H), 4.24 (dddd, *J* = 2.8, 5.5, 7.6, 49.2 Hz, 1H), 7.20–7.40 (m, 10H). ^{13}C NMR: δ 16.6 (d, *J* = 7.0 Hz), 18.5 (d, *J* = 5.1 Hz), 30.7 (d, *J* = 19.8 Hz), 52.3 (d, *J* = 22.0 Hz), 55.8, 58.9, 62.8, 72.7, 98.1 (d, *J* = 172.8 Hz), 126.8, 127.1, 128.1, 128.2, 128.5, 128.7, 139.5, 140.2. ^{19}F NMR: δ −189.4 (tdd, *J* = 18.8, 31.5, 70.1 Hz). HRMS (ESI+) Calcd. for $C_{21}H_{28}FNNaO$ $(M+Na)^+$: 352.2053, Found: 352.2051. $[\alpha]_D$ −40.9 (*c* 1.00, EtOH). IR (film): 2963, 1494, 1453, 1117 cm^{-1}.

(*R*)-*N*-Benzyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-4-methylpentylamine (11c) The compound

was purified by silica gel chromatography (*n*-hexane : AcOEt = 8 : 1) to afford product as a colorless oil (78%). ^{1}H NMR: δ 0.80 (d, *J* = 4.9 Hz, 3H), 0.82 (d, *J* = 5.0 Hz, 3H), 1.05–1.24 (m, 1H), 1.36–1.47 (m, 1H), 1.56–1.69 (m, 1H), 2.54 (ddd, *J* = 3.5, 14.6, 28.0 Hz, 1H), 2.85 (ddd, *J* = 7.2, 14.6, 18.3 Hz, 1H), 3.34 (s, 3H), 3.65 (d, *J* = 14.3 Hz, 1H), 3.75–3.91 (m, 3H), 4.07 (dd, *J* = 5.9, 7.0 Hz, 1H), 4.40–4.61 (m, 1H), 7.20–7.44 (m, 10H). ^{13}C NMR: δ 21.9, 23.2, 24.4 (d, *J* = 3.7 Hz), 42.0 (d, *J* = 19.8 Hz), 55.3 (d, *J* = 21.6 Hz), 56.2, 58.9, 63.2, 72.9, 92.4 (d, *J* = 168.4 Hz), 126.9, 127.2, 128.1, 128.2, 128.5, 128.7, 139.4, 140.2. ^{19}F NMR: δ −183.4–−183.0 (m). HRMS (ESI+) Calcd. for $C_{22}H_{31}FNO$ $(M+H)^+$: 344.2390, Found: 344.2392. $[\alpha]_D$ −36.9 (*c* 0.67, $CHCl_3$). IR (film): 2956, 1486, 1451 cm^{-1}.

(*R*)-*N*-Benzyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)octylamine (11d) The compound was purified by silica gel chromatography (*n*-hexane : AcOEt = 10 : 1) to afford product as a colorless oil (72%). ^{1}H NMR: δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.19–1.56 (m, 10H), 2.57 (ddd, *J* = 3.5, 14.6, 27.7 Hz, 1H), 2.86 (ddd, *J* = 7.0, 14.6, 18.8 Hz, 1H), 3.34 (s, 3H), 3.63 (d, *J* = 14.0 Hz, 1H), 3.78–3.89 (m, 3H), 4.07 (dd, *J* = 6.0, 7.0 Hz, 1H), 4.35–4.53 (m, 1H), 7.20–7.37 (m, 10H). ^{13}C NMR: δ 14.1, 22.5, 24.8 (d, *J* = 4.8 Hz), 29.0, 31.6, 33.0 (d, *J* = 20.2 Hz), 54.6 (d, *J* = 22.0 Hz), 56.0, 58.9, 63.0, 72.8, 94.0 (d, *J* = 169.1 Hz), 126.9, 127.1, 128.1, 128.2, 128.5, 128.7, 139.4, 140.2. ^{19}F NMR: δ −182.9–−182.5 (m). HRMS (ESI+) Calcd. for $C_{24}H_{35}FNO$ $(M+H)^+$: 372.2703, Found: 372.2691. $[\alpha]_D$ −10.1 (*c* 0.72, $CHCl_3$). IR (film): 2928, 1453 cm^{-1}.

(*R*)-*N*-Benzyl-2-cyclopentyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (11e) The compound was purified by silica gel chromatography (toluene) to afford product as a colorless oil (54%). ^{1}H NMR: δ 1.31–1.55 (m, 8H), 1.84–1.98 (m, 1H), 2.58 (ddd, *J* = 2.5, 14.8, 32.6 Hz, 1H), 2.87 (ddd, *J* = 7.6, 14.8, 18.9 Hz, 1H), 3.34 (s, 3H), 3.67 (d, *J* = 14.0 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 1H), 3.83–3.89 (m, 2H), 4.08 (dd, *J* = 5.8, 7.1 Hz, 1H), 4.30 (ddt, *J* = 2.5, 7.6, 47.5 Hz, 1H), 7.21–7.38, (m, 10H). ^{13}C NMR: δ 25.5 (d, *J* = 4.8 Hz), 27.7 (d, *J* = 3.7 Hz), 28.5 (d, *J* = 6.6 Hz), 42.1 (d, *J* = 19.1 Hz), 53.8 (d, *J* = 21.6 Hz), 55.8, 62.8, 72.8, 97.2 (d, *J* = 171.7 Hz), 126.8, 127.1, 128.1, 128.2, 128.5, 128.7, 139.5, 140.2. ^{19}F NMR: δ −184.6–−184.2 (m). HRMS (ESI+) Calcd. for $C_{23}H_{31}FNO$ $(M+H)^+$: 356.2390, Found: 356.2395. $[\alpha]_D$ −46.2 (*c* 1.07, $CHCl_3$). IR (film): 2954, 2869, 1604, 1452 cm^{-1}.

(*R*)-*N*-Benzyl-2-cyclohexyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)ethylamine (11f) The compound was purified by silica gel chromatography (toluene) to afford product as a colorless oil (73%). ^{1}H NMR: δ 0.88–1.65 (m, 11H), 2.61 (ddd, *J* = 2.8, 14.7, 31.7 Hz, 1H), 2.87 (ddd, *J* = 7.5, 14.7, 19.6 Hz, 1H), 3.34 (s, 3H), 3.65 (d, *J* = 14.0 Hz, 1H), 3.77 (d, *J* = 14.0 Hz, 1H), 3.81–3.89 (m, 2H), 4.07 (dd, *J* = 5.8, 7.0 Hz, 1H), 4.16–4.32 (m, 1H), 7.21–7.37 (m, 10H). ^{13}C NMR: δ 25.8, 26.0, 26.2, 26.8 (d, *J* = 6.2 Hz), 28.8 (d, *J* = 4.4 Hz), 40.3 (d, *J* = 19.1 Hz), 52.2 (d, *J* = 22.4 Hz), 55.8, 58.9, 62.7, 72.7, 97.4 (d, *J* = 171.7 Hz), 126.8, 127.1, 128.1, 128.2, 128.5, 128.7, 139.5, 140.2. ^{19}F NMR: δ −189.5 (qt, *J* = 18.4, 32.0

Hz). HRMS (ESI+) Calcd. for $C_{24}H_{33}FNO$ $(M+H)^+$: 370.2546, Found: 370.2550. $[\alpha]_D$ −51.0 (*c* 0.50, $CHCl_3$). IR (film): 2926, 2853, 1601, 1451 cm^{-1}.

(*R*)-*N*-Benzyl-2-fluoro-*N*-((*R*)-2-methoxy-1-phenylethyl)-3,3-dimethylbutylamine (11g) The compound was purified by silica gel chromatography (*n*-hexane : Et_2O = 10 : 1) to afford product as a colorless oil (23%). ^1H NMR: δ 0.77 (s, 9H), 2.60 (dd, *J* = 15.0, 39.4 Hz, 1H), 2.87 (ddd, *J* = 8.4, 15.0, 20.2 Hz, 1H), 3.38 (s, 3H), 3.77 (s, 2H), 3.84–3.86 (m, 2H), 4.06–4.22 (m, 2H), 7.20–7.34 (m, 10H). ^{13}C NMR: δ 25.2 (d, *J* = 4.8 Hz), 34.1 (d, *J* =19.4 Hz), 50.6 (d, *J* = 21.3 Hz), 55.6, 58.9, 62.6, 72.1, 100.9 (d, *J* = 175.7 Hz), 126.8, 127.0, 128.1, 128.2, 128.5, 128.7, 139.8, 140.2. ^{19}F NMR: δ −188.3 (ddd, *J* = 20.4, 39.3, 49.2 Hz). HRMS (ESI+) Calcd. for $C_{22}H_{31}FNO$ $(M+H)^+$: 344.2390, Found: 344.2395. $[\alpha]_D$ −71.2 (*c* 0.52 $CHCl_3$). IR (film): 3028, 2961, 1600, 1453 cm^{-1}.

5. Synthesis of **18**

(*S*)-2-Isopropyl-1-((*R*)-2-(4-methoxybenzyloxy)-1-phenylethyl)aziridine (12) A solution of *n*-butyllithium (18.4 mL, 1.6 M in hexane, 29.5 mmol) was added dropwise over several minutes to a stirred solution of powdered trimethylsulfonium iodide (6.02 g, 29.5 mmol) and HMPA (5.1 mL, 29.5 mmol) in 53 mL of dry THF under nitrogen at 0 °C. After stirring for 20 min, a solution of imine in 10 mL of dry THF, which was prepared from **3** (3.04 g, 11.8 mmol) and isobutyraldehyde (1.29 mL, 14.1 mmol), was added. After stirring for 12 h at rt, the resulting mixture was diluted with 50 mL of water and extracted with AcOEt (50 mL × 3 times). The combined organic layer was washed with brine (50 mL × 2 times), dried over Na_2SO_4, and evaporated to give the residue, which was purified by silica gel chromatography (*n*-hexane : AcOEt = 1 : 1) to afford **12** as a colorless oil (3.68 g, 11.3 mmol, 95%). ^1H NMR: δ 0.53 (d, *J* = 6.3 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H), 1.05–1.13 (m, 2H), 1.65 (d, *J* = 6.1 Hz, 1H), 1.76 (d, *J* = 3.4 Hz, 1H), 2.55 (dd, *J* = 5.7, 6.9 Hz, 1H), 3.67 (dd, *J* = 5.7, 9.8 Hz, 1H), 3.80 (s, 3H), 3.85 (dd, *J* = 6.9, 9.7 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 2H), 7.25–7.37 (m, 5H). ^{13}C NMR: δ 19.6, 20.2, 31.4, 34.4, 44.0, 55.1, 72.9, 74.4, 74.6, 113.6, 127.4, 128.0 (C × 2), 129.0, 130.4, 141.0, 158.9. HRMS (ESI+) Calcd. for $C_{21}H_{28}NO_2$ $(M+H)^+$: 326.2120, Found: 326.2162. $[\alpha]_D$ −27.3 (*c* 1.00, $CHCl_3$). IR (film): 2955, 2857, 1612, 1586, 1512 cm^{-1}.

(*R*)-*N*-Benzyl-2-bromo-*N*-((*R*)-2-(4-methoxybenzyloxy)-1-phenylethyl)-3-methylbutylamine (13) A mixture of **12** (3.44 g, 10.58 mmol) and benzyl bromide (10 equiv., 12.6 mL, 105.8 mmol) in acetone (32 mL) was refluxed for 12 h under nitrogen atmosphere. After cooling, the reaction mixture was evaporated to give the crude product, which was purified by silica gel chromatography (*n*-hexane : AcOEt = 16 : 1) to afford **13** as a colorless oil (3.87 g, 7.79 mmol, 74%). ^1H NMR: δ 0.49 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* =

6.7 Hz, 3H), 1.83–1.90 (m, 1H), 2.85 (dd, *J* = 7.9, 14.0 Hz, 1H), 3.08 (dd, *J* = 6.4, 14.0 Hz, 1H), 3.64 (d, *J* = 13.8 Hz, 1H), 3.74 (d, *J* = 13.8 Hz, 1H), 3.81 (s, 3H), 3.87–4.06 (m, 4H), 4.40 (s, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.22–7.35 (m, 12H). ^{13}C NMR: δ 16.2, 21.5, 29.9, 55.0, 55.9, 56.6, 62.7, 64.8, 68.7, 72.6, 113.5, 126.9, 127.0, 127.9, 128.1, 128.5, 128.7, 129.1, 130.1, 139.3, 139.9, 159.0. HRMS (ESI+) Calcd. for $C_{28}H_{35}{}^{79}BrNO_2$ $(M+H)^+$: 496.1851, Found: 496.182. $[\alpha]_D$ −28.6 (*c* 1.00, $CHCl_3$). IR (film): 3028, 2963, 1614 cm^{-1}.

(*R*)-*N*-Benzyl-2-fluoro-*N*-((*R*)-2-(4-methoxybenzyloxy)-1-phenylethyl)-3-methylbutylamine (15) To a stirred solution of fleshly prepared **13** (510 mg, 1.04 mmol) in dry toluene (5.2 mL) was added $Et_3N{\cdot}3HF$ (3.3 equiv. 0.56 mL, 3.43 mmol) in Teflon® vessel at rt. The reaction mixture was then heated at 90 °C, and stirred for 96 h. After cooling, the reaction mixture was slowly poured into 1M NaOH aqueous solution (30 mL) and the organic layer was separated, the aqueous layer was extracted with $CHCl_3$ (30 mL × 3 times), and the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 5 : 1) to afford **15** as a colorless oil (359 mg, 0.82 mmol, 79%). ^{1}H NMR: δ 0.73–0.76 (m, 6H), 1.65–1.77 (m, 1H), 2.60 (ddd, *J* = 2.8, 14.6, 31.6 Hz, 1H), 2.86 (ddd, *J* = 7.6, 14.6, 19.1 Hz, 1H), 3.67 (d, *J* = 14.0 Hz, 1H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.85–3.95 (m, 2H), 4.11 (t, *J* = 6.3 Hz, 1H), 4.23 (dddd, *J* = 2.8, 5.4, 7.6, 49.2 Hz, 1H), 4.42–4.49 (m, 2H). 6.86 (d, *J* = 8.6 Hz, 2H), 7.12–7.34 (m, 12H). ^{13}C NMR: δ 16.4 (d, *J* = 6.97 Hz), 18.5 (d, *J* = 4.8 Hz), 30.5 (d, *J* = 20.2 Hz), 52.2 (d, *J* = 22.4 Hz), 55.0, 55.7, 62.8, 69.5, 72.6, 98.1(d, *J* = 172.8 Hz), 113.6, 126.7, 126.9, 127.9, 128.1, 128.5, 128.6, 129.1, 130.3, 139.7, 140.2, 159.0. ^{19}F NMR: δ −148.5 (tdd, *J* = 19.8, 32.7, 49.1 Hz). HRMS (ESI+) Calcd. for $C_{28}H_{35}FNO_2$ $(M+H)^+$: 436.2652, Found: 436.2632. $[\alpha]_D$ −28.2 (*c* 1.17, $CHCl_3$). IR (film): 3029, 2962, 1613, 1454 cm^{-1}.

(*R*)-2-(Benzyl((*R*)-2-fluoro-3-methylbutyl)amino)-2-phenylethanol (16) To a stirred solution of **15** (359 mg, 0.82 mmol) in DCM (0.82 mL) was added TFA (0.82 mL) at −10 °C and stirred for 20 h. The reaction mixture was quenched with 1N NaOH aqueous solution (30 mL), and extracted with $CHCl_3$ (30 mL × 3 times). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product. The residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 3 : 1) to afford **16** as a colorless oil (240 mg, 0.76 mmol, 92%). ^{1}H NMR: δ 0.86 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 0.8 Hz, 3H), 1.77–1.83 (m, 1H), 2.36 (ddd, *J* = 1.3, 14.6, 34.9 Hz, 1H), 3.03 (ddd, *J* = 9.2, 14.6, 18.8 Hz, 1H), 3.24–3.28 (m, 1H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.60 (dt, *J* = 4.3, 10.5 Hz, 1H), 3.83 (d, *J* = 13.7 Hz, 1H), 3.87–4.07 (m, 2H), 4.27 (dddd, *J* = 1.3, 6.1, 9.2, 49.7 Hz, 1H), 7.19–7.41 (m, 10H). ^{13}C NMR: δ 17.3 (d, *J* = 6.6 Hz), 18.4 (d, *J* = 5.1 Hz), 31.0 (d, *J* = 19.4 Hz), 50.8 (d, *J* = 20.2 Hz), 55.8, 60.7, 64.1, 96.2 (d, *J* = 173.1 Hz), 127.3, 127.9, 128.4, 128.5, 128.8 (C × 2), 135.9, 138.9. ^{19}F NMR:

δ −188.6–−188.3 (m). HRMS (ESI+) Calcd. for $C_{20}H_{27}FNO$ $(M+H)^+$: 316.2077, Found: 316.2089. $[\alpha]_D$ −111.5 (*c* 0.79, $CHCl_3$). IR (film): 3035, 2964, 1454 cm^{-1}.

(*R*)-*N*-((*S*)-2-Azido-2-phenylethyl)-*N*-benzyl-2-fluoro-3-methylbutylamine (17) To the stirred solution of **16** (806 mg, 2.55 mmol) and PPh_3 (1.2 equiv. 804 mg, 3.06mmol) in dry THF (12.5 mL) was added DIAD (1.2 equiv. 0.50 mL, 3.06 mmol) at −10 °C and reaction mixture was stirred for 30 min. Then DPPA (1.2 equiv. 0.60 mL, 2.55 mmol) in dry THF (12.5 mL) was added and the reaction mixture was allowed to stir for 3 h at rt. After evaporation of all the volatiles, the residue was purified by silica gel chromatography (*n*-hexane : AcOEt = 4 : 1) to afford **17** as a colorless oil (544 mg, 1.60 mmol, 63%). ^{1}H NMR: δ 0.85–0.88 (m, 6H), 1.76–1.83 (m, 4H), 2.69–2.99 (m, 4H), 3.72 (d, *J* = 13.6 Hz, 1H), 3.88 (d, *J* = 13.6 Hz, 1H), 4.33–4.49 (m, 1H), 4.56 (dd, *J* = 4.9, 8.8 Hz, 1H), 7.22–7.34 (m, 10H). ^{13}C NMR: δ 16.6 (d, *J* = 7.0 Hz), 18.5 (d, *J* = 4.8 Hz), 30.9 (d, *J* = 19.8 Hz), 55.8 (d, *J* = 21.6 Hz), 59.9 (d, *J* = 1.5 Hz), 61.4 (d, *J* = 1.8 Hz), 64.4, 97.5 (d, *J* = 172.3 Hz), 126.8, 127.1, 128.0, 128.3, 128.6, 128.9, 138.5, 138.8. ^{19}F NMR: δ −188.2–−187.8 (m). HRMS (ESI+) Calcd. for $C_{20}H_{26}FN_4$ $(M+H)^+$: 341.2142, Found: 341.2178. $[\alpha]_D$ +68.9 (*c* 0.97, $CHCl_3$). IR (film): 2964, 2097, 1454 cm^{-1}.

***N*-((*S*)-2-(Benzyl((*R*)-2-fluoro-3-methylbutyl)amino)-1-phenylethyl)-4-bromobenzenesulfonamide (18)** The solution of **17** (463 mg, 1.36 mmol) and PPh_3 (1.2 equiv. 428 mg, 1.63mmol) and H_2O (5 equiv. 0.12 mL, 6.8 mmol) in THF was heated at 45 °C. After being stirred for 16 h, the mixture was diluted with Et_2O (47 mL), and extracted with 2M HCl aqueous solution (40 mL × 3 times) and brine (20 mL × 1 time). The combined aqueous layer was washed with Et_2O (70 mL × 1 time), followed by alkalized with NaOH. The aqueous layer was extracted with $CHCl_3$ (60 mL × 3 times). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude primary amine (410 mg) as a colorless oil which was used in the next step without further purification. (^{1}H NMR: δ 0.86 (dd, *J* = 1.0, 6.8 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H), 1.67–1.83 (m, 3H), 2.61–2.80 (m, 4H), 3.61 (d, *J* = 13.7 Hz, 1H), 3.88 (d, *J* = 13.7 Hz, 1H), 4.06 (dd, *J* = 4.0, 9.9 Hz, 1H), 4.34–4.53 (m, 1H), 7.21–7.36 (m, 10H))

To a solution of primary amine (410 mg, *ca*. 1.30 mmol) and Et_3N (3.0 equiv. 0.54 mL, 3.91 mmol) in dry DCM (3.3 mL) at 0 °C was added 4-bromobenzenesulfonyl chloride (1.5 equiv. 501mg, 1.96 mmol) in dry DCM (3.3 mL) and the solution was stirred at rt for 6 h. The resulting mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL) and extracted with $CHCl_3$ (30 mL × 3 times). The combined organic layer was washed with saturated $NaHCO_3$ (50 mL × 1 time) and brine (50 mL × 1 time), dried over anhydrous Na_2SO_4, and evaporated to give the crude product. The residue was purified by silica gel chromatography ($CHCl_3$) to afford product as a colorless oil (980.5 mg, 1.27 mmol, 93%). ^{1}H NMR: δ 0.83–0.87 (m, 6H), 1.63–1.76 (m, 1H), 2.55–2.80 (m, 4H), 3.49 (d, *J* = 13.4 Hz, 1H), 3.81 (d, *J* = 13.4 Hz, 1H), 4.26–4.43 (m, 2H), 5.88 (br s, 1H), 7.04–7.17 (m, 4H), 7.27–7.38 (m, 10H). ^{13}C NMR: δ 16.8 (d, *J* =

7.0 Hz), 18.3 (d, *J* = 5.1 Hz), 31.2 (d, *J* = 19.8 Hz), 54.9 (d, *J* = 19.8 Hz), 55.7, 58.7 (d, *J* = 1.5 Hz), 60.5 (d, *J* = 2.6 Hz), 98.0 (d, *J* = 172.8 Hz), 127.0, 127.2, 127.5, 127.7, 128.2, 128.6, 128.8, 129.1, 131.6, 137.8, 138.5, 139.30. ^{19}F NMR: δ −188.1 (br s). HRMS (ESI+) Cald. for $C_{26}H_{31}{}^{79}BrFN_2O_2S$ $(M+H)^+$: 533.1274, Found: 533.1245. $[\alpha]_D$ +20.4 (*c* 0.87, $CHCl_3$). IR (film): 3281, 2966, 1576, 1455, 1333, 1165 cm^{-1}.

Crystalline hydrochlorides **18**·HCl were obtained in quantitative yield by treatment with HCl (1M in Et_2O) followed by evaporation.

6. X-Ray structure determination of compound **18**·HCl

A colorless crystal of **18**·HCl having an approximate dimension of 0.3 x 0.1 x 0.1 mm grown from acetone/toluene was used for the data collection of a Rigaku R-AXIS RAPD diffractometer with graphcic monochromated Cu-Kα radiation (λ = 1.54187 Å). The crystal data is as follow: $C_{26}H_{31}BrClFN_2O_2S$, M = 569.96, colorless prism, triclinic, space group P1 (#1), a = 6.5690 (2), b = 9.0206 (3), c = 12.2192 (4) Å, V = 666.39(6) $Å^3$, Z = 1, D_{calc} = 1.420 g/cm^3, μ(CuKα) = 40.260 cm^{-1}, 7480 collected data, 3969 unique (R_{int} = 0.0338). All calculations were performed using the Crystal Structure program. Structure solved SIR-2004 and refined by SHELXL[15], R_1 = 0.0407 (I>2.00σ(I)) and wR_2 = 0.1044. Crystallographic data for the structural analysis of **18**·HCl have been deposited with Cambridge Crystallographic Data Center (CCDC) under the depositry No. 1831935. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, e-mail deposit@ccdc,cam.ac.uk.

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