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# Preparation of Optically Pure α-Trifluoromethyl-α-amino Acids from *N*-Tosyl-2-trifluoromethyl-2-alkyloxycarbonyl Aziridine

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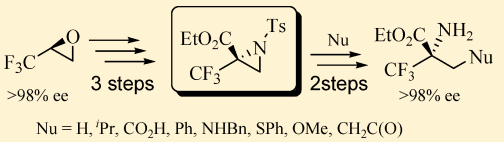
Supporting Information

**ABSTRACT:** The preparation of optically pure α-trifluoromethyl-α-amino acids from *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonylaziridine is described. Optically pure aziridine was prepared with a 60% yield via three steps from optically pure 2,3-epoxy-1,1,1-trifluoropropane (TFPO). Ring-opening reactions of the aziridine with a variety of nucleophiles and subsequent deprotection of the *N*-tosyl moieties gave the optically pure β-substituted-α-trifluoromethyl-α-amino acids in moderate to good yields (up to 85%) without racemization at the quaternary stereogenic center of the amino acid.



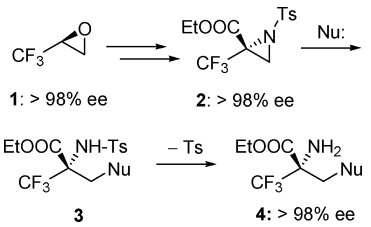

## INTRODUCTION

The importance of the preparative method for fluorinated amino acids need not be repeated here.[1] Among fluorinated amino acids, α-trifluoromethylated amino acids have altered properties of the functional groups.[1i,2] and fix the conformations of the peptides in which they are incorporated;[1l,q,s] thus, these amino acids have been the synthetic targets of recent stereoselective organic syntheses.[1a,r,2] Despite the remarkable developments in the syntheses of α-trifluoromethylated amino acids, there have been few reports on the bioactivities of peptides incorporating α-trifluoromethyl-α-amino acids.[2,3] The poor knowledge of the chemistry and biological activities of α-trifluoromethyl-α-amino acids is due to the difficulty in preparing α-trifluoromethyl-α-amino acids that are optically pure. Automatic syntheses of peptides are demanding an optimization-free preparation for the optically pure α-trifluoromethyl-α-amino acids.

To date, many racemic[2,a,4] and optically active[1d,5] α-trifluoromethyl-α-amino acids have been prepared, independently. Many of these compounds have been prepared by the addition of nucleophiles to imino-carbons, for example, the addition of an alkyl moiety to trifluoromethyl imino-esters,[3a,f,g,j−z,ab,ad,b−j,l−o,t,v] the nucleophilic addition of $CF_3$ to imino-esters,[4h,ac] and the Strecker-type addition of cyanide to alkyl trifluoromethyl imines followed by hydrolysis of the cyano group.[4af,m,q,u,w] Some of these amino acids have been prepared by the addition of electrophiles to an enamine form of trifluoroalanine. These strategies construct the stereogenic quaternary C-atoms via the addition of a variety of nucleophiles or electrophiles. Therefore, these strategies require the optimization of the asymmetric reaction or optical resolution of the products. These conventional strategies are not suitable for the general synthesis of a series of optically pure α-trifluoromethyl-α-amino acids.

We hypothesized that our optically pure *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonylaziridine (**2**), which was prepared from optically pure 2,3-epoxy-1,1,1-trifluoropropane (TFPO, **1**),[6,7] could be a common precursor of optically pure α-trifluoromethyl-α-amino acids (**4**) (Scheme 1).[8]

**Scheme 1. A Strategy for the Preparation of Optically Pure α-Trifluoromethyl-α-amino Acids**[8]




Our syntheses of α-trifluoromethyl-α-amino acid **4** from optically pure aziridine **2** involve nucleophilic addition without modification of the stereogenic center. Thus, the product requires no further optical purification, which is the advantage of our strategy. However, we experienced a few problems to overcome before the implementation of this strategy. (1) The preparation of the aziridine from the optically pure epoxide (4 steps, 27%, see Scheme 2) should be condensed. (2) Aziridine **2** has two electrophilic centers: the aziridine ring and the ester moiety. Thus, the nucleophilic attack should be chemoselective (Scheme 1). (3) Although the tosyl group on the aziridine *N*-atom is essential for the nucleophilic ring-opening reaction of the aziridine, it should be removed at the last stage. Therefore, a method for the facile detosylation from the nitrogen of the ring-opening products should be developed.

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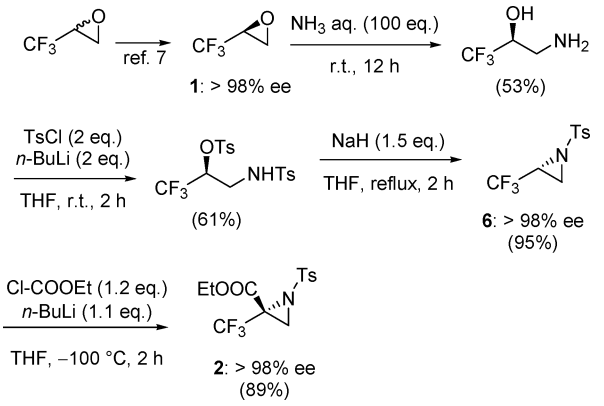
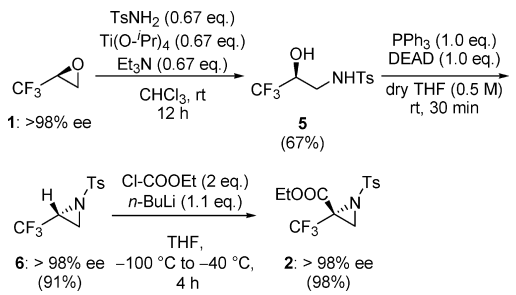
**Scheme 2. Our Conventional Method for Preparation of the Aziridine 2 (See Ref 6)**




Herein, we report an improved method for the preparation of *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonyl aziridine **2** (Scheme 3), including the scope of the relevant nucleophilic

**Scheme 3. Improved Preparation of Aziridine 2**




ring-opening reactions and the detosylation of the aziridine *N*-atom (Scheme 4), for the preparation of optically pure $\alpha$-trifluoromethyl-$\alpha$-amino acids.

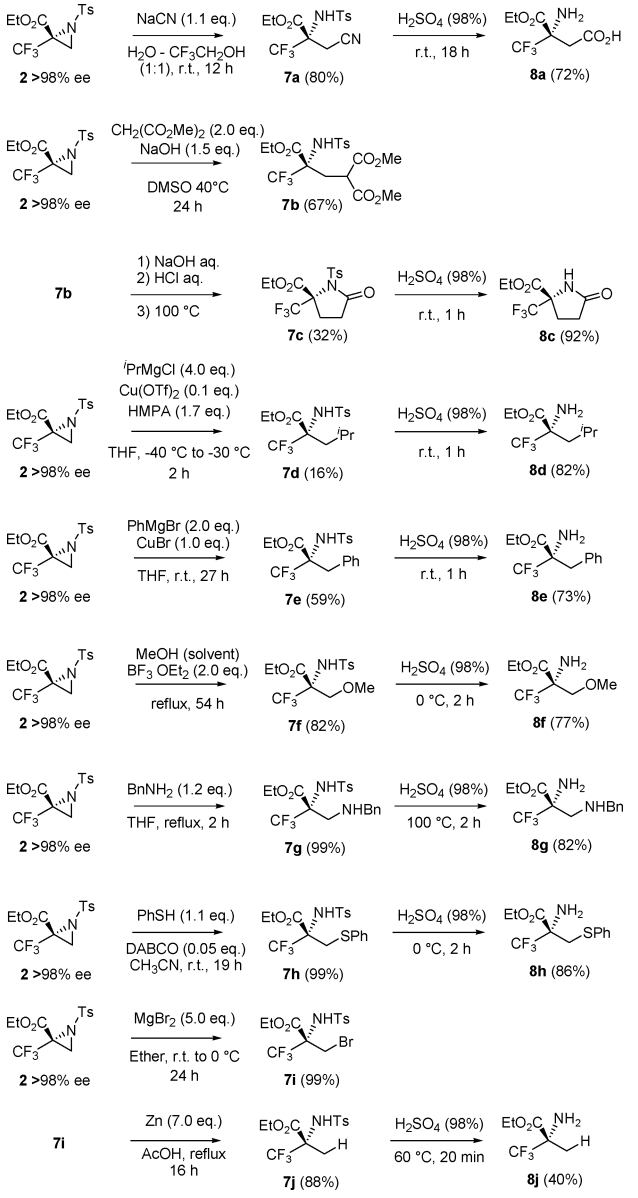
## RESULTS AND DISCUSSION

**An Improved Preparation of Aziridine 2.** As illustrated in Scheme 2, the total yield of the conventional synthesis of aziridine **2** from epoxide **1** was 27%.[8b] The low yield was the result of the low yield of the ring-opening reaction of **1** and of the following tosylation of the amino alcohol. Thus, a reduction of these processes would give a better total yield of aziridine **2**. Therefore, the direct ring-opening reaction of epoxide **1** with *p*-toluenesulfonamide ($TsNH_2$) was investigated.

The direct ring-opening reaction of epoxide **1** with $TsNH_2$ and Lewis acid catalysis ($Ti(O^iPr)_4$)/$Et_3N$[9] gave amide alcohol **5** with a 67% yield. Here, the yield is based on the amount of epoxide **1** used. Therefore, the yield of the product was essentially quantitative based on the amount of $TsNH_2$. To avoid the problematic separation of tosylated amide alcohol **5** from the remaining $TsNH_2$, an excess amount (1.5 equiv.) of epoxide **1** was used to ensure complete consumption of the $TsNH_2$ present.

The amino alcohol derivative **5** was converted into aziridine **6** by an intramolecular Mitsunobu reaction[10] with a 91% yield. This improvement of the process for the synthesis of aziridine **2** resulted in a better total yield (60%). Further reduction of technical losses of the volatile epoxide **1** in the first step could increase the total yield up to 90%.

**Scheme 4. Nucleophilic Additions to the Aziridine 2 and Subsequent Detosylation**




**Ring-Opening Reactions of Aziridine 2 and Subsequent Detosylation.** Aziridine **2** has two nucleophile-reactive sites: the aziridine ring and the ester moiety. Therefore, there would be two competing reactions with the nucleophile. However, except for some nucleophiles, the nucleophilic additions were regioselective with the nucleophiles attacking the aziridine ring to give ring-opening products **7** in good to moderate yields (Scheme 4). This regioselectivity could be due to the high hindrance of the nucleophilic attack on the carbonyl carbon, which is shielded by the bulky and negatively charged trifluoromethyl group (Figure 1).[6d,11]

In our experiments, the hydride ($NaBH_4$) and the stabilized carbanion of acetonitrile reacted with the ester group of **2** (Scheme 5). This means that the sterically small nucleophiles reacted with the highly hindered ester moiety.

Although the cyanide ion is also a small nucleophile, its addition led selectively to the ring-opening product **7a**. Among these three small nucleophiles, only the cyanide ion could be a leaving group from an initially formed ester addition product.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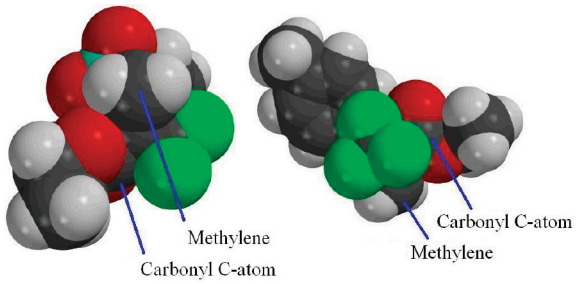
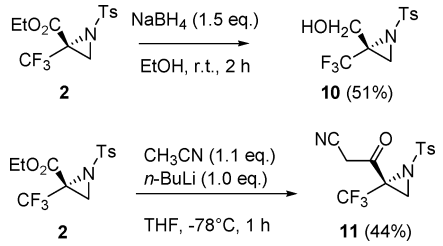



**Figure 1.** Steric hindrance around the carbonyl C-atom.

**Scheme 5. Reaction of Aziridine 2 with the Hydride and the Carbanion of Acetonitrile**

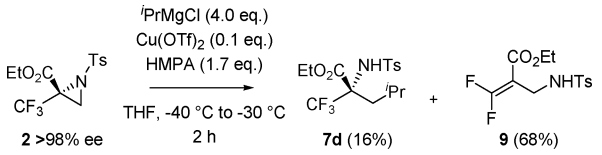



That is, the cyanide ion could react with ester group reversibly, while the ring-opening reaction is irreversible.

To prepare the $\alpha$-trifluoromethyl glutamic acid precursor, we allowed the aziridine **2** to react with the carbanion of dimethyl malonate to give compound **7c** via **7b**. Detosylation proceeded smoothly to give **7c**.

It is noteworthy that the ring-opening reaction of aziridine **2** with $^{i}$PrMgBr gave, in addition to the product **7d** (16%), difluoroolefin **9** (68%) via cleavage of the N(1)−C(2) bond of **2**, followed by defluorination, along with recovered aziridine **2** (Scheme 6).

**Scheme 6. Reaction of the Aziridine 2 with $^{i}$PrMgBr**




The reaction would be initiated by electron transfer(s)[12a] from the Grignard reagent[12b,c] to the aziridine **2**, followed by defluorination.[12d] The product olefin could be a precursor of $\beta,\beta$-difluoro-$\beta$-amino acids via nucleophilic addition to the difluoromethylene carbon.[13]

Detosylation of **7** was attained by reaction with concentrated sulfuric acid, with 62−86% yields.[14] Fortunately, the stereogenic centers of amino acids **7** and **8** were quarternary; thus, the reactions proceeded without racemization. Popular reductive detosylations, such as the Birch-type reduction,[15] resulted in the defluorination or decomposition of the products, and no amino acid **8** was obtained.

## CONCLUSION

In conclusion, we have developed a method of preparation of $\alpha$-trifluoromethyl-$\alpha$-amino acids from optically pure epoxide **1** via optically pure aziridine **2**. This process retains the configuration of the stereogenic center; the use of optically pure epoxide **1** resulted in preparation of optically pure $\alpha$-trifluoromethyl-$\alpha$-amino acids **8** without the need to optimize a stereoselective processes.

## EXPERIMENTAL SECTION

**(*S*)-*N*-(3,3,3-Trifluoro-2-hydroxypropyl)toluenesulfonamide (5).** To a solution of $TsNH_2$ (17.144 g, 100.1 mmol) in $CHCl_3$ (180 mL), $Ti(O^{i}Pr)_4$ (29.3 mL, 100 mmol), 2,3-epoxy-1,1,1-trifluoropropane **1** (10.3 mL, 150 mmol), and $Et_3N$ (13.9 mL, 100 mmol) were added. The reaction mixture was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure, reaction mixture was dissolved in AcOEt and 10% HCl(aq). After extraction with AcOEt, the combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was washed with hexane to give product **5** as a white solid in <99% yield from $TsNH_2$ (in 67% yield from epoxide **1**). Optical purity was >99% ee confirmed by comparison of the HPLC results (see Supporting Information). $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 7.76 (m, 2H), 7.35 (m, 2H), 4.93 (dd, $J$ = 9, 5 Hz, 1H), 4.14 (m, 1H), 3.36 (ddd, $J$ = 14, 9, 3 Hz, 1H), 3.13 (d, $J$ = 5 Hz, 1H), 3.07 (ddd, $J$ = 14, 9, 5 Hz, 1H), 2.45 (s, 3H). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 83.2 (d, 7 Hz, 3F). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm) 144.3, 135.9, 130.0, 127.1, 123.9, 69.3, 42.5, 21.5. IR (KBr): 3500, 3280, 1320, 1140 cm$^{-1}$. GC/MS $m/z$ (%): 184 (41), 155 (50), 91 (100). Anal. calcd for $C_{10}H_{12}F_3NO_3S$: C, 42.40; H, 4.27; N, 4.94. Found: C, 42.46; H, 4.05; N, 5.07. $[\alpha]^{D}_{25}$ = −30.6° ($c$ = 1.64, AcOEt).

**(*R*)-1-Tosyl-2-trifluoromethylaziridine (6).**[8] To a solution of **5** (0.283 g, 1.0 mmol) and $PPh_3$ (0.286 g, 1.09 mmol) in dry THF (4 mL) was added dropwise 40% DEAD (0.45 mL, 1.0 mmol) in toluene at room temperature under an Ar atmosphere. After stirring for 30 min at room temperature, water was added. The reaction mixture was extracted with $Et_2O$, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by short column chromatography on silica gel (eluent hexane/$Et_2O$ = 1/1) to give product **6** as white solid in 91% yield. Mp: 87.8 °C. $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 7.85 (d, $J$ = 8 Hz, 2H), 7.38 (d, $J$ = 9 Hz, 2H), 3.27 (m, 1H), 2.82 (d, $J$ = 7 Hz,1H), 2.53 (d, $J$ = 7 Hz, 1H), 2.47 (s, 3H). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 90.8 (s, 3F). IR(KBr): 1340, 1130 cm$^{-1}$. GC-MS $m/z$ (rel. int): 265 (7, $M^+$), 155 (50), 110 (15), 91 (100), 69 (6), 65 (35). Anal. Calcd. for $C_{10}H_{10}F_3NO_2S$: C, 45.28; H, 3.80; N, 5.28. Found: C, 45.36; H, 3.91; N, 5.28. $[\alpha]^{D}_{25}$= −16.3° ($c$ = 1.37, THF).

**(*S*)-Ethyl 1-Tosyl-2-(trifluoromethyl)aziridine-2-carboxylate (2).**[8] $n$-BuLi (1.1 equiv., 2.66 M in hexane) was added dropwise to a solution of **6** (5 mmol) in THF (25 mL) at −102 °C, and the solution was stirred at this temperature for 20 min to generate aziridinyl anion. Then, ClCOOEt (10 mmol, 2.0 equiv) was added dropwise to the solution at this temperature. After the reaction mixture was allowed to warm to −40 °C for 3 h, $Et_2O$ (5 mL) was added. The solution was warmed to room temperature followed by addition of sat. $NH_4Cl$ (8 mL). The combined organic layer was separated; then the aqueous layer was extracted with $Et_2O$. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/$Et_2O$ = 5/1) to give products **2** as a white solid in 95% yield. $^{1}$H NMR ($CDCl_3$): $\delta$ (ppm) 7.85 (d, $J$ = 8.0 Hz, 2H), 7.36 (d, $J$ = 9 Hz, 2H), 4.39 (q, $J$ = 7 Hz, 2H), 3.52 (br, 1H), 2.77 (s, 1H), 2.45 (s, 3H), 1.38 (t, $J$ = 7 Hz, 3H) {lit.[8] 7.84 (d, $J$ = 8 Hz, 2H), 7.36 (d, $J$ = 8 Hz, 2H), 4.38 (q, $J$ = 7 Hz, 2H), 3.52 (br, 1H), 2.77 (s, 1H), 2.45 (s, 3H), 1.37 (t, $J$ = 7 Hz, 3H)}. $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 90.8 (s, 3F); {lit.[8] 89.8 (s, 3F)}.

**(*S*)-Ethyl 3-Cyano-2-trifluoromethyl-2-tosylaminopropanoate (7a).** A solution of aziridine **2** (1.349 g, 4 mmol) and NaCN (0.217 g, 4.4 mmol) in $H_2O$ (16 mL) and $CF_3CH_2OH$ (16 mL) was stirred for 12 h. Then, sat. $NH_4Cl$ was added, the mixture was extracted with AcOEt, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified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by column chromatography on silica gel (eluent hexane/$Et_2O$ = 5/1) to give product **7a** in 80% yield as colorless oil. Mp: 50 °C. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 7.81 (d, $J$ = 8 Hz, 2H), 7.34 (d, $J$ = 8 Hz, 2H), 6.03 (s, 1H), 4.38 (dq, $J$ = 11, 7 Hz, 1H), 4.29 (dq, $J$ = 11, 7 Hz, 1H), 3.67 (d, $J$ = 17 Hz, 1H), 3.31 (d, $J$ = 17 Hz, 1H), 2.43 (s, 3H), 1.32 (t, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ (ppm) 87.9 (s, 3F). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) 163.3, 144.4, 137.2, 129.5, 126.9, 121.9, 113.9, 65.0, 65.0, 21.4, 20.9, 13.5. IR(KBr): 3290, 1740 $cm^{-1}$. GC/MS $m/z$ (%): 364 (tr $M^+$), 155(48), 91 (100), 65 (31). Anal. calcd for $C_{14}H_{15}F_3N_2O_4S$: C, 46.15; H, 4.15; N, 7.69. Found: C, 46.13; H, 4.30; N, 7.53. $[\alpha]^D_{25}$ = −25.9° ($c$ = 1.27, $Et_2O$).

**(*S*)-3-Amino-3-(ethoxycarbonyl)-4,4,4-trifluorobutanoic Acid (8a).** Compound **7a** (1.0 mmol) was dissolved in 98% $H_2SO_4$ (1 mL), and the resulting solution was kept at room temperature for 18 h. The solution was cooled to 0 °C and then added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel to give product **8a** in 72% yield as a colorless oil. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 4.11 (q, $J$ = 7 Hz, 2H), 3.11 (d, $J$ = 19 Hz, 1H), 2.74 (d, $J$ = 19 Hz, 1H), 1.25 (t, $J$ = 7 Hz, 1H) {lit.[5n] ($D_2O$) $\delta$ (ppm) 4.16 (q, $J$ = 7.1 Hz, 2H), 2.78 (q, $J$ = 16.7 Hz, 2H), 1.14 (t, $J$ = 7.1 Hz, 3H)}. $^{19}F$ NMR ($CDCl_3$): $\delta$ (ppm) 82.3 (s, 3F) {lit.[5n] ($D_2O$) $\delta$ (ppm) 87.2 (s)}. GC/MS $m/z$ (%): 156 (5), 154 (100) 69 (4), 59 (5). IR(neat): 1730, 1190 $cm^{-1}$.

**(*S*)-Ethyl 4,4-Bis(methoxycarbonyl)-2-tosylamino-2-trifluoromethylbutanoate (7b).** To NaOH (0.1219 g, 3.0 mmol) powder in DMSO (3 mL) in a flame-dried flask under Ar, a mixture of aziridine **2** (0.3303 g, 0.98 mmol) and $CH_2(CO_2Me)_2$ (0.24 mL, 2.1 mmol) in DMSO (3 mL) was added; the suspension was stirred for 2 h at room temperature. Then, 10% HCl(aq) was added, the mixture was extracted with AcOEt, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/AcOEt = 3/1) gave product **7b** in 67% yield as a white solid. Further purification was attained by recrystallization in 18% yield. Mp: 137−138 °C. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 7.73 (d, $J$ = 8 Hz, 2H), 7.28 (d, $J$ = 8 Hz, 2H), 5.85 (s, 1H), 4.34 (dq, $J$ = 11, 7 Hz, 1H), 4.23 (dq, $J$ = 11, 7 Hz, 1H), 3.94 (dd, $J$ = 8, 5 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.01 (dd, $J$ = 15, 5 Hz, 1H), 2.78 (dd, $J$ = 15, 8 Hz), 2.42 (s, 3H), 1.31 (t, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ (ppm) 88.6 (s, 3F). GC/MS $m/z$ (%): 396 (9), 224 (68), 155 (53), 91 (100). IR(KBr): 3280, 1770 $cm^{-1}$. Anal. calcd for $C_{18}H_{22}F_3NO_8S$: C, 46.05; H, 4.72; N, 2.98. Found: C, 45.96; H, 4.62; N, 2.99. $[\alpha]^D_{20}$ = +29.6° ($c$ = 0.04, $Et_2O$).

**(*S*)-Ethyl 5-Oxo-2-(trifluoromethyl)-*N*-tosylpyrrolidine-2-carboxylate (7c).** To **7b** (0.56 mmol), 1 M NaOH(aq) was added at room temperature. After the solution was stirred for 4 h, 10% HCl(aq) was added at 0 °C, the mixture was extracted with $Et_2O$, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. After the crude mixture of the product was heated at 150 °C for 4 h, it was purified by column chromatography on silica gel (eluent hexane/AcOEt = 5/1) to give product **7c** in 32% as a white solid. Mp: 113.2−113.8 °C. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 8.01 (d, $J$ = 9 Hz, 2H), 7.34 (d, $J$ = 8 Hz, 2H), 4.44 (dq, $J$ = 7, 1 Hz, 2H), 2.5 (m, 4H), 2.44 (s, 3H), 1.42 (t, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ (ppm) 89.4 (s, 3F). $^{13}C$ NMR ($CDCl_3$): $\delta$ (ppm) 172.6, 165.9, 145.8, 134.6, 129.6, 129.3, 123.8 (q, $J$ = 284 Hz), 70.5(q, $J$ = 20 Hz), 63.6, 29.1, 27.1, 21.7, 12.8. GC/MS $m/z$ (%): 315 (17), 242 (100), 155 (20), 91 (65). IR(KBr): 1750 $cm^{-1}$. Anal. calcd for $C_{15}H_{16}F_3NO_5S$: C, 47.49; H, 4.25; N, 3.69. Found: C, 47.35; H, 4.21; N, 3.66. $[\alpha]^D_{20}$ = +34.3° ($c$ = 0.014, AcOEt).

**(*S*)-Ethyl 5-Oxo-2-(trifluoromethyl)pyrrolidine-2-carboxate (8c).** Compound **7c** (0.22 g, 0.58 mmol) was dissolved in 98% $H_2SO_4$ (0.5 mL), and the resulting solution was kept at 50 °C for 3 h. The solution was cooled to 0 °C, then added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/AcOEt = 5/1) to give product **8c** in 92% as white solid. Mp: 78.2−79.0 °C. $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 6.36 (br, 1H), 4.33 (q, $J$ = 7 Hz, 2H), 2.5 (m, 4H), 1.33 (t, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ (ppm) 83.9 (s, 3F). GC/MS $m/z$ (%): 225 (<1), 152 (100), 132 (11), 104 (9), 54 (16). IR(KBr): 3200, 1760, 1710 $cm^{-1}$. Anal. calcd for $C_8H_{10}F_3NO_3$: C, 42.67; H, 4.48; N, 6.22. Found: C, 42.66; H, 4.51; N, 6.19.

**(*S*)-Ethyl 3,3,3-Trifluoro-2-(2-methylpropyl)-2-tosylaminopropanoate (7d) and Ethyl 3,3-Difluoro-2-tosylamino-2-propenoate (9).** To $Cu(OTf)_2$ (0.037 g, 0.1 mmol) in a flame-dried flask under Ar, THF (1.5 mL) and HMPA (0.3 mL, 1.7 mmol) were added at −40 °C. Then, isopropyl magnesium chloride ($^i$PrMgCl) (2.1 mL, 4.0 mmol) was added dropwise. The mixture was stirred for 2 h at −30 °C. The reaction was quenched by $NH_4Cl$(aq) and extracted with $Et_2O$. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/$Et_2O$ = 5/1) to give product **7d** in 16% yield as colorless oil. The main product was difluoroolefin **9** (68%).

*(S)-Ethyl 3,3,3-Trifluoro-2-(2-methylpropyl)-2-tosylaminopropanoate (7d).* $^1H$ NMR ($CDCl_3$): $\delta$ (ppm) 7.73 (d, $J$ = 8 Hz, 2H), 7.27 (d, $J$ = 8 Hz, 2H), 5.95 (s,1H), 4.38 (dq, $J$ = 11, 7 Hz, 1H), 4.27 (dq, $J$ = 11, 7 Hz, 1H), 2.57 (dd, $J$ = 14, 4 Hz, 1H), 2.41 (s, 3H), 2.10 (m, 1H), 1.94 (dd, $J$ = 14, 4 Hz, 1H), 1.33 (t, $J$ = 7 Hz, 3H), 1.05 (d, $J$ = 7 Hz, 3H), 0.83 (d, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ (ppm) 88.8 (s, 3F). GC/MS $m/z$ (%): 308 (6), 170 (11), 155 (66), 91 (100). IR(neat): 2970, 1750 $cm^{-1}$. Anal. calcd for $C_{16}H_{22}F_3NO_4S$: C, 50.38; H, 5.81; N, 3.67. Found: C, 50.42; H, 5.68; N, 3.57. $[\alpha]^D_{20}$ = +36.0° ($c$ = 0.005, $Et_2O$).

*Ethyl 3,3-Difluoro-2-tosylamino-2-propenoate (9).* Mp: 65.5−66.0 °C. $^1H$ NMR ($CDCl_3$): $\delta$ 7.76 (d, $J$ = 8 Hz, 2H), 7.32 (d, $J$ = 8 Hz, 2H), 5.86 (s, 1H), 4.16(q, $J$ = 7 Hz, 2H), 3.14 (t, $J$ = 3 Hz, 2H), 2.44 (s, 3H), 1.26 (t, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ 73.7(d, $J$ = 32 Hz, 1F), 68.3 (d, $J$ = 32 Hz, 1F). IR(KBr): 3200, 1770, 1740 $cm^{-1}$. GC/MS $m/z$ (%): 274 (tr), 246 (1), 178(5), 155 (22), 136 (24), 91 (100). Anal. calcd for $C_{13}H_{15}F_2NO_4S$: C, 48.90; H, 4.73; N, 4.39. Found: C, 48.95; H, 4.75; N, 4.41.

**(*S*)-Ethyl 2-Amino-4-methyl-2-trifluoromethylpentanoate (8d).** Compound **7d** (1.0 mmol) was dissolved in 98% $H_2SO_4$ (1 mL), and the resulting solution was kept at room temperature for 1 h. Then the solution was added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/$Et_2O$ = 5/1) to give product **8d** in 57% as colorless oil. $^1H$ NMR ($CDCl_3$): $\delta$ 4.27 (m, 2H), 2.03 (dd, $J$ = 14, 8 Hz, 1H), 1.7 (m, 1H), 1.65 (dd, $J$ = 14, 5 Hz, 1H), 1.32 (t, $J$ = 7 Hz, 3H), 0.99 (d, $J$ = 7 Hz, 3H), 0.86 (d, $J$ = 7 Hz, 3H). $^{19}F$ NMR ($CDCl_3$): $\delta$ 83.2 (s, 3F). IR(neat): 1750 $cm^{-1}$. GC/MS $m/z$ (%): 154 (97), 112 (100). Anal. calcd for $C_9H_{16}F_3NO_2$: C, 47.57; H, 7.10; N, 6.16. Found: C, 47.54; H, 7.11; N, 6.26. $[\alpha]^D_{20}$ = −30.0° ($c$ = 0.002, $Et_2O$).

**(*S*)-Ethyl 2-Benzyl-3,3,3-trifluoro-2-tosylaminopropanoate (7e).** CuBr (0.0137 g, 0.095 mmol) was added to the solution of PhMgBr (5.3 mL, 2 mmol); then the solution was cooled to 0 °C. To the solution of Grignard reagent, a solution of aziridine **2** (0.331 g, 0.99 mmol) in dry THF (5 mL) was added dropwise. The suspension was stirred at room temperature for 27 h; then sat. $NH_4Cl$ was added to quench, and the mixture was extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (hexane/$Et_2O$ = 5/1) to give product **7e** in 59% yield as a colorless oil. Optical purity was confirmed by comparison of the HPLC results (see Supporting Information). The product was submitted to the

detosylation without further purification. Mp: 85.0−85.7 °C. $^1$H NMR ($CDCl_3$): δ (ppm) 7.73 (d, J = 8.4 Hz, 2H), 7.39 (m, 2H), 7.30 (m, 5H), 5.83 (s, 1H), 4.26 (dq, J = 11, 7 Hz, 1H), 4.17 (dq, J = 11, 7 Hz, 1H), 3.97 (d, J = 14 Hz, 1H), 3.35 (d, J = 14 Hz, 1H), 2.41 (s, 3H), 1.24 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 90.4 (s, 3F). $^{13}$C NMR ($CDCl_3$): δ (ppm) 165.4, 143.2, 138.9, 132.6, 130.5, 129.2, 128.4, 127.7, 126.6, 122.9, 68.9, 63.9, 36.1, 21.4, 13.6. IR(KBr): 3280, 1750, 1160 cm$^{-1}$. GC/MS *m*/*z* (%): 342 (tr), 244 (19), 155 (28), 91 (100). $[\alpha]^D_{25}$ = +31.6° (*c* = 1.28, AcOEt).

**(*S*)-Ethyl 2-Amino-2-benzyl-3,3,3-trifluoropropanoate (8e).** Compound **7e** (1.0 mmol) was dissolved in 98% $H_2SO_4$ (1 mL), and the resulting solution was kept at room temperature for 1 h. Then the solution was added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (hexane/$Et_2O$ = 5/1) to give product **8e** in 73% yield as a colorless oil. $^1$H NMR ($CDCl_3$): δ (ppm) 7.23 (m, 5H), 4.27 (dq, J = 11, 7 Hz, 1H). 4.22 (dq, J = 11, 7 Hz, 1H), 3.47 (d, J = 14 Hz, 1H), 2.98 (d, J = 14 Hz, 1H), 1.85 (br, 2H), 1.30 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 84.9 (s, 3F). IR(neat): 1750 cm$^{-1}$. GC/MS *m*/*z* (%): 188 (43), 91(100). Anal. calcd for $C_{12}H_{14}F_3NO_2$: C, 55.17; H, 5.40; N, 5.36. Found: C, 55.24; H, 5.42; N, 5.40.

**(*S*)-Ethyl 3-Methoxy-2-tosylamino-2-trifluoromethylpropanoate (7f).** To an ice-cooled solution of aziridine **2** (3.376 g, 10 mmol) in MeOH (50 mL), $BF_3$·$OEt_2$ (47%) (5.1 mL, 20 mmol) was added dropwise. After the mixture was refluxed (54 h), water was added. The reaction mixture was exacted with $Et_2O$, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/$Et_2O$ = 3/1) to give product **7f** in 82% yield as a white solid. Optical purity was confirmed by comparison of the HPLC results (see Supporting Information). The product was submitted to the detosylation without further purification. Mp: 69.0−70.5 °C. $^1$H NMR ($CDCl_3$): δ (ppm) 7.76 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 5.84 (s, 1H), 4.31 (q, J = 7 Hz, 2H), 4.23 (d, J = 10 Hz, 1H), 3.91 (d, J = 10 Hz, 1H), 3.18 (s, 3H), 2.41 (s, 3H), 1.28 (t, *d* = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 89.5 (s, 3F). $^{13}$C NMR ($CDCl_3$): δ (ppm) 164.7, 143.2, 139.0, 129.1, 126.6, 122.3, 68.3, 68.0, 63.9, 59.0, 21.5, 13.8. IR(KBr): 3300, 1760 cm$^{-1}$. GC/MS *m*/*z* (%): 369 (tr M$^+$), 214 (9), 155 (9), 91 (32), 45 (100). $[\alpha]^D_{25}$ = −12.3° (*c* = 1.02, $Et_2O$).

**(*S*)-Ethyl 2-Amino-3-methoxy-2-trifluoromethylpropanoate (8f).** Compound **7f** (1.0 mmol) was dissolved in 98% $H_2SO_4$ (1 mL), and the resulting solution was kept at 0 °C for 2 h. The solution was added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel to give product **8f** in 77% as a colorless oil. Optical purity was confirmed by comparison of the HPLC results (see Supporting Information). $^1$H NMR ($CDCl_3$): δ (ppm) 4.29 (q, J = 7 Hz, 2H), 3.86 (d, J = 9 Hz, 1H), 3.63 (d, J = 9 Hz, 1H), 3.39 (s, 3H), 2.04 (br, 2H), 1.31 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$) δ (ppm) 86.0 (s, 3F). IR(neat): 1750 cm$^{-1}$. GC/MS *m*/*z* (%): 142 (63), 69 (2), 45 (100). Anal. calcd for $C_7H_{12}F_3NO_3$: C, 39.07; H, 5.62; N, 6.51. Found: C, 38.81; H, 5.90; N, 6.52. $[\alpha]^D_{25}$ = −6.6° (*c* = 1.67, $Et_2O$).

**(*S*)-Ethyl 3-Benzylamino-2-tosylamino-2-trifluoromethyl propionate (7g).** To a solution of aziridine **2** (2.703 g, 8.02 mmol) in THF (80 mL), $BnNH_2$ (1.31 mL, 12.0 mmol) was added dropwise. After 2 h refluxing, the reaction mixture was concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/$Et_2O$ = 3/1) to give product **7g** in 99% yield as colorless oil. Optical purity was confirmed by comparison of the HPLC results (see Supporting Information). $^1$H NMR ($CDCl_3$): δ (ppm) 7.76 (d, J = 8 Hz, 2H), 7.34 (m, 2H), 7.27 (m, 5H), 4.29 (dq, J = 7, 14 Hz, 1H), 3.84 (d, J = 14 Hz, 1H), 3.76 (d, J = 14 Hz, 1H), 3.49 (d, J = 13 Hz, 1H), 3.14 (d, J = 13 Hz, 1H), 2.40 (s, 3H), 1.27 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 89.7(s, 3F). $^{13}$C NMR ($CDCl_3$): δ (ppm) 166.0, 143.4, 139.1, 138.4, 129.3, 128.4, 127.9, 127.2, 126.4, 122.8, 67.6, 63.6, 53.7, 47.9, 21.5, 13.8. IR(neat): 3290, 1750, 1600 cm$^{-1}$. GC/MS *m*/*z* (%): 301 (19), 274 (4), 155 (7), 91 (100). Anal. calcd for $C_{20}H_{23}F_3N_2O_4S$: C, 54.05; H, 5.22; N, 6.30. Found: C, 54.12; H, 5.21; N, 6.24. $[\alpha]^D_{25}$ = +5.0° (*c* = 3.21, AcOEt).

**(*S*)-Ethyl-2-amino-3-benzylamino-2-trifluoromethylpropanoate (8g).** Compound **7g** (1.0 mmol) was dissolved in 98% $H_2SO_4$ (1 mL), and the resulting solution was kept at 100 °C for 2 h. The solution was cooled to 0 °C, then added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel to give product **8g** in 82% yield as colorless oil. $^1$H NMR ($CDCl_3$): δ (ppm) 7.30 (m, 5H), 4.23 (m, 2H), 3.81 (d, J = 2 Hz, 2H), 3.26 (d, J = 12 Hz, 1H), 2.84 (d, J = 12 Hz, 1H), 1.29 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 85.2(s, 3F). IR(neat): 1750 cm$^{-1}$. GC/MS *m*/*z* (%): 291 (tr M$^+$), 217 (1), 120 (21), 91 (100). Anal. calcd for $C_{13}H_{17}F_3N_2O_2$: C, 53.79; H, 5.90; N, 9.65. Found: C, 54.03; H, 6.07; N, 9.70. $[\alpha]^D_{25}$ = −13.56° (*c* = 0.05, AcOEt).

**(*S*)-Ethyl 3-Phenylthio-2-tosylamino-2-trifluoromethylpropanoate (7h).** To a solution of aziridine **2** (2.704 g, 8.02 mmol) and DABCO (0.050 g, 0.44 mmol) in $CH_3CN$ (64 mL), PhSH (0.99 mL, 9.6 mmol) was added dropwise. After stirring at room temperature for 19 h, the reaction mixture was concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/AcOEt = 5/1) to give product **7h** in 99% yield as a colorless oil. Optical purity was confirmed by comparison of the HPLC results (see Supporting Information). $^1$H NMR ($CDCl_3$): δ (ppm) 7.77 (d, J = 8 Hz, 2H), 7.44 (d, J = 7 Hz, 2H), 7.30 (m, 5H), 6.08 (s, 1H), 4.22 (d, J = 14 Hz, 1H), 4.08 (dq, J = 10, 7 Hz, 1H), 3.61 (d, J = 14 Hz, 1H), 3.67 (dq, J = 10, 7 Hz, 1H), 2.42 (s, 3H), 1.03 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 89.5 (s, 3F). $^{13}$C NMR ($CDCl_3$): δ (ppm) 164.6, 143.5, 138.7, 134.5, 131.8, 129.1, 128.9, 127.4, 126.7, 122.1, 68.4, 64.1, 36.4, 21.4, 13.3. IR(neat): 3300, 1750, 1060 cm$^{-1}$. GC/MS *m*/*z* (%): 447 (2: M+), 276 (16), 123 (100), 91 (37). Anal. calcd for $C_{19}H_{20}F_3NO_4S_2$: C, 51.00; H, 4.50; N, 3.13. Found: C, 51.02; H, 4.41; N, 3.12. $[\alpha]^D_{25}$ = +43.1° (*c* = 1.08, AcOEt).

**(*S*)-Ethyl 2-Amino-3-phenylthio-2-trifluoromethylpropanoate (8h).** Compound **7h** (1.0 mmol) was dissolved in 98% $H_2SO_4$ (1 mL), and the resulting solution was kept at 0 °C for 2 h. Then the solution was added dropwise into $Et_2O$ with stirring, and ice−water was added to the solution. The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel to give product **8h** in 86% as colorless oil. $^1$H NMR ($CDCl_3$): δ (ppm) 7.43 (m, 2H), 7.32 (m, 3H), 4.13 (dq, J = 11, 7 Hz, 1H), 3.90 (dq, J = 11, 7 Hz, 1H), 3.68 (d, J = 14 Hz, 1H), 3.26 (d, J = 14 Hz, 1H), 2.09 (br, 2H), 1.16 (t, J = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): δ (ppm) 84.8 (s, 3F). IR(neat): 1750 cm$^{-1}$. GC/MS *m*/*z* (%): 293 (6, M), 220 (2), 123 (100), 109(25), 69 (3). Anal. calcd for $C_{12}H_{14}F_3NO_2S$: C, 49.14; H, 4.81; N, 4.78. Found: C, 49.20; H, 4.77; N, 4.90. $[\alpha]^D_{25}$ = +26.8° (*c* = 1.37, $Et_2O$).

**(*S*)-Ethyl 3-Bromo-2-tosylamino-2-trifluoromethylpropanoate (7i).** To a mixture of aziridine **2** (0.7557 g, 2.23 mmol) and $MgBr_2$·$Et_2O$ (1.0386 g, 4.02 mmol) placed in an oven-dried round-bottom flask under Ar, $Et_2O$ (20 mL) was added. After refluxing for 24 h, 10% HCl(aq) (2 mmol) was added at 0 °C. The reaction mixture was exacted with $Et_2O$, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/$Et_2O$ = 5/1)

to give product **7i** in 99% yield as colorless crystal. Mp: 104.5−105.5 °C. $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 7.79 (d, $J$ = 8 Hz, 2H), 7.30 (d, $J$ = 8 Hz, 2H), 5.97 (s, 1H), 4.52 (d, $J$ = 11 Hz, 1H), 4.39 (m, 2H), 3.97 (d, $J$ = 11 Hz, 1H), 2.42 (s, 3H), 1.34 (t, 3H). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 90.4 (s, 3F). IR(KBr): 3270, 1770 cm$^{-1}$. GC/MS $m/z$ (%): 346 (5), 344 (5), 155 (84), 91 (100). Anal. calcd for $C_{13}H_{15}BrF_3NO_4S$: C, 37.33; H, 3.62; N, 3.35. Found: C, 37.39; H, 3.45; N, 3.32. $[\alpha]^D_{20}$ = −8.23° ($c$ = 7.20, $Et_2O$).

**(*S*)-Ethyl 2-Tosylamino-2-trifluoromethylpropanoate (7j).** To a mixture of compound **7i** (0.9868 g, 2.4 mmol) and Zn (0.7480 g, 11.4 mmol), AcOH (3 mL) was added. After the solution was stirred at 130 °C for 16 h, AcOH (3 mL) was added. After completion (6 h) of the reaction, AcOH was removed under reduced pressure. The reaction mixture was dissolved in $Et_2O$ and 10% HCl(aq) and then extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/dichloroethane =3/1) to give product **7j** in 88% yield as a white solid. Mp: 115.5−116.0 °C. $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 7.76 (d, $J$ = 8 Hz, 2H), 7.31 (d, $J$ = 8 Hz, 2H), 5.65 (s, 1H), 4.23 (q, $J$ = 7 Hz, 2H), 2.43 (s, 3H), 1.65 (s, 3H), 1.28 (t, $J$ = 7 Hz, 3H). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 83.9 (s, 3F). GC/MS $m/z$ (%): 266 (15), 155 (76), 139 (4), 112 (6), 91 (100), 65 (30). IR(KBr): 3280, 1600 cm$^{-1}$. Anal. calcd for $C_{13}H_{16}F_3NO_4S$: C, 46.01; H, 4.75; N, 4.13. Found: C, 46.23; H, 5.00; N, 4.11. $[\alpha]^D_{20}$ = 0.0° ($c$ = 1.37, $Et_2O$).

**$\alpha$-$CF_3$-Ala (8j).**[50] Compound **7j** (0.1005 g 0.30 mmol) was dissolved in 98% $H_2SO_4$ (0.5 mL), and the resulting solution was kept at 50 °C for 10 min. The solution was cooled to 0 °C, and ice−water was added to the solution. The combined organic phase was extracted with $Et_2O$ and washed with 10% HCl(aq). The aqueous layer was made alkaline by addition of NaOH(aq) and was then extracted with $Et_2O$. After being concentrated under reduced pressure, the crude mixture of the product was added to KOH(aq). After the mixture was stirred for 3 h, HCl(aq) was added until the aqueous layer was made acidic. After being concentrated under reduced pressure, the crude mixture of the product was purified by column chromatography on ion-exchange regins (DOWEX 50W-X8) to give product $\alpha$-$CF_3$-Ala (**8j**) as a yellowish white powder. $^1$H NMR ($D_2O$): $\delta$ (ppm) 1.57 (s, 3H) {lit.[50] ($D_2O$) $\delta$ (ppm) 1.55 (s, 3H)}.$^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 86.3 (s, 3F) {lit.[50] ($D_2O$) $\delta$ (ppm) 87.1 (s, 3F)}.GC/MS $m/z$ (%): 112 (100).

**(*R*)-2-Hydroxymethyl-2-trifluoromethyl-*N*-tosylaziridine (10).** To a mixture of compound **2** (0.3362 g, 1.0 mmol) and $NaBH_4$ (0.0593 g, 1.6 mmol), EtOH (3 mL) was added. After the solution was stirred for 2 h, $NH_4Cl$(aq) was added, and the solution was extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (hexane/AcOEt = 5/1) to give product **10** in 51% yield as a white solid. $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 7.86 (d, $J$ = 8 Hz, 2H), 7.38 (d, $J$ = 8 Hz, 2H), 4.56 (d, $J$ = 14 Hz, 1H), 4.21 (d, $J$ = 14 Hz, 2H), 3.13 (br, 1H), 2.98 (s, 1H), 2.63 (s, 1H), 2.47 (s, 3H). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 88.9 (s. 3F). GC/MS $m/z$ (%): 295 (<1), 155 (29), 140 (20), 91 (100). IR(KBr): 3540, 1600 cm$^{-1}$. Anal. calcd for $C_{11}H_{12}F_3NO_3S$: C, 44.74; H, 4.10; N, 4.74. Found: C, 44.75; H, 4.06; N, 4.81.

**2-Cyanomethylcarbonyl-2-trifluoromethyl-*N*-tosylaziridine (11).** The reaction was influenced by the possible existence of a small amount of water. Under a highly dried condition, aziridine **6** with cyanoacetate was the main product.

To acetonitrile (0.035 mL, 0.6 mmol) in THF (0.5 mL) at −78 °C, $n$-BuLi (0.19 mL, 0.5 mmol) was added. After the mixture was stirred for 20 min, a solution of **2** (0.1684 g, 0.5 mmol) in THF (1.0 mL) was added dropwise. After the mixture was stirred for 10 min, $NH_4Cl$(aq) was added, and the solution was extracted with $Et_2O$. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture of the product was purified by column chromatography on silica gel (eluent hexane/AcOEt = 3/1) and recrystallization to give product **11** in 44% yield as a yellowish white crystal. $^1$H NMR ($CDCl_3$): $\delta$ (ppm) 7.82 (d, $J$ = 8 Hz, 2H), 7.40 (d, $J$ = 8 Hz, 2H), 4.24 (d, $J$ = 20 Hz, 1H), 3.98 (d, $J$ = 20 Hz, 1H), 3.48 (d, $J$ = 1 Hz, 1H), 2.80 (s, 1H), 2.48 (s, 3H). $^{19}$F NMR ($CDCl_3$): $\delta$ (ppm) 92.0 (s. 3F). GC/MS $m/z$ (%): 332(6), 155(50), 91(100). IR(KBr): 1750 cm$^{-1}$. Anal. calcd for $C_{13}H_{11}F_3N_2O_3S$: C, 46.99; H, 3.34; N, 8.43. Found: C, 46.99; H, 3.38; N, 8.39. $[\alpha]^D_{20}$ = 19.3° ($c$ =0.01, $Et_2O$).

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Spectroscopic data ($^1$H NMR, $^{19}$F NMR, $^{13}$C NMR, and chiral LC charts). This material is available free of charge via the Internet at http://pubs.acs.org.

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