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Trifluoromethyl-stabilized optically active oxiranyl and aziridinyl anions for stereospecific syntheses of trifluoromethylated compounds

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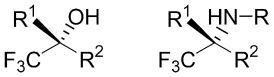
Abstract—Optically active 2,3-epoxy-1,1,1-trifluoropropane was converted into the corresponding oxiranyl anion and reacted with electrophiles such as aldehydes, ketones and halides to give the corresponding adducts in moderate to good yields. The whole reaction occurred with retention of configuration at the stereogenic carbon center. In a similar manner, trifluoromethyl stabilizing aziridinyl anions were generated from the optically active *N*-tosyl and *N*-anisyl-2-trifluoromethylaziridines. They also reacted well with various electrophiles. The products of these reactions are versatile synthetic intermediates useful for the synthesis of a variety of trifluoromethylated compounds with quaternary chiral carbon centers.

1. Introduction

The biological and pharmaceutical importance of optically active fluorinated organic compounds has been well described.[1–5] However, the poor availability of optically active fluorinated starting materials, which stems from a lack of natural fluoro-organics, has made the preparations of optically active fluoro-organic compounds difficult. Moreover, the unique reactivity of such fluorinated compounds makes the construction of the desired structure difficult. Therefore, a smart strategy and an effective device for construction of the fluorinated organic compounds have been desired. A stereocontrolled preparation of fluorinated organic compounds remains not only a demand for biochemists and medicinal chemists, but also a challenge of synthetic organo-fluorine chemistry.[2–5]

Among the challenging themes in fluoro-organic synthesis, construction of chiral quaternary carbon atoms bearing a trifluoromethyl group such as those in structures **1** and **2**, is one of the most challenging. Such carbons are the key chiral centers of inhibitory pharmaceuticals[6] and chiral derivatizing agents.[7] To date, the construction of the chiral carbon involved in **1** and **2** has been attained by stereoselective and/or diastereoselective alkylations of ketones and imines,[6,8] or separations of the corresponding racemates.[7]



1 **2**

Recent progress in enantioselective and/or diastereoselective alkylations enabled us to utilize a conventional strategy to construct such quaternary carbons via stereoselective alkylations, although they require some elaborate effort for the individual alkylation to attain a satisfactory stereoselectivity. Thus, an alternative synthetic strategy using a common synthetic intermediate having a chiral quaternary carbon and reactive functional group(s) would be much more practical for preparations of a variety of quaternary chiral derivatives.

Here, we describe our new strategy for preparation of the common synthetic intermediates, which contain quaternary carbons bearing trifluoromethyl groups as well as reactive three membered rings such as epoxide and aziridine by stereospecific alkylation of optically active 2-trifluoromethylated oxiranyl and the aziridinyl anions.

2. Results and discussion

Among the optically active fluorinated compounds, compounds with structure **3** in Scheme 1 are exceptionally reliable and highly available.[9] Thus, the stereospecific substitution of the proton on the chiral carbon in these

Keywords: trifluoromethyl group; oxiranyl anion; aziridinyl anion; 2,3-epoxy-1,1,1-trifluoropropane; quarternary chiral carbon center; fluorinated amino acid.
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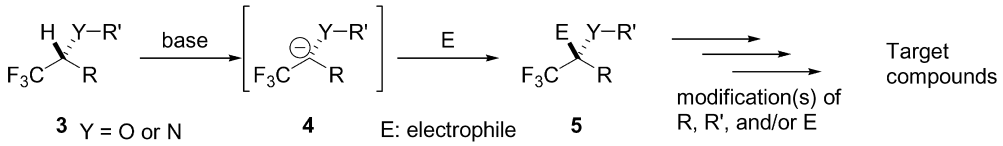
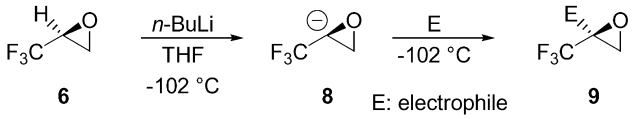


Scheme 1.

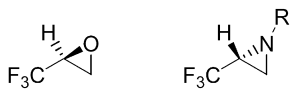


Scheme 2.

compounds would give a general synthetic intermediate **5** for optically active compounds having chiral quaternary carbons bearing trifluoromethyl groups.[10] The strategy is illustrated in Scheme 1.

However, the sp^3 carbanion at this chiral carbon is notorious for its unstable nature; it spontaneously undertakes defluorination to give difluoroolefins.[11] Except for our oxiranyl and aziridinyl anions,[12] and the organozinc species, CF_3CCl_2-ZnX,[13] conventional α-trifluoromethylated carbanions are sp^2 carbanions, and are stabilized by either π-conjugation such as enol forms or a neighboring effect by heteroatoms;[14] thus, they can not be optically active themselves.

The general starting material for our oxiranyl and aziridinyl anions chemistry is 2,3-epoxy-1,1,1-trifluoropropane **6**, which is a highly available chiral trifluoromethylated compound.[15] Although commercially available **6** is 75% ee (*S*) form,[15c] recently reported Jacobsen's enantioselective hydrolysis of the racemate enables us to utilize the optically pure **6**.[16] Optically pure aziridines **7** were synthesized in a few steps from the epoxide **6**.[9,12b]



The oxiranyl anion **8** was generated from optically active **6** under the conditions shown in Scheme 2. The reaction of the oxiranyl anion **8** with PhCHO gave the substituted epoxide **9a** in an excellent yield. The anion was generated regioselectively at the α-carbon to trifluoromethyl group; that is, the trifluoromethyl group acts as 'the oxiranyl anion stabilizing group'.[17]

The oxiranyl anion is sensitive to temperature. Thus, the reaction should be performed under low temperature conditions. This oxiranyl anion **8** was found to be stable at −78°C even for 1 h and to react well with PhCHO, but to decompose at around −70°C. The oxiranyl anion **8** was completely decomposed at a reaction temperature above −40°C; an ^{19}F NMR analysis of the reacting solution showed that the reaction performed at −40°C gave no **9a** as well as no appreciable amount of fluorinated organic compounds.

Table 1. Scope of the reaction of trifluoromethylated oxiranyl anion **8** with carbonyl compounds

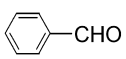
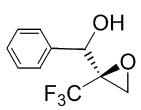
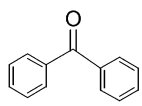
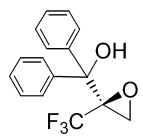
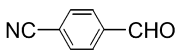
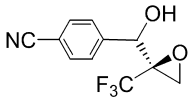
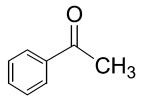
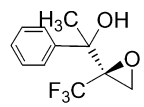
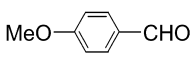
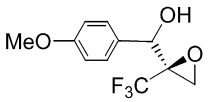
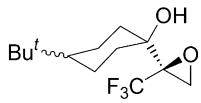
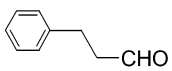
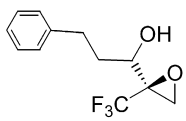
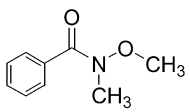
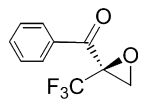
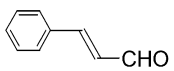
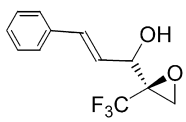
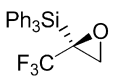
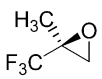
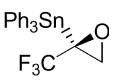
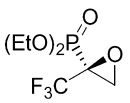
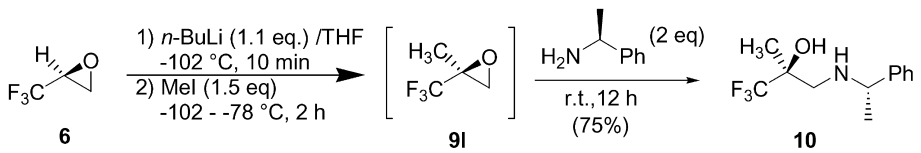
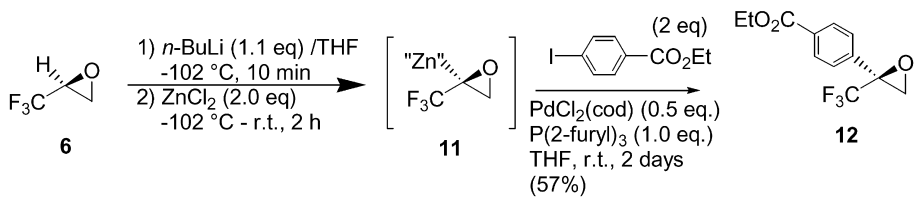
Electrophile	Products (yield, %)	Electrophile	Products (yield, %)
	 **9a** (91) ds=83/17		 **9f** (85)
	 **9b** (88) ds=78/22		 **9g** (78) ds=84/16
	 **9c** (99) ds=85/15		 **9h** (87) ds=83/17
	 **9d** (85) ds=51/49		 **9i** (82)
	 **9e** (77) ds=81/19		

Table 2. Scope of the reaction of trifluoromethylated oxiranyl anion **8** with halides

Electrophile	Products (yield, %)		Electrophile	Products (yield, %)	
Ph_3Si-Cl		**9j** (70)	CH3-I		**9l** (75) see Scheme 3
Ph_3Sn-Cl		**9k** (87)	$(EtO)_2P(O)$-Cl		**9m** (42)



Scheme 3.



Scheme 4.

The oxiranyl anion **8** reacts with a variety of carbonyl compounds to give a series of epoxides **9** with retention of the configuration at the quaternary carbon center. The results are summarized in Table 1. The anion is so reactive that the reaction with acid halides is uncontrollable; the reaction gave many products. Therefore, instead of acid halides, synthesis of the product with a carbonyl moiety, **9i**, needed the utilization of the Weinreb amide.[18]

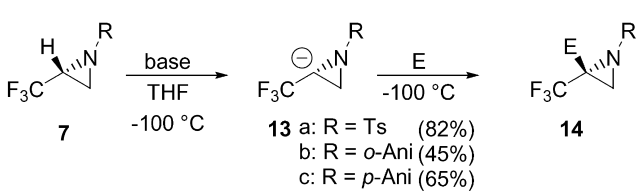
The oxiranyl anion **8** reacted with halides, likewise, to give other products including heteroatom substituted epoxides (Table 2).

Although the methylation of the anion **8** with MeI appears to go in good yield, the product **9l** was lost in the usual workup procedure due to its high volatility. Thus, the yield was estimated by that of the further ring-opened compound **10** (Scheme 3). Other alkylations, such as vinylation, allylation, and benzylation with corresponding halides have not yet been successful.

A metal exchange by $ZnCl_2$ gave thermally stable species **11**, of which the detailed structure is unknown. The zinc species **11** underwent a coupling reaction with aryl halide with the aid of a Pd catalyst at room temperature to give arylated compound **12** (Scheme 4).

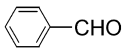
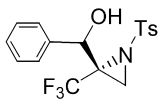
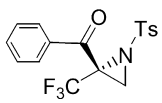
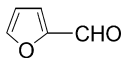
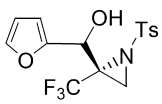
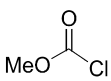
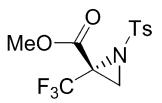
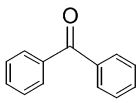
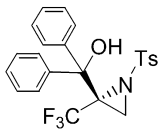
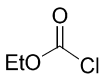
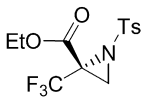
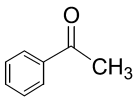
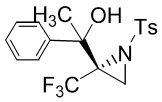
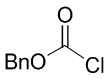
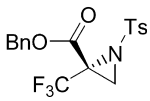
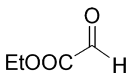
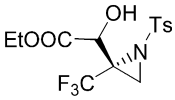
As described above, oxiranyl anion chemistry enabled us to access a wide variety of highly functionalized α-trifluoromethylated alcohols.[19] The aziridinyl anions would allow access to a wide variety of optically active amines with α-quaternary carbons with an attached trifluoromethyl group. Such amines would be pharmaceutically as well as biochemically interesting compounds.[10,20]

Similarly to that of the oxiranyl anion, the anions produced from 2-trifluoromethyl aziridines **7** were the α-carbon to the trifluoromethyl group. Generation of this anion species **13** depended on the *N*-substituents on the aziridine and the base. The reaction of the *N*-tosyl aziridine with *n*-BuLi generated anion **13a** in good yield (82%), which could be trapped by electrophile PhCHO to give **14** with *E*=–CH(OH)–Ph (Scheme 5). In contrast, the *N*-(*o*-anisyl) and *N*-(*p*-anisyl) aziridinyl anions (**13b** and **13c**) needed *sec*-BuLi, a stronger base, for generation of a certain amount (45 and 65%, respectively) of them, which was also trapped by PhCHO.[21] Generation of the aziridinyl anions of the *N*-benzyl aziridine with *sec*-BuLi was unsuccessful. The present results suggested that the electron-withdrawing property of *N*-substituents and the basicity of the alkyllithium are essential to generate the aziridinyl anions. Thus, the tosyl group acts as the best *N*-substituent among those tested.[12b]



Scheme 5.

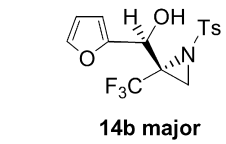
Table 3. Scope of the reaction of trifluoromethylated aziridinyl anion **13** with carbonyl compounds

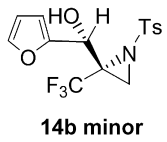
Electrophile	Products (yield, %)	Electrophile	Products (yield, %)
	 **14a** (82) ds=76/24		 **14f** (67)
	 **14b** (95) ds=72/28		 **14g** (85)
	 **14c** (45)		 **14h** (89)
	 **14d** (73) ds=92/8		 **14i** (95)
	 **14e** (27) ds=67/33		

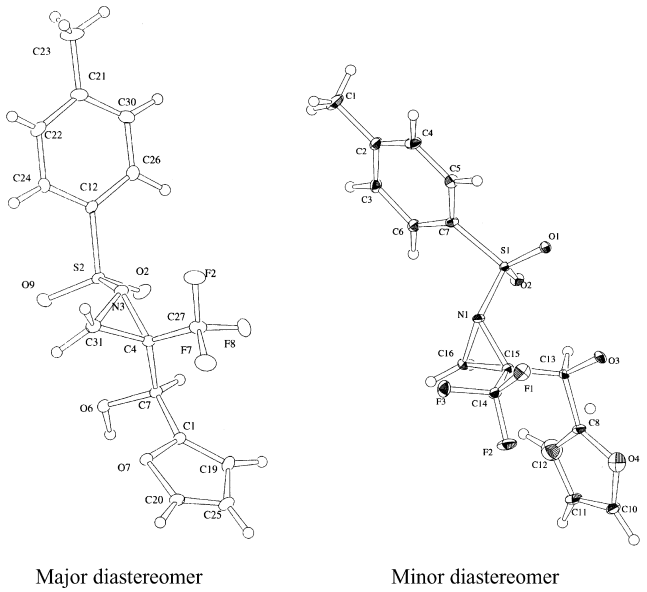
The aziridinyl anion **13a** from optically pure *N*-tosyl aziridine **7a** reacted with a variety of carbonyl compounds to give optically pure and highly substituted aziridines **14** in moderate to excellent yields. The results are summarized in Table 3.

The major and the minor isomers of **14b** were separated and subjected to X-ray crystallographic analyses. The major isomer has *S* configuration at the newly generated diastereomeric center. The ORTEPs are shown in Figure 1.

The stereochemistry of the product was confirmed by an X-ray crystallographic analysis of the ring opened derivative, **15a**, from **14g**. The compound **14g** was allowed to react with optically pure (*R*)-phenethylamine to give the compound **15a**, α-trifluoromethyl-α,β-diamino acid (Scheme 6). The ORTEP view of the **15a** is shown in

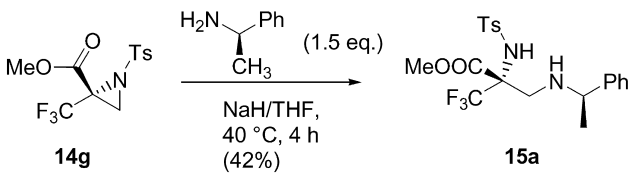






Major diastereomer Minor diastereomer

Figure 1. ORTEPs of **14b**.



Scheme 6.

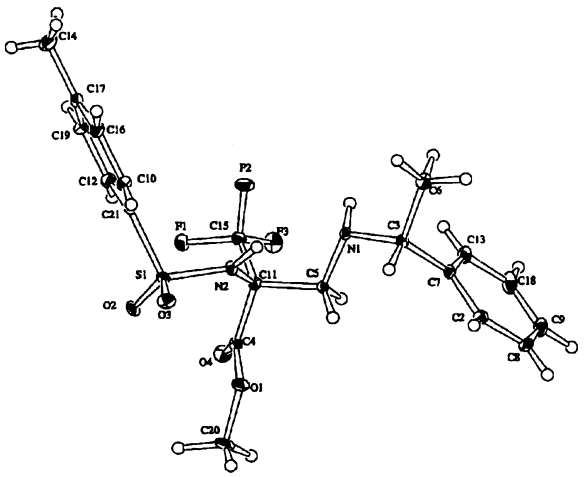
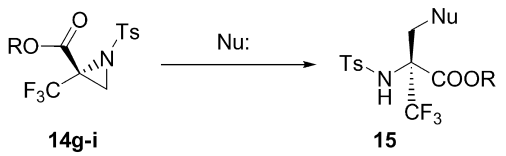
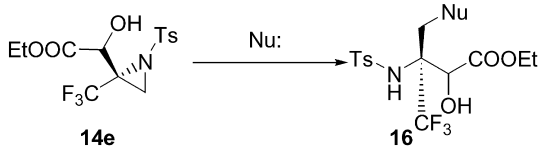


Figure 2. ORTEP of **15a**.



Scheme 7.



Scheme 8.

Table 4. Scope of the reaction of trifluoromethylated aziridinyl anion **13** with halides and disulfide

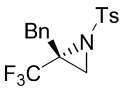
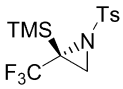
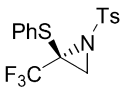
Electrophile	Products (yield, %)
BNbR	 **14j** (13)
TMS-Cl	 **14k** (99)
Phs-sph	 **14l** (87)

Figure 2. Retention of the configuration at the trifluoromethylated quaternary carbon center in the course of the reaction was confirmed.

The ester products **14g–i** are universal synthetic intermediates for α-trifluoromethyl-α-amino acid derivatives **15**, which could be derived by nucleophilic aziridine ring opening reactions (Scheme 7). In addition, **14e** could be that of α-hydroxy-β-trifluoromethyl-β-amino acid derivatives **16** (Scheme 8).

In a similar fashion to the oxiranyl anion **8**, the aziridinyl anion **13a** (R=Ts) reacted with halides and disulfide to give heteroatom substituted aziridines (Table 4).

A rich chemistry of the optically pure aziridinyl anion would provide a promising way to obtain a wide variety of α/β-amino acid derivatives.[10]

3. Conclusion

We have reported a new strategy to give optically active common synthetic intermediates, epoxides **9** and aziridines **14** with chiral quaternary carbons bearing a trifluoromethyl group; the strategy is characterized by stereospecific alkylation of the highly available optically active epoxide **6** and the aziridines **7** via the corresponding oxiranyl and aziridinyl anions with sp^3 carbon center. These common synthetic intermediates can undertake nucleophilic reactions at their three membered ring to give a series of trifluoromethylated highly functionalized alcohols and amines. In particular, the aziridines **14g–i** could be common synthetic intermediates for the synthesis of optically active α-trifluoromethyl-α-amino acids.

4. Experimental

4.1. General

All reactions were performed under an Ar or N_2 atmosphere. (*S*)-TFPO **6** (75% ee) was gifted by Japan Energy Corporation, Pharmaceuticals and Biotechnology Laboratory, and the same grade compound could be bought from Tokyo Kasei Kogyo Co. (Cat. code: T1557. e-mail: international@tokyokasei.co.jp). Optically active (*S* enriched, 75% ee)-TFPO **6** was used as it is, except for the preparation of **9m**. Optically pure (*S*)-TFPO was prepared by the Jacobsen kinetic resolution procedure.[16] Spectroscopic data for compound **9a–k** had been already published in our previous report as supporting information (see http://pubs3.acs.org/acs/journals/supporting_information.page?in_manuscript=ol016829f).[12a] Preparations of the optically pure 2-trifluoromethylated aziridines **7** were described in our previous report.[12b] THF was distilled from sodium-benzophenone ketyl solution under nitrogen. All other chemicals were of commercial grade and used without further purification. A commercial solution of *n*/*sec*-BuLi was titrated by using *l*-menthol and 2,2′-bipyridyl prior to use.[22] Glassware and syringes used for the reaction were oven dried before use.

All chromatographic purifications were performed on E. Merck silica gel (Kieselgel 60) using the indicated solvent systems. GC analyses were performed using Shimadzu GC-12A system connected to GL-Science CP-Cyclodex-β-256M capillary column. Melting points were obtained on Yanagimoto MP-S3 apparatus and were uncorrected.

^1H (200, 300, 500 MHz) and ^{19}F (188 and 282 MHz) NMR spectra were recorded on Varian VXR-200, Mercury-300, and VXR-500 spectrometers. Chemical shifts are reported in δ ppm from tetramethylsilane (δ 0.0 ppm for ^1H) and C_6F_6 (δ 0.0 ppm for ^{19}F NMR). For quantitative analyses of yields by NMR integration, 1,3-bis(trifluoromethyl)benzene was used as an internal standard for ^{19}F NMR. Coupling constants (*J*) are reported in hertz. IR spectra were taken on a Hitachi 270-30 spectrometer. Elemental analyses were performed on Perkin–Elmer series II CHNS/O Analyzer 2400. GC/MS spectra were recorded on a Hewlett–Packard HP5971A. Intensity measurements for X-ray crystallographic analyses were made on a Rigaku RAXIS-IV imaging plate area detector with graphite monochromated Mo Kα radiation.

4.2. Typical procedure for the reactions of oxiranyl anion

Typical procedure for the reaction of (*S*)-2,3-epoxy-1,1,1-trifluoro-propane ((*S*)-TFPO, **6** 75% ee) with electrophiles is as follows: an 1.1 equiv. amount of *n*-BuLi (1.56 M in hexane) was added dropwise to a solution of (*S*)-TFPO **6** (1.0 mmol) in THF (5 mL) at −102°C, and the solution was

stirred at this temperature for 10 min to generate oxiranyl anion **8**. Then electrophile (1.5 mmol) was added dropwise to the solution at this temperature. After the reaction mixture had been stirred for a further 10 min at −102°C, ether (1 mL) was added. The solution was warmed to rt, followed by addition of sat. aq. NH_4Cl (2 mL). The organic phase was separated, and then the aqueous layer was extracted by ether (5 mL, three times). The combined organic layer was washed with brine (5 mL, three times), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt 10/1) to give products **9**.

4.2.1. Preparation of (2*S*,5*S*)-2-methyl-5-phenyl-1,1,1-trifluoro-4-azahexane-2-ol (10, ring opened product of 9l). The product, 2,3-epoxy-1,1,1-trifluoro-2-methylpropane **9l** generated by the procedure shown above (NMR yield=82%) cannot be isolated due to its high volatility. Thus, the THF solution of **9l** was submitted for further ring opening reaction by the following procedure. To an ice cooled solution of **9l** (ca. 1 mmol) in 5 mL of THF, (*S*)-1-phenethylamine (2 mmol) was added dropwise. The reaction mixture was stirred at rt over night. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane/AcOEt 10/1) to give corresponding ring opened product **10** as a mixture of diastereomers.

Overall yield from **6** was 75%, ds=90/10 (theoretical, 87.5/12.5), a pale yellow liquid. IR (neat) 3350 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (m, 3H, minor), 1.27 (m, 3H, major), 1.40 (d, J=6 Hz, 3H), 2.29 (m, 1H), 2.96 (d, J=14 Hz, 1H), 3.79 (q, J=7 Hz, 1H, minor), 3.72 (q, J=7 Hz, 1H, major), 7.22–7.41 (m, 5H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 83.2 (s, CF_3, minor), 84.0 (s, CF_3, major) ppm; GC/MS *m*/*z* (%) 246 (1: M^+-1), 105 (100), 77 (12), 44 (21); Anal. calcd for $C_{12}H_{16}F_3NO$: C, 58.29; H, 6.52; N, 5.66. Found: C, 57.89; H, 6.66; N, 5.91.

4.2.2. 2-(Diethoxyphosphoryl)-1,2-epoxy-3,3,3-trifluoropropane (9m). This compound was prepared from optically pure epoxide **6**. Overall yield was 42%, a colorless liquid. IR (neat) 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, J=7 Hz, 3H), 1.37 (t, J=7 Hz, 3H), 4.20 (q, J=7 Hz, 2H), 4.23 (q, J=7 Hz, 2H), 5.43–5.40 (m, 1H), 5.54–5.50 (m, 1H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 87.8 (s or br, CF_3) ppm; GC/MS *m*/*z* (%) 248 (3: M^+), 221 (32), 192 (20), 109 (100), 98 (21), 91 (40), 81 (85); Anal. calcd for $C_7H_{12}F_3O_4P$: C, 33.88; H, 4.87. Found: C, 33.54; H, 4.96. $[\alpha]_D^{31}$=−14.7 (diastereo mixture, c=0.54, ether).

4.2.3. Procedure for Aryl coupling to 2-(*p*-ethoxycarbonylphenyl-1,2-epoxy-3,3,3-trifluoropropane (12). The oxiranyl anion was generated similarly from the 1 mmol of epoxide **6**. To a solution containing oxiranyl anion **8**, was added $ZnCl_2$ (273 mg, 2.0 mmol) dissolved in THF (5 mL) at −102°C. The solution was stirred for 1 h at this temperature then heated to 0°C. The solution containing zinc species **11** was then added dropwise into the mixture of $PdCl_2$(cod) (142 mg, 0.5 mmol), tri-2-furylphosphine (232 mg, 1.0 mmol), and ethyl 4-iodobenzoate (552 mg, 2.0 mmol) in THF (5 mL) via cannular tube. The reacting solution was stirred for 1 day at rt, then quenched by water, and the solution was extracted by ether twice. The combined etherial solution was washed by sat. NH_4Cl aq. and brine, then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane/AcOEt 10/1) to give arylated epoxide **12** in 57% yield.

Overall yield of **12** was 57%, a yellowish liquid. IR (neat) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, J=7 Hz, 3H), 2.93 (dq, J=5, 2 Hz, 1H), 3.45 (d, J=5 Hz, 1H), 4.39 (q, J=7 Hz, 2H), 7.62–7.59 (m, 2H), 8.10–8.06 (m, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 86.9 (s, CF_3) ppm; GC/MS *m*/*z* (%) 260 (7: M^+), 231 (25), 215 (52), 201 (10), 187 (100), 159 (10), 137 (16), 109 (17); Anal. calcd for $C_{12}H_{11}F_3O_3$: C, 55.39; H, 4.26. Found: C, 55.37; H, 4.58.

4.3. Typical procedure for the reaction of aziridinyl anion

Typical procedure for the reaction of (*R*)-1-tosyl-2-trifluoromethylaziridine **7** with electrophiles is as follows: An 1.1 equiv. amount of *n*-BuLi (2.66 M in hexane) was added dropwise to a solution of **7** in THF (5 mL) at −102°C, and the solution was stirred at this temperature for 20 min to generate aziridinyl anion. Then electrophile was added dropwise to the solution at this temperature. After the reaction mixture was allowed to warm to −40°C for 3 h, then ether (1 mL) was added. The solution was warmed to rt, followed by addition of sat. aq. NH_4Cl (2 mL). The combined organic layer was separated, and then the aqueous layer was extracted by ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ether 5/1) to give products **14**.

4.3.1. (2*S*)-2-(1-Hydroxy-1-phenylmethyl)-1-tosyl-2-trifluoromethylaziridine (14a major). Overall yield was 62%, white solid. Mp=131–132°C; IR (KBr) 3500 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.70 (s, 1H), 3.35 (s, 1H), 3.45 (d, J=6 Hz, 1H), 5.63 (d, J=6 Hz, 1H), 7.34–7.44 (m, 7H), 7.87 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 93.3 (s, CF_3) ppm; GC/MS *m*/*z* (%) 265 (2), 155 (18), 107 (100), 91 (71), 79 (33), 65 (25); Anal. calcd for $C_{17}H_{16}F_3NO_3S$: C, 54.98; H, 4.34; N, 3.77. Found: C, 55.22; H, 4.49; N, 4.02; $[\alpha]_D^{25}$=−30.1 (c=0.91, MeOH).

4.3.2. (2*S*)-2-(1-Hydroxy-1-phenylmethyl)-1-tosyl-2-trifluoromethylaziridine (14a minor). Overall yield was 20%, a white solid. IR (KBr) 3580 cm^{-1}; mp=161–162°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.81 (s, 1H), 3.28 (br, 1H), 4.01 (d, J=3 Hz, 1H), 5.47 (br, 1H), 7.32–7.42 (m, 5H), 7.52 (d, J=7 Hz, 2H),7.91 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 94.7 (s, CF_3) ppm; GC/MS *m*/*z* (%) 265 (tr), 171 (22), 155 (11), 107 (100), 91 (51), 79 (38), 77 (26); Anal. calcd for $C_{17}H_{16}F_3NO_3S$: C, 54.98; H, 4.34; N, 3.77. Found: C, 54.69; H, 4.74; N, 3.97; $[\alpha]_D^{25}$=+6.4 (c=1.20, MeOH).

4.3.3. (2*S*,1′*S*)-2-(1-Fur-2-yl-1-hydroxymethyl)-1-tosyl-2-trifluoromethyl-aziridine (14b major). Overall yield was

68%, a white solid. IR (KBr) 3560 cm^{-1}; Mp=76–77°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.73 (s, 1H), 3.37 (s, 1H), 3.53 (d, *J*=7 Hz, 1H), 5.69 (d, *J*=7 Hz, 1H), 6.39 (dd, *J*=3, 2 Hz, 1H), 6.50 (d, *J*=3 Hz, 1H), 7.35 (d, *J*=8 Hz, 2H), 7.44 (dd, *J*=2, 1 Hz, 1H), 7.84 (d, *J*=8 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 89.8 (s, CF_3) ppm; GC/MS *m/z* (%) 361 (tr: M^+), 206 (36), 190 (23), 171 (13), 155 (13), 97 (100), 91 (61). Anal. calcd for $C_{15}H_{14}F_3NO_4S$: C, 49.86; H, 3.91; N, 3.88. Found: C, 49.84; H, 3.80; N, 3.62; $[\alpha]_D^{25}=-10.8$ (*c*=1.02, MeOH).

Crystallographic data for **14b-major** *at 150 K.* $C_{15}H_{14}F_3NO_4S$; Mr=361.34; monoclinic; $P2_1$ (#4); *a*=15.629(2), *b*=5.8787(4), *c*=17.209(3) Å, β=103.275(2)°, *V*=1538.93(2) $Å^3$, *Z*=4, Dx=1.559 g/cm^3, μ=2.64 cm^{-1} for Mo Kα radiation (λ=0.7107 Å). The structure was solved by a direct method (SIR92), expanded using Fourier techniques (DIRDIF94), and refined by a full-matrix least-squares method. Final *R* was 0.037 and *Rw* was 0.044 for 3469 reflection with $I_0>1.00\sigma$ (I_0). Reflection/parameter ratio was 7.52, Goodness of fit indicator was 15.44. Max shift/error in final cycle was 0.00.

4.3.4. (2*S*,1′*R*)-2-(1-Fur-2-yl-1-hydroxymethyl)-1-tosyl-2-trifluoromethylaziridine (14b minor). Overall yield was 27%, white solid. IR (KBr) 3570 cm^{-1}; mp=135–136°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.84 (s, 1H), 3.25 (s, 1H), 3.83 (d, *J*=4 Hz, 1H), 5.47 (br, 1H), 6.41 (dd, *J*=3, 2 Hz, 1H), 6.51 (d, *J*=3 Hz, 1H), 7.39 (d, *J*=7 Hz, 3H), 7.89 (d, *J*=8 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 91.8 (s, CF_3) ppm; GC/MS *m/z* (%), 361 (tr: M^+), 206 (44), 190 (15), 186 (12), 155 (17), 97 (100), 91 (75); Anal. calcd for $C_{15}H_{14}F_3NO_4S$: C, 49.86; H, 3.91; N, 3.88. Found: C, 50.14; H, 3.71; N, 3.87; $[\alpha]_D^{25}=-30.2$ (*c*=1.04, MeOH).

Crystallographic data for **14b-minor** *at 150 K.* $C_{15}H_{14}F_3NO_4S$; Mr=361.34; monoclinic; $P2_1$ (#4); *a*=11.486(2), *b*=5.9188(4), *c*=11.896(2) Å, β=106.595(3)°, *V*=775.0(2) $Å^3$, *Z*=2, Dx=1.548 g/cm^3, μ=2.62 cm^{-1} for Mo Kα radiation (λ=0.7107 Å). The structure was solved by a direct method (SIR92), expanded using Fourier techniques (DIRDIF94), and refined by a full-matrix least-squares method. Final *R* was 0.076 and *Rw* was 0.087 for 1760 reflection with $I_0>3.00\sigma$ (I_0). Reflection/parameter ratio was 6.57, Goodness of fit indicator was 32.40. Max shift/error in final cycle was 2.64.

4.3.5. (2*S*)-2-(1-Hydroxy-1,1-diphenylmethyl)-1-tosyl-2-trifluoromethylaziridine (14c). Overall yield was 45%, a white solid. IR (KBr) 3580 cm^{-1}; Mp=187–188°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.79 (s, 1H), 3.01 (s, 1H), 3.20 (s, 1H), 7.29–7.35 (m, 8H), 7.41–7.44 (m, 2H), 7.52–7.56 (m, 2H), 7.77 (d, *J*=8 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 104.0 (s, CF_3) ppm; DI/MS *m/z* (%) 447 (tr: M^+), 183 (100), 155 (7), 105 (62), 91 (38), 77 (43), 65 (15); Anal. calcd for $C_{23}H_{20}F_3NO_3S$: C, 61.73; H, 4.51; N, 3.13. Found: C, 61.55; H, 4.72; N, 3.09; $[\alpha]_D^{25}=+19.1$ (*c*=1.20, MeOH).

4.3.6. (2*S*)-2-(1-Hydroxy-1-phenylethyl)-1-tosyl-2-trifluoromethylaziridine (14d, mixture of diastereomer). Overall yield was 73%, ds=92/8, a viscous colorless liquid. IR (neat) 3540 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.78 (s, 3H, minor), 2.03 (s, 3H, major), 2.47 (s, 3H, major), 2.94 (s, 1H, major), 3.03 (s, 1H, major), 3.07 (s, 1H, minor), 3.28 (br, 1H, major), 7.31–7.40 (m, 5H), 7.46–7.51 (m, 2H), 7.87 (d, *J*=8 Hz, 2H, minor), 7.90 (d, *J*=8 Hz, 2H, major) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 98.8 (s, CF_3, major), 100.9 (s, CF_3, minor) ppm; GC/MS *m/z* (%) major: 370 (tr), 155 (4), 121 (100), 91 (22); minor: 370 (tr), 155 (3), 121 (100), 91 (23); Anal. calcd for $C_{23}H_{20}F_3NO_3S$: C, 56.10; H, 4.71; N, 3.63. Found: C, 56.28; H, 5.10; N, 3.74; $[\alpha]_D^{25}=+7.3$ (diastereo mixture, *c*=0.78, MeOH).

4.3.7. (2*S*)-2-(1-Ethoxycarbonyl-1-hydroxymethyl)-1-tosyl-2-trifluoromethylaziridine (14e, mixture of diastereomer). Overall yield was 27%, ds=67/33, a viscous colorless liquid. IR (neat) 3520, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.28 (t, *J*=7 Hz, 3H, major), 1.33 (t, *J*=7 Hz, 3H, minor), 2.46 (s overlap, 3H, major and minor), 2.74 (s, 1H, major), 2.85 (s, 1H, minor), 3.02 (d, *J*=2 Hz, 1H, major), 3.16 (s, 1H, minor), 3.55 (d, *J*=7 Hz, 1H, major), 3.61 (d, *J*=4 Hz, 1H, minor), 4.22–4.38 (m, 2H, major and minor), 5.02 (br, 1H, minor), 5.04 (d, *J*=7 Hz, 1H, major), 7.35–7.38 (m, 2H, major and minor), 7.87 (d, *J*=9 Hz, 2H, major), 7.90 (d, *J*=9 Hz, 2H, minor) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 91.1 (s, CF_3, major), 91.4 (s, CF_3, minor) ppm; DI/MS *m/z* (%) 367 (tr: M^+), 294 (7), 212 (5), 195 (4), 155 (47), 138 (27), 91 (100), 65 (30); Anal. calcd for $C_{14}H_{16}F_3NO_5S$: C, 45.77; H, 4.39; N, 3.81. Found: C, 45.78; H, 4.58; N, 4.15; $[\alpha]_D^{25}=-0.4$ (diastereo mixture, *c*=1.06, MeOH).

4.3.8. (2*S*)-Phenyl 1-tosyl-2-trifluoromethyl-2-aziridinyl ketone (14f). Overall yield was 67%, a white solid. IR (KBr) 1690 cm^{-1}; mp=145–146°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.02 (s, 1H), 3.27 (q, *J*=2 Hz, 1H), 7.38 (d, *J*=9 Hz, 2H), 7.48–7.55 (m, 2H), 7.62–7.68 (m, 1H), 7.87 (d, *J*=9 Hz, 2H), 8.00 (d, *J*=7 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 91.6 (s, CF_3) ppm; DI/MS *m/z* (%) 369 (tr: M^+), 214 (3), 154 (2), 105 (100), 91 (23), 77 (28); Anal. calcd for $C_{17}H_{14}F_3NO_3S$: C, 55.28; H, 3.82; N, 3.79. Found: C, 55.10; H, 3.99; N, 3.84; $[\alpha]_D^{25}=-27.6$ (*c*=1.18, MeOH).

4.3.9. (2*S*)-Methyl 1-tosyl-2-trifluoromethylaziridine-2-carboxylate (14g). Overall yield was 85%, white solid. IR (KBr) 1760 cm^{-1}; mp=81–82°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.79 (s, 1H), 3.54 (q, *J*=2 Hz, 1H), 3.93 (s, 3H), 7.26–7.39 (m, 2H), 7.82–7.86 (m, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 89.0 (s, CF_3) ppm; GC/MS *m/z* (%) 323 (2: M^+), 292 (2), 168 (20), 155 (56), 91 (100), 65 (23); Anal. calcd for $C_{12}H_{12}F_3NO_4S$: C, 44.58; H, 3.74; N, 4.33. Found: C, 44.63; H, 4.03; N, 4.31; $[\alpha]_D^{25}=-60.7$ (*c*=1.16, MeOH).

4.3.10. (2*S*)-Ethyl 1-tosyl-2-trifluoromethylaziridine-2-carboxylate (14h). Overall yield was 89%, a white solid. IR (KBr) 1760 cm^{-1}; mp=69–70°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, *J*=7 Hz, 3H), 2.45 (s, 3H), 2.77 (s, 1H), 3.52 (br, 1H), 4.38 (q, *J*=7 Hz, 2H), 7.36 (d, *J*=8 Hz, 2H), 7.84 (d, *J*=8 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 89.8 (s, CF_3) ppm; GC/MS *m/z* (%) 337 (2: M^+), 292 (2), 155 (79), 91 (100), 65 (25); Anal. calcd for $C_{13}H_{14}F_3NO_4S$: C, 46.29; H, 4.18; N, 4.15. Found: C, 45.91; H, 4.54; N, 4.31; $[\alpha]_D^{25}=-42.5$ (*c*=0.92, Et_2O).

4.3.11. (2*S*)-Benzyl 1-tosyl-2-trifluoromethylaziridine-2-carboxylate (14i). Overall yield was 95%, a white solid. IR (KBr) 1750 cm^{-1}; mp=71–72°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.79 (s, 1H), 3.55 (br, J=2 Hz, 1H), 5.29 (d, J=12 Hz, 1H), 5.37 (d, J=12 Hz, 1H), 7.31 (d, J=8 Hz, 2H), 7.36–7.44 (m, 5H), 7.81 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 89.2 (s, CF_3) ppm; GC/MS *m/z* (%) 293 (2), 244 (3), 155 (16), 107 (10), 91 (100), 65 (16); Anal. calcd for $C_{18}H_{16}F_3NO_4S$: C, 54.13; H, 4.04; N, 3.51. Found: C, 54.16; H, 4.40; N, 3.37; $[\alpha]_D^{25}$=−59.9 (c=1.72, MeOH).

4.3.12. (2*R*)-2-Benzyl-1-tosyl-2-trifluoromethylaziridine (14j). Overall yield was 13%, a white solid. Mp=165–166°C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.61 (s, 1H), 2.99 (s, 1H), 3.59 (d, J=16 Hz, 1H), 3.70 (d, J=15 Hz, 1H), 7.32 (s, 5H), 7.37 (d, J=8 Hz, 2H), 7.88 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (188 MHz, $CDCl_3$) δ 88.6 (s, CF_3) ppm; GC/MS *m/z* (%) 355 (13: M^+), 200 (60), 155 (11), 130 (14), 91 (100); Anal. calcd for $C_{17}H_{16}F_3NO_2S$: C, 57.46; H, 4.54; N, 3.94. Found: C, 57.65; H, 4.17; N, 3.69; $[\alpha]_D^{25}$=−37.8 (c=0.91, Et_2O).

4.3.13. (2*S*)-1-Tosyl-2-trifluoromethyl-2-trimethylsilylaziridine (14k). Overall yield was 99%, a white solid. Mp=61–62°C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.40 (q, J=1 Hz, 9H), 2.45 (s, 3H), 2.55 (s, 1H), 2.74 (br, 1H), 7.33 (d, J=8 Hz, 2H), 7.83 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 93.9 (s, CF_3) ppm; GC/MS *m/z* (%) 200 (5), 155 (30), 142 (63), 91 (100), 65 (40); Anal. calcd for $C_{13}H_{18}F_3NO_2SSi$: C, 46.27; H, 5.38; N, 4.15. Found: C, 46.55; H, 5.35; N, 4.40; $[\alpha]_D^{25}$=−1.67 (c=1.00, MeOH).

4.3.14. (2*S*)-2-Phenylthio-1-tosyl-2-trifluoromethylaziridine (14l). Overall yield was 87%, a white solid. Mp=106–108°C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.72 (s, 1H), 2.87 (q, J=1 Hz, 1H), 7.34–7.42 (m, 5H), 7.67–7.70 (m, 2H), 7.88 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 87.2 (s, CF_3) ppm; GC/MS *m/z* (%) 373 (3: M^+), 264 (27), 218 (57), 155 (23), 123 (60), 109 (18), 91 (100), 65 (42); Anal. calcd for $C_{16}H_{14}F_3NO_2S_2$: C, 51.46; H, 3.78; N, 3.75. Found: C, 51.25; H, 3.70; N, 3.48; $[\alpha]_D^{25}$=−67.6 (c=1.39, MeOH).

4.3.15. (2*S*,2′*R*)-Methyl 3-(2′-phenetyl)amino-2-tosylamino-2-(trifluoromethyl)propionate (15a). Oily NaH (49 mg 60% in oil, 1.2 mmol) was washed with hexane, then dried in vacuo. To an ice cooled suspension of the NaH in THF (3 mL), (*R*)-1-phenethylamine (0.2 mL, 1.6 mmol) was added and stirred for 40°C for 30 min. The THF (5 mL) solution of the aziridine **14g** (329 mg, 1.0 mmol) was added dropwise at 40°C. The reaction mixture was stirred at this temperature for 6 h, then quenched by sat. NH_4Cl aq. The reaction mixture was extracted by Et_2O three times and the ether layers were combined, washed by brine, and dried over $MgSO_4$. After a removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane/ether 3/1) to give corresponding ring opened product **15a** in 42% yield.

White solid. IR (KBr) 3340, 3270, 1750 cm^{-1}; mp=112–114°C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, J=7 Hz, 3H), 2.41 (s, 3H), 2.99 (d, J=13 Hz, 1H), 3.22 (d, J=13 Hz, 1H), 3.72 (q, J=7 Hz, 1H), 3.87 (s, 3H), 7.22–7.30 (m, 5H), 7.32–7.38 (m, 2H), 7.71 (d, J=8 Hz, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ 88.9 (s, CF_3) ppm; GC/MS *m/z* (%) 441 (6), 351 (6), 197 (6), 155 (17), 105 (100), 91 (43); Anal. calcd for $C_{20}H_{23}F_3N_2O_4S$: C, 54.05; H, 5.22; N, 6.30. Found: C, 54.06; H, 5.29; N, 6.39; $[\alpha]_D^{25}$=+26.7 (c=1.22, MeOH).

Crystallographic data for **15a**. $C_{20}H_{23}F_3N_2O_4S$; Mr=444.47; orthorhombic; $P2_12_12_1$; a=7.2660(2), b=13.3922(4), c=21.2120(9) Å, V=2064.1(1) $Å^3$, Z=4, Dx=1.430 g/cm^3, μ=2.13 cm^{-1} for Mo Kα radiation (λ=0.71069 Å). The structure was solved by a direct method (SIR92), and refined by a full-matrix least-squares method. Final R was 0.030 and Rw was 0.033 for 2290 reflection with $I_0>3.00\sigma$ (I_0). Reflection/parameter ratio was 6.31. Goodness of fit indicator was 1.73. Max shift/error in final cycle was 0.06.

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References

1. Peters, R. *Carbon–fluorine compounds chemistry, biochemistry and biological activities. A Ciba Foundation Symposium*; Elsevier: Amsterdam, 1972.
2. *EnantioControlled Synthesis of Fluoro-organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999.
3. *Fluorine-containing amino acids: synthesis and properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994.
4. Welch, J. T. Advances in the preparation of biologically active organofluorine compounds. *Tetrahedron* **1987**, *43*, 3123.
5. *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, 1991.
6. For recent example: (a) Magnus, N. A.; Confalone, P. N.; Storace, L. *Tetrahedron Lett.* **2000**, *41*, 3015. (b) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L., Jr.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119. (c) Corbett, J. W.; Kresge, K. J.; Pan, S.; Cordova, B. C.; Klabe, R. M.; Rodgers, J. D.; Erickson-Viitanen, S. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 309. (d) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711.
7. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
8. (a) Prakash, G. K. S.; Mandal, M. *J. Fluorine. Chem.* **2001**, *123*, 112. (b) Aiet-Mohand, S.; Takechi, N.; Medebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2001**, *3*, 4271. (c) Petrov, V. A. *Tetrahedron Lett.* **2001**, *42*, 3267. (d) Ramachandran, P. V.; Jennings, M. P. *Org. Lett.* **2001**, *3*, 3789. (e) Uneyama, K.; Yan, F.; Hirama, S.; Katagiri, T. *Tetrahedron Lett.* **1996**, *37*,

2045. (f) Bravo, P.; Capelli, S.; Meille, S. V.; Seresini, P.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2321. (g) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (h) Assensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Soler, J. G.; Meille, S. V.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449. (i) Volonterio, A.; Bravo, P.; Panzeri, W.; Pesenti, C.; Zanda, M. *Eur. J. Org. Chem.* **2002**, 3336. (j) Bravo, P.; Soloshonok, V.; Farina, A.; Frigerio, M.; Meille, S. V.; Viani, F. *Tetrahedron: Asymm.* **1994**, *5*, 987. (k) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771. (l) Bravo, P.; Fustero, S.; Guidetti, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1999**, *64*, 8731.

9. For our recent review, see: Katagiri, T.; Uneyama, K. *Chirality* **2003**, *15*, 4.
10. For review on construction of α-amino acids with α-quaternary carbon, see: (a) Ctiviela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (b) Ctiviela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645.
11. (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 11327. (b) Howarth, J. A.; Owton, W. M.; Percy, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 757. (c) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 1641.
12. Yamauchi, Y.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2002**, *4*, 173. Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6319.
13. An example of sp^3 organometallics, CF_3CCl_2-ZnCl, without chirality, had been reported: Fujita, M.; Hiyama, T. *Bull. Chem. Soc. Jpn* **1987**, *60*, 4377.
14. (a) Jiang, B.; Xu, Y. *Tetrahedron Lett.* **1992**, *33*, 511. (b) Jiang, B.; Xu, Y. *J. Org. Chem.* **1991**, *56*, 7336. (c) Shi, G.-Q.; Huang, X.-H.; Hong, F. *J. Org. Chem.* **1996**, *61*, 3200. (d) Watanabe, H.; Yan, F.-Y.; Sakai, T.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 758. (e) Watanabe, H.; Yamashita, F.; Uneyama, K. *Tetrahedron Lett.* **1993**, *34*, 1941. (f) Uneyama, K.; Noritake, C.; Sadamune, K. *J. Org. Chem.* **1996**, *61*, 6055. (g) Heinze, P. L.; Burton, D. J. *J. Org. Chem.* **1988**, *53*, 2714. (h) Morken, P. A.; Lu, H.; Nakamura, A.; Burton, D. J. *Tetrahedron Lett.* **1991**, *32*, 4271. (i) Knunyants, I. L.; Stelin, R. N.; Bogachev, V. E. *Izv. Akad. Nauk. Ser. Khim.* **1958**, *22*, 407. (j) Spawn, T. D.; Burton, D. J. *Bull. Soc. Chim. Fr.* **1986**, 876. (k) Miller, W.; Snider, R. H.; Hummel, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 6532. (l) Banks, R. E.; Haszeldine, R. N.; Taylor, D. R.; Webb, G. *Tetrahedron Lett.* **1970**, 5215. (m) Drakesmith, F. G.; Stwert, O. J.; Tarrant, P. *J. Org. Chem.* **1967**, *33*, 280. (n) Fuchikami, T.; Ojima, I. *Tetrahedron Lett.* **1982**, *23*, 4099. (o) Fuchikami, T.; Yamanouchi, A.; Ojima, I. *Synthesis* **1984**, 766. (p) Ishikawa, N.; Yokozawa, T. *Bull. Chem. Soc. Jpn* **1983**, *56*, 724. (q) Seebach, D.; Beck, A. K.; Renaud, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 98. (r) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276. (s) Fuchigami, T.; Nakagawa, Y.; Nonaka, T. *J. Org. Chem.* **1987**, *52*, 5489. (t) Uneyama, K.; Momota, M. *Bull. Chem. Soc. Jpn* **1989**, *62*, 3378. (u) Qian, C.-P.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 7043. (v) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897. (w) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369.
15. For review on this epoxide see: (a) Katagiri, T. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, 1999; p 161. (b) Katagiri, T.; Uneyama, K. *J. Fluorine Chem.* **2000**, *105*, 285. (c) Furuhashi, K. In *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; Wiley: New York, 1992.
16. Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307.
17. (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (c) Capriati, V.; Degennaro, L.; Favia, R.; Florio, S.; Luisi, R. *Org. Lett.* **2002**, *4*, 1551. (d) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445.
18. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
19. Coppola, G. A.; Schuster, H. F. *α-Hydroxy Acids in Enantioselecctive Syntheses*; VCH: Weinheim, 1997.
20. The strategy for preparation of non-fluorinated amino acids, see: (a) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790. (b) Dodd, R. H. *Molecules* **2000**, *5*, 293.
21. A stronger base, *sec*-BuLi with TMEDA had been used for generation of aziridinyl and oxiranyl anions: see Ref. 17c and d, also see Luisi, R.; Capriati, V.; Florio, S.; Ranaldo, R. *Tetrahedron. Lett.* **2003**, *44*, 2677.
22. (a) Yamamoto, K.; Miyazawa, M.; 4th ed. *Jikken Kagaku Koza*; Maruzen: Tokyo, 1992; Vol. 24. p. 14. This method is a modification of the conventional method using *sec*-BuOH, see: (b) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.