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The Synthesis and Strecker Reaction of 2-Chlorotetrafluoroethanesulfinyl Ketimines

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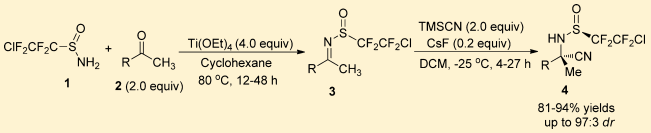
Supporting Information

ABSTRACT: A series of 2-chlorotetrafluoroethanesulfinyl ketimines were prepared from 2-chlorotetrafluoroethanesulfinamide and ketones in high yields, and their Strecker reactions with TMSCN have been investigated. High yields and excellent diastereoselectivities were achieved in the presence of a catalytic amount of CsF under mild conditions. The six-membered chairlike models were proposed to account for the high stereoselective Strecker reaction.



The chiral auxiliary strategy has been developed as an important technology in asymmetric synthesis.[1] Among various chiral auxiliaries, *N*-*tert*-butanesulfinimines (*t*-BS-imines)[1a,b,2] and *N*-*p*-toluenesulfinimines (*p*-TS-imines)[1c,3] are two typical ones and have found wide applications as versatile chiral amine templates. Recently, a novel fluorinated chiral auxiliary, polyfluoroalkanesulfinamide, was developed in our laboratory and applied successfully in the Strecker reaction,[4a] three-component aza-Diels–Alder reaction,[4b] and aminoallylation of aldehydes.[4c] Due to the strong electron-withdrawing effect of polyfluoroalkyl groups, imines derived from polyfluoroalkanesulfinamides showed high reactivity in the above reactions, and the reactions usually took place under mild conditions to achieve good yields and high diastereoselectivities. Among various polyfluoroalkanesulfinamides investigated in our previous work,[4] 2-chlorotetrafluoroethanesulfinamide (CTFSA) is a promising one due to its easy availability and high performance.

The Strecker reaction is an efficient approach for the formation of the C–C bond.[5,6] It has been reported that the Strecker reaction of aldimines could achieve good yields and stereoselectivities using TBSA[7] and *p*-TSA[8] as auxiliaries. However, the corresponding ketimines[9] derived from TBSA and *p*-TSA showed much less reactivity than their aldimine counterparts.[10] Therefore, the application of ketimines in the Strecker reaction still remains a challenge in organic synthesis.[11] In 2006, Lu's group demonstrated that the reaction of trifluoromethylketimines, prepared from trifluoroacetophenone and TBSA, with TMSCN could occur in the absence of additive and gave the adducts with excellent diastereoselectivities.[12] Obviously, the reinforced electrophilicity of the ketimines was attributed to the strong electron-withdrawing effect of trifluoromethyl group. Recently, Han's group also succeeded in developing the asymmetric application of trifluoromethylated *N*-*tert*-butanesulfinylimine.[13] Encouraged by their work, we envisioned that CTFSA[4a] might serve as a superior auxiliary for ketimines due to the strong electron-withdrawing effect of the fluoroalkyl group. Therefore, we studied the synthesis of 2-chlorotetrafluoroethanesulfinyl ketimines from CTFSA and ketones and investigated their application in the Strecker reaction. The results are reported in this contribution.

In our initial experiments, 2-chlorotetrafluoroethanesulfinamide (**1**) was treated with 1.1 equiv of acetophenone (**2a**) and 2.0 equiv of $Ti(OEt)_4$ in toluene at 90 °C. After 12 h, ^{19}F NMR spectrum of the reaction mixture showed that 63% of **1** converted and the desired ketimine **3a** was formed in 47% yield. When the reaction was carried out at 80 °C, the corresponding conversion and yield were reduced to 42% and 38%, respectively. Further decrease of temperature led to much lower conversion and yield. Taking into account the reaction efficiency, we chose 80 °C as the reaction temperature in the following experiments. Screening of solvent revealed that 1,4-dioxane, acetonitrile, and dimethylsulfoxide (DMSO) could not afford ketimine **3a**, and only trace product was observed in 1,2-dichloroethane (DCE). When cyclohexane was used as solvent, the yield of **3a** was improved to 64% (Table SI-1 in Supporting Information (SI)).

Next, the ratio of reagents was screened to find a suitable protocol for the formation of ketimines. The data revealed that increasing the amount of **2a** and $Ti(OEt)_4$ was beneficial for the formation of **3a** (Table SI-2 in SI). The yield of **3a** could be improved to 92% in the presence of 2.0 equiv of **2a** and 4.0 equiv of $Ti(OEt)_4$. Therefore, the optimal reaction conditions were set to using 2.0 equiv of **2a** and 4.0 equiv of $Ti(OEt)_4$ in cyclohexane at 80 °C.

It is worth mentioning that ketimine **3a** is stable in the refrigerator, and no decomposition is detected for weeks. Purification by flash column chromatography afforded **3a** in 81% yield (Table 1, entry 1). Under the optimized conditions, various ketones **2** were examined and a series of ketimines were synthesized. As shown in Table 1, the reaction of electron-deficient ketones proceeded well to afford the corresponding

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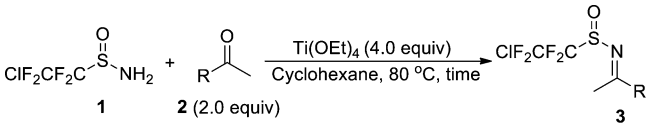
Table 1. Synthesis of Fluoroalkanesulfinyl Ketimines 3



entry[a]	2, R	time (h)	3	yield (%)[b]
1	**2a**, C_6H_5	20	**3a**	81 (92)
2	**2b**, *p*-$CF_3C_6H_4$	12	**3b**	68 (97)
3	**2c**, *p*-FC_6H_4	24	**3c**	70 (87)
4	**2d**, *p*-ClC_6H_4	24	**3d**	77 (95)
5	**2e**, *p*-BrC_6H_4	24	**3e**	71 (86)
6	**2f**, *m*-$CF_3C_6H_4$	12	**3f**	69
7	**2g**, *p*-MeC_6H_4	24	**3g**	63 (82)
8	**2h**, *p*-$MeOC_6H_4$	36	**3h**	69 (86)
9	**2i**, *p*-$O(CH_2CH_2)_2N-C_6H_4$	48	**3i**	41 (55)
10	**2j**, $C_6H_5CH{=}CH$	36	**3j**	75 (99)
11[c]	**2k**, $(CH_3)_2CHCH_2$	12	**3k**	56 (86)

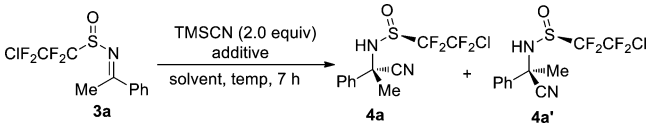
[a]The concentration of **1** was 0.1 M. [b]Yields in parentheses were determined by ^{19}F NMR spectroscopy using *p*-$BrC_6H_4CF_3$ as internal standard. [c]The reaction was carried out at 70 °C (oil bath).

products **2b**–**2f** in high yields (Table 1, entries 2–6). The ketones containing electron-donating substituted groups had lower reactivity and required longer reaction time. For example, it took 36 h for 4-methoxy acetophenone (**2h**) to achieve full conversion (Table 1, entry 8). In the case of ketone **2i**, the reaction time was prolonged to 48 h, and only 41% yield was obtained (Table 1, entry 9). Ketone **2j** containing a styryl group also reacted smoothly to give the corresponding ketimine **3j** in good yield (Table 1, entry 10). Under similar conditions, aliphatic ketone **2k** reacted with **1** readily at 70 °C to give the corresponding ketimine **3k**, but the isolated yield of **3k** was relatively lower (56%) due to its sensitivity to moisture (Table 1, entry 11).

Having the desired ketimines in hand, we next investigated their Strecker reactions. When **3a** was treated with TMSCN (2.0 equiv) without additive in dimethylformamide (DMF) at room temperature, ^{19}F NMR analysis of the reaction mixture showed that **3a** remained unchanged (Table 2, entry 1). When hexamethylphosphoramide (HMPA) was used as solvent, no desired product was obtained (Table 2, entry 2). Running the reaction in a mixed solvent of DMF and HMPA (1:1), the isomers **4a** and **4a′** were obtained in a total yield of 36% with a ratio of 33:67 (Table 2, entry 3). Attempts to use 2.0 equiv of $Ti(OEt)_4$ or CsF as additives failed to afford the products in 1,2-dichloromethane (DCM) at room temperature (Table 2, entries 4–5). However, when the reaction was carried out at −25 °C in the presence of CsF (2.0 equiv), adducts with *syn*-configuration as major isomer, were obtained in a total yield of 95% with 95:5 dr (Table 2, entry 6). Further experiments indicated that the additive loading could be lowered down to 0.2 equiv without any erosion in yield and stereoselectivity (Table 2, entries 7–8). Therefore, the optimized conditions of the Strecker reaction were set as follows: treating **3a** with TMSCN (2.0 equiv) in the presence of catalytic amount of CsF (0.2 equiv) in DCM at −25 °C.

Under the optimized conditions, the scope of Strecker reaction was then examined. The data in Table 3 showed that the reaction of various ketimines **3** worked well to afford the corresponding products in good yields with excellent diastereoselectivities. It is worth mentioning that the Strecker reaction was very sensitive to the electronic property of the

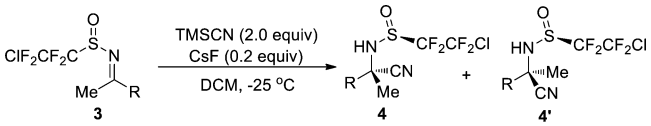
Table 2. Optimization of Reaction Parameters for the Strecker Reaction of 3a



entry[a]	solvent	temp (°C)	additive (equiv)	yield (%)[b]	dr (**4a**/**4a′**)[b]
1	DMF	rt	–	NR	–
2	HMPA	rt	–	0	–
3	DMF/HMPA (1/1)	rt	–	36	33:67
4	DCM	rt	$Ti(OEt)_4$ (2.0)	trace	–
5	DCM	rt	CsF (2.0)	complex	–
6	DCM	−25	CsF (2.0)	95	97:3
7	DCM	−25	CsF (0.2)	94	97:3
8	DCM	−25	CsF (0.1)	90	97:3

[a]Conditions: Ketimine **3a** (0.1 mmol), TMSCN (0.2 mmol) and 1 mL solvent at room temperature or −25 °C. [b]Determined by ^{19}F NMR using $PhCF_3$ as internal standard.

Table 3. Strecker Reaction of Fluoroalkanesulfinyl Ketimines



entry[a]	3, R	time (h)	products	yield (%)[b]	dr (4:4′)[c]
1	**3a**, C_6H_5	7	**4a, 4a′**	93	97:3
2	**3b**, *p*-$CF_3C_6H_4$	4	**4b, 4b′**	84	96:4
3	**3c**, *p*-FC_6H_4	9	**4c, 4c′**	85	94:6
4	**3d**, *p*-ClC_6H_4	7	**4d, 4d′**	87	96:4
5	**3e**, *p*-BrC_6H_4	6	**4e, 4e′**	81	93:7
6	**3f**, *m*-$CF_3C_6H_4$	7	**4f, 4f′**	83	96:4
7	**3g**, *p*-MeC_6H_4	15	**4g, 4g′**	89	97:3
8	**3h**, *p*-$MeOC_6H_4$	17	**4h, 4h′**	89	96:4
9[d]	**3i**, *p*-$O(CH_2CH_2)_2N-C_6H_4$	27	**4i, 4i′**	84	>97:3
10	**3j**, $C_6H_5CH{=}CH$	17	**4j, 4j′**	82	97:3
11	**3k**, $(CH_3)_2CHCH_2$	4	**4k, 4k′**	94	96:4

[a]Reaction conditions: **3** (0.2 mmol), TMSCN (0.4 mmol), CsF (0.04 mmol) in 3 mL DCM at −25 °C for 7 h. [b]Isolated yield. [c]Determined by ^{19}F NMR spectra of the crude reaction mixture. [d]15% of **3i** was recovered, and the reaction was performed at −5 °C.

substituent on the aromatic ring. It took a much shorter time for electron-deficient aromatic ketimines **3b**–**3f** and aliphatic ketimine **3k** (Table 3, entries 2–6, 11). The reaction of ketimine **3i** with a morpholine-substituent was carried out at −5 °C, and the corresponding adducts **4i** and **4i′** were obtained in 82% yield with 15% recovery of ketimine **3i** (Table 3, entry 9).

To further demonstrate the application of 2-chlorotetrafluoroethanesulfinyl ketimines in asymmetric synthesis, (*S*)-**3a** with 97.8% ee was prepared from (*S*)-2-chlorotetrafluoroethanesulfinamide (99% ee) and allowed to react with TMSCN under standard conditions to make optically pure **4a** (Scheme 1). HPLC analysis confirmed the excellent de value (94.0%) and ee value (97.5%) of the reaction. It was reported that the asymmetric strecker reaction of *tert*-butanesulfinyl and *p*-toluenesulfinyl ketimines derived from acetophenone gave the

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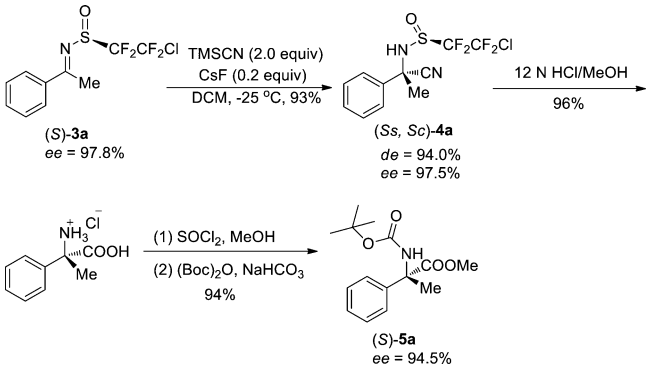
Scheme 1. Preparation of (*S*)-5a from (*S*)-3a



corresponding adducts with 84% de[11a] and 78% de,[11b] respectively. Furthermore, the X-ray crystal structure of **4a** was obtained, indicating that the absolute configuration of **4a** was (*Ss*,*Sc*) (Figure SI-1 in SI).[14] No racemization was observed during the deprotection of (*Ss*,*Sc*)-**4a** and the formation of (*S*)-**5a**.

On the basis of the above experimental results, the six-membered chairlike models[15] T^1 and T^2 were proposed to account for the high stereoselectivity of the Strecker reaction. As shown in Figure 1, transition state T^2 was an unfavored one

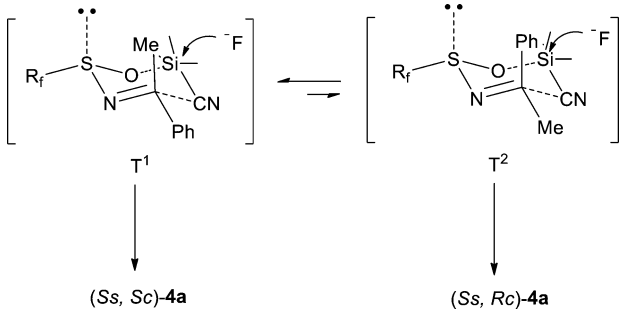


Figure 1. Proposed transition states for the Strecker reaction.

because of the predominant steric hindrance raised by the phenyl group. Therefore, the transition state T^1 predominated in this reaction and afforded the *syn*-adduct as a major product.

In summary, 2-chlorotetrafluoroethanesulfinyl ketimines **3** have been synthesized successfully from 2-chlorotetrafluoroethanesulfinamide, and their Strecker reaction with TMSCN was achieved in the presence of a catalytic amount of CsF, affording the corresponding adducts in good yields with excellent stereoselectivities. Compared with *tert*-butanesulfinyl and *p*-toluenesulfinyl ketimines, these fluoroalkanesulfinyl ketimines showed much higher diastereoselectivity in these Strecker reactions.

EXPERIMENTAL SECTION

General Information. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. CH_2Cl_2 was freshly distilled by standard procedure prior to use. Melting points were measured on a Melt-Temp apparatus and uncorrected. IR spectra were recorded with an infrared spectrometer. ^{1}H NMR and ^{19}F NMR were recorded on ^{1}H at 300 Hz (or 400 MHz) and ^{19}F at 282 MHz (or 376 MHz), respectively. ^{13}C NMR spectra were recorded on ^{13}C at 100 MHz. The mass analyzer type was FTICR-MS used for the HRMS measurements. Enantiomeric excesses were determined by chiral HPLC.

Procedure for the Synthesis of Racemic 1. To a flask containing HMDS (0.075 mol) was added 2-chlorotetrafluoroethanesulfinyl chloride (0.075 mol) dropwise at 0 °C. After addition, stirring was continued for 2 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was treated with 50 mL of saturated NH_4Cl (aq) for 2 h at room temperature. The resulting mixture was extracted with Et_2O (30 mL × 4) and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether 1:5).

Compound ***1***. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.96 (s, 2H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −67.27 to −67.32 (m, 2F), −119.74 (d, J_{FF} = 243.6 Hz, 1F), −122.47 (d, J_{FF} = 243.6 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 122.4 (tt, J = 298.4, 33.4 Hz), 116.3 (ddt, J = 306.0, 302.0, 35.1 Hz) ppm; HRMS (EI) calcd for $C_2H_2ClF_4NOS$ (M^+) requires 198.9482, found 198.9480.

Procedure for the Synthesis of (*S*)-1. n-BuLi (2.64 mL, 2.5 M in hexane) was added dropwise to the solution of (*S*)-4-phenyloxazolidin-2-one (6 mmol) in THF (30 mL) at −78 °C under the protection of N_2. After addition, the mixture was stirred for 0.5 h. Then 2-chlorotetrafluoroethanesulfinyl chloride (19.8 mmol) in 10 mL of THF was added. After being stirred for 3 h, the mixture was allowed to warm to room temperature. Solvent was removed, and the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether, 1:7). (*Rs*, *Sc*)-4-Phenyl-*N*-(2-chlorotetrafluoroethanesulfinyl)oxazolidin-2-one was obtained as a white solid.

A solution of (*Rs*,*Sc*)-4-phenyl-*N*-(2-chlorotetrafluoroethanesulfinyl)oxazolidin −2-one (0.5 mmol) in CH_2Cl_2 (7 mL) was added slowly to a solution of LiHMDS (1.0 mmol) in CH_2Cl_2 (3 mL) in 3 h at −78 °C under the protection of N_2. After addition, saturated NH_4Cl (aq) (5 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (10 mL × 3), and the organic solution was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel (EtOAc/petroleum ether, 1:5).

*Compound (S)-**1**:* yield 72%; white solid; mp 42−43 °C; $[\alpha]^{20}_D$ = −15.5 (c = 1.0, $CHCl_3$, 99% ee).

Typical Procedure for the Preparation of Ketimines 3. To a solution of 2-chlorotetrafluoroethanesulfinamide (0.2 mmol) and titanium(IV) ethoxide (0.8 mmol) in cyclohexane (2.0 mL) was added ketone **2** (0.4 mmol). The mixture was stirred at 80 °C and monitored by TLC. After the reaction was completed, brine (5 mL) was added, and the resulting mixture was filtered through Celite. The filter cake was washed with EtOAc. The aqueous phase was extracted with EtOAc (5.0 mL × 3), and the combined organic phase was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel to give ketimine **3** (EtOAc/petroleum ether, 1:20).

Typical Procedure for the Strecker Reaction. To a solution of 2-chlorotetrafluoroethanesulfinyl ketimine **3** (0.1 mmol) and CsF (0.02 mmol) in anhydrous DCM (1.0 mL) was added TMSCN (0.2 mmol) dropwise via a syringe at −25 °C. The resulting mixture was stirred at −25 °C and monitored by ^{19}F NMR. After the reaction was completed, the solvent was evaporated, and the residue was purified by column chromatography on silica gel (EtOAc/petroleum ether, 1:10) to give the corresponding products **4a** and **4a′**.

Compound ***3a***: 48.8 mg, 81%; yellow oil; IR (film): 3067, 1610, 1594, 1573, 1285, 1174, 1014, 800, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94−7.91 (m, 2H), 7.58−7.55 (m, 1H), 7.50−7.45 (m, 2H), 2.85 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.94 (s, 2 F), −115.48 (d, J_{FF} = 231.7 Hz, 1F), −116.91 (d, J_{FF} = 231.7 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 137.2, 133.0, 128.7, 127.8, 122.3 (tt, J_{C-F} = 248.8, 25.1 Hz), 117.0 (tt, J_{C-F} = 253.5, 25.1 Hz), 20.3 ppm; ESI-MS (m/z, %): 302.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{10}H_8ClF_4NNaOS$ $[M + Na]^+$ requires 323.9843, found 323.9828.

*Compound (S)-**3a**:* 48.4 mg, 80%; yellow oil; $[\alpha]^{20}_D$ = −79.6 (c = 1.0, $CHCl_3$, 97.8% ee).

Compound ***3b***: 50.0 mg, 68%; yellow oil; IR (film): 3085, 2925, 1608, 1570, 1408, 1328, 1177, 1014, 847, 795, 606 cm^{-1}; ^{1}H NMR

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(300 MHz, $CDCl_3$): δ 8.01 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 3H), 2.90 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.60 (s, 3F), −65.44 (s, 2F), −114.32 (d, J_{FF} = 230.2 Hz, 1F), −115.64 (d, J_{FF} = 230.2 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 140.4, 134.4 (q, J_{C-F} = 32.7 Hz), 128.1, 125.7 (q, J_{C-F} = 3.5 Hz), 123.5 (q, J_{C-F} = 270.6 Hz), 122.3 (tt, J_{C-F} = 298.5, 35.9 Hz), 117.3 (tt, J_{C-F} = 308.1, 35.8 Hz), 20.4 ppm; ESI-MS (m/z, %): 370.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{11}H_8ClF_7NOS$ $[M + H]^+$ requires 369.9898, found 369.9893.

Compound ***3c:*** 44.7 mg, 70%; yellow oil; IR (film): 3079, 2930, 1600, 1507, 1300, 1135, 1012, 841, 577 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, J = 8.6, 5.6 Hz, 2H), 7.73 (t, J = 8.6 Hz, 2H), 2.84 (s, 3H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.76 (s, 2F), −104.69 (d, J = 3.4 Hz, 1F), −115.38 (d, J_{FF} = 229.9 Hz, 1F), −116.51 (d, J_{FF} = 229.9 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.3, 165.8 (d, J_{C-F} = 255.8 Hz), 133.5 (d, J_{C-F} = 3.6 Hz), 130.4 (d, J = 8.9 Hz), 115.9 (d, J = 21.8 Hz), 20.3 ppm; ESI-MS (m/z, %): 320.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{10}H_7ClF_5NNaOS$ $[M + Na]^+$ requires 341.9749, found 341.9735.

Compound ***3d:*** 51.7 mg, 77%; yellow oil; IR (film): 3104, 1682, 1587, 1488, 1398, 1265, 1176, 1013, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 2.85 (s, 3H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.71 (d, J = 2.5 Hz, 2F), −115.10 (d, J_{FF} = 231.0 Hz, 1F), −116.29 (d, J_{FF} = 231.0 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 139.6, 135.6, 129.2, 129.1, 20.2 ppm; ESI-MS (m/z, %): 336.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{10}H_7Cl_2F_4NNaOS$ $[M + Na]^+$ requires 357.9453, found 357.9448.

Compound ***3e:*** 54.0 mg, 71%; yellow oil; FT-IR (film): 3085, 2927, 2856, 1609, 1557, 1302, 1136, 1009, 829, 688, 576 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H), 2.83 (s, 3H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.42 (s, 2F), −114.89 (d, J_{FF} = 231.0 Hz, 1F), −116.05 (d, J_{FF} = 231.0 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 136.1, 132.1, 129.3, 128.3, 20.2 ppm; ESI-MS (m/z, %): 379.9 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{10}H_7BrClF_4NNaOS$ $[M + Na]^+$ requires 401.8949, found 401.8949.

Compound ***3f:*** 50.0 mg, 69%; yellow oil; IR (film): 3074, 2930, 2359, 1614, 1435, 1337, 1133, 905, 797, 693, 565 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15−8.09 (m, 2H), 7.82 (d, J = 8.1 Hz, 1H), 7.60 (t, J = 8.1 Hz, 1H), 2.89 (s, 3H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.37 to −62.47 (m, 3F), −65.61 (s, 2F), −114.89 (d, J_{FF} = 231.0 Hz, 1F), −116.05 (d, J_{FF} = 231.0 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 138.1, 131.5 (q, J_{C-F} = 33.1 Hz), 130.8, 129.5, 129.4 (q, J_{C-F} = 3.6 Hz), 124.6 (q, J_{C-F} = 4.6 Hz), 123.6 (q, J_{C-F} = 271.3 Hz), 20.2 ppm; ESI-MS (m/z, %): 370.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{11}H_8ClF_7NOS$ $[M + H]^+$ requires 369.9893, found 369.9892.

Compound ***3g:*** 39.8 mg, 63%; yellow oil; IR (film): 3037, 2924, 1596, 1439, 1284, 1174, 1011, 817, 579 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 2.83 (s, 3H), 2,42 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.38 (s, 2F), −116.32 (d, J_{FF} = 233.7 Hz, 1F), −117.48 (d, J_{FF} = 233.7 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 144.2, 134.6, 129.5, 128.0, 21.6, 20.3 ppm; ESI-MS (m/z, %): 316.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{11}H_{11}ClF_4NOS$ $[M + H]^+$ requires 316.0176, found 316.0181.

Compound ***3h:*** 45.8 mg, 69%; yellow oil; IR (film): 2936, 2842, 1589, 1560, 1420, 1290, 1261, 1177, 1027, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, J = 9 Hz, 2H), 6.94 (d, J = 9 Hz, 2H), 3.90 (s, 3H), 2.82 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.43 (s, 2 F), −115.70 (d, J_{FF} = 232.4 Hz, 1F), −116.80 (d, J_{FF} = 232.4 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 163.8, 130.2, 129.7, 113.9, 55.5, 20.1 ppm; ESI-MS (m/z, %): 332.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{11}H_{11}ClF_4NO_2S$ $[M + H]^+$ requires 332.0129, found 332.0121.

Compound ***3i:*** 37.1 mg, 41%; yellow solid; mp: 103−104 °C; IR (KBr): 3432, 3136, 1607, 1526, 1399, 1181, 1109, 788 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 3.86 (t, J = 5.4 Hz, 2H), 3.34 (t, J = 4.8 Hz, 2H), 2,76 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.36 (s, 2F), −117.16 (d, J_{FF} = 234.3 Hz, 1F), −118.10 (d, J_{FF} = 234.3 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 154.4, 130.2, 127.2, 113.3, 66.5, 47.3, 19.9 ppm; ESI-MS (m/z, %): 387.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{14}H_{15}ClF_4N_2NaO_2S$ $[M + Na]^+$ requires 409.0371, found 409.0381.

Compound ***3j:*** 49.2 mg, 75%; yellow oil; IR (film): 3060, 1668, 1609, 1257, 975, 749, 690, 559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53−7.48 (m, 3H), 7.40 (d, J = 3.0 Hz, 3H), 6.70 (d, J = 16.2 Hz, 1H), 2.38 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.95 (d, J = 24.6 Hz, 2F), −115.64 to −116.70 (m, 2F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 143.5, 134.4, 130.5, 129.0, 128.3, 127.1, 27.4 ppm; ESI-MS (m/z, %): 327.9 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{12}H_{11}ClF_4NOS$ $[M + H]^+$ requires 328.0181, found 328.0176.

Compound ***3k:*** 31.5 mg, 56%; yellow oil; IR (film): 2963, 1625, 1370,1174, 1127, 1015, 910, 801 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.37−2.29 (m, 5H), 2.16−2.07 (m, 1H), 0.94 (dd, J = 12.3, 3.0 Hz, 6H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −65.69 (s, 2F), −116.58 (d, J_{FF} = 230.7 Hz, 1F), −117.08 (d, J_{FF} = 230.7 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.2, 120.6 (tt, J_{C-F} = 299.9, 33.6 Hz), 117.5 (tt, J_{C-F} = 251.3, 33.3 Hz), 52.7, 29.6, 25.8, 22.2 ppm; ESI-MS (m/z, %): 282.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_8H_{13}ClF_4NOS$ $[M + H]^+$ requires 282.0337, found 282.0327.

Compound ***4a:*** 30.5 mg, 93%; yellow solid; mp: 87−88 °C; IR (KBr): 3433, 3171, 1624, 1400, 1175, 1130, 1018, 803, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63−7.60 (m, 2H), 7.49−7.46 (m, 3H), 5.33 (s, 1H), 2.06 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.55 to −66.95 (m, 2F), −116.08 (d, J_{FF} = 232.1 Hz, 1F), −118.00 (d, J_{FF} = 232.1 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5, 130.2, 129.5, 126.0, 119.6, 57.7, 30.3 ppm; ESI-MS (m/z, %): 346.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_9ClF_4N_2NaOS$ $[M + Na]^+$ requires 350.9952, found 350.9965. (*Ss*,*Sc*)-**4a**: yield 93%; 97.5% ee; $[\alpha]_D^{20}$ = −20.7 (c = 1.0 in $CHCl_3$)

Compound ***4b:*** 33.3 mg, 84%; yellow oil; IR (film): 3465, 3161, 1621, 1416, 1329, 1176, 1127, 1015, 801 cm^{-1} ; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 4H), 5.73 (s, 1H), 2.07 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.50 (s, 3F), −66.14 to −66.20 (m, 2F), −115.06 (ddd, J_{FF} = 232.1, 5.4, 2.5 Hz, 1F), −118.89 (dd, J_{FF} = 232.1, 2.0 Hz, 1F) ppm; ^{13}C NMR (100 MHz, CDCl3): δ 141.2, 132.5 (q, J_{C-F} = 33.3 Hz), 126.7 (q, J_{C-F} = 3.5 Hz), 126.2, 123.4 (q, J_{C-F} = 270.8 Hz), 119.0, 57.4, 29.7 ppm; ESI-MS (m/z, %): 414.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{12}H_8ClF_7N_2NaOS$ $[M + Na]^+$ requires 418.9826, found 418.9838.

Compound ***4c:*** 29.5 mg, 85%; yellow oil; IR (film): 3203, 2824, 2359, 1605, 1511, 1239, 1167, 1129, 1016, 838, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63−7.58 (m, 2H), 7.19−7.13 (m, 2H), 5.58 (s, 1H), 2.04 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ-66.37 to −66.43 (m, 2F), −109.99 to −110.09 (m, 1F), −115.62 (dt, J = 231.8, 3.9 Hz, 1F), −119.03 (dt, J = 231.8, 3.1 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (d, J_{C-F} = 249.1 Hz), 133.0 (d, J_{C-F} = 3.7 Hz), 127.9 (d, J_{C-F} = 8.6 Hz), 119.4, 116.6 (d, J_{C-F} = 21.3 Hz), 57.1, 30.0 ppm; ESI-MS (m/z, %): 364.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_8ClF_5N_2NaOS$ $[M + Na]^+$ requires 368.9858, found 368.9864.

Compound ***4d:*** 31.6 mg, 87%; white solid; mp: 77−79 °C; IR (KBr): 3442, 3187, 1493, 1402, 1179, 1132, 1013, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 5.71 (s, 1H), 2.02 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.63 to −66.97 (m, 2F), −116.22 (d, J_{FF} = 231.8 Hz, 1F), −118.09 (d, J_{FF} = 231.8 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 135.7, 129.8, 127.1, 119.3, 57.2, 29.9 ppm; ESI-MS (m/z, %): 380.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_8Cl_2F_4N_2NaOS$ $[M + Na]^+$ requires 384.9562, found 384.9574.

Compound ***4e:*** 33.0 mg, 81%; colorless oil; IR (film): 3200, 2920, 2361, 1590, 1490, 1398, 1264, 1180, 1009, 801, 520 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.63−7.59 (m, 2H), 7.50−7.46 (m, 2H), 5.51 (s, 1H), 2.02 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.21 to −66.24 (m, 2F), −116.09 (d, J_{FF} = 232.0 Hz, 1F), −119.80 (d, J_{FF} = 232.0 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 132.8, 127.3, 124.5, 119.2, 57.3, 29.9 ppm; ESI-MS (m/z, %): 423.9 (100)

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$[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{11}H_8BrClF_4N_2NaOS$ $[M + Na]^+$ requires 428.9057, found 428.9067.

Compound ***4f:*** 32.9 mg, 83%; yellow oil; IR (film): 3202, 2926, 2853, 1492, 1437, 1331, 1177, 803, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.86−7.83 (m, 2H), 7.75 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 5.36 (s, 1H), 2.09 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −62.50 (s, 3F), −66.21 to −66.24 (m, 2F), −115.83 (d, J_{FF} = 233.3 Hz, 1F), −118.43 (d, J_{FF} = 233.3 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 132.2 (q, J_{C-F} = 32.6 Hz), 130.3, 129.0, 127.1 (q, J_{C-F} = 3.1 Hz), 123.4 (q, J_{C-F} = 271.3 Hz), 122.5 (q, J_{C-F} = 13.6 Hz), 118.9, 57.3, 29.8 ppm; ESI-MS (m/z, %): 413.9 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{12}H_8ClF_7N_2NaOS$ $[M + Na]^+$ requires 418.9826, found 418.9838.

Compound ***4g:*** 30.5 mg, 89%; colorless oil; IR (film): 3212, 2926, 1513, 1451, 1377, 1264, 1176, 1018, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 5.57 (s, 1H), 2.38 (s, 3H), 2.03 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.90 to −67.06 (m, 2F), −116.44 (dd, J_{FF} = 228.7, 5.4 Hz, 1F), −119.78 (dd, J_{FF} = 228.7, 2.5 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 134.0, 130.2, 125.6, 119.7, 57.5, 29.9, 21.1 ppm; ESI-MS (m/z, %): 360.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{12}H_{11}ClF_4N_2NaOS$ $[M + Na]^+$ requires 365.0109, found 365.0114.

Compound ***4h:*** 31.9 mg, 89%; colorless oil; IR (film): 3213, 2937, 1609, 1514, 1180, 1017, 801 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 9.0 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 5.56 (s, 1H), 3.84 (s, 1H), 2.04 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.64 to −67.00 (m, 2F), −115.92 (d, J = 284.1 Hz, 1F), −118.83 (d, J = 284.1 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 128.6, 127.3, 119.8, 114.8, 57.3, 55.4, 29.9 ppm; ESI-MS (m/z, %): 376.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{12}H_{11}ClF_4N_2NaO_2S$ $[M + Na]^+$ requires 381.0058, found 381.0061.

Compound ***4i:*** 34.8 mg, 84%; colorless solid; mp: 133−135 °C; IR (KBr): 3447, 3125, 1610, 1517, 1384, 1227, 1170, 1117, 1015, 802, 535 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 5.46 (s, 1H), 3.85 (s, 4H), 3.20 (s, 4H), 2.03 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −66.95 (d, J = 23.4 Hz, 2F), −116.08 (d, J = 232.6 Hz, 1F), −119.38 (d, J = 232.6 Hz, 1F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 126.9, 126.7, 119.9, 115.3, 66.6, 57.2, 48.2, 29.8 ppm; ESI-MS (m/z, %): 414.0 (100) $[M + H]^+$; HRMS (ESI) Calcd for $C_{15}H_{17}ClF_4N_3O_2S$ $[M + H]^+$ requires 414.0660, found 414.0669.

Compound ***4j:*** 29.1 mg, 82%; colorless oil; IR (film): 3419, 3202, 2921, 1401, 1172, 1138, 960, 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.36 (m, 5H), 7.07 (d, J = 15.9 Hz, 1H), 6.31 (d, J = 15.9 Hz, 1H), 5.62−5.59 (m, 1H), 1.91 (s, 3H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −65.55 to −66.90 (m, 2F), −115.75 (d, J = 232.4 Hz, 1F), −118.69 (ddd, J = 232.4, 5.6, 3.7 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 134.1, 129.4, 128.9, 127.3, 125.2, 118.6, 55.8, 28.0 ppm; ESI-MS (m/z, %): 372.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_{13}H_{11}ClF_4N_2NaOS$ $[M + Na]^+$ requires 377.0106, found 377.0113.

Compound ***4k:*** 29.0 mg, 94%; yellow oil; IR (film): 3208, 2965, 2877, 1471, 1382, 1264, 1127, 1016, 910, 799, 605 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.35 (s, 1H), 1.95−1.74 (m, 3H), 1.70 (s, 3H), 1.07−1.04 (m, 6H) ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ −67.02 to −67.06 (m, 2F), −116.91 (dd, J = 236.0, 2.8 Hz, 1F), −119.95 (d, J = 236.0 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.4, 53.6, 49.6, 26.9, 24.6, 23.6, 23.5 ppm; ESI-MS (m/z, %): 326.0 (100) $[M + NH_4]^+$; HRMS (ESI) Calcd for $C_9H_{13}ClF_4N_2NaOS$ $[M + Na]^+$ requires 331.0265, found 331.0281.

Procedure for the Preparation of (*S*)-5a from (*Ss, Sc*)-4a. A suspension of (*Ss, Sc*)-**4a** (0.0482 mmol) in the mixture of conc. HCl (1 mL) and MeOH (0.1 mL) was stirred at 80 °C for 8 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was dissolved in dry MeOH (0.5 mL). To this mixture, $SOCl_2$ (50 μL) was added dropwise at room temperature, and the resulting mixture was refluxed for 9 h. After cooling to room temperature, the solvent was removed in vacuo, and the residue was dissolved in CH_3CN (2 mL). $NaHCO_3$ (3.6 mmol) and Boc_2O (0.206 mmol) were added, and the mixture was stirred at 70 °C for 12 h. After cooling to room temperature, the precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (AcOEt/hexane, 1/6) to give the Boc-protected amino acid (*S*)-**5a** (11.4 mg, 84% from (*Ss,Sc*)-**4a**, 94.5% ee) as a white solid.

Compound ***5a:*** This is a known compound.[15] 94.5% ee, colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ 7.46−7.28 (m, 5H), 5.82 (s, br, 1H), 3.69 (s, 3H), 1.99 (s, 3H), 1.37 (s, 9H) ppm; $[\alpha]_D^{20}$ = −17.9 (c = 1.00 in $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The crystal data of (*Ss, Sc*)-**4a**; ^1H, ^{19}F, and ^{13}C NMR spectra for compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The crystal data of (*Ss*,*Sc*)-**4a** have been deposited at the Cambridge Crystallographic Data Center. CCDC: 965936. Empirical Formula: $C_{11}H_9ClF_4N_2OS$; Formula Weight: 328.71; Crystal Color, Habit: yellow, prismatic; Crystal Dimensions: 0.342 × 0.213 × 0.116 mm^3; Crystal System: Trigonal; Lattice Type: Primitive; Lattice Parameters: a = 10.278(5)Å, b = 10.278(5)Å, c = 11.406(4)Å, α = 90°, β = 90°, γ = 120°, V = 1043.5(9)$Å^3$; Space group: $P3(1)/n$; Z = 3; D_{calc} = 1.569 g/cm^3; F_{000} = 498; Residuals: R; Rw: 0.0466, 0.0503.

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