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Asymmetric Synthesis of Both Enantiomers of *anti*-4,4,4-Trifluorothreonine and 2-Amino-4,4,4-trifluorobutanoic Acid

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Received April 6, 2003

Abstract: A short and efficient enantioselective synthesis of both enantiomers of *anti*-4,4,4-trifluorothreonine and 2-amino-4,4,4-trifluorobutanoic acid was successfully developed. Trifluoromethylation of benzyl-protected bromoalkene **4** provided key intermediate trifluoromethylated *trans*-disubstituted alkene **2** in good yield. The sequence then involved Sharpless asymmetric dihydroxylation, nucleophilic opening of cyclic sulfate with NaN_3, palladium-catalyzed selective hydrogenation, and oxidation.

Fluorinated analogues and derivatives of naturally occurring amino acids have proved to be of fundamental interest because the introduction of fluorine atoms into bioactive targets often produces significant changes in physical properties, physiological activities, and metabolic profiles of these compounds.[1] In recent years, more and more fluorinated amino acids have been used as probes to follow biochemical reactions,[2] as inhibitors of enzymes,[3] as antitumor and antibacterial agents,[4] and as conformational modifiers in physiologically active proteins and enzymes.[5] One recent example is that Tirrell and Kumar found that fluorinated coil−coil protein prepared from trifluoroleucine and trifluorovaline displays enhanced thermal and chemical stability. [5a−c]

4,4,4-Trifluorothreonines are widely studied because of not only their potentially pharmaceutical utility but also their versatility as chiral building blocks with three distinguishable functionalities. The first synthesis of racemic 4,4,4-trifluorothreonines was published in 1957 by Walborsky and Baum.[6] From then on, many methods have been reported on the preparation of stereoisomers of 4,4,4-trifluorothreonine.[7,8] However, all of the methodologies for the synthesis of enantiomerically pure 4,4,4-trifluorothreonines required either resolution of racemates[7] or a preformed chiral center's stereoinduction.[8] Therefore, it is still of great importance to develop new routes to enantiomerically pure 4,4,4-trifluorothreonines. The Sharpless asymmetric dihydroxylation (AD) provided easy access to enantiopure vicinal diols with high levels of enantioselectivity and practicality, which led to numerous synthetic applications.[9] Recently, the Sharpless AD has been applied to many enantiopure amino acid syntheses.[10] However, to the best of our knowledge, there are only two reports on the Sharpless AD of trifluoromethyl-containing alkenes with moderate enantiomeric excess,[11] which inspired us to explore this reaction and apply the resulting chiral 1,2-diol to the synthesis of trifluoromethylated amino acids and other biologically active compounds. Herein, we report an efficient and highly diastereoselective synthesis of both enantiomers of *anti*-4,4,4-trifluorothrenine and 2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutanoic acid using the Sharpless AD of trifluoromethylated trans-disubstituted alkene **2** as key step.

To prepare the trifluoromethylated trans-disubstituted alkene **2**, two strategies were investigated (Scheme 1). The 3,3,3-trifluoropropynyl anion generated from 2-bromo-3,3,3-trifluoropropene reacted with aldehydes and ketones produced secondary and tertiary trifluoromethylated propargylic alcohols in excellent isolated yields.[12] We were interested in extending this reaction to paraformaldehyde for the preparation of 4,4,4-trifluoro-2-butyn-

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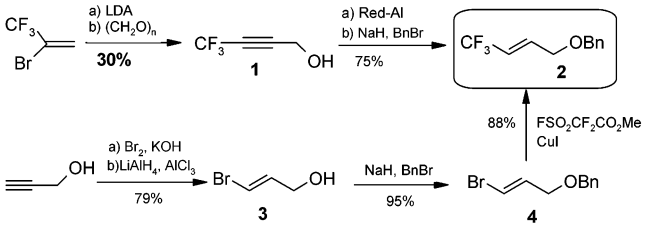
10.1021/jo0344384 CCC: $25.00
Published on Web 08/22/2003

SCHEME 1



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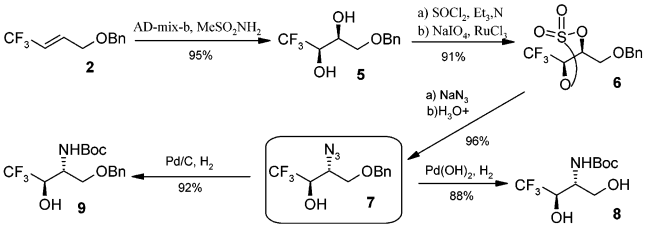
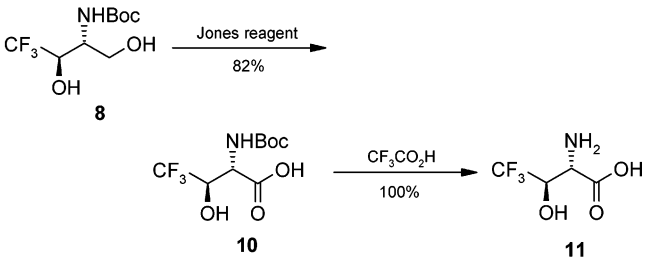


1-ol **1**, which was easily converted to **2** by Red-Al reduction and followed by protection of hydroxyl group with benzyl bromide. However, treatment of 2-bromo-3,3,3-trifluoropropene with LDA at −78 °C followed by addition of paraformaldehyde resulted in the isolation of 4,4,4-trifluoro-2-butyn-1-ol **1** in low yield (30%). Thus, an alternative convenient and efficient route to **2** was developed. Adapting a known protocol,[13] the propargylic alcohol was converted to the benzyl-protected bromoalkene **4** with good yield. Trifluoromethylation of **4** was easily accomplished with $FSO_2CF_2CO_2Me$/CuI[14] to give the key intermediate **2** in 88% yield on a 30-g scale.

With trifluoromethylated trans-disubstituted alkene **2** in hand, the Sharpless AD reaction was then carried out on compound **2** in the presence of AD-mix-β and methanesulfonamide at room temperature to yield (2*S*,3*R*)-1-benzyloxy-4,4,4-trifluoro-2,3-butanediol **5** in 95% yield (Scheme 2). The enantiomeric excess of compound **5** was determined to be 93% by HPLC on a Chiralcel OD column. However, the Sharpless AD reaction of **2** proceeded quite slowly (3−4 days) due to the strong electron-withdrawing effect of trifluoromethyl group. The resulting vicinal diol **5** was first converted to its 2,3-cyclic sulfite with $SOCl_2$, and then the 2,3-cyclic sulfite was further oxidized to the cyclic sulfate **6** with RuO_4 (generated in situ from $NaIO_4$/catalytic $RuCl_3$) in excellent yield (91%). Ring opening of trifluoromethylated cyclic sulfate **6** with NaN_3 in DMF occurred exclusively at C2 with clean inversion of chirality followed by acidic hydrolysis to provide **7** in high yield. The structure of **7** was confirmed by its further transformation. However, in the case of the cyclic sulfate-2-carboxylic esters, the azide anion attacked at the carbon atom that is adjacent to carboxylic ester.[10] From this point, we can see that the regioselectivity of trifluoromethylated cyclic sulfate **6** was different from that of cyclic sulfate-2-carboxylic esters in the ring-opening reaction by sodium azide. The catalytic hydrogenation of **7** in the presence of di-*tert*-butyl dicarbonate with different palladium catalysts resulted in quite different products. When $Pd(OH)_2$ was used as catalyst,[15] compound **7** readily underwent the reduction of azido group and the removal of the benzyl group to generate **8** in 88% yield, whereas only the azido group of compound **7** was hydrogenated to produce **9** in 92% yield in the case of Pd/C. Both compounds **8** and **9** were important intermediates for the synthesis of trifluoromethylated amino acids.

SCHEME 3



The conversion of the amino alcohol **8** into (2*S*,3*R*)-4,4,4-trifluorothreonine **11** was then investigated. The selective oxidation of the primary hydroxyl group of **8** was carried out under a number of reaction conditions. Treatment of **8** with TEMPO/NaOCl[16] and Pt/O_2[17] resulted in no reaction. Fortunately, compound **8** was subjected to Jones reagent to afford the desired amino acid **10** in 82% yield (Scheme 3). It was noteworthy that the secondary hydroxyl group of **8** was inert under Jones oxidation, which was probably due to the steric and inductive effect of trifluoromethyl group. Beaulieu reported a similar selective oxidation of trichloromethylated diol to 4,4,4-trichlorothreonine with Jones reagent.[18] The protected amino acid **10** was easily deprotected with trifluoroacetic acid in dichloromethane at room temperature to give (2*S*,3*R*)-4,4,4-trifluorothreonine **11** in quantitative yield. The optical rotation of compound **11** ($[\alpha]^{20}_D = -11.7$ (*c* 0.68, H_2O) was identical with that reported ($[\alpha]^{20}_D = -11.9$ (*c* 1.00, H_2O)).[7] This result further proved the absolute configuration of the vicinal diol **5** resulting from the Sharpless AD reaction of **2**.

Recently, the enantioselective preparation of (*R*)/(*S*)-2-amino-4,4,4-trifluorobutanoic acid has been reported.[19] With compound **9** in hand, we turned our attention to synthesize (*S*)-2-amino-4,4,4-trifluorobutanoic acid from **9**. First, the radical-based dehydroxylation of **9** was examined. Treatment of **9** with phenylthiochloroformate in the presence of DMAP resulted in no reaction. To our delight, when 4 Å molecular sieves were added to the reaction mixture, **9** was completely converted and *O*-phenylthioate **12** was isolated in 78% yield (Scheme 4).

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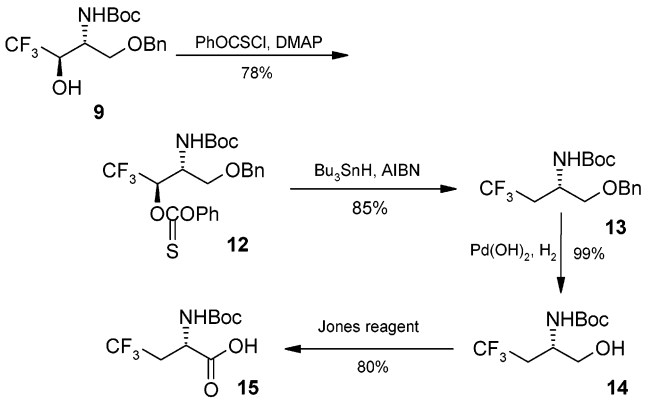
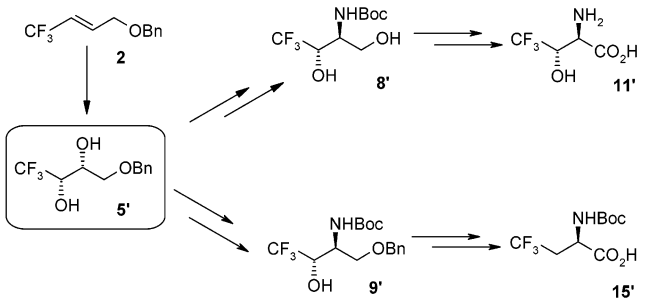
SCHEME 4



SCHEME 5



Then radical-mediated dehydroxylation of **12** with Bu_3SnH and AIBN in toluene at 80 °C gave **13** in 85% yield. Hydrogenation of **13** under the catalysis of palladium hydroxide on carbon afforded alcohol **14** in 99% yield. Finally, the oxidation of **14** provided the desired (*S*)-2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutanoic acid **15** in 80% yield.

We also wanted to extend this methodology to the synthesis of enantiomers of **11** and **15**. The Sharpless AD of trifluoromethylated trans-disubstituted alkene **2** with AD-mix-α and methanesulfonamide provided (2*R*,3*S*)-1-benzyloxy-4,4,4-trifluoro-2,3-butanediol **5′** in 93% ee (Scheme 5). The same procedure as described above can smoothly convert **5′** to (2*R*,3*S*)-4,4,4-trifluorothreonine **11′** and (2*R*)-2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutanoic acid **15′** from the key intermediates **8′** and **9′,** respectively.

It was noteworthy that the regioseletivity of the nucleophilic opening of cyclic sulfate **6** (Scheme 2) was confirmed by the ^{19}F NMR spectrum of radical-mediated dehydroxylation product **13**. A triplet appeared at −63.9 ppm (J = 10.0 Hz). It indicated the trifluoromethyl group (CF_3) of **13** was adjacent to the *gem*-methylene group (CH_2). Therefore, nucleophilic opening of cyclic sulfate **6** took place exclusively at C2 with clean inversion of chirality.

In summary, we have described an efficient procedure for high enantioselective synthesis of both enantiomers of *anti*-4,4,4-trifluorothreonine and 2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutanoic acid. Trifluoromethylation of benzyl-protected bromoalkene **4** provided trifluoromethylated trans-disubstituted alkene **2** in good yield on a 30-g scale. The Sharpless asymmetric dihydroxylation of **2** gave chiral 1,2-diol **5** and **5′** with high enantioselectivity. The nucleophilic opening of cyclic sulfate **6** and **6′** took place exclusively at C2 with clean inversion of chirality.

Experimental Section

(*E*)-1-Benzyloxy-4,4,4-trifluoro-2-butene (2). A solution of $FSO_2CF_2CO_2Me$ (25 mL, 200 mmol) in anhydrous DMF (50 mL) was added dropwise at 80 °C for 15 h to a mixture of **4** (22.80 g, 100 mmol), HMPA (40 mL), CuI (3.81 g, 20 mmol), and DMF (300 mL). The reaction mixture was stirred at 80 °C for 10 h and then was cooled to room temperature. The saturated aqueous NH_4Cl was added. The reaction mixture was extracted with diethyl ether. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give **2** (19.18 g, 88%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.39 (m, 5H), 6.36−6.48 (m, 1H), 5.93−6.00 (m, 1H), 4.57 (s, 2H), 4.10−4.15 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −64.22 (m); IR (thin film) ν_{max} 3091, 3035, 2860, 1687, 1498, 1455, 1315, 1119 cm^{-1}; MS (EI) m/z 216 (M^+, <1), 91 (100), 77 (15), 69 (3); HRMS (EI) calcd for $C_{11}H_{11}OF_3$ 216.0762, found 216.0745.

(2*S*,3*R*)-1-Benzyloxy-4,4,4-trifluoro-2,3-butanediol (5). To a stirring mixture of *t*-BuOH (25 mL), water (25 mL), and AD-mix-β (7.00 g) was added $MeSO_2NH_2$ (0.48 g, 5 mmol). Then the mixture was cooled to 0 °C. Compound **2** (1.08 g, 5 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at room temperature for 4 days. Na_2SO_3 was added. The mixture was stirred for 30 min and then extracted with ethyl acetate. The combined organic layer was washed with 2 N KOH and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **5** (1.20 g, 95% yield, 93% ee): mp 71−72 °C; $[\alpha]^{20}_D = -13.5$ (c 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.42 (m, 5H), 4.59 (s, 2H), 4.16 (dt, J = 2.1 Hz, 6.0 Hz, 1H), 3.97 (dq, J = 2.1 Hz, 9.0 Hz, 1H), 3.63 (d, J = 6.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −77.45 (d, J = 9.0 Hz); IR (KBr) ν_{max} 3337, 3036, 1588, 1499, 1455, 1164, 1143 cm^{-1}; MS (EI) m/z 250 (M^+, 15), 107 (16), 91 (100), 77 (5), 69 (1); HRMS (EI) calcd for $C_{11}H_{13}O_3F_3$ 250.0817, found 250.0843.

(3*R*,4*S*)-3-Benzyloxymethyl-4-trifluoromethyl-2,2-dioxo-1,3,2-dioxathiolane (6). To a solution of **5** (0.81 g, 3.24 mmol) and triethylamine (1.31 g, 13 mmol) in methylene chloride (15 mL) was added dropwise thionyl chloride (0.77 g, 6.48 mmol) at 0 °C during 10 min. The reaction mixture was stirred for another 10 min at 0 °C and then was diluted with cold ether. The aqueous phase was extracted with ether. The combined organic phases were washed with brine and concentrated in vacuo. The crude cyclic sulfite was purified by a short silica gel column. $NaIO_4$ (0.83 g, 3.89 mmol) and $RuCl_3 \cdot 3H_2O$ (1.0 mg) were added to the mixture of the cyclic sulfite, water (7.5 mL), CH_3CN (5 mL), and CCl_4 (5 mL). The reaction mixture was vigorously stirred for 1 h at room temperature and then diluted with ether. The organic layer was filtered through a pad of Celite. The filtrate was washed with water, saturated aqueous sodium bicarbonate, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give **6** (0.92 g, 91%): $[\alpha]^{20}_D = +22.6$ (c 1.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.41(m, 5H), 5.18 (dq, J = 5.9 Hz, 6.0 Hz, 1H), 5.03 (dt, J = 6.3 Hz, 3.6 Hz, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 11.7 Hz, 1H), 3.92 (dd, J = 3.6 Hz, 12.0 Hz, 1H), 3.78 (dd, J = 3.6 Hz, 12.0 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.81 (d, J = 5.9 Hz); IR (thin film) ν_{max} 3035, 1498, 1456, 1409, 1220, 1160 cm^{-1}; MS (EI) m/z 312 (M^+, 64), 107 (32), 91 (100), 77 (10), 69 (2). Anal. Calcd for $C_{11}H_{11}O_5F_3S$: C, 42.31; H, 3.55. Found: C, 42.64; H, 3.36.

(2*R*,3*R*)-1-Benzyloxy-2-azido-4,4,4-trifluorobutan-3-ol (7). A solution of cyclic sulfate **6** (0.90 g, 2.89 mmol) and sodium azide (38 g, 5.77 mmol) in DMF (10 mL) was stirred for 4 h at 80 °C. The solvent was carefully removed by distillation under reduced pressure. THF (20 mL), water (54 μL), and sulfuric acid (150 μL) were added, and the resulting suspention was stirred for 1 h. Then $NaHSO_3$ was added. The reaction mixture was

stirred for 20 min and filtered on silica gel. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 8:1) to give **7** (0.76 g, 96%): $[\alpha]^{20}_D = +16.9$ (*c* 1.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.42 (m, 5H), 4.62 (s, 2H), 4.18−4.26 (m, 1H), 3.98 (dd, *J* = 4.2 Hz, 10.2 Hz, 1H), 3.90 (dd, *J* = 3.3 Hz, 10.2 Hz, 1H), 3.0.64−3.69 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.90 (d, *J* = 6.6 Hz); IR (thin film) ν_{max} 3424, 3035, 2116, 1456, 1271, 1142 cm^{-1}, MS (EI) *m*/*z* 247 (1), 107 (1), 91 (100), 77 (4), 69 (1); HRMS (ESI) calcd for $C_{11}H_{12}O_2F_3N_3Na$ 298.0773, found 298.0764.

(2*R*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-4,4,4-trifluoro-1,3-butandiol (8). A suspension of 20% palladium hydroxide on carbon (1.34 g) in THF (10 mL) was stirred under a hydrogen atmosphere for 30 min. To this suspension was added a mixture of **7** (1.34 g, 4.87 mmol) and di-*tert*-butyl dicarbonate (1.27 g, 5.84 mmol) in THF (20 mL). The resulting mixture was stirred under hydrogen at room temperature for 10 h. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **8** (1.11 g, 88%): mp 94−95 °C; $[\alpha]^{20}_D = -3.7$ (*c* 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 4.01−4.07 (m, 1H), 3.80−3.86 (m, 1H), 3.68−3.77 (m, 2H), 1.46 (s, 9H); ^{19}F NMR (282 MHz, CD_3OD) δ −77.22 (d, *J* = 6.5 Hz); IR (KBr) ν_{max} 3371, 2990, 1689, 1532, 1164 cm^{-1}; MS (EI) *m*/*z* 228 (2), 160 (10), 99 (1), 69 (1), 57 (100). Anal. Calcd for $C_9H_{16}O_4NF_3$: C, 41.70; H, 6.22; N, 5.40. Found: C, 41.75; H, 6.25; N, 5.35.

(2*S*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-hydroxy-4,4,4-trifluorobutanoic Acid (10). To a mixture of **8** (0.21 g mg, 0.8 mmol) in acetone (20 mL) at 0 °C was added Jones reagent (1 M, 5 mL, 5 mmol). The mixture was stirred for 20 min at 0 °C under nitrogen. The reaction was quenched with isopropyl alcohol (5 mL) and then diluted with water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to give **10** (0.18 g, 82%): mp 106−107 °C; $[\alpha]^{20}_D = -34.2$ (*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, CD_3OD) δ 4.36 (d, *J* = 7.2 Hz, 1H), 4.17−4.26 (m, 1H), 1.36 (s, 9H); ^{19}F NMR (282 MHz, CD_3-OD) δ −77.17 (d, *J* = 7.1 Hz); IR (KBr) ν_{max} 3346, 2993, 1761, 1692, 1534, 1164 cm^{-1}; MS (EI) *m*/*z* 243 (1), 174 (6), 172 (1), 99 (1), 69 (21), 57 (100). Anal. Calcd for $C_9H_{14}O_5NF_3$: C, 39.57; H, 5.16; N, 5.13. Found: C, 39.37; H, 5.12; N, 5.15.

(2*S*,3*R*)-2-Amino-3-hydroxy-4,4,4-trifluorobutanoic acid (11). Trifluoroacetic acid (2.5 mL) was added to a solution of **10** (0.22 g, 0.9 mmol) in dichloromethane (4 mL) at 0 °C. The resulting mixture was stirred at room temperature for 6 h at 0 °C. The solvent was removed under reduced pressure. The crude product was purified by heating at 60 °C in vacuo for 3 h to give **11** (0.16 g, 100%): $[\alpha]^{20}_D = -11.7$ (*c* 0.68, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 4.36 (dq, *J* = 4.2 Hz, 6.3 Hz, 1H), 3.73 (d, *J* = 4.2 Hz, 1H); ^{19}F NMR (282 MHz, D_2O) δ −74.92 (d, *J* = 6.3 Hz).

(2*R*,3*R*)-1-Benzyloxyl-2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutan-3-ol (9). A mixture of 10% palladium on charcoal (0.11 g), di-*tert*-butyl dicarbonate (0.52 g, 2.4 mmol) and **7** (0.55 g, 2 mmol) in THF (15 mL) was stirred under hydrogen at room temperature for 10 h. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to give **9** (0.70 g, 92%): mp 59−60 °C; $[\alpha]^{20}_D = +7.9$ (*c* 1.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.42 (m, 5H), 5.40 (d, *J* = 8.7 Hz, 1H), 4.55 (d, *J* = 12.8 Hz, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.06−4.17 (m, 2H), 3.94 (dd, *J* = 3.0 Hz, 9.9 Hz, 1H), 3.69 (dd, *J* = 2.1 Hz, 9.9 Hz, 1H), 1.45 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −76.81 (d, *J* = 9.6 Hz); IR (KBr) ν_{max} 3358, 2984, 1690, 1533, 1170 cm^{-1}; MS (EI) *m*/*z* 350 (M + 1, 55), 91 (100), 77 (3), 69 (1), 57 (88). Anal. Calcd for $C_{16}H_{22}O_4NF_3$: C, 55.01; H, 6.36; N, 4.01. Found: C, 54.86; H, 6.27; N, 3.89.

(2*R*,3*R*)-1-Benzyloxyl-2-(*tert*-butoxycarbonyl)amino-3-oxylthiocarbonylphenyl-4,4,4-trifluorobutane (12). Phenylthiochloroformate (0.44 g, 2.51 mmol) was added to a mixture of **9** (0.56 g, 1.67 mmol), DMAP (0.41 g, 3.35 mmol), 4 Å molecular sieves (0.59 g), and toluene (20 mL). The reaction mixture was stirred at room temperature overnight and then filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) to give **12** (0.64 g, 78%): $[\alpha]^{20}_D = +43.7$ (*c* 0.64, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dt, *J* = 1.8 Hz, 7.5 Hz, 2H), 7.31−7.36 (m, 5H), 7.09 (d, *J* = 7.5 Hz, 2H), 7.11−7.18 (m, 1H), 5.12 (d, *J* = 9.0 Hz, 1H), 4.56 (s, 2H), 4.48−4.54 (m, 2H), 3.65−3.72 (m, 2H), 1.47 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.75 (d, *J* = 8.5 Hz); IR (thin film) ν_{max} 3430, 2980, 1717, 1529, 1269, 1170 cm^{-1}; MS (EI) *m*/*z* 428 (1), 107 (17), 91 (100), 77 (12), 69 (1), 57 (79). Anal. Calcd for $C_{23}H_{26}O_5NF_3S$: C, 56.90; H, 5.40; N, 2.89. Found: C, 57.05; H, 5.43; N, 2.63.

(2*S*)-1-Benzyloxyl-2-(*tert*-butoxycarbonyl)amino-4,4,4-trifluorobutane (13). A solution of **12** (0.41 g, 0.84 mmol) in toluene (15 mL) was degassed for 15 min under Ar atmosphere. A mixture of Bu_3SnH (0.9 mL, 3.36 mmol) and AIBN (84 mg, 0.52 mmol) in toluene (8 mL) was then added dropwise to the above solution at 80 °C. The reaction mixture was stirred at 80 °C for 1 h, cooled to room temperature, and then quenched by addition of water (0.2 mL). The solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to give **13** (0.24 g, 85%): mp 56−57 °C; $[\alpha]^{20}_D = +25.3$ (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.41 (m, 5H), 4.93 (d, *J* = 6.9 Hz, 1H), 4.56 (d, *J* = 12.3 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 4.12−4.14 (m, 1H), 3.52−3.61 (m, 2H), 2.39−2.52 (m, 2H), 1.44 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.99 (t, *J* = 10.7 Hz); IR (KBr) ν_{max} 3365, 2990, 1683, 1533, 1244, 1170 cm^{-1}; MS (EI) *m*/*z* 278 (28), 277 (17), 107 (26), 91 (100), 77 (12), 69 (2), 57 (100); HRMS (EI) calcd for $C_{12}H_{13}O_3NF_3$ 276.0920, found 276.0881.

(2*S*)-2-(*tert*-Butoxycarbonyl)amino-4,4,4-trifluorobutan-1-ol (14). A suspension of 20% $Pd(OH)_2$ (0.28 g) and **13** (0.28 g, 0.84 mmol) in THF (10 mL) was stirred under a hydrogen atmosphere for 2 h. Filtration and removal of the solvent gave the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give **14** (0.21 g, 99%): mp 94−95 °C; $[\alpha]^{20}_D = +19.3$ (*c* 0.59, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (m, 1H), 3.69 (m, 2H), 2.34−2.47 (m, 2H), 1.43 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.60 (t, *J* = 9.6 Hz); IR (KBr) ν_{max} 3358, 2984, 1690, 1533, 1170 cm^{-1}; MS (EI) *m*/*z* 350 (M + 1, 55), 91 (100), 77 (3), 69 (1), 57 (88). Anal. Calcd for $C_9H_{16}O_3NF_3$: C, 44.44; H, 6.63; N, 5.76. Found: C, 44.57; H, 6.89; N, 5.56.

(2*S*)-2-(*tert*-Butoxycarbonyl)amino-4,4,4-trifluorobutanoic acid (15). Alcohol **14** (0.15 g, 0.63 mmol) was treated with Jones reagent according to the general procedure outlined for acid **10**. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to give **15** (0.13 g, 80%): $[\alpha]^{20}_D = -7.6$ (*c* 0.41, $CHCl_3$); ^{1}H NMR (300 MHz, acetone-d_6) δ 6.41 (d, *J* = 8.4 Hz, 1H), 4.51 (dt, *J* = 4.2 Hz, 8.4 Hz, 1H), 2.72−2.93 (m, 2H), 1.42 (s, 9H); ^{19}F NMR (282 MHz, Acetone-d_6) δ −65.09 (t, *J* = 12.4 Hz); IR (thin film) ν_{max} 3374, 2990, 1715, 1693, 1529, 1144 cm^{-1}; MS (EI) *m*/*z* 212 (9), 112 (21), 69 (2), 57 (100). Anal. Calcd for $C_9H_{14}O_4NF_3$: C, 42.03; H, 5.49; N, 5.45. Found: C, 42.45; H, 5.38; N, 5.21.

Acknowledgment. We thank the National Natural Science Foundation of China and Shanghai Municipal Scientific Committee for funding this work.

Supporting Information Available: Experimental procedures for **2** and **4** prepared from 2-bromo-3,3,3-trifluoropropane and propargyl alcohol, respectively, and characterization data for **1**, **5′**, **6′**, **7′**, **8′**, **9′**, **10′**, **11′**, **12′**, **13′**, **14′**, and **15′**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0344384