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Asymmetric Reduction of Trifluoromethyl Ketones Containing a Sulfur Functionality by the Alcohol Dehydrogenase from *Geotrichum*

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Abstract: The reduction of trifluoromethyl ketones containing a sulfur functionality by the crude alcohol dehydrogenase from *Geotrichum* proceeded successfully, and the corresponding optically active alcohols were synthesized with high yields and excellent enantioselectivities. © 1998 Elsevier Science Ltd. All rights reserved.

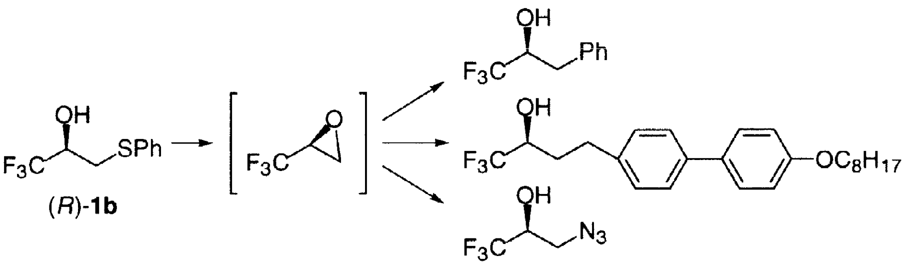
Keywords: Asymmetric reactions, Reduction, Fluorine and compounds, Sulfur compounds

Introduction

Research on optically active fluorinated compounds for ferroelectric liquid crystals or bioactive fluorinated compounds has received much attention in the last few years because of the unique physical and biological features induced by fluorine atoms.[1] As the demand for optically active fluorinated compounds increases, the importance of the development of asymmetric synthetic methods for fluorinated building blocks grows.

On the other hand, sulfur functionalities such as phenylthio and dithianyl groups have been used as useful reactive groups for a variety of chemical transformations.[2] For example, (*R*)-1,1,1-trifluoro-3-phenylthio-2-propanol (*R*)-**1b** prepared by lipase-mediated kinetic resolution can be transformed by an one-pot reaction to several useful classes of compounds without any loss in optical purity[3] as shown in Fig. 1. However, only a few reports on the synthesis of chiral fluorinated compounds bearing sulfur functionalities by chemical and biological methods have been published so far,[1a, 4] and an investigation in this field is awaited. Therefore, trifluoromethyl ketones containing a sulfur functionality were chosen as substrates for asymmetric reduction.

Fig. 1. A one-pot reaction of (*R*)-1,1,1-trifluoro-3-phenylthio-2-propanol (*R*)-**1b** to useful compounds



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Previously, we have reported on an asymmetric reduction system by a crude alcohol dehydrogenase (the APG4 system) as one of methodologies for obtaining optically pure secondary alcohols.[5] For example, acetophenone derivatives, 2-alkanones, and 1,1,1-trifluoro-2-alkanones are reduced to the corresponding (*S*)-alcohols with 96 - >99% ee. This system consists of a crude enzyme (an acetone powder of *Geotrichum candidum* IFO4597, APG4), a catalytic amount of a coenzyme, and a reducing agent. As the substrate, a ketone, is reduced to an alcohol, NAD(P)$^+$ is formed, which in turn is reduced to NAD(P)H by the coupled oxidation of 2-alkanol or cyclopentanol as shown in Scheme 1. To prepare useful chiral building blocks bearing a trifluoromethyl group and a sulfur functionality, the substrate specificity of the APG4 system has been expanded particularly to trifluoromethyl ketones containing a sulfur functionality. We report here that the reduction of trifluoromethyl ketones with a phenylthio, octylthio, thienyl or dithianyl group by the APG4 system proceeded successfully, and chiral trifluorinated alcohols **1b-5b** shown in Fig. 2 were synthesized with high yields and excellent enantioselectivities. For example, (*R*)-**1b** was prepared in 90% yield (91 mg) with 98% ee and (*R*)-**4b** in 84% yield (1.32 g) with >99% ee.

Scheme 1

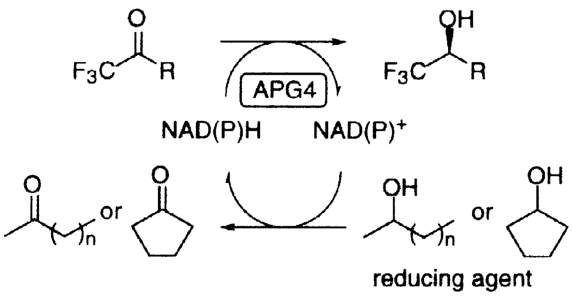
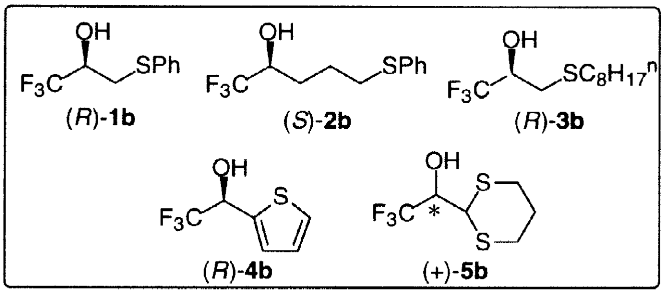


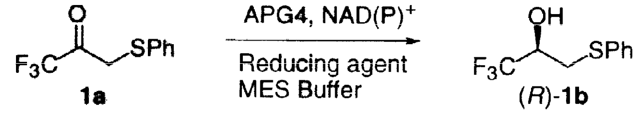
Fig. 2. Useful optically active alcohols containing a trifluoromethyl group and a sulfur functionality obtained by the reduction of the corresponding ketones by the APG4 system



Results and Discussions

Firstly, the reaction conditions for the reduction of 1,1,1-trifluoro-3-(phenylthio)propan-2-one **1a** by the APG4 system were examined. Since both of NAD$^+$ and NADP$^+$ are effective as a coenzyme and any 2-alkanol from 2-propanol to 2-octanol and cyclopentanol can be used as a reducing agent for the recycling of the coenzyme,[5] the reduction of **1a** by various conditions was tested (Table 1). The yield was higher when NAD$^+$ was used than when NADP$^+$ was used, while the selectivity did not depend on the kind of coenzyme. Furthermore, a higher selectivity was obtained when cyclopentanol was used than when 2-propanol was used. As a result, the combination of NAD$^+$ and cyclopentanol gave the best result out of four combinations. The change in the selectivity is caused by the change in the kind of reducing agents probably because of the presence of plural enzymes in APG4 which catalyze the reduction to different configurational alcohols, and cyclopentanol inhibits the activity of the unnecessary enzyme(s) since it has been reported that an excess amount of cyclopentanol inhibits the activity of alcohol dehydrogenase(s) from *Geotrichum*.[6]

Table 1. **Reduction of 1a by the APG4 System**



Coenzyme	Reducing Agent	Yield(%)[a,b]	ee(%)[a]
NAD$^+$	2-propanol	53	95
NADP$^+$	2-propanol	28	93
NAD$^+$	cyclopentanol	73	98
NADP$^+$	cyclopentanol	41	98

Reaction Conditions: 20 h at 30 °C at 130 rpm in MES buffer (pH 7.0, 0.1 M, 3 mL). Substrate: 0.08 mmol, APG4: 20 mg, NAD(P)$^+$: 0.007 mmol, Reducing agent: 0.65 mmol. [a] Determined by GC analysis (CP-Cyclodextrin-B-2,3,6-M-19, 150 °C, He: 2 mL/min). [b] not optimized. Higher yields can be obtained with more enzyme or coenzyme, longer reaction times or reaction under an argon atmosphere.

The usefulness of the APG4 system in synthesizing chiral building blocks containing a trifluoromethyl group and a sulfur functionality was demonstrated by preparative scale synthesis as listed in Table 2. Under the conditions using the best combination of the coenzyme and the reducing agent, which depends on the substrate, trifluoromethyl ketones **1a** - **5a** were reduced with excellent selectivities with high to moderate yields. Concerning reduction of **4a** by the APG4 system, a perfect enantioselectivity and an excellent yield were obtained even when the substrate concentration was increased from 27 mM to 57 mM. The reduction in the gram scale proceeded quantitatively and yielded the optically pure alcohol (*R*)-**4b** in 84% yield after purifications (1.32 g, ee >99%). However, a limitation in the substrate specificity of the APG4 system was also found; the reduction of a substrate with dithianyl moiety **5a** did not proceed smoothly. Only when the amount of APG4 was increased, (+)-**5b** was obtained in 67% yield (GC Yield) with >99% ee. The substrate specificity of the APG4 system is summarized in Fig. 3. Thienyl ketone **4a** was reduced smoothly with an even higher substrate concentration than the others. Sulfides **1a**, **2a** and **3a** can be reduced successfully, but dithianyl ketone **5a** was reduced with difficulty.

Absolute configurations of **2b** and **4b** were determined as in Scheme 2. Absolute configuration of **2b** was determined by synthesizing the authentic sample (*S*)-**2b** from (*S*)-epoxide (*S*)-**7** of which the sign of the optical rotation was compared with that of the APG4 product. For the determination of absolute configuration of **4b**, protected (*R*)-**4b** was desulfurated by Raney Ni to give (*S*)-**11**, of which the sign of the optical rotation was compared with the authentic sample prepared from (*S*)-**7**.

In conclusion, the APG4 reduction of trifluoromethyl ketones containing a sulfur functionality was investigated. The reduction of the substrates with a phenylthio group **1a** or **2a**, octylthio group **3a** or thienyl group **4a** by the APG4 system proceeds with excellent enantioselectivities. In particular, **4a** as a substrate affords an optically pure alcohol (*R*)-**4b** with high yield. The reduction products are important starting materials for synthesizing ferroelectric liquid crystals, natural product analogues, or other useful materials due to the unique characteristics of the trifluoromethyl group, the high optical purity, and usefulness of the sulfur functionalities for the conversion to other functionalities.

Table 2 Preparative Enzymatic Synthesis of Optically Active Trifluoromethyl Alcohols Containing a Sulfur Functionality.

Substrate	Coenzyme	Reducing Agent	Yield(%)[a]	ee(%)	Config.	$[\alpha]_D$
1a	NAD^+	cyclopentanol	90(97)	98	*R*	-79.0
2a	NAD^+	2-propanol	78(98)	>99	*S*	-18.7
3a	$NADP^+$	cyclopentanol	35(60)	96	*R*	-39.9
4a	NAD^+	cyclopentanol	84(99)	>99	*R*	+27.6
5a	NAD^+	cyclopentanol	42(67)	>99	-[b]	+4.86

Reaction conditions are described in the experimental section. [a] Isolated yields after purification. The yields determined by GC are shown in the parenthesis. [b]not determined.

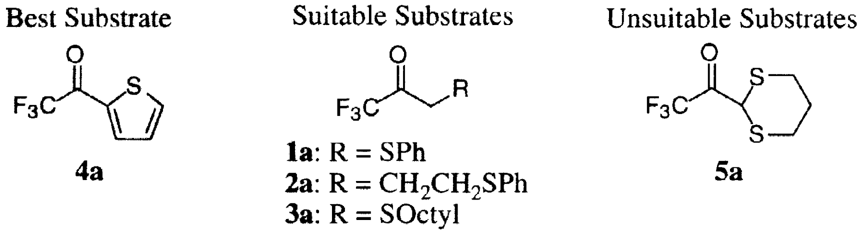


Fig. 3. Suitable substrates and unsuitable substrates of the APG4 system

Experimental

Instruments. Gas chromatographic analyses were performed using a Shimadzu GC-9A or GC-14B gas chromatograph with a Shimadzu C-R6A Chromatopac equipped with a chiral GC-column (Chiraldex G-TA; 30 m; He 2 mL/ min or CP-Cyclodextrin-B-2,3,6-M-19; 25 m; He 2 mL/ min). HPLC analyses were performed using a Hitachi 655 Liquid Chromatograph equipped with a Hitachi D-2000 Chromato-Integrator, a Spectrophotometer 852 III, and a Chiralcel OD (0.46 cm x 25 cm). ^1H NMR spectra were recorded at 200 MHz on a Varian VXR-200 spectrometer in $CDCl_3$. ^{19}F NMR spectra were recorded at 188 MHz on a Varian VXR-200 spectrometer in $CDCl_3$ using $CFCl_3$ as an internal standard. IR spectra were obtained from a JASCO FT/IR-5300. The optical rotations were measured with a 10 cm path-length cell on a JASCO DIP-181 Digital Polarimeter.

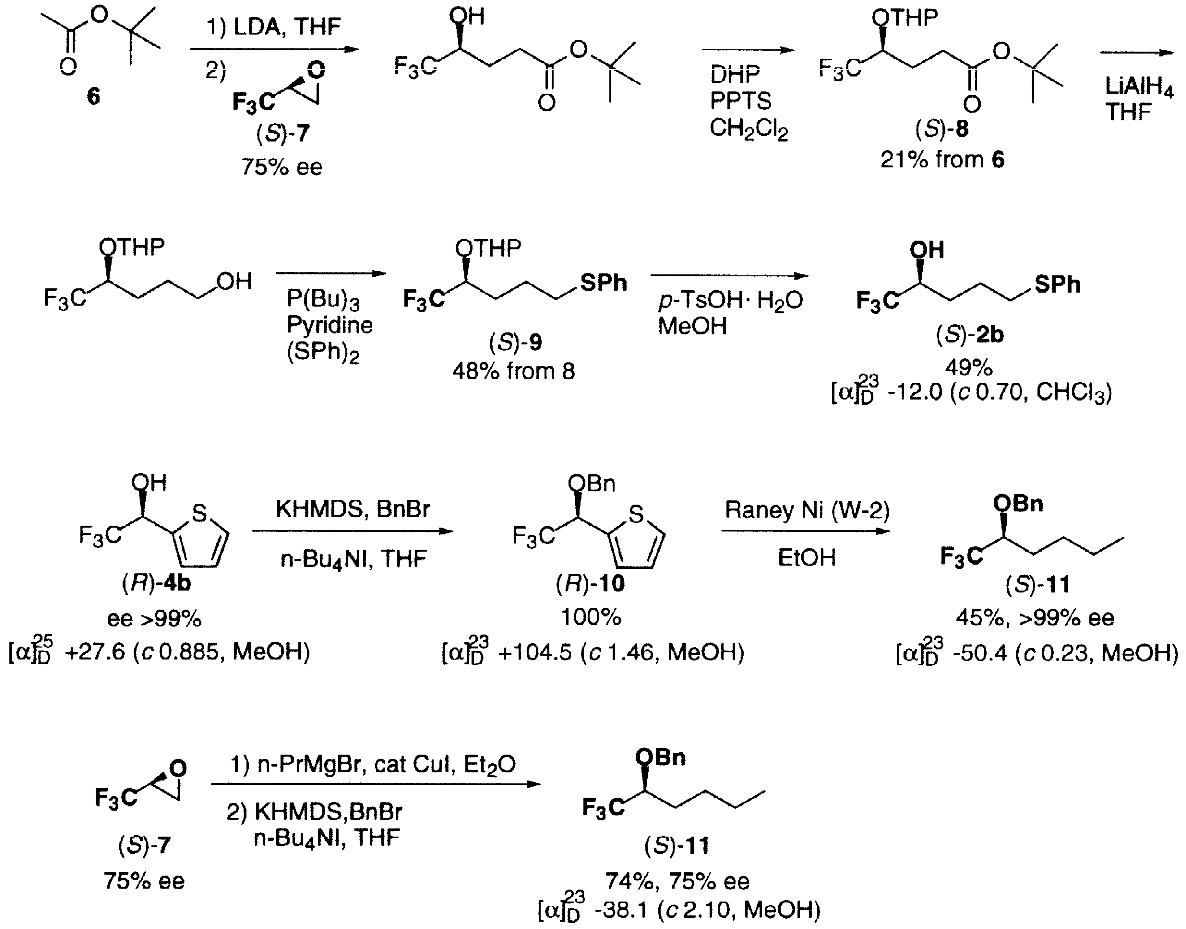
Chemicals. Organic reagents were purchased from Nakalai Tesque, Inc., Wako Pure Chemical Industries, Ltd., or Aldrich Chemical Company, Inc. unless otherwise noted.

Preparations of the Enzyme (APG4). *Geotrichum candidum* IFO 4597 was grown as described previously.[7] The cells (18 g wet wt) were mixed with cold acetone (-20 °C) and filtered. The procedure was repeated five times and then dried under reduced pressure. The dried cells (3.8 g) were obtained and used without further purification.

Preparations of Ketones.

1,1,1-Trifluoro-3-phenylthiopropan-2-one (1a) This ketone was prepared as described previously.[3]

Scheme 2



1,1,1-Trifluoro-5-phenylthiopentan-2-one (2a) To a solution of potassium phenylthiolate prepared from thiophenol (1.02 mL, 10 mmol) and KOH (85% purity, 725 mg, 11 mmol) in EtOH (7 mL), 1,3-dibromopropane (2.03 mL, 20 mmol) was added at 0 °C, and the mixture was stirred at rt for 26 h. The crude mixture was concentrated in vacuo, and the resulting oil was dissolved in ethyl acetate (20 mL). The solution was washed with saturated aq brine (10 mL x 2), dried over Na_2SO_4 and concentrated in vacuo to give crude 1-bromo-3-phenylthiopropane (2.65 g) as an oil. To a suspension of Mg (288 mg, 12 mgatm) activated with a small amount of iodine in THF (2 mL), a solution of the crude 1-bromo-3-phenylthiopropane (2.65 g) in THF (8 mL) was added dropwise at rt for 1 h and the mixture was heated at reflux for 16 h. The resulting Grignard reagent was cooled to -78 °C and ethyl trifluoroacetate (1.79 mL, 15 mmol) was added at -78 °C to the reaction mixture. After being stirred at rt for 19 h, the reaction was quenched by saturated aq NH_4Cl (5 mL) and the mixture was extracted with ether (10 mL x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil (1.5 g), which was then purified by silica gel column chromatography (eluent: *n*-Hex / AcOEt = 10 / 1) to give the title compound **2a** as a colorless oil (726 mg, 29%).

1,1,1-Trifluoro-3-octylthiopropan-2-one (3a) To a mixture of DABCO (2.24 g, 20.0 mmol) and 1-methylthiooctane (3.2 g, 20.0 mol) in THF (30 mL), *n*-BuLi (14.0 mL, 1.72 M in *n*-hexane, 24.0 mmol) was added dropwise at -20 °C and the mixture was stirred at 0 °C for 3 h. To the resulting mixture was added ethyl trifluoroacetate (2.62 mL, 22.0 mmol) at -78 °C and the whole mixture was stirred at -78 °C for 3 h. Saturated aq NH_4Cl (5 mL) was added and the mixture was extracted with ether (5 mL x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil which was then purified by silica gel column chromatography (eluent: *n*-Hex / AcOEt = 10 / 1) to give the title compound **3a** as a colorless oil (722 mg, 14%).

1,1,1-Trifluoro-3-(1,3-dithian-2-yl)propan-2-one (5a) To a solution of 1,3-dithiane (1.01 g, 8.32 mmol) in THF (15 mL), *n*-BuLi (4.89 mL, 1.7 M in *n*-hexane, 8.32 mmol) was added dropwise at -15 °C and the mixture was stirred at -15 °C for 2 h. The resulting mixture was added to a solution of ethyl trifluoroacetate (1.02 mL, 8.57 mmol) in THF (5 mL) at -90 °C and the whole mixture was stirred at -78 °C for 1 h and then at 0 °C for 3 h. Saturated aq NH_4Cl (5 mL) was added and the mixture was extracted with ether (5 mL x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil, which was then purified by silica gel column chromatography (eluent: *n*-Hex / AcOEt = 10 / 1) to give the title compound **5a** as a colorless oil (790 mg, 43%).

Asymmetric Reduction of Ketones by the APG4 System

(*R*)-1,1,1-Trifluoro-3-phenylthiopropan-2-ol ((*R*)-1b). To a mixture of **1a** (0.45 mmol, 100 mg), cyclopentanol (1.0 mL) and MES (2-(*N*-morpholino)ethanesulfonic acid) buffer (60 mL, 0.1 M, pH 7.0), NAD^+ (100 mg) and APG4 (200 mg) were added. The mixture was shaken at 130 rpm at 30 °C under an argon atmosphere in the dark for 24 h and additional cyclopentanol (0.25 mL), NAD^+ (50 mg) and APG4 (100 mg) were added. The mixture was shaken at 130 rpm at 30 °C under an argon atmosphere in the dark for additional 36 h and filtered through Extrelut which was washed with ether. The filtrate was extracted with ether (50 mL x 4), and the combined extracts were washed with water, saturated aq $NaHCO_3$ and water, successively, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent: n-Hex / AcOEt = 4 / 1), followed by distillation with a Kugelrohr apparatus (120 °C/0.6 mmHg), giving (*R*)-**1b** (91 mg, 90%). Ee was determined to be 98% from GC analysis (CP-Cyclodextrin-B-2,3,6-M-19, 150 °C, He: 2 mL/min). $[\alpha]^{25}_{D}$ -79.0 (*c* 0.428, MeOH), *lit.*[3] $[\alpha]^{23}_{D}$ -77.7 (c 0.38, MeOH, >99% ee (*R*)); ^1H NMR ($CDCl_3$) δ 2.86 (d, 1H, OH, *J* = 4.4 Hz), 3.01 (dd, 1H, SCH_2, *J* = 14.2, 10.0), 3.32 (dd, 1H, SCH_2, *J* = 14.2, 2.9 Hz), 3.98 (m, 1H, CH), 7.25-7.45 (m, 5H, Ph); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ -79.3 (d, *J* = 6.4 Hz); IR (neat) 3416, 1584, 1481, 1441, 1273, 1169, 1128, 866, 741 cm^{-1}; Anal. Calcd. for $C_9H_9OF_3S$: C, 48.64%; H, 4.08%. Found: C, 48.71%; H, 4.06%.

(*S*)-1,1,1-Trifluoro-5-phenylthiopentan-2-ol ((*S*)-2b). To a mixture of **2a** (0.40 mmol, 100 mg), 2-propanol (1.0 mL) and MES buffer (60 mL, 0.1 M, pH 7.0), NAD^+ (100 mg) and APG4 (400 mg) were added. The mixture was shaken at 130 rpm at 30 °C for 12 h and filtered through Extrelut which was washed with ether. The filtrate was extracted with ether (50 mL x 4) and the combined extracts were washed with water, saturated aq $NaHCO_3$ and water, successively, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent, n-Hex / AcOEt = 4 / 1), giving (*S*)-**2b** (79 mg, 78%). Ee was determined to be >99% from HPLC analysis (OD, eluent, n-Hex / 2-propanol = 4 / 1, 0.5 mL/min). $[\alpha]^{25}_{D}$ -18.7 (*c* 0.705, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.68-1.94 (m, 4H, CH_2), 2.12 (d, 1H, OH, *J* = 5.8 Hz), 2.91-3.00 (m, 2H, CH_2), 3.87-3.94 (m, 1H, CH), 7.14-7.37 (m, 5H, Ph); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ -80.6 (d, *J* = 6.8 Hz); IR (neat) 3409, 1584, 1481, 1439, 1279, 1173, 1127, 1026, 741, 693 cm^{-1}; Anal. Calcd for $C_{11}H_{13}OF_3S$: C, 52.79%; H, 5.24%. Found: C, 52.81%; H, 5.35%.

(*R*)-1,1,1-trifluoro-3-octylthiopropan-2-ol ((*R*)-3b). To a mixture of **3a** (0.60 mmol, 153 mg), cyclopentanol (1.5 mL) and MES buffer (90 mL, 0.1 M, pH 7.0), NADP$^+$ (150 mg) and APG4 (600 mg) were added. The mixture was shaken at 130 rpm at 30 °C under an argon atmosphere for 18 h and filtered through Extrelut which was washed with ether. The filtrate was extracted with ether (70 mL x 4) and the combined extracts were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (eluent, n-Hex / isopropyl ether = 3 / 1), followed by distillation with a Kugelrohr apparatus (130 °C/0.8 mmHg), giving (*R*)-**3b** (54 mg, 35%). Ee was determined to be 96% from GC analysis (G-TA, 105 °C for 100 min followed by 5 °C/min, He: 2 mL/min). $[\alpha]_D^{25}$ -39.9 (c 0.456, $CHCl_3$), *lit.*[1a] $[\alpha]_D^{24}$ -36.5 (*c* 2.17, $CHCl_3$, >95% ee(*R*)); ^1H NMR ($CDCl_3$) δ 0.87 (t, 3H, CH3, *J* = 6.4 Hz), 1.14 - 1.40 (m, 10H, CH_2), 1.51 - 1.59 (m, 2H, CH_2), 2.55 (t, 2H, SCH_2, *J* = 7.3 Hz), 2.71 (dd, 1H, CH_aH_bCHOH, J = 9.4, 14.4 Hz), 2.89 (dd, 1H, CH_aH_bCHOH, *J* = 3.4, 14.4 Hz), 3.0 (d, 1H, OH, *J* = 4.8), 3.95 - 4.10 (m, 1H, CH); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ -79.5 (d, *J* = 6.2 Hz); IR (neat) 3418, 2928, 2857, 1273, 1169, 1128 cm^{-1}; Anal. Calcd. for $C_{11}H_{21}OF_3S$: C, 51.14%; H, 8.19%. Found: C, 50.85%; H, 8.43%.

(*R*)-2,2,2-trifluoro-1-(2-thienyl)ethanol ((*R*)-4b). To a mixture of **4a** (8.6 mmol, 1.55 g), cyclopentanol (2.5 mL) and MES buffer (150 mL, 0.1 M, pH 7.0), NAD$^+$ (150 mg) and APG4 (250 mg) were added. The mixture was shaken at 130 rpm at 30 °C for 18 h, and filtered through Extrelut which was washed with ether. The filtrate was extracted with ether (100 mL x 4) and the combined extracts were concentrated in vacuo. The residue was dissolved in benzene and washed with water and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography (eluent, *n*-Hex / isopropyl ether = 3 / 1) followed by distillation with a Kugelrohr apparatus (125 °C/15 mmHg), giving (*R*)-**4b** (1.32 g, 84%). Ee was determined to be >99% by GC analysis (CP-Cyclodextrin-B-2,3,6-M-19, 120 °C, He: 2 mL/min). $[\alpha]_D^{25}$ +27.6 (*c* 0.885, MeOH); ^1H NMR ($CDCl_3$) δ 2.91 (d, 1H, OH, *J* = 4.8 Hz), 5.21-5.32 (m, 1H, CH), 7.02-7.07 (m, 1H), 7.19-7.21 (m, 1H), 7.37-7.41 (m, 1H); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ -79.2 (d, *J* = 6.2 Hz); IR (KBr) 3422, 1447, 1354, 1260, 1217, 1182, 1127, 1065, 860, 833, 712 cm^{-1}; Anal. Calcd for $C_6H_5OF_3S$: C, 39.56%; H, 2.77%. Found: C, 39.33%; H, 2.75%.

(+)-1,1,1-Trifluoro-3-(1,3-dithian-2-yl)propan-2-ol ((+)-5b). To a mixture of **5a** (0.48 mmol, 103 mg), cyclopentanol (0.8 mL) and MES buffer (20 mL, 0.1 M, pH 7.0), NAD$^+$ (100 mg) and APG4 (2.0 g) were added. The mixture was shaken at 130 rpm at 30 °C for 24 h followed by addition of Extrelut. The product was extracted with ether from the Extrelut and the extract was concentrated in vacuo. The residue was dissolved in benzene, washed with water, and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography (eluent, *n*-Hex / AcOEt = 3 / 1) followed by distillation with a Kugelrohr apparatus (110 °C/0.8 mmHg), giving (+)-**5b** (44 mg, 42%). The absolute configuration of the product is unknown at the moment. Ee was determined to be >99% from GC analysis (CP-Cyclodextrin-B-2,3,6-M-19, 160 °C, He: 2 mL/min). $[\alpha]_D^{24}$ +4.86 (*c* 0.617, $CHCl_3$) ^1H NMR ($CDCl_3$) δ 1.94-2.16 (m, 2H, CH_2), 2.71-3.04 (m, 4H, SCH_2), 3.09 (d, 1H, OH, *J* = 5.8 Hz), 4.16 (d, 1H, CH, *J* = 5.6 Hz), 4.20-4.32 (m, 1H, $CHCF_3$); ^{19}F NMR ($CDCl_3$-$CFCl_3$) δ -75.8 (d, *J* = 6.0 Hz); IR (neat) 3320, 2915, 1426, 1281, 1263, 1169, 1121 cm^{-1}; Anal. Calcd for $C_6H_9OF_3S_2$: C, 33.02%; H, 4.16%. Found: C, 32.79%; H, 4.22%.

Determination of Absolute Configurations

(*S*)-1,1,1-Trifluoro-5-phenylthiopentan-2-ol ((*S*)-2b) (Prepared from (*S*)-1,1,1-trifluoro-2,3-epoxypropane): To a solution of diisopropylamine (0.433 μL, 3.3 mmol) in THF (3 mL), a solution of *n*-

BuLi (2.00 ml, 1.65 M in *n*-hexane, 3.3 mmol) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 30 min. To the resulting LDA solution, a solution of *t*-butyl acetate **6** (348 mg, 3.0 mmol) in THF (5 mL) was added at -78 °C and the mixture was stirred at -78 °C for 2h. (*S*)-1,1,1-Trifluoro-2,3-epoxypropane (*S*)-**7** (75% ee, 344 μL, 4.0 mmol) was added to the resulting enolate solution at -78 °C, and the reaction mixture was allowed to stand at rt for 19 h. Saturated aq NH_4Cl (5 mL) was added, and the mixture was extracted with ether (10 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give an oil (238 mg). To a solution of the crude product in CH_2Cl_2 (1 mL), a solution of 3,4-dihydro-2*H*-pyran (455 μL, 5.0 mmol) in CH_2Cl_2 (2 mL) and pyridinium *p*-toluenesulfonate (50 mg, 0.2 mmol) were added at rt, and the mixture was allowed to stand at rt for 22 h. Saturated aq $NaHCO_3$ (3 mL) was added and the mixture was extracted with ethyl acetate (5 ml x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil, which was then purified on silica gel TLC (eluent: *n*-Hex / AcOEt = 5 / 1) to give *t*-butyl (4*S*)-5,5,5-trifluoro-4-(tetrahydropyran-2-yloxy)pentanoate (*S*)-**8** as a colorless oil (200 mg, 21%).

To a suspension of $LiAlH_4$ (73 mg, 1.92 mmol) in THF (2 mL) was added dropwise a solution of *t*-butyl (4*S*)-5,5,5-trifluoro-4-(tetrahydropyran-2-yloxy)pentanoate (*S*)-**8** (200 mg, 0.64 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Saturated aq Na_2SO_4 (0.2 mL) was added followed by ethyl acetate (5 mL), and the resulting suspension was filtered through celite with the aid of ethyl acetate. The filtrate was concentrated in vacuo to give a crude oil (143 mg). To a solution of the crude product and tributylphosphine (388 mg, 1.92 mmol) in pyridine (0.5 mL), diphenyl disulfide (418 mg, 1.92 mmol) was added at rt and the mixture was stirred at rt for 20 h. Saturated aq brine (5 mL) was added and the mixture was extracted with ethyl acetate (5 mL x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude solution gave an oil, which was purified on silica gel TLC (eluent: *n*-Hex / AcOEt = 15 / 1) to give (2*S*)-1,1,1-trifluoro-5-phenylthio-2-(tetrahydropyran-2-yloxy)pentane (*S*)-**9** as a colorless oil (108 mg, 48%).

To a solution of (2*S*)-1,1,1-trifluoro-5-phenylthio-2-(tetrahydropyran-2-yloxy)pentane (*S*)-**9** (108 mg, 0.31 mmol) in MeOH (2 mL), *p*-TsOH•H_2O (11 mg, 0.058 mmol) was added at rt and the mixture was stirred at rt for 17 h. Saturated aq $NaHCO_3$ (3 mL) was added and the mixture was extracted with ethyl acetate (5 mL x 3). The combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which was then purified on silica gel TLC (eluent: *n*-Hex / AcOEt = 4 / 1) to give the title compound (*S*)-**2b** as a colorless oil (40 mg, 49%). $[\alpha]_D^{23}$ -12.0 (*c* 0.70, $CHCl_3$).

(*R*)-2,2,2-trifluoro-1-(2-thienyl)ethanol

(*R*)-1-Benzyloxy-2,2,2-trifluoro-1-(2-thienyl)ethane ((*R*)-10): To a solution of (*R*)-2,2,2-trifluoro-1-(2-thienyl)ethanol (*R*)-**4b** (50 mg, 0.27 mmol) prepared by the APG4 reduction system in THF (1 mL), a solution of potassium hexamethyldisilazanide (0.82 ml, 0.5 M in toluene, 0.41 mmol) was added dropwise at 0 °C, and the mixture was stirred at 0 °C for 30 min. To the resulting mixture was added tetrabutylammonium iodide (11 mg, 0.03 mmol) and a solution of benzyl bromide (92 mg, 0.54 mmol) in THF (1 mL) successively at 0 °C, and the whole was stirred at rt for 2 h. Saturated aq brine (5 mL) was added, and the mixture was extracted with ether (5 ml x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil, which was then purified on silica gel TLC (eluent: n-Hex / AcOEt = 20 / 1) to give the title compound (*R*)-**10** as a colorless oil (73 mg, 100%); $[\alpha]_D^{23}$ +104.5 (*c* 1.46, CH_3OH); ^1H NMR (CCl_4) δ = 4.37 (d, 1H, *J* = 13.0 Hz), 4.67 (d, 1H, *J* = 13.0 Hz), 4.77 (q, 1H, *J* = 6.5 Hz), 6.80-7.41 (m, 3H), 7.25 (s, 5H); IR (neat) 2950, 1605, 1500, 1370, 1345, 1265, 1220, 1175, 1130, 1080 cm^{-1}.

(*S*)-2-Benzyloxy-1,1,1-trifluorohexane ((*S*)-11) : A mixture of (*R*)-1-benzyloxy-2,2,2-trifluoro-1-(2 thienyl)ethane (*R*)-**10** (73 mg, 0.27 mmol) and Raney Ni (W-2, 800 mg) in ethanol (7 mL) was heated at reflux for 3.5 h. The reaction mixture was filtered through a celite pad and the filtrate was concentrated to give an oil. Purification on preparative silica gel TLC (eluent: *n*-Hex / AcOEt = 50 / 1) gave the title compound (*S*)-**11** as a colorless oil (30 mg, 45%); $[\alpha]_D^{23}$ -50.4 (*c* 0.23, CH_3OH); ^1H NMR (CCl_4) δ = 0.89 (t, 3H, *J* = 6.5 Hz), 1.13-1.93 (m, 6H), 3.40-3.90 (m, 1H), 4.53 (d, 1H, *J* = 12.0 Hz), 4.87 (d, 1H, *J* = 12.0 Hz), 7.30 (s, 5H); ^{19}F NMR (CCl_4-$CFCl_3$) -78.5 ppm (d, *J* = 6.5 Hz); IR (neat) 3025, 2950, 1600, 1495, 1460, 1400, 1380, 1275, 1210, 1160, 1120, 730, 695 cm^{-1}.

(*S*)-2-Benzyloxy-1,1,1-trifluorohexane ((*S*)-11) (Prepared from (*S*)-1,1,1-trifluoro-2,3-epoxypropane (*S*)-7): Propylmagnesium bromide was prepared from 1-bromopropane (1.23 g, 10.0 mmol) and magnesium (264 mg, 11 mgatm) in ether (12 mL) in the usual manner, and to it was added (*S*)-1,1,1-trifluoro-2,3-epoxypropane (*S*)-**7** (75% ee, 517 µl, 6 mmol) and CuI (23 mg, 0.12 mmol) at -60 °C. The cooling bath was removed and the whole was stirred at rt for 12 h. Saturated aq NH_4Cl (5 mL) was added and the mixture was extracted with ether (10 mL x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil, which was dissolved in THF (20 mL). To the crude oil was added dropwise a solution of potassium hexamethyldisilazanide (12.0 ml, 0.5 M in toluene, 6.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. To the resulting mixture was added tetrabutylammonium iodide (221 mg, 0.6 mmol) and a solution of benzyl bromide (1.02 g, 6.0 mmol) in THF (10 mL) successively at 0 °C, and the whole mixture was stirred at rt for 2 h. Saturated aq brine (20 mL) was added, and the entire mixture was extracted with ether (20 ml x 3). The combined extracts were dried over Na_2SO_4. Concentration of the crude mixture gave an oil, which was then purified on silica gel TLC (eluent: n-Hex / AcOEt = 50 / 1) to give the title compound (*S*)-**11** as a colorless oil (1.09 g, 74%); $[\alpha]_D^{23}$ -38.10 (*c* 2.10, CH_3OH). The spectral properties are identical to those of the above material.

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