Chiral Synthesis via Organoboranes. 40. Selective Reductions. 55. A Simple One-Pot Synthesis of the Enantiomers of (Trifluoromethyl)oxirane. A General Synthesis in High Optical Purities of α-Trifluoromethyl Secondary Alcohols via the Ring-Cleavage Reactions of the Epoxide[1]

P. Veeraraghavan Ramachandran, Baoqing Gong,[2] and Herbert C. Brown*

Herbert C. Brown and R. B. Wetherill Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907

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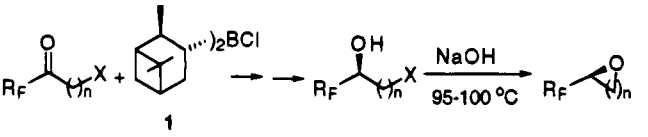
An extremely efficient one-pot asymmetric synthesis of either enantiomer of (trifluoromethyl)oxirane (3,3,3-trifluoro-1,2-epoxypropane, **4**) in 64% yield and 96% ee has been achieved via the asymmetric reduction of the commercially available 1-bromo-3,3,3-trifluoro-2-propanone with either (+)- or (−)-*B*-chlorodiisopinocampheylborane (Aldrich: DIP-Chloride), followed by ring closure of the intermediate chloroborinate, IpcBCl[OCH(CH_2Br)CF_3]. The ring cleavage reactions of **4** provide a general synthesis of chiral trifluoromethyl carbinols without loss of optical activity. Thus we have synthesized 1-amino-3,3,3-trifluoro-2-propanol, 1-azido-3,3,3-trifluoro-2-propanol, 1-(diethylamino)-3,3,3-trifluoro-2-propanol, 1-cyano-3,3,3-trifluoro-2-propanol, 1,1,1-trifluoro-2-propanol, 1,1,1-trifluoro-2-octanol, 1-phenyl-3,3,3-trifluoro-2-propanol, 1-ethoxy-3,3,3-trifluoro-2-propanol, and 1,2-dihydroxy-3,3,3-trifluoropropane, in 61–88% yields and in 96% ee by the cleavage of **4** with the appropriate nucleophile.

Introduction

The growing importance of chiral fluoroorganic molecules in modern organic chemistry[3] compelled us to include them in our general program of asymmetric synthesis via chiral organoboranes. Accordingly, we studied the asymmetric reduction of fluorinated ketones with one of the successful asymmetric reducing agents introduced by us a decade ago,[4] *B*-chlorodiisopinocampheylborane (DIP-Chloride, **1**).[5] Apart from revealing several very interesting theoretical aspects of the reduction of fluoro ketones, we achieved an efficient synthesis of optically active α-perfluoroalkyl secondary alcohols in excellent enantiomeric excess (ee). Whenever the carbonyl moiety is flanked by a perfluoroalkyl (R_F) group on one side, the product alcohol is obtained in very high ee (≥90%), with the R_F group always acting as the enantiocontrolling group.

Epoxides are important synthons in organic chemistry.[6] Our successful synthesis of chiral cyclic ethers via asymmetric reduction of aryl ω-haloalkyl ketones with **1**[7] convinced us that a similar reduction of perfluoroalkyl ω-haloalkyl ketones should provide an easy route to α-perfluoroalkyl cyclic ethers (Scheme 1).

Scheme 1



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R_F = CF_3, *n*-C_2F_5, *n*-C_3F_7, etc. n = 1, 2, 3, etc. X = Cl, Br, I

There are several methods available in the literature for the synthesis of perfluoroalkyl epoxides. Systematic research carried out by McBee and co-workers four decades ago has shown that 1-bromo-3,3,3-trifluoro-2-propanone (**2**) could be reduced to the corresponding bromohydrin **3** and cyclized to the epoxide **4**.[8] Rausch and co-workers adopted this procedure for the synthesis of internal epoxides as well.[9] Knunyants *et al.* prepared the bromoacetate from 1,1,1-trifluoropropene and cyclized it using sodium hydroxide to give the epoxide.[10] The Arndt–Eistert reaction of aldehydes substituted with an α-electron-withdrawing group provides the epoxide as the major or sole product.[11] Groth applied this observation for the synthesis of **4** by treating fluoral with diazomethane.[12] Coudures and co-workers showed that α-perfluoroalkyl terminal olefins do not undergo ready epoxidation and developed a lengthy and cumbersome procedure to synthesize higher homologs of perfluoroalkyl epoxides.[13] However, Bégué *et al.* have shown that enol ethers of fluorinated structures undergo ready epoxidation with *m*-chloroperoxybenzoic acid at room temperature (rt).[14]

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(2) Postdoctoral Research Associate on a Grant from the U.S. Army Research Office.

(3) All the articles contained in a special issue entitled Enantiocontrolled Synthesis of Fluoroorganic Compounds. *Tetrahedron: Asym.* **1994**, *5*, June issue. Hayashi, T., Soloshonok, V. A., Eds.; Elsevier Science: Oxford, U.K.

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Table 1. Asymmetric Reduction of 1-Bromo-3,3,3-trifluoro-2-propanone and Synthesis of (Trifluoromethyl)oxirane

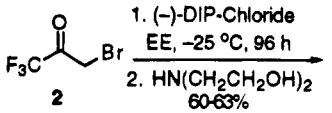
	reduction conditions			bromohydrin 3			epoxide 4		
reagent	solvent	temp, °C	time, h	yield, %	ee,[a] %	config[b]	yield, %	ee,[c] %	config[d]
(−)-DIP-Chloride	neat	25	8	61	88	*R*	82	88	*S*
(−)-DIP-Chloride	EE	0	16	62	92	*R*	83	92	*S*
(−)-DIP-Chloride	EE	−25	96	60	96	*R*	82	96	*S*
(+)-DIP-Chloride	EE	0	16	65	95	*S*	85	95	*R*
(+)-DIP-Chloride	EE	−25	96	63	97	*S*	81	96	*R*

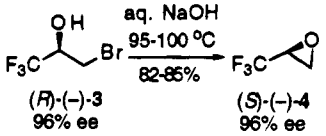
[a] Determined as the MTPA ester on a SPB-5 capillary column. [b] Based on the rotation of **3** reported in the literature: ref 22. [c] Based on the % ee of the ring-cleaved products. [d] Based on the rotation of **4** reported in the literature: ref 17.

Though the synthesis and properties of racemic perfluoroalkyl epoxides have been studied for a long time, the corresponding optically active epoxides received the attention of organic chemists only recently. Aerobic oxidation of olefins by microorganisms to produce epoxides with yields ranging from 36 to 52% has been achieved.[15] This procedure is substrate specific and solvent dependent. Takahashi carried out such an enzymatic oxidation of 1,1,1-trifluoropropene to obtain **4** in an unspecified yield and 75% ee.[16] Recently, Seebach reported a multistep, low-yielding procedure, starting with hexafluoropropylene oxide, for the synthesis of optically pure **4**.[17] Bravo and co-workers have reported the syntheses and reactions of optically active α-substituted fluoroalkyl oxiranes by the addition of diazomethane to the corresponding β-keto-γ-fluoro-substituted sulfoxides.[18] Asymmetric reduction of perfluoroalkyl haloalkyl ketone as a possible step for the preparation of the corresponding chiral cyclic ethers has not been reported thus far. We undertook this approach, and the results of our systematic investigation of the synthesis and ring-opening reactions of the parent epoxide **4** are presented herein.

Results and Discussion

Synthesis of the Oxirane. The reduction of **2** with (−)-**1** at rt was complete in 8 h, and the usual diethanolamine workup[3] provided **3** in 61% yield (eq 1). The decreased yield of the product is probably due to the reaction of diethanolamine with the bromine in **3**. Our modified acetaldehyde–NaOH workup[19] was avoided since **3** is known to be converted to the diol at low temperature.[20] The analysis of **3** for the optical purity as its methoxy(trifluoromethyl)phenylacetate (MTPA ester)[21] or as the trifluoroacetate ester using a gas chromatograph with a SPB-5 or Chiraldex GTA capillary column, respectively, showed it to be 88% ee.[22] Lowering the reaction temperature to 0 °C provided **3** of 92% ee and a product of 96% ee was produced at −25 °C. Dehydrobromination of the above product under McBee's conditions (15 N NaOH, 95–100 °C)[23] provided the required epoxide in 82% yield.

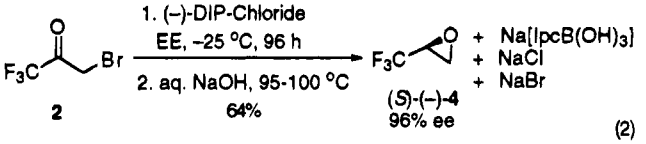




(1)

The opposite enantiomer of **4** was synthesized from **2** by reduction with (+)-**1**. The effect of the reduction temperature on the % ee of the oxirane is summarized in Table 1.

One-Pot Synthesis. We took advantage of the volatility (bp 38 °C) of **4** and modified the workup procedure to isolate the product directly from the chloroborinate intermediate, IpcBCl(OR*), obtained after the reduction. Upon completion of the reduction, the solvent was removed and the intermediate was added to aqueous sodium hydroxide and heated to distill **4** from the reaction pot. This procedure avoids the isolation of **3** which increases the yield of the oxirane without affecting the enantiomeric purity (eq 2).



(2)

Ring-Cleavage Reactions. With the optically active **4** in hand, we decided to carry out several ring-opening reactions. This was imperative not only to demonstrate the synthetic utility of our procedure but also to study the effect of the trifluoromethyl group on the regioisomeric and enantiomeric purity of the product. McBee had carried out several ring-cleavage reactions with racemic **4**,[20] and Szonyi had opened up several racemic perfluoroalkyl epoxides with various amines and sulfides to synthesize fluorinated surface active agents.[24] Takahashi cleaved (−)-**4** of 75% ee with Grignard-type and Friedel–Crafts-type reactions.[16] He observed a reversal in regioselectivity in the ring opening Friedel–Crafts-type reaction as compared to the hydrocarbon analog of the oxirane which was explained using molecular orbital calculations. Kubota and Yamamoto had recently carried

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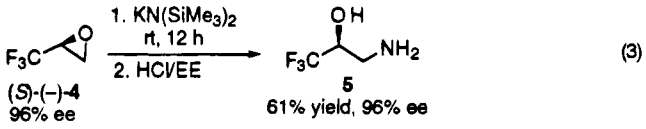
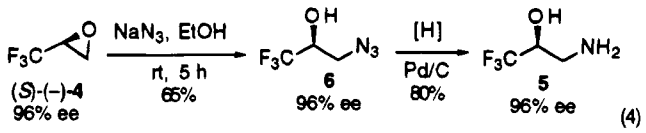
out Wittig-type reactions with **4**.[25] Katagiri and coworkers oxidized **4** with nitric acid in the presence of copper catalyst to prepare optically active trifluorolactic acid.[26] We utilized a wide variety of nucleophiles to open the oxirane. In all the cases studied, including the Friedel–Crafts-type ring-opening,[16] we obtained the secondary alcohol as the sole product.

Synthesis of Amino Alcohols. Chiral 1,2- and 1,3-amino alcohols constitute the backbone of several natural products.[27] Recently, organic chemists have been synthesizing new chiral 1,2-amino alcohols[28] to be used for catalysts in asymmetric reductions[29] and the reaction of dialkylzinc with aldehydes.[30] The reaction of amines with epoxides is a standard procedure for the synthesis of 1,2-amino alcohols. However, the syntheses of optically active perfluorinated amino alcohols have not been studied. McBee had demonstrated the reaction of anhydrous ammonia with racemic **4** for the synthesis of 1-amino-3,3,3-trifluoro-2-propanol (**5**) in 27% yield.[20] We approached this amine *via* a different route. Treatment of **4** with the potassium salt of 1,1,1,3,3,3-hexamethyldisilazane[31] and workup with anhydrous HCl provided **5** in 61% yield (eq 3). Analysis showed that the enantiomeric purity had not changed.



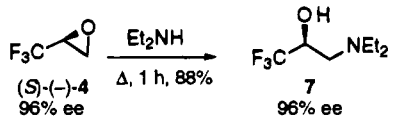
(3)

Alternately, we synthesized **5** by the ring-cleavage of **4** with sodium azide followed by hydrogenation (eq 4). The literature reports that the reaction of azide in ethanol in the presence of ammonium chloride is the best condition for the synthesis of the azido alcohol **6**.[14,32] We utilized a similar procedure, and the reaction was complete in 5 h.



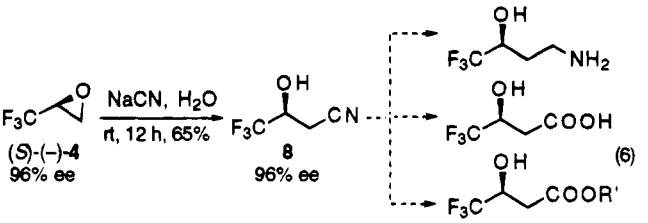
(4)

Following the procedure of McBee, the treatment of **4** with excess diethylamine in a sealed tube at 55 °C provides optically active 1-(diethylamino)-3,3,3-trifluoro-2-propanol (**7**) in 88% yield (eq 5). Analysis of the menthyl chloroformate (MCF) derivative,[33] showed complete retention of optical activity, 96% ee. This can be a general method for the synthesis of chiral trifluoromethyl β-amino alcohols. By the proper choice of the dialkylamine, we can prepare the desired amino alcohol.



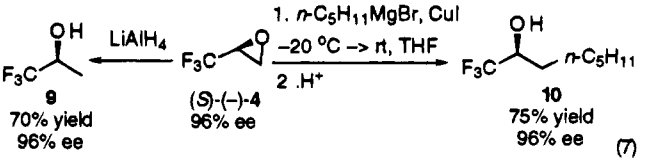
(5)

We achieved the synthesis of 1-cyano-3,3,3-trifluoro-2-propanol (**8**) by the treatment of **4** with NaCN. This cyanohydrin should be transformable into the corresponding γ-amino alcohol, β-hydroxy acid or ester, etc. (eq 6).



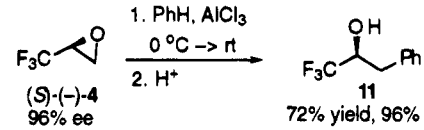
(6)

Synthesis of 1,1,1-Trifluoro-2-alkanols. Asymmetric reduction of 1,1,1-trifluoro-2-alkanones provides an excellent synthesis of the corresponding secondary alcohols in very high ee.[5a] We utilized the ring-opening reactions of **4** as an alternate route to these alcohols. Thus, 1,1,1-trifluoro-2-propanol (**9**) and 1,1,1-trifluoro-2-octanol (**10**) were synthesized by the reaction of lithium aluminum hydride (LAH)[20] and *n*-pentylcopper,[16] respectively (eq 7).



(7)

In contrast to the Friedel–Crafts reaction of methyloxirane with benzene, which opens the epoxide ring so as to place the phenyl group at C_2, in the reaction of **4** the epoxide ring opens up to place the phenyl group at C_1 to provide the trifluoromethyl benzyl carbinol **11**. This reaction has been studied in detail by Takahashi using molecular modeling (eq 8).[16]



(8)

Hydrolysis Reactions. It is known that the nucleophilic ring-opening of **4** and its hydrocarbon analog under basic conditions occurs exclusively at C_1 to provide the substituted secondary alcohol as the sole product.[20] However, the ring cleavage under acidic conditions does not show uniformity in the products obtained. While methyloxirane provides a mixture of products, **4** undergoes regiospecific cleavage to provide a single product. For example, ethanolysis of **4** gives the β-ethoxy alcohol **12**. Hydrolysis under similar conditions provides the diol **13** (eq 9).

The results of the ring-cleavage reactions are summarized in Table 2. All of these reactions provide a general synthesis of both isomers of optically pure α-trifluoromethyl secondary alcohols.

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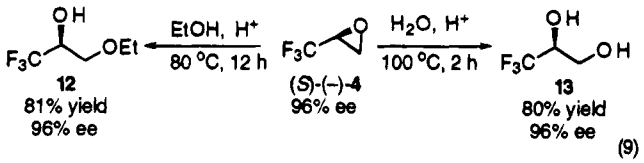
Table 2. Ring-Cleavage Reactions of (*S*)-(Trifluoromethyl)oxirane

reagent	product	react. temp, °C	react. time, h	yield, %	$[\alpha]_D$, deg	ee, %	config[a]
$KN(SiMe_3)_2$	$CF_3CH(OH)CH_2NH_2$ (**5**)	25	12	61	−19.54 (*c* 1.3, MeOH)	≥99[b,c]	*S*
NaN_3	$CF_3CH(OH)CH_2N_3$ (**6**)	25	5	65	+12.87 (*c* 1.9, MeOH)	96[d]	*S*
Et_2NH	$CF_3CH(OH)CH_2NEt_2$ (**7**)	55	1	88	−29.79 (*c*, 1.4, MeOH)	96[e]	*S*
NaCN	$CF_3CH(OH)CH_2CN$ (**8**)	25	12	65	−16.78 (*c* 1.5, MeOH)	96[f]	*S*
$LiAlH_4$	$CF_3CH(OH)CH_3$ (**9**)	25	1.5	70	−6.24 (neat)[g]	96[e]	*S*
n-$C_5H_{11}MgBr$	$CF_3CH(OH)C_6H_{13}$ (**10**)	−20−25	3	75	−25.52 (*c* 1.5, $CHCl_3$)[h]	96[b]	*S*
PhH, $AlCl_3$	$CF_3CH(OH)CH_2Ph$ (**11**)	0−25	3	72	−50.24 (*c* 1.8, MeOH)	96[f]	*S*
$EtOH/H^+$	$CF_3CH(OH)CH_2OEt$ (**12**)	80	12	81	−11.20 (*c* 1.4, MeOH)	96[f]	*S*
H_2O/H^+	$CF_3CH(OH)CH_2OH$ (**13**)	100	2	80	−10.95 (*c* 1.4, MeOH)	96[f]	*S*

[a] Based on the reaction mechanism. [b] Determined as the MTPA ester on a SPB-5 capillary column. [c] The initial product was crystallized in EE. [d] Determined by converting the azide to the amine. [e] Determined as the MCF derivative on a SPB-5 capillary column. [f] Determined as the TFA derivative on a Chiraldex-GTA column. [g] From ref 5a. [h] From ref 5c.



(9)

Conclusions

We have achieved the syntheses of both isomers of optically active (trifluoromethyl)oxirane in a one-pot reaction in 64% yield and in 96% ee. The ring-cleavage reactions of this epoxide with a variety of nucleophiles have been carried out to show the general synthetic utility for the preparation of α-trifluoromethyl secondary alcohols. The easy synthesis of optically active trifluoromethyl β-amino alcohols **5** and **7** should find valuable applications in organic synthesis. The trifluoromethyl cyanohydrin **8** provides possible synthetic routes to γ-amino alcohols, β-hydroxy acids, esters, etc. Since we know that **1** is an excellent asymmetric reagent for the reduction of aryl and alkyl perfluoroalkyl ketones,[5] this should provide a general route to the synthesis of several other perfluoroalkyl cyclic ethers (Scheme 1) and perfluoroalkyl secondary alcohols bearing functional groups. We are continuing our studies on the asymmetric reduction of different classes of fluorinated ketones with **1**.

Experimental Section

General Methods. Techniques for handling air-sensitive compounds have been previously described.[34] ^1H, ^{13}C, ^{11}B, and ^{19}F NMR (CF_3COOH as external standard at δ −76.5 ppm) spectra were plotted on a Varian Gemini-300 spectrometer with a Nalorac Quad-Nucleus probe, and IR spectra were plotted on a Perkin-Elmer 1420 ratio recording spectrophotometer. Analyses of the MTPA esters or MCF derivatives were performed on a Hewlett-Packard 5890A gas chromatograph using a SPB-5 capillary column (30 m), at appropriate temperatures, and integrated using a Hewlett-Packard 3390A integrator. Some of the product alcohols were converted to the trifluoroacetates and analyzed on a Chiraldex-GTA capillary column (23 m). Optical rotations were measured using a Rudolph Autopol III polarimeter.

Materials. Ethyl ether (Mallinckrodt) was used as such. Aluminum chloride, benzene, 1-bromo-3,3,3-trifluoro-2-propanone, cuprous iodide, (+)- and (−)-DIP-Chloride, diethanolamine, diethylamine, 1,1,1,3,3,3-hexamethyldisilazane, lithium aluminum hydride, menthyl chloroformate, 10% palladium on activated carbon, *n*-pentylmagnesium bromide, potassium hydride, sodium azide, sodium cyanide, and trifluoroacetic anhydride were all obtained from Aldrich Chemical Co. (*R*)-(+)-Methoxy(trifluoromethyl)phenylacetic acid (MTPA) was obtained from Aldrich Chemical Co. and converted to the acid chloride using Mosher's procedure.[21]

Synthesis of (*S*)-(−)-(Trifluoromethyl)oxirane (4). (a) Stepwise Procedure. (*R*)-(−)-1-Bromo-3,3,3-trifluoro-2-propanol (3). An oven-dried, 100 mL round-bottom flask equipped with a side arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. (−)-DIP-Chloride (8.8 g, 27.5 mmol) was transferred to the flask in a glove bag and dissolved in EE (25 mL). The solution was cooled to −25 °C, and **2** (4.7 g, 25 mmol) was added using a syringe. The reaction was followed by ^{11}B NMR after aliquots were methanolyzed at the reaction temperature at periodic intervals. When the reaction was complete (^{11}B δ: 32 ppm, 96 h), the mixture was warmed to 0 °C and diethanolamine (5.3 mL, 55 mmol) was added dropwise. The mixture was then warmed to rt and stirred for 2 h, whereupon the boranes precipitated as a complex which was filtered and washed with pentane. The solvents were removed by distillation, and the residue was passed through a silica gel column to separate α-pinene and the product (pentane and CH_2Cl_2 as eluents). The fraction containing the product was concentrated and distilled at 122−23 °C to yield 2.9 g (60%) of **3** (lit.[8] bp 122−23 °C). The alcohol was further purified by preparative GC using an SE-30 column. The rotation was measured. α_D^{22} = −51.06 (neat) which corresponded to the *R*-isomer.[22] The MTPA ester of the alcohol was prepared by a standard procedure.[21] Racemic **3** obtained by the reaction of **2** with borane−methyl sulfide complex was converted to the MTPA ester and analyzed on a SPB-5 capillary column to obtain the diastereomeric pair of peaks. Then the optically active ester was analyzed which showed a composition of 98% of the *R*-isomer and 2% of the *S*-isomer, i.e. an ee of 96% in the *R*-isomer. The % ee was also confirmed by analysis of the trifluoroacetate of the alcohol on a Chiraldex-GTA capillary column. IR ν_{max} cm^{-1} neat: 3380 (OH). ^1H NMR δ ($CDCl_3$): 2.72−2.82 (m, 1H, O*H*), 3.48 (dd, *J* = 11.2, 8.5 Hz, 1H, −C*H*′H″Br), 3.64 (dd, *J* = 11.2, 3.0 Hz, 1H, −CH′*H*″Br), 4.20−4.30 (m, 1H, C*H*(OH)CF_3). ^{13}C NMR δ($CDCl_3$): 29.69 (C_1), 70.53 (q, *J* = 31.8 Hz, C_2), 123.39 (q, *J* = 282.8 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −78.07 (d, *J* = 5.0 Hz).

A similar reaction of 1-bromo-3,3,3-trifluoro-2-propanone with (−)-**1** at rt was complete in 8 h and workup provided **3** of 88% ee in 61% yield. Another reaction at 0 °C was complete in 16 h, and the product, obtained in 65% yield, showed 92% ee.

(*S*)-(−)-(Trifluoromethyl)oxirane ((−)-4). The epoxide was prepared from (*R*)-(−)-**3** (96% ee) using a procedure reported in the literature for the racemic material.[8] The bromohydrin (2.9 g, 15 mmol) was added, dropwise, to an ice-cold solution of aqueous NaOH (15 N, 60 mmol) contained in a 15 mL round bottom flask fitted with a distillation set up. The mixture was stirred at 95−100 °C; then **4** distilled at 37−38 °C (lit.[8] bp 38 °C) and was collected in a flask cooled in a dry ice−acetone bath. Yield: 1.38 g (82%). $[\alpha]_D^{22}$ = −10.92 (*c* 5.0, $CHCl_3$), which corresponds to an optical purity of 91% in the *S*-isomer on the basis of the maximum rotation reported in the literature.[17] However, the material is of 96% ee as confirmed by the ring-cleavage reactions. ^1H NMR δ ($CDCl_3$): 2.90−3.02 (m, 2H, CH_2), 3.40−3.50 (m, 1H, C*H*). ^{13}C

(34) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975; Chapter 9.

NMR δ ($CDCl_3$): 43.11 (C_1), 48.16 (q, J = 41.7 Hz, C_2), 122.84 (q, J = 274.8 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −75.04 (d, J = 4.6 Hz).

(b) One-Pot Procedure. The reduction of **2** with (−)-**1** was carried out as above. After the completion of the reduction, the solvent was removed, added to aqueous NaOH (15 N, 10.0 equiv), and heated at 95−100 °C to distill the epoxide **4**. Yield: 64%. The product showed the same physical characteristics as the product obtained from the above reaction.

(*R*)-(+)-(Trifluoromethyl)oxirane ((+)-4). The reduction of **2** with (+)-**1** at −25 °C, as above, provided (*S*)-(+)-**3** of 96% ee. Treatment of this bromohydrin with NaOH at 95−100 °C provided the (*R*)-oxirane in 81% yield, bp 37−39 °C, $[\alpha]^{23}_D$ = +11.28 (*c* 4.9, $CHCl_3$), which corresponds to 95% ee on the basis of the maximum rotation reported in the literature.[17] This product is also of 96% ee as was confirmed by the ring-cleavage reactions.

(*S*)-(−)-1-Amino-3,3,3-trifluoro-2-propanol (5). (a) Direct Synthesis. Under stirring, (−)-**4** (1.12 g, 10 mmol, 96% ee) was added, dropwise, to an ice-cold solution of $KN(SiMe_3)_2$ (12.5 mmol)[28] and stirring at rt was continued for 12 h. Methanol (2 mL) was added to this dark brown mixture, which was stirred for an additional 2 h. Removal of the volatiles under vacuum provided a dark oil which was dissolved in EE (30 mL), followed by the addition of HCl in EE (12.5 mmol) at 0 °C. The solid (KCl) was filtered off and washed with EE, and the combined washings were concentrated to obtain 0.79 g (61%) of solid **5**, mp 120−121 °C. Analysis of the MTPA ester using a SPB-5 capillary column showed it to be of 96% ee. Crystallization of this material from EE increased the ee to ≥99%. $[\alpha]^{23}_D$ = −19.54 (*c* 1.3, MeOH). IR ν_{mac} cm^{-1} Nujol: 3370 (OH), 3298 (NH_2). ^1H NMR δ ($CDCl_3$): 1.85 (br s, 3H, O*H*, N*H*$_2$), 2.98 (dd, J = 13.5, 5.2 Hz, 1H, −C*H*′H″NH_2), 3.08 (dd, J = 13.5, 4.9 Hz, 1H, −CH′*H*″NH_2), 3.82−3.92 (m, 1H, C*H*). ^{13}C NMR δ (acetone-d_6): 47.45 (C_1), 74.55 (q, J = 31.0 Hz, C_2), 126.15 (q, J = 280.3 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −78.44 (d, J = 7.3 Hz).

(b) Indirect Synthesis: (*S*)-(+)-1-Azido-3,3,3-trifluoro-2-propanol (6). A solution containing 0.56 g (5.0 mmol) of (*S*)-(−)-**4**, NH_4Cl (0.54 g, 10 mmol), and NaN_3 (0.65 g, 10 mmol) in 5 mL of 80% EtOH was stirred at rt for 5 h. Water (5 mL) was added to this mixture, which was extracted with ether, dried over $MgSO_4$, and concentrated to obtain 0.50 g (65%) of **6**. The optical purity of **6** was determined by converting it to the amine **5** (see below). $[\alpha]^{24}_D$ = +12.87 (*c* 1.9, MeOH). IR ν_{max} cm^{-1} neat: 3380 (OH), 2112 (N_3). ^1H NMR δ ($CDCl_3$): 2.70 (br s, 1H, O*H*), 3.46−3.61 (m, 2H, C*H*$_2$), 4.10−4.20 (m, 1H, C*H*). ^{13}C NMR δ ($CDCl_3$): 50.18 (C_1), 69.83 (q, J = 31.1 Hz, C_2), 123.73 (q, J = 282.2 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −78.39 (d, J = 6.5 Hz).

Hydrogenation. The azide **6** obtained from the above reaction (0.463 g, 3 mmol) in methanol (10 mL) was hydrogenated in the presence of 5 mol % of 10% Pd on activated carbon (0.05 g). The suspension was filtered through Celite and washed with 20 mL of methanol. The combined washings were concentrated to yield 0.31 g (80%) of **5**. Analysis of the MTPA ester showed it to be 96% ee. The physical properties of this material matched those of the material obtained from the direct synthesis of **5** given above.

(*S*)-(−)-1-(Diethylamino)-3,3,3-trifluoro-2-propanol (7). A sealed tube containing 0.67 g (6.0 mmol) of (*S*)-(−)-**4** and excess (10 equiv) diethylamine was heated at 55 °C for 1 h and maintained at rt for 10 h. The tube was cooled and broken, and the contents were dissolved in EE. The solvent and excess diethylamine were removed under vacuum, and the residue was distilled using a Kugelrohr apparatus (pot temperature 100 °C/40 mmHg) to obtain 0.98 g (88%) of **7**. $[\alpha]^{22}_D$ = −29.79 (*c* 1.4, MeOH). Analysis of the MCF derivative on a SPB-5 capillary column showed it to be of 96% ee. IR ν_{max} cm^{-1} neat: 3360 (OH). ^1H NMR δ ($CDCl_3$): 1.05 (t, J = 7.2 Hz, 6 H, C*H*$_3$), 2.52−2.72 (m, 6H, −C*H*$_2$CH$_3$, −C*H*$_2$N), 3.85−4.00 (m, 1H, C*H*). ^{13}C NMR δ ($CDCl_3$): 11.42, 47.38, 51.89, 66.13 (q, J = 30.5 Hz, C_2), 125.11 (q, J = 280.8 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −78.86 (d, J = 6.4 Hz).

(*S*)-(−)-1-Cyano-3,3,3-trifluoro-2-propanol (8). Magnesium sulfate (1.2 g, 10 mmol) was dissolved in 3.5 mL of water at rt followed by the addition of sodium cyanide (0.54 g, 11 mmol) and 0.56 g (5.0 mmol) of (−)-**4** (96% ee). Stirring was continued for 12 h. HCl (2 N, 5 mL) (Caution: Poison!) was added, the product was extracted with ethyl acetate, and the solvents were removed and then distilled using a Kugelrohr apparatus (pot temperature 90−100 °C/35 mmHg). Yield: 0.45 g (65%). $[\alpha]^{25}_D$ = −16.78 (*c* 1.5, MeOH). Analysis of the TFA derivative on a Chiraldex-GTA capillary column showed it to be of 96% ee. IR ν_{max} cm^{-1} neat: 3407 (OH), 2269 (CN). ^1H NMR δ ($CDCl_3$ + acetone-d_6): 2.70−2.86 (m, 2H, C*H*$_2$), 4.30−4.41 (m, 1H, C*H*), 5.25 (br s, 1H, O*H*). ^{13}C NMR δ ($CDCl_3$ + acetone-d_6): 19.84 (C_1), 66.06 (q, J = 32.7 Hz, C_2), 115.77, 123.68 (q, J = 282.3 Hz, C_3). ^{19}F NMR: δ ($CDCl_3$): −80.00 (d, J = 5.8 Hz).

(*S*)-1,1,1-Trifluoro-2-propanol (9). A solution of (*S*)-(−)-**4** (0.56 g, 5 mmol) (96% ee) in EE (5 mL) was added dropwise to a stirred solution of LAH in EE (2.5 mmol of 1.0 M) under nitrogen atmosphere. After 1.5 h at rt, the mixture was added dropwise to wet ether, treated with dilute H_2SO_4, extracted with EE, and dried ($MgSO_4$). Removal of EE and distillation provided 0.4 g (70%) of **9**, bp 77−78 °C.[5a] Analysis of the MCF derivative on a SPB-5 capillary column showed it to be 96% ee in the *S*-isomer. The ^1H NMR and ^{13}C NMR are identical to those of the product obtained from the reduction of 1,1,1-trifluoroacetone.[5a]

(*S*)-1,1,1-Trifluoro-2-octanol (10). (*S*)-(−)-**4** (0.56 g, 5.0 mmol) (96% ee) was added to a mixture of *n*-pentylmagnesium bromide (7.5 mmol of 2.0 M in EE) and copper iodide (0.02 g, 0.10 mmol) in 10 mL of THF at −20 °C. The mixture was allowed to warm to rt, stirred for 3 h, hydrolyzed, extracted with EE, dried ($MgSO_4$), concentrated, and distilled to provide 1,1,1-trifluoro-2-octanol in 75% yield, bp 167−169 °C/740 mmHg.[5c] The ^1H, ^{13}C, and ^{19}F NMR spectra of this product are identical to those obtained from the reduction of the corresponding ketone with **1**.[5c] Analysis of the MTPA ester of the product on a SPB-5 capillary column showed it to be of 96% ee in the *S*-isomer.

(*S*)-(−)-1-Phenyl-3,3,3-trifluoro-2-propanol (11). (*S*)-(−)-**4** (0.63 g, 5.6 mmol) (96% ee) was added to a mixture of aluminum chloride (0.86 g, 6.44 mmol) and benzene (11.4 g, 26 equiv) at 0 °C. The reaction mixture was stirred at rt for 3 h, hydrolyzed, extracted with EE, dried ($MgSO_4$), concentrated, and distilled using a Kugelrohr apparatus (pot temperature 95−100 °C/1 mmHg) to provide 0.76 g (72%) of **11**. Analysis of the TFA ester on a Chiraldex-GTA capillary column showed no loss of optical activity. $[\alpha]^{22}_D$ = −50.24 (*c* 1.8, MeOH), which corresponds to 96% ee in the *S*-isomer. IR ν_{max} cm^{-1} neat: 3397 (OH). ^1H NMR δ ($CDCl_3$): 2.38 (br s, 1H, O*H*), 2.77 (dd, J = 14.4, 10.3 Hz, 1H, −C*H*H″Ph), 3.00 (dd, J = 14.4, 3.0 Hz, 1H, −CH′*H*″Ph), 4.02 (br s, 1H, C*H*), 7.19−7.31 (m, 5H, Ph). ^{13}C NMR δ ($CDCl_3$): 36.01, 71.38 (q, J = 30.9 Hz, C_2), 124.81 (q, J = 282.2 Hz, C_3), 127.11, 128.67, 129.37, 135.77. ^{19}F NMR δ ($CDCl_3$): −79.62 (d, J = 6.6 Hz).

(*S*)-(−)-1-Ethoxy-3,3,3-trifluoro-2-propanol (12). A mixture of (*S*)-(−)-**4** (0.67 g, 6.0 mmol) (96% ee) and ethanol (3 mL) containing 0.75% H_2SO_4 was heated in a sealed tube at 80 °C for 12 h. Distillation of the product mixture using a Kugelrohr appratus (pot temperature 100 °C/40 mmHg) provided 0.76 g (81%) of **12**. Analysis of the TFA derivative on a Chiraldex GTA capillary column showed it to be 96% ee. $[\alpha]^{22}_D$ = −11.20 (*c*, 1.4, MeOH). IR ν_{max} cm^{-1} neat: 3408 (OH). ^1H NMR δ ($CDCl_3$): 1.23 (t, J = 7.0 Hz, 3H, C*H*$_3$), 3.55−3.72 (m, 4H, C*H*$_2$CH$_3$, C*H*$_2$OEt), 3.85 (br s, 1H, O*H*), 4.10−4.20 (m, 1H, C*H*OH). ^{13}C NMR δ ($CDCl_3$): 14.58, 67.27, 68.11, 69.33 (q, J = 30.9 Hz, C_2), 124.21 (q, J = 281.7 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −77.94 (d, J = 4.9 Hz).

(*S*)-(−)-1,2-Dihydroxy-3,3,3-trifluoropropane (13). A mixture of (*S*)-(−)-**4** (0.79 g, 7.0 mmol) (96% ee) and water (3.5 mL) containing 1% H_2SO_4 was heated in a sealed tube at 100 °C for 2 h. The product mixture was extracted with ethyl acetate, dried over $MgSO_4$, concentrated, and distilled using a Kugelrohr appratus (pot temperature 100 °C/25 mmHg) to provide 0.73 g (80%) of **13**. Analysis of the TFA derivative on a Chiraldex-GTA capillary column showed it to be of 96% ee. $[\alpha]^{24}_D$ = −10.95 (*c* 1.4, MeOH). IR ν_{max} cm^{-1} neat: 3373 (OH). ^1H NMR δ ($CDCl_3$): 3.5 (br s, 1H, O*H*), 3.75−3.90 (m, 2H,

CH_2), 4.0–4.15 (m, 1H, C*H*), 4.58 (br s, 1H, O*H*). ^{13}C NMR δ ($CDCl_3$ + acetone-d_6): 60.27, 70.40 (q, J = 30.1 Hz, C_2), 124.26 (q, J = 282.0 Hz, C_3). ^{19}F NMR δ ($CDCl_3$): −77.82 (d, J = 6.8 Hz).

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Supplementary Material Available: ^1H and ^{13}C NMR data of compounds **3**–**8** and **11**–**13** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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