Efficient Synthesis of Optically Pure 1,1,1-Trifluoro-2-alkanols through Lipase-Catalyzed Acylation in Organic Media

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Lipase-catalyzed esterification was successfully utilized for the optical resolution of 1,1,1-trifluoro-2-alkanol **1** when racemic **1** was treated with lipase from *Candida antarctica* in hexane in the presence of molecular sieves (4 Å) to provide the corresponding (*S*)-acetate **2** in an optically pure state. Alkanol **1** is known as an important component of liquid crystal compounds which display remarkable ferroelectric liquid crystal (FLC) characteristics. Five types of *optically pure* alkanols, i.e., 1,1,1-trifluoro-2-octanol (**1a**), 1,1,1-trifluoro-2-nonanol (**1b**), 1,1,1-trifluoro-2-decanol (**1c**), 1,1,1-trifluoro-2-undecanol (**1d**), and 1,1,1-trifluoro-8-(benzyloxy)-2-octanol (**1e**), were thus obtained by the lipase-catalyzed acylation.

Introduction

Ferroelectric liquid crystals (FLC) are known to be important high-speed switching devices,[1] and their response time strongly depends on the magnitude of their spontaneous polarization (P_s). A recent study revealed that chiral FLC compounds, which involve optically active 1,1,1-trifluoroalkanols **1**, possess remarkable characteristics such as a wide temperature range of the Sc* phase, a large spontaneous polarization, and a short response time (Figure 1).[1c] Only three preparation methods have been reported for optically active **1**.[2] The first example is optical resolution through the lipase-catalyzed hydrolysis of the corresponding racemic esters, though high enantioselection was allowed for a limited number of compounds.[2a] The second example is the enantioselective reduction of trifluoromethyl ketones by bakers' yeast,[2b] or plant tissue cultures from *Nicotiana tabacum* which we recently reported.[2c] The third method is the classical resolution of racemic **1** as diastereomeric esters using optically pure *trans*-2-benzamidocyclohexanoic acid.[2d]

Because the target compounds are FLC compounds, large scale preparation is particularly desired. The lipase-catalyzed reaction is obviously superior to the others in total efficiency.[3] We wish to report the highly efficient enzymatic resolution of 1,1,1-trifluoroalkanols, which have a long linear alkyl chain, through enantioselective acylation in organic media using *Candida antarctica* lipase.

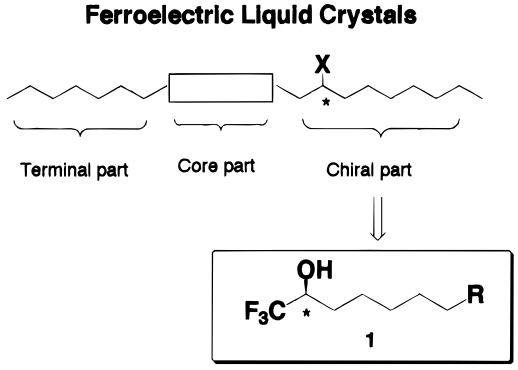

Figure 1. Model structure of ferroelectric liquid crystals.[1c]

Results and Discussion

The racemic 1,1,1-trifluoroalkanols were prepared as shown in Scheme 1. Initially, we prepared trifluoromethyl ketones **2** by a known method.[2d] The substitution reaction of the magnesium bromide salt of trifluoroacetic acid (TFA) with a Grignard reagent was attempted; however, the reaction provided **2** in poor chemical yield (20−30%), and also required an excess amount of the reagent. We found that the one-pot procedure described in Scheme 1 was superior to this method for synthesizing trifluoromethyl ketones. TFA was first converted to the corresponding lithium salt by hydrolysis with lithium hydroxide.[4] The salt was thoroughly dried under reduced pressure prior to the next reaction and then treated with 1 equiv of the Grignard reagent to produce the desired ketones **2**. Ketones **2** were immediately subjected to reduction with sodium borohydride ($NaBH_4$) without purification, because a significant loss of material, due to the volatility of **2**, was observed during the purification process using silica gel flash column chromatography. After the reduction of **2** with $NaBH_4$, distillation under reduced pressure provided the corresponding alcohol

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(1) (a) Clark, N. A.; Lagerwal, S. T. *Appl. Phys. Lett.* **1980**, *36*, 899. (b) Skarp, K.; Handschy, M. A. *Mol. Cryst. Liq. Cryst.* **1988**, *165*, 439. (c) Nohira, H. *J. Synth. Org. Chem., Jpn.* **1991**, *49*, 467 and references cited therein.

(2) (a) Tain Lin. J.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211. (b) Kitazume, T.; Ishikawa, N. *Chem. Lett.* **1983**, 237. (c) Hamada, H.; Imura, M.; Okano, T. *J. Biotechnology* **1994**, *32*, 89. (d) Ishizuka, T.; Miura, H.; Nohira, H. *Nippon Kagaku Kaishi* **1990**, 1171.

(3) Transesterification-based enzymatic resolution of secondary alcohols is now widely regarded as one of the best methods of choice for the synthesis of an enantiomer of an alcohol with high enantiomeric purity. For reviews see: (a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071. (b) Faber, K.; Riva, S. *Synthesis* **1992**, 895.

(4) The lithium salt of TFA could be kept at room temperature for several months, though it was a deliquescent compound.

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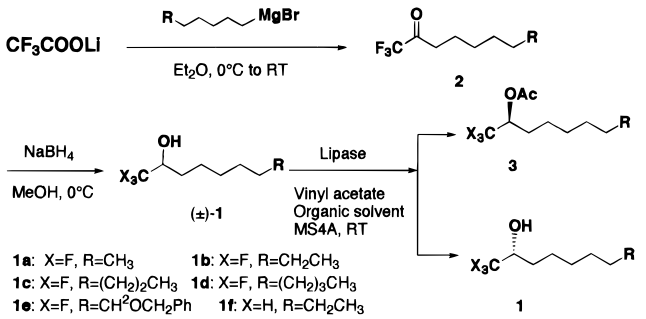
Scheme 1



(±)-**1** in 60−80% overall yield. Five types of (trifluoromethyl)alkanols, **1a**−**e**, were thus successfully obtained using these procedures from TFA.

Initially several kinds of lipases were tested using 1,1,1-trifluoro-2-nonanol (**1b**) as the model substrate to find a lipase that ensured high enantioselection. The reaction was performed using the following procedure: To a suspension of (±)-**1b** in organic medium was added the lipase (50 wt % of the alcohol), and the mixture was then stirred at room temperature. Progress of the reaction was monitored by GC analysis, and the reaction was stopped when the peak of the produced acetate and the unreacted alcohol reached the same intensity. Purification was carried out using silica gel flash column chromatography. Optical purity of the produced acetate **3b** and the remaining alcohol **1b** was determined as the acetate by capillary GC analysis using the chiral phase of Chiraldex G-Ta. To identify the absolute configuration of the produced acetate, authentic alcohol (*S*)-**1b**; $[\alpha]^{22}_{D}$ −19.0° (*c* 1.0, $CHCl_3$), 75% ee, was derived from commercial (*S*)-(trifluoromethyl)oxirane (75% ee). After comparing the value of the optical rotation of alcohol **1b**, $[\alpha]^{18}_{D}$ +17.8° (*c* 1.01, $CHCl_3$), with the authentic sample, the configuration of the 2-position of **1b** remaining after acylation was assigned as *R*, and the acetate **3d** produced was therefore assigned as *S*. From the diastereomeric differences in retention time on GC analysis, the configuration was postulated. The results are summarized in Table 1.

Preliminary experiments involving the acetylation of **1b** (R = Et, X = F) showed that six types of lipases: lipase PS, lipase AY, LPL, CAL, lipase AK, and CCL catalyzed the acylation using vinyl acetate[5] as an acyl donor in hexane.[6]

Typical results are summarized in Table 1. In these reactions, lipases from *Pseudomonas* sp. (PS, AK) were not stereospecific to the acylation with 1,1,1-trifluoro-2-nonanol (**1b**) (entries 1 and 3), though they catalyzed the acylation of 2-nonanol (**1f**) with moderate enantioselectivity (entries 2 and 5). Lipase from *Candida rugosa* (AY), from *Candida cylindracea* (CCL), and from *Candida antarctica* (CAL) were more promising than the other tested enzymes (entries 7, 9, and 11), providing ester **3b** with extremely high optical purity. As seen in Table 1, CAL has the highest acylation efficiency of **1b** among all tested enzymes. It also catalyzed the acylation with excellent enantioselectivity toward both **1b** and **1f** (entries 11 and 12), though CCL and AY acylated **1f** with poor enantioselectivity (entries 8 and 10). It is particularly interesting that CAL displayed completely the opposite enantioselectivity to lipases AY and CCL, though all three of these enzymes are obtained from *Candida* species. A moderate effect on optical purity was observed when the organic solvent was changed (entries 11, 13−17).[7] Obviously, hexane is the best solvent system in which to obtain the optically pure alcohol **1b** and acetate **3b** based on a comparison of the reaction time and *E* value (entry 11).[8]

The enantiomer favoritism of these enzymes is summarized in Figure 2. The alcohol pair (*S*)-**1b** and (*R*)-**1f**, or (*R*)-**1b** and (*S*)-**1f**, have the same geometry in the chiral center, though they are assigned to the opposite configuration due to the sequence rule. As can be seen in the figure, CAL catalyzed the acylation of alcohols **1b** and **1f** with the same enantiomer favoritism. CCL and AY also displayed the same enantiomer favoritism during the acylation of alcohols **1b** and **1f**. On the contrary, the opposite enantiomer favoritism was observed during the acylation of these substrates by lipases PS and AK, though the selectivity was not an efficient one. It is interesting that influenced favoritism in the geometry of **1b** and **1f** was observed in the reaction of lipases from *Pseudomonas* species (PS and AK), whereas it was not observed in the reaction of lipases from *Candida* species (AY, CAL, and CCL). The lipase-catalyzed acylation has been reported to proceed through a ping-pong mechanism.[9] Lively discussions have taken place about the molecular structure of the active site of the lipase during the hydrolysis of esters.[10] On the other hand, there has been no reputable theory offered for the mechanism of enantiomer favoritism in the lipase-catalyzed acylation, though two "pockets" of different sizes are generally assigned for the active domain of a lipase in order to explain the substrate selectivity and enantioselectivity.[7c,10,11] It is reported that *Pseudomonas* lipases all have similar sequences.[12] This fact may indicate the presence of a special functional group, which is sensitive to the electron rich trifluoromethyl group, such as the hydroxyl group of the serine part, at the medium-sized pocket or the large-sized pocket close to the active center of the enzymes of the *Pseudomonas* species.[13] Enzymes from *Candida* species, on the other hand, seem to lack such a functional group. Results of the present reaction seem to offer a very interesting point from which to consider the molecular structure of these enzymes.

(5) Vinyl acetate was found better as acyl donor than vinyl propionate in enantioselectivity.

(6) List of lipases tested: Lipase PS (*Pseudomonas cepacia*), LPL (*Pseudomonas aeruginosa*), Lipase AK (*Pseudomonas* sp.), CAL (*Candida antarctica*), Lipase AY (*Candida rugosa*), CCL (*Candida rugosa*), Immobilized Lipase from *Pseudomonas fluorescence*, Lipase CES (*Pseudomonas* sp.) PPL (Porcine pancreas), PLE (Pig liver), Lipozyme (*Mucor miehei*), Lipase L (*Candida lipolytica*), Lipase A (*Aspergillus niger*), Lipase GC (*Geotrichum candidum*), Protease A, Lipase F (*Rizopus javanicus*), Lipase R (*Penicillium roqueforti*), Lipase N (*Rhizopus niveus*), Lipase CE (*Humicola lanuginosa*), Protease S, Lipase M (*Mucor javanicus*), Protease P, Lipase G (*Penicillium* sp.), and Lipase D (*Rhizopus delemar*).

(7) Examples, see: (a) Sakurai, T.; Margolin, A. L.; Russell, A. J.; Klivanov, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 7236. (b) Parida, S.; Dordick, J. S. *Ibid.* **1991**, *113*, 2253. (c) Parida, S.; Dordick, J. S. *J. Org. Chem.* **1993**, *58*, 3238. (d) Kamat, S. *Biotechnol. Bioengin.* **1992**, *40*, 158. (e) Arroyo, M.; Sinisterra, J. V. *J. Org. Chem.* **1994**, *59*, 4410.

(8) Chen, C.-S.; Fujimoto, Y.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *112*, 7294.

(9) Mitsuda, S.; Nabeshima, S. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 151.

(10) For a recent example see: Cygler, M.; Grochulski, P.; Kazlauskas, R. J.; Schrag, J. D.; Bouthillier, F.; Rubin, B.; Serreqi, A. N.; Gupta, A. K. *J. Am. Chem. Soc.* **1994**, *116*, 3180. References cited therein.

(11) (a) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656. (b) Kim, M. J.; Cho, H. *J. Chem. Soc., Chem. Commun.* **1992**, 1411.

(12) Gilbert, E. J. *Enzyme Microb. Technol.* **1993**, *15*, 634.

(13) Nakamura, K.; Kawasaki, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3053.

Table 1. Enzymatic Resolution of 1,1,1-Trifluoro-2-alkanol 1 through Lipase-Catalyzed Esterification Vinyl Acetate as an Acyl Donor[a]

entry	substrate	enzyme	solvent	time (h)	% conv	% ee of **3** (config)	*E* value[b]
1	**1b** (R = Et, X = F)	PS	hexane	6	27	17 (S)	2
2	**1f** (R = Et, X = H)	PS	hexane	6	20	83 (S)	13
3	**1b** (R = Et, X = F)	AK	hexane	6	27	36 (S)	2
4	**1f** (R = Et, X = H)	AK	hexane	6	39	76 (S)	12
5	**1b** (R = Et, X = F)	LPL	hexane	6	45	99 (S)	15
6	**1f** (R = Et, X = H)	LPL	hexane	6	10	37 (R)	2
7	**1b** (R = Et, X = F)	CCL	hexane	6	9	99 (R)	322
8	**1f** (R = Et, X = H)	CCL	hexane	6	20	37 (S)	2
9	**1b** (R = Et, X = F)	AY	hexane	6	14	99 (R)	255
10	**1f** (R = Et, X = H)	AY	hexane	6	37	24 (S)	2
11	**1b** (R = Et, X = F)	CAL	hexane	6	28	98 (S)	118
12	**1f** (R = Et, X = H)	CAL	hexane	6	36	99 (R)	350
13	**1b** (R = Et, X = F)	CAL	iPr_2O	240	26	>99 (S)	>280
14	**1b** (R = Et, X = F)	CAL	THF	240	0	0	–
15	**1b** (R = Et, X = F)	CAL	Et_2O	240	31	96 (S)	75
16	**1b** (R = Et, X = F)	CAL	$CHCl_3$	240	9	>99 (S)	>220
17	**1b** (R = Et, X = F)	CAL	CH_3CN	240	22	98 (S)	130

[a] Substrate **1** (1 mmol), vinyl acetate (1.5 equiv), solvent (5 mL), enzyme (50 wt %), reaction temperature 35 °C. [b] Calculated by the acylated conversion and % ee of the product, see reference 8. $E = \ln[(1 - c)(1 - ee\mathbf{3})]/\ln[(1 - c)(1 + ee\mathbf{3})]$, where $c = ee\mathbf{3}/(ee\mathbf{3} + ee\mathbf{1})$.

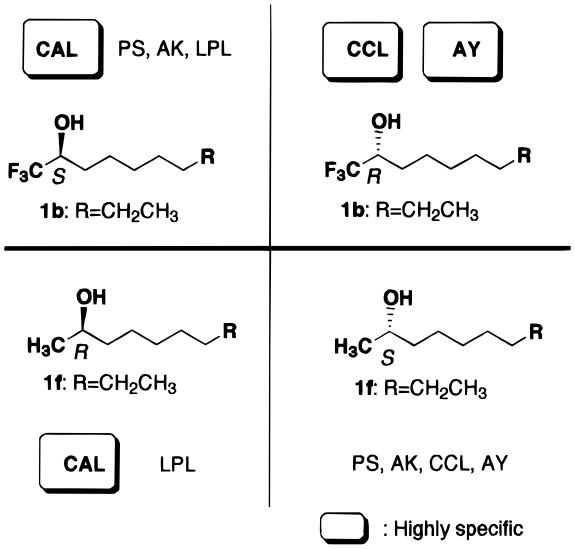


Figure 2. Map of favorite substrates of six types of lipases.

Table 2. Optical Resolution of 1,1,1-Trifluoro-2-alkanols 1 through *Candida antarctica* Lipase-Catalyzed Esterification[a]

entry	substrate	time (days)	% conv	% ee of **1**	% ee of **3** (config)	*E*
1	**1a** (R = Me)	7	25	33 (R)	>99 (S)	>274
2	**1b** (R = Et)	8	35	52 (R)	96.6 (S)	97
3	**1c** (R = Pr)	6	25	33 (R)	>99 (S)	>274
4	**1d** (R = Bu)	11	32	12 (R)	>99 (S)	>317
5	**1e** (R = CH_2OBn)	6	14	25 (R)	>99 (S)	>253

[a] Reaction was carried out under the following conditions: substrate **1** (1 g), vinyl acetate (1.5 equiv), hexane (5 mL), enzyme (0.1 g), molecular sieves 4 Å (0.5 g), reaction temperature 18−20 °C.

The optical resolution of various types of 1,1,1-trifluoro-2-alkanols using CAL are summarized in Table 2. Although all entries of the reaction proceeded slowly, CAL catalyzed the acylation of all compounds tested with perfect enantioselectivity, affording optically pure **3**. Further prolongation of the reaction significantly reduced the total amounts of product and substrate recovered because of the high volatility of the product, hence the reaction was stopped at the levels listed in the table. The (trans)esterification reaction actually involves the reaction of an alcohol with an acyl enzyme. Although we tried to increase the reaction rate by applying several acyl donors such as vinyl butyrate, vinyl chloroacetate, or isopropenyl acetate, no acceleration of the esterification was observed. The concentration of vinyl acetate also did not affect the reaction rate. Because the reaction rate was not influenced by the nature of the acyl donor or concentration of the acyl donor, the slow speed of the esterification seemed to depend on the low nucleophilicity of the trifluoromethyl alkanols. We also tested the CAL-catalyzed hydrolysis of the corresponding acetate (±)-**3d**. The present method was superior to the hydrolysis method for two reasons, though the hydrolysis reaction proceeded smoothly. The first is that we could not obtain the alcohols in an optically pure form by the hydrolysis method. This was probably due to the ease of hydrolysis of the acetates of the trifluoromethyl alkanols under the reaction conditions. Secondly, the total amount of product and substrate recovered were worth more than that of the (trans)esterification method. Trifluoromethyl alkanols are very volatile compounds. The simplicity of the procedure is essential for obtaining products in good yield during the reaction of such volatile compounds.

It should be emphasized that the present lipase resolution is the only method for preparing **1** in the *optically pure state*.[14] It is of particular importance that compound **1e** was obtained in the optically pure state. Because **1e** possesses a benzyloxy group at the terminal position, this compound is converted to various types of 1,1,1-trifluoro-2-alkanols. The lipase-catalyzed reaction in organic media can be used in large scale preparations, and the present method offers a valuable technique for preparing optically pure trifluoro-2-alkanol. Key compounds for making ferroelectric liquid crystals are thus easily obtained.

Experimental Section

Instrument and Materials. Reagents and solvents were purchased from a common commercial source and were used as received following purification by distillation from appropriate drying agents. Boiling points are uncorrected. Reactions requiring anhydrous conditions were run under an atmosphere

(14) Preparation of optically active (trifluoromethyl)oxirane was reported recently through enantioselective reduction of 1,1,1-trifluoro-3-chloro-2-propanone by chlorodisiopinocamphenylborane. Various types of 1,1,1-trifluoro-2-alkanols were derived from the oxirane, though the optical purity was, at best, 96% ee: Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org. Chem.* **1995**, *60*, 41.

of dry argon. Silica gel (Wako gel C-300) was used for column chromatography, and TLC analyses were done on Merck 60 F_{254} silica gel plates and Wako gel B5F. Chemical shifts are expressed in δ value (ppm) downfield from tetramethylsilane (TMS) in $CDCl_3$ as an internal reference. ^{19}F NMR spectra were reported in ppm downfield from C_6F_6 as an internal reference.

(±)-1,1,1-Trifluoro-2-undecanol (1d). To an ether (Et_2O) (83 mL) solution of TFA (82.8 mmol) was carefully added lithium hydroxide (82.8 mmol) at 0 °C, and the mixture was evaporated to dryness after neutralization was completed. The residue was thoroughly dried under reduced pressure at room temperature overnight and then diluted with 50 mL of Et_2O. To this solution was added a Et_2O (100 mL) solution of nonylmagnesium bromide (100 mmol) at 0 °C, and the mixture was allowed to warm to rt with stirring for 14 h. The reaction was quenched by addition of 2 M HCl and extracted with ether. The combined organic layers were dried over $MgSO_4$ and evaporated to give **2d** (22.5 g) as a colorless oil. To a methanol (100 mL) solution of **2d** was added $NaBH_4$ (3.783 g, 100 mmol) in several portions at 0 °C. After being stirred for 2 h at 0 °C, solvent was evaporated off. Purification by silica gel flash column chromatography (hexane:ethyl acetate = 10:1) gave **1d** (12.2 g, 53.8 mmol) in 65% yield: bp 65 °C/4 Torr (Kugelrohr); R_f 0.38 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.88 (3H, t, J = 6.4 Hz) 1.15−1.43 (14H, m) 1.51−1.76 (2H, m) 2.57 (1H, OH, t, J = 4.2 Hz) 3.78−4.00 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.04, 22.67, 24.91, 29.01, 29.28, 29.40, 29.45, 29.45, 29.50, 31.87, 70.52 (q, J_{C-F} = 30.8 Hz) 125.21 (q, J_{C-F} = 280.1 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 81.77 (d, J = 6.2 Hz); IR (neat) 3350, 2970, 2860, 1460, 1270, 1170, and 1140 cm^{-1}.

1,1,1-Trifluoro-2-alkanols 1a, **1b**, **1c**, and **1e** were prepared with a yield of 60−80% by the above procedure.

(±)-1,1,1-Trifluoro-2-octanol (1a): bp 45 °C/4 Torr (Kugelrohr); R_f 0.38 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.89 (3H, t, J = 6.5 Hz) 1.12−1.48 (8H, m) 1.53−1.72 (2H, m) 2.38 (1H, OH, t, J = 6.4 Hz) 3.79−4.00 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.97, 22.52, 24.85, 28.85, 29.54, 31.56, 70.52 (q, J_{C-F} = 30.7 Hz) 125.21 (q, J_{C-F} = 280.3 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 81.73 (d, J = 6.6 Hz); IR (neat) 3350, 2925, 2850, 1450, 1270, 1170, and 1140 cm^{-1}.

(±)-1,1,1-Trifluoro-2-nonanol (1b): bp 52 °C/4 Torr (Kugelrohr); R_f 0.41 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.88 (3H, t, J = 6.5 Hz) 1.16−1.43 (10H, m) 1.51−1.70 (2H, m) 2.52 (1H, OH, brs) 3.78−3.98 (1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.00, 22.59, 24.90, 29.15, 29.33, 29.56, 31.72, 70.50 (q, J_{C-F} = 30.8 Hz) 125.21 (q, J_{C-F} = 281.8 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 81.77 (d, J = 6.6 Hz); IR (neat) 3350, 2940, 2850, 1460, 1280, 1170, and 1140 cm^{-1}.

(±)-1,1,1-Trifluoro-2-decanol (1c):[2a] bp 60 °C/5 Torr (Kugelrohr); R_f 0.37 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.88 (3H, t, J = 7.0 Hz) 1.16−1.45 (12H, m) 1.51−1.80 (2H, m) 2.29 (1H, OH, brs) 3.78−3.99(1H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.06, 22.64, 24.90, 29.19, 29.34, 29.56, 31.81, 70.54 (q, J_{C-F} = 30.8 Hz) 125.21 (q, J_{C-F} = 280.2 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 81.68 (d, J = 6.5 Hz); IR (neat) 3350, 2900, 2850, 1460, 1270, 1170, and 1130 cm^{-1}.

(±)-1,1,1-Trifluoro-8-(benzyloxy)-2-octanol (1e): bp 160 °C/5 Torr (Kugelrohr); R_f 0.12 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 1.20−1.46 (4H, m) 1.46−1.75 (4H, m) 2.53 (1H, brs, OH) 3.47 (2H, t, J = 6.5 Hz) 3.81 (1H, dt, J = 3.4 Hz, 16.2 Hz) 4.50 (2H, s), 7.20−7.40 (5H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 24.78, 25.89, 28.92, 29.46, 29.58, 70.34 (q, J_{C-F} = 30.7 Hz), 72.84, 125.2 (q, J_{C-F} = 282.0 Hz), 127.54, 127.66, 128.03, 128.34, 138.42; ^{19}F NMR (188 MHz, δ, $CDCl_3$) 81.77 (d, J = 6.4 Hz); IR (neat) 3375, 3000, 1450, 1270, 1140 cm^{-1}.

Lipase-Catalyzed Acylations. Preparation of (*S*)-1,1,1-Trifluoroundecan-2-yl Acetate (3d). Alcohol (±)-**1d** (3.432 g, 15 mmol), vinyl acetate (12.9 g, 150 mmol), lipase CAL (787 mg, Novo Nordisk Co., Ltd.,) in hexane (150 mL), and 4 Å molecular sieves (3.75 g) were stirred at room temperature for 11 days. The mixture was filtered through a glass sintered filter with a Celite pad, and the filtrate was chromatographed on silica gel flash column, hexane/ethyl acetate = 100:1 to 10:1, and gave **3d** ($[\alpha]^{17}_D$ +5.6° (*c* 1.09, Et_2O); 1.29 g, 4.80 mmol; 32%) and unreacted **1d** ($[\alpha]^{19}_D$ +8.16° (*c* 0.80, Et_2O); 2.05 g, 9.06 mmol; 60%), respectively. The optical purity of the produced acetate **3d** was found to be >99% ee (*S*) by GPC analysis using a capillary column on chiral phase. Optical purity of the remaining alcohol **1d** was measured by GPC analysis to be 46.7% ee as the corresponding acetate **3d**.

Using the same procedure, acetates **3a**, **3b**, **3c**, and **3e** were prepared. Retention time on GC analyses and $[\alpha]_D$ values of the remaining alcohols are summarized as follows: t_R of **3**. Chiraldex G-Ta, ∅ 0.25 mm × 20 m, carrier gas: He 40 mL/min, temp: 100 °C, inlet pressure: 1.35 kg/cm^2, amount 400 ng, detection: FID; **3a**: $t_{R(R)}$ = 1.6 min, $t_{R(S)}$ = 1.9 min; **3b**: $t_{R(R)}$ = 1.9 min, $t_{R(S)}$ = 2.5 min; **3c**: $t_{R(R)}$ = 2.5 min, $t_{R(S)}$ = 2.9 min; **3d**: $t_{R(R)}$ = 7.5 min, $t_{R(S)}$ = 9.5 min; **3e**: $t_{R(R)}$ = 19.1 min, $t_{R(S)}$ = 20.0 min (oven temperature was 150 °C). $[\alpha]_D$ values of alcohols **1a**−**e**; (*R*)-**1a**: $[\alpha]^{19}_D$ +8.0° (*c* 0.96, Et_2O), 33% ee; (*R*)-**1b**: $[\alpha]^{21}_D$ +17.8° (*c* 1.23, Et_2O), 52% ee; (*R*)-**1c**: $[\alpha]^{19}_D$ +8.2° (*c* 0.97, Et_2O), 34% ee; (*R*)-**1d**: $[\alpha]^{17}_D$ +11.3° (*c* 1.53, Et_2O), 47% ee; (*R*)-**1e** : $[\alpha]^{19}_D$ −0.11° (*c* 1.06, MeOH), 25% ee.

(*S*)-1,1,1-Trifluoroundecan-2-yl acetate (3d): $[\alpha]^{17}_D$ +5.6° (*c* 1.46, Et_2O), >99% ee; bp 65 °C/4 Torr (Kugelrohr); R_f 0.60 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.87 (3H, t, J = 6.3 Hz) 1.17−1.41 (14H, m) 1.63−1.80 (2H, m) 2.13 (3H, s) 5.28 (1H, dt, J = 20.1 Hz, 6.8 Hz); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.01, 20.37, 22.64, 24.52, 27.77, 29.05, 29.27, 29.41, 31.83, 69.54 (q, J_{C-F} = 32.0 Hz) 123.84 (q, J_{C-F} = 280.6 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 84.57 (d, J = 6.8 Hz); IR (neat) 2950, 2850, 1760(CO), 1460, 1220, 1020 cm^{-1}. Anal. Calcd for $C_{13}H_{23}O_2F_3$: C, 58.19; H, 8.64%. Found: C, 58.19; H, 8.77%.

(*S*)-1,1,1-Trifluorooctan-2-yl acetate (3a): $[\alpha]^{18}_D$ +7.2° (*c* 0.9, Et_2O), >99% ee; bp 45 °C/4 Torr (Kugelrohr); R_f 0.48 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.87 (3H, t, J = 6.6 Hz) 1.14−1.43 (8H, m) 1.63−1.81 (2H, m) 2.14 (3H, s) 5.28 (1H, dt, J = 20.1 Hz, 6.8 Hz); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 13.96, 20.46, 22.47, 24.48, 27.76, 28.72, 31.45, 69.56 (q, J_{C-F} = 31.7 Hz) 123.84 (q, J_{C-F} = 278.9 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 84.48 (d, J = 6.4 Hz); IR (neat) 2950, 2850, 1755(CO), 1370, 1210, 1070 cm^{-1}. Anal. Calcd for $C_{10}H_{17}O_2F_3$: C, 53.09; H, 7.57%. Found: C, 52.85; H, 7.65%.

(*S*)-1,1,1-Trifluorononan-2-yl acetate (3b): $[\alpha]^{18}_D$ +3.69° (*c* 1.42, Et_2O), 96.6% ee; bp 55 °C/4 Torr (Kugelrohr); R_f 0.57 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.85 (3H, t, J = 6.4 Hz) 1.12−1.40 (10H, m) 1.60−1.79 (2H, m) 2.12 (3H, s) 5.26 (1H, dt, J = 20.2 Hz, 6.7 Hz); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.02, 20.48, 22.57, 24.53, 27.77, 28.94, 29.01, 31.65, 69.56 (q, J_{C-F} = 31.7 Hz) 123.84 (q, J_{C-F} = 276.3 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 84.48 (d, J = 6.6 Hz); IR (neat) 2910, 2850, 1775(CO), 1460, 1370, 1210, 1080 cm^{-1}. Anal. Calcd for $C_{11}H_{19}O_2F_3$: C, 54.99; H, 7.97%. Found: C, 55.35; H, 7.98%.

(*S*)-1,1,1-Trifluorodecan-2-yl acetate (3c): $[\alpha]^{19}_D$ +3.4° (*c* 1.20, Et_2O), >99% ee; bp 110 °C/42 Torr (Kugelrohr); R_f 0.54 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 0.87 (3H, t, J = 6.4 Hz) 1.17−1.42 (12H, m) 1.62−1.83 (2H, m) 2.14 (3H, s) 5.28 (1H, dt, J = 20.1 Hz, 6.8 Hz); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 14.04, 20.46, 22.61, 24.51, 27.74, 29.04, 29.10, 29.22, 31.76, 69.55 (q, J_{C-F} = 31.9 Hz) 123.83 (q, J_{C-F} = 278.5 Hz); ^{19}F NMR (188 MHz, δ, $CDCl_3$) 84.48 (d, J = 6.6 Hz); IR (neat) 2920, 2850, 1760(CO), 1460, 1280, 1220, 1080 cm^{-1}. Anal. Calcd for $C_{12}H_{21}O_2F_3$: C, 56.68; H, 8.32%. Found: C, 56.54; H, 8.28%.

(*S*)-1,1,1-Trifluoro-8-(benzyloxy)octan-2-yl acetate (3e): $[\alpha]^{26}_D$ +2.7° (*c* 1.25, MeOH), >99% ee; bp 135 °C/2 Torr (Kugelrohr); R_f 0.36 (hexane/ethyl acetate = 10:1); ^1H NMR (200 MHz, δ, $CDCl_3$) 1.15−1.42 (6H, m) 1.42−1.75 (4H, m) 2.05 (3H, s) 3.38 (2H, t, J = 6.5 Hz) 4.42 (2H, s) 5.11−5.31 (1H, m) 7.12−7.35 (5H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) 20.41, 24.44, 25.85, 27.70, 28.83, 29.53, 69.30 (q, J_{C-F} = 32.0 Hz), 70.18, 72.85, 123.82 (q, J_{C-F} = 278.1 Hz), 127.45, 127.57, 128.30, 138.57, 169.40; ^{19}F NMR (188 MHz, δ, $CDCl_3$) 84.56

(d, J = 6.8 Hz); IR (neat) 3375, 3000, 1450, 1270, 1140 cm^{-1}. Anal. Calcd for $C_{17}H_{23}O_3F_3$: C, 61.43; H, 6.98%. Found: C, 61.45; H, 6.97%.

Preparation of (*S*)-1,1,1-Trifluoro-2-decanol ((*S*)-1c). To a solution of CuI (114 mg, 0.6 mmol) in a mixed solvent of THF (13 mL) and dimethyl sulfide (1.0 mL) was added a THF (2 mL) solution of (*S*)-1,1,1-trifluoropropene oxide (336 mg, 3.0 mmol) and a THF (4.4 mL) solution of hexylmagnesium bromide (3.6 mmol) at −15 °C under argon, and then the mixture was stirred for 7 h at the same temperature. The reaction was quenched by addition of 2 M HCl and was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated to dryness. Purification using Kugelrohr distillation under reduced pressure gave (*S*)-**1c** (362 mg) as a colorless liquid in 61% yield: $[\alpha]^{22}_D$ −19.0° (*c* 1.0, $CHCl_3$), 75.4% ee.

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Supporting Information Available: IR, ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectra for **1b**−**e** and **3a**−**e** (36 pages). These materials are contained in libraries on microfiche, immediately follow 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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