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Highly Enantioselective Synthesis of Long Chain Alkyl Trifluoromethyl Carbinols and β-Thiotrifluoromethyl Carbinols Through Lipases

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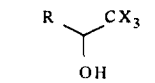
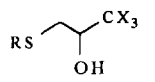
Abstract: Among a variety of lipases tested, *Candida antarctica* lipase has been found to promote the enantioselective acylation of long chain alkyl trifluoromethyl carbinols **1a-4a** and β-thiotrifluoromethyl carbinols **5a-7a**, producing both *R* and *S* enantiomeric alcohols in good to excellent chemical yield and enantioselectivity. In all cases the lipase preferentially acylates the *S* enantiomer, irrespective the presence or not of a sulfur atom in β position to the hydroxyl group. When the reaction was carried out on the non-fluorinated substrates **1c-2c**, the process occurred much faster and with higher e.e. of the less reacting enantiomer than when conducted on the fluorinated substrates. Copyright © 1996 Elsevier Science Ltd

Research on bioactive fluorinated compounds has received much attention in the last few years because of the unique physical and biological features induced by fluorine[1]. In this regard, trifluoromethyl carbinols have been found applications as renin inhibitors[2], as synthons in the construction of ferroelectric crystals[3] or as intermediates in the synthesis of polyfunctional bioactive molecules[4]. They are also precursors of trifluoromethyl ketones, which are potent inhibitors of a variety of serine esterases[5].

Utilization of biocatalysts in preparative organic chemistry has been receiving increasing importance[6]. In the course of our ongoing program directed to the development of inhibitors of antennal esterases of the Egyptian armyworm *Spodoptera littoralis*[7], we have recently described the lipase-catalysed enantioselective synthesis of naphthyl trifluoromethyl carbinols as probes to determine the potential chiral recognition of the substrate by the antennal esterase of the insect[8]. Along this line, we now want to report on the enantioselective synthesis of long chain alkyl trifluoromethyl carbinols **1a-4a** and β-thiotrifluoromethyl carbinols **5a-7a**, through acylation of the corresponding racemic alcohols by lipases. A very recent paper of Nakamura and coworkers[9] prompted us to disclose our own results on the synthesis of these biologically relevant compounds. In our study we have included some representative examples of the sulfur-containing derivatives, since it has been shown that two racemic alcohols, i.e. 3-octylthio-1,1,1-trifluoropropan-2-ol and 3-octylthio-1,1,1-trifluorobutan-2-ol, have also displayed potent activity as inhibitors of JH esterase[10]. The effect of the presence of fluorine atoms on the extent and enantioselectivity of the acylation reaction was also investigated by running the biotransformation on the non-fluorinated parent compounds **1c-2c** (Figure 1).



$R = C_8H_{17}$ X = F: **1a**
$R = C_8H_{17}$ X = H: **1c**
$R = C_{12}H_{25}$ X = F: **2a**
$R = C_{12}H_{25}$ X = H: **2c**
$R = C_{13}H_{27}$ X = F: **3a**
$R = C_{16}H_{31}$ X = F: **4a**



$R = C_6H_{13}$ X = F: **5a**
$R = C_8H_{17}$ X = F: **6a**
$R = C_{10}H_{21}$ X = F: **7a**

Figure 1

Besides Nakamura's work[9] only one report by Kitazume[11] has been found in the literature on the synthesis of non-racemic chiral trifluoromethyl carbinols. The procedure involved hydrolysis of the corresponding racemic acetates with lipase MY. In our case, we initially atempted hydrolysis of the acetate of **3a** using lipase PS and acetone/phosphate buffer as solvent[12]. However, after 8 h reaction (54% conversion) disappointing e.e. values of 7 and 6% of both enantiomeric alcohols (*R*) and (*S*)-**3a** were obtained. Likewise, transesterification of **2a** using porcine pancreatic lipase (PPL) in ether and trifluoroethyl laurate[13] also failed, although the same process on **1c** afforded, in contrast, good e.e. values of alcohols (*S*)-**1c** and (*R*)-**1c** (78% and >95%, respectively, E=133), pointing in the former case to a clear detrimental effect exerted by fluorine on the chiral recognition by the enzyme.

A preliminary screening of a number of commercially available lipases, i.e. *Candida cylindracea* (AY), *Aspergillus niger* (AP6), and *Pseudomonas cepacia* (PS) from Amano, *Candida cylindracea* (CCL) and porcine pancreatic lipase (PPL) from Sigma, *Aspergillus niger*, *Rhizopus arrhizus* and *Pseudomonas fluorescens* lipase (PFL) from Fluka, *Chromobacterium viscosum* from Biocatalysts, and *Candida antarctica* lipase (CAL) from Novo Nordisk, showed that only lipase PS, PFL and CAL successfully acylated the model substrate **2a** in a reasonable time (25-45 h for 40-56% conversion). Because of the easier availability to us of lipase PS and in order to optimize the enantioselectivity of the acylation reaction, we carried out the process under different solvents using vinyl acetate as acylating agent. In contrast to most literature reports wherein only one particular enantiomer is commonly pursued, we directed our efforts to obtain the highest e.e. of *both* enantiomeric alcohols in one single transformation. In most solvents the e.e. of (*R*) and (*S*)-**2a** were relatively poor and only in CH_2Cl_2 or $CHCl_3$ moderate e.e. values were obtained (60-76%) (Table 1). Here again and confirming the above results on the effect of the fluorine atom, acylation of the non-fluorinated compounds **1c** and **2c** with lipase PS in hexane required shorter conversion times and afforded better enantiomeric discrimination than on fluorinated derivative **2a**. Use of PFL in CH_2Cl_2 also afforded promising results of the *S* enantiomer but the time required for only 28% conversion (11 days) was unsuitable for further optimization.

We were delighted to find that utilization of CAL yielded good to excellent e.e. of *both* alcohols (*R*)-**2a** and (*S*)-**2a** in a reasonable time. The reaction was applied to other aliphatic long chain trifluoromethyl carbinols **1a-4a** to

study the effect of the chain length on the enantioselectivity of the process (Table 2). The reaction was monitored by GC analysis and stopped when ca. 50% transformation was achieved. After filtration, the non-reactive *R* alcohol was separated from the acetate and the ester hydrolysed under basic conditions to obtain

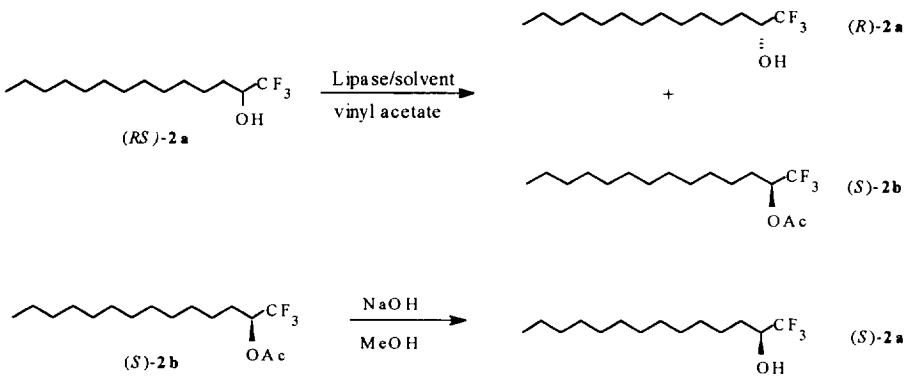


Figure 2

the preferentially recognised *S* enantiomer by the enzyme (Figure 2). Both alcohols were purified by column chromatography and their enantiomeric purity assessed by ^{19}F NMR analysis of the corresponding Mosher ester[14] and/or by GC chiral column of the free alcohol or GC capillary column of the diastereomeric Mosher ester. In the cases assayed, the three methods showed reliable results with only very small differences in the estimated e.e. values (±2-3%). Longer reaction times were required for substrates of longer chain, but even for **4a** (n=C_{16}) only a reasonable period of 62 h was needed for a 47% conversion. In all cases excellent e.e. values were obtained, particularly of the more reactive *S* enantiomer (Table 2). The non-fluorinated substrates **1c-2c** were also very efficiently discriminated by the enzyme in a very short time and, interestingly, the less reactive *S* enantiomers were obtained in higher e.e. than the more reactive *R* enantiomers. It should be noted the reverse absolute configuration of the non-fluorinated substrates because of the sequence rule. In a similar manner to what we observed on lipase PS[8], CAL active site appears to preferentially recognise the parent secondary alcohols over the corresponding fluorinated derivatives. Our results matched with the very recently report by Nakamura and coworkers[9], although their reaction conditions required longer reaction times (usually several days) to achieve a 25-35% conversion. The Japanese group, therefore, obtained excellent e.e. values but only of the reacting *S* enantiomer.

When we extended the reaction to β-thiotrifluoromethyl carbinols **5a-7a**, no apparent effect resulting from introduction of the sulfur atom in β position to the hydroxyl group was observed. Thus, similar good to excellent results in terms of chemical yield and enantioselectivity of both enantiomeric alcohols were attained and, again, the preferentially reacting enantiomer appeared to have the *S* configuration.

Table 1. Enantioselective acylation of alcohols (*R,S*)-**2a**, (*R,S*)-**1c** and (*R,S*)-**2c** catalysed by different lipases.

Lipase[a]	Solvent	Substrate	Time (h)	Conv.[b] (%)	Yield[c] alcohol	e.e.[d] (conf.)	Yield[c,e] alcohol	e.e.[d] (conf.)	E[f]
PS	Hexane	**2a**	25	56	43	38 (R)	35	30 (S)	3
PS	Hexane	**1c**	3.75	61	29.5	88 (S)	41	55 (R)	10
PPL[g]	EE[h]	**1c**	23	45	26	78 (S)	22	>95 (R)	133
PS	Hexane	**2c**	2.75	49	55	70 (S)	27.5	72 (R)	12
PS	THF	**2a**	330	20	77	14 (R)	15	56 (S)	4
PS	Benzene	**2a**	42	48	48	29 (R)	30	32 (S)	3
PS	Acetone	**2a**	286	54	45	42 (R)	35	36 (S)	3
PS	EE[h]	**2a**	122	55	44	44 (R)	39	36 (S)	3
PS	CH_2Cl_2	**2a**	91	44	52	60 (R)	44	76 (S)	13
PS	$CHCl_3$	**2a**	190	41	50	48 (R)	30	70 (S)	9
PS	CCl_4	**2a**	24	53	44	32 (R)	40	28 (S)	2
PS	VA[h]	**2a**	167	49	45	42 (R)	46	44 (S)	4
PS	Toluene	**2a**	165	39	57	28 (R)	35	44 (S)	3
PFL	Hexane	**2a**	25	39	52	22 (R)	45	35 (S)	2
PFL	CH_2Cl_2	**2a**	261	28	68	32 (R)	22	82 (S)	14
CAL	Hexane	**2a**	45	47	48	86 (R)	40	>95 (S)	131

[a]Substrate:lipase:vinyl acetate ratio was 1:2:10.
[b]Percentage of conversion was calculated from the e.e. values according to Sih et al. (Chen, Ch.-Sh.; Wu, Sh.-H.; Girdaukas, G.; Sih, Ch.J. *J. Am. Chem. Soc.* 1987, *109*, 2812).
[c]Yields refer to pure isolated products after column chromatography purification.
[d]Calculated by ^{19}F NMR analysis of the corresponding Mosher ester[14]. The absolute configuration of the alcohols was assigned in based to the specific rotation of (R)-1,1,1-trifluoro-2-decanol reported in the literature.[11a]
[e]Overall yield of alcohol derived from hydrolysis of the initially formed chiral acetate.
[f]Enantiomeric ratio (E) values were determined from the e.e. of the residual substrate and the extent of conversion (Chen, Ch.-Sh.; Fujimoto, Y.; Girdaukas, G.; Sih, Ch.J. *J. Am. Chem. Soc.* 1982, *104*, 7294).
[g]Trifluoroethyl laurate was used as acylating agent.
[h]EE = diethyl ether; VA = vinyl acetate.

Table 2. Enantioselective acylation of trifluoromethyl carbinols **1a-7a** and β-thiotrifluoromethyl carbinols **1c-2c** catalysed by *Candida antarctica*[a] lipase.

Substrate	Time (h)	Conv.[b] (%)	Yield[c] alcohol	e.e.[d] (conf.)	Yield[c,e] alcohol	e.e.[d] (conf.)	E[f]
1a	25	40	58	66[g] (R)	26	>95[g] (S)	197
2a	45	47	48	86 (R)	40	>95 (S)	131
3a	46	43	40	68 (R)	36	92 (S)	50
4a	62	47	31	84 (R)	32	>95 (S)	131
5a	77	41	45	68[h] (R)	32	>95[h] (S)	100
6a	23	45	50	80 (R)	33	>95 (S)	121
7a	24	42	48	70[h] (R)	40	>95[h] (S)	208
1c	0.75	52	42	>95[h] (S)	42	92[h] (R)	126
2c	3	53	40	>95 (S)	40	86 (R)	69

[a]In hexane at 37°C using vinyl acetate as acylating agent. The ratio substrate:lipase:vinyl acetate was 1:2:10.
[b]Percentage of conversion was calculated from the ee values according to Sih *et al.* (Chen, Ch.-Sh.; Wu, Sh.-H.; Girdaukas, G.; Sih, Ch.J. *J. Am. Chem. Soc.* 1987, *109*, 2812).
[c]Yields refer to pure isolated products after purification on column chromatography.
[d]Determined by ^{19}F NMR analysis of the corresponding Mosher ester[14].
[e]Overall yield of alcohol obtained by hydrolysis of the initially formed chiral acetate.
[f]Enantiomeric ratio (E) values were determined from the e.e. of the residual substrate and the extent of conversion (Chen, Ch.-Sh.; Fujimoto, Y.; Girdaukas, G.; Sih, Ch.J. *J. Am. Chem. Soc.* 1982, *104*, 7294).
[g]E.e. values of 63% (*R*)-**1a** and >98% (*S*)-**1a** were determined by GC on Cydex-B quiral column.
[h]Analysis by GC capillary column of the diastereomeric Mosher esters gave the following e.e. values: (*R*)-**5a**: 73%, (*S*)-**5a**: 98%; (*R*)-**7a**: 75%, (*S*)-**7a**: 98%; (*S*)-**1c**: ≥99%, (*R*)-**1c**: 96%.

In summary, we have shown that CAL is able to resolve racemic long chain trifluoromethyl carbinols in a very efficient manner, the more reacting enantiomers being obtained in almost enantiomerically pure state after hydrolysis of the corresponding acetates. The alcohols are now ready for biological assays.

Experimental

Elemental analyses were determined on Carlo Erba models 1106 and 1500. IR spectra were recorded on a Bomem MB-120 with Fourier transform instrument. [^1H] and [^{13}C]NMR spectra were obtained in $CDCl_3$ solutions on a Varian Unity 300 spectrometer, operating at 300 MHz for [^1H] and 75 MHz for [^{13}C]. The values are expressed in δ scale relative to internal Me_4Si. [^{19}F]NMR spectra were recorded on a Varian Unity 300 instrument at 282 MHz

and the values are reported in δ scale relative to trichlorofluoromethane as internal standard. Low resolution mass spectra were run on a HP 5995 mass spectrometer using a SPB-5 30m x 0,32μm ID fused silica capillary column. GC analyses were performed on Carlo Erba model 4130, equipped with a FID detector, using a crosslinked fused silica capillary column (5% phenylmethyl silicone) and hydrogen as carrier gas. In some cases determination of the enantiomeric excess was also determined by GC on Cydex-B 25m x 0.22 μm ID chiral fused silica capillary column or on the SPB capillary column for the diastereomeric Mosher esters. Optical rotations were measured on a Perkin Elmer 141 polarimeter.

Commercial analytical-grade reagents were obtained from commercial suppliers (Aldrich Chemie, Fluka Chemie, Carlo Erba) and were used directly without further purification. Anhydrous tetrahydrofuran and diethyl ether were prepared by drying with solid KOH followed by distillation from Na/benzophenone under N_2, methylene chloride by distillation from P_2O_5, and triethylamine by distillation from KOH.

Synthesis of alkyl trifluoromethyl carbinols 1a-4a. General procedure. The alkyl trifluoromethyl carbinols were obtained by reduction of the corresponding trifluoromethyl ketones, which were obtained as previously described[15]. In a previously flamed 2-neck round-bottomed flask was introduced the trifluoromethyl ketone (3.79 mmol) in 20 mL of absolute ethyl alcohol, then $NaBH_4$ (10 equiv.) was added and the mixture stirred at room temperature until no starting material left by GC analysis (generally 2-5 h). The solvent was removed under vacuum and the residue treated with H_2O and extracted with ether. The organic phase was washed with aqueous NH_4Cl soln. and brine, dried ($MgSO_4$) and the solvent evaporated off. The crude alcohol was purified by column chromatography on silica gel eluting with mixtures of hexane:ether to yield 89-96% of pure **1a-4a**.

(RS)-*n*-**Octyl trifluoromethyl carbinol**[11a] **1a**. IR: 3383, 2956, 2927, 1467, 1278, 1168 cm^{-1}. ^1H NMR δ: 3.91 (m, 1H, C*H*OH), 1.97 (d J=6.3 Hz, 1H, CHO*H*), 1.78-1.44 (c 2H, $CH_2CHOHCF_3$), 1.26 (b, 12H, $6CH_2$), 0.88 (t J=6.9 Hz, 3H, CH_3). ^{19}F NMR δ: -80.61 (d J=6.2 Hz, CF_3). ^{13}C NMR δ: 125.2 (q J=282 Hz, CF_3), 70.6 (q J=30.8 Hz, *C*HOH), 31.8, 29.6 (q J=1.7 Hz, $CH_2CHOHCF_3$), 29.3, 29.2 (2C), 24.9, 22.6, 14.1 (CH_3). MS m/z (%): 165 (9), 141 (18), 123 (20), 98 (22), 97 (21), 84 (24), 83 (47), 71 (21), 70 (90), 69 (40), 57 (73), 56 (100), 55 (74).

(RS)-*n*-Dodecyl trifluoromethyl carbinol 2a. IR: 3372, 2954, 2925, 1465, 1278, 1170 cm^{-1}. ^1H NMR δ: 3.91 (m, 1H, C*H*OH), 1.97 (d J=6.3 Hz, 1H, CHO*H*), 1.8-1.5 (c, 2H, $CH_2CHOHCF_3$), 1.26 (b, 20H, $10CH_2$), 0.88 (t J=6.3 Hz, 3H, CH_3). ^{19}F NMR δ: -80.62 (d J=7 Hz, CF_3). ^{13}C NMR δ: 125.2 (q J=282 Hz, CF_3), 70.6 (q J=30.8 Hz, *C*HOH), 31.9, 29.6-29.2, 29.5, 29.4, 29.3, 29.2, 24.9, 22.7, 14.1 (CH_3). MS m/z (%): 165 (4), 141 (12), 137 (11), 111 (17), 98 (12), 97 (26), 85 (21), 84 (23), 83 (29), 71 (41), 70 (39), 69 (36), 57 (100), 56 (43), 55 (45). Elemental Analysis: Calculated for $C_{14}H_{27}OF_3$: C, 62.66; H, 10.14; F, 21.24. Found: C, 62.69; H, 10.26; F, 21.33.

(RS)-*n*-Tridecyl trifluoromethyl carbinol 3a. IR: 3375, 3291, 2952, 2918, 1465, 1272, 1168 cm^{-1}. ^1H NMR δ: 3.90 (m, 1H, C*H*OH), 1.99 (d J=6.0 Hz, 1H, CHO*H*), 1.8-1.5 (c, 2H, $CH_2CHOHCF_3$), 1.26 (b, 22H, $11CH_2$), 0.88 (t J=6.9 Hz, 3H, CH_3). ^{19}F NMR δ: -80.61 (d J=6.8 Hz, CF_3). ^{13}C NMR δ: 123.4 (q J=282 Hz, CF_3), 70.6 (q J=30.8 Hz, *C*HOH), 31.9, 29.68, 29.65 (3C), 29.61, 29.5, 29.4, 29.36, 29.2, 24.9, 22.7, 14.1 (CH_3). MS m/z (%): 165 (5), 141 (11), 137 (19), 111 (15), 97 (23), 85 (23), 84 (18), 83 (25), 71 (43), 70 (28), 69 (30), 57 (100), 56 (35),

55 (52). Elemental Analysis: Calculated for $C_{15}H_{29}OF_3$: C, 63.80; H, 10.35; F, 20.18. Found: C, 63.85; H, 10.36; F, 20.22.

(RS)-*n*-Hexadecyl trifluoromethyl carbinol 4a. IR: 3372, 3295, 2949, 2918, 1463, 1271, 1178 cm^{-1}. ^1H NMR δ: 3.91 (m, 1H, C*H*OH), 2.0 (d J=6.3 Hz, 1H, CHO*H*), 1.8-1.5 (c, 2H, $CH_2CHOHCF_3$), 1.26 (b, 28H, $14CH_2$), 0.88 (t J=6.9 Hz, 3H, CH_3). ^{19}F NMR δ: -80.61 (d J=6.5 Hz, CF_3). ^{13}C NMR δ: 125.2 (q J=282 Hz, CF_3), 70.6 (q J=30.8 Hz, *C*HOH), 31.9, 29.7-29.6, 29.5, 29.39, 29.37, 29.2, 24.9, 22.7, 14.1 (CH_3). MS m/z (%): 169 (5), 165 (5), 111 (13), 97 (21), 85 (32), 84 (14), 83 (19), 71 (51), 70 (21), 69 (26), 57 (100), 56 (26), 55 (47). Elemental Analysis: Calculated for $C_{18}H_{35}OF_3$: C, 66.63; H, 10.87; F, 17.57. Found: C, 66.61; H, 10.86; F, 17.79.

Synthesis of alkylthio trifluoromethyl carbinols 5a-7a. General procedure. In a previously flamed round bottomed flask was introduced $LiAlH_4$ (0.275 g; 7.25 mmol), diethyl ether (50 ml) and the mixture cooled to 0°C. Then, the alkylthio trifluoromethyl ketone, prepared by alkylation of the corresponding thiol with 3-bromo-1,1,1-trifluoropropan-2-one[7b] (6.1 mmol referred to non-hydrated trifluoromethyl ketone), was added dropwise and allowed to react for 3 h at room temperature. The reaction mixture was quenched with water (0.67 ml), 15% NaOH soln. (0.67 ml) and again with water (2 ml). The mixture was magnetically stirred for 1 h, filtered off and the organic phase dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography on silica gel eluting with hexane:ether 9:1 affording the expected alkylthio trifluoromethyl carbinols **5a-7a** in 74-91% yield.

(RS)-*n*-Hexylthio trifluoromethyl carbinol 5a. IR: 3426, 2929, 2857, 1272, 1166, 1127, 1100 cm^{-1}. ^1H NMR δ: 4.03 (m, 1H, C*H*OH), 3.23 (d J=3.0 Hz, 1H, CHO*H*), 2.89 (dd J=14.4 J'=3.3 Hz, 1H, CH_aH_bCHOH), 2.72 (dd J=14.1 J'=9.6 Hz, 1H, CH_aH_bCHOH), 2.57 (t J=7.5 Hz, 2H, CH_2S), 1.6 (m, 2H, CH_2CH_2S), 1.48-1.2 (c, 6H, $3CH_2$), 0.89 (t J=6.8 Hz, 3H, CH_3). ^{19}F NMR δ: -79.46 (d J=6.5 Hz, CF_3). ^{13}C NMR δ: 124.3 (q J=282 Hz, CF_3), 68.6 (q J=31.0 Hz, *C*HOH), 32.6 (q J=1.6 Hz, $CH_2CHOHCF_3$), 32.4, 31.3, 29.4, 28.4, 22.4, 13.9 (CH_3). MS m/z (%): 230 (M^+, 21), 159 (17), 131 (64), 129 (30), 128 (17), 117 (100), 84 (20), 83 (62), 69 (46), 61 (94), 56 (97), 55 (98). Elemental Analysis: Calculated for $C_9H_{17}OF_3S$: C, 46.93; H, 7.44; F, 24.74; S, 13.92. Found: C, 46.87; H, 7.58; F, 24.68; S, 13.73.

(RS)-*n*-Octylthio trifluoromethyl carbinol[10] 6a IR: 3420, 2927, 2856, 1463, 1272, 1166 cm^{-1}. ^1H NMR δ: 4.02 (m, 1H, C*H*OH), 3.02 (d J=4.4 Hz, 1H, CHO*H*), 2.90 (dd J=14.3 J'=3.6 Hz, 1H, CH_aH_bCHOH), 2.71 (dd J=14.3 J'=9.4 Hz, 1H, CH_aH_bCHOH), 2.56 (t J=7.4 Hz, 2H, CH_2S), 1.6 (m, 2H, CH_2CH_2S), 1.27 (b, 10H, $5CH_2$), 0.88 (t J=6.8 Hz, 3H, CH_3). ^{19}F NMR δ: -79.48 (d J=6.8 Hz, CF_3). ^{13}C NMR δ: 124.4 (q J=282 Hz, CF_3), 68.5 (q J=31.0 Hz, *C*HOH), 32.7 (q J=1.7 Hz, $CH_2CHOHCF_3$), 32.4, 31.8, 29.4, 29.12, 29.09, 28.7, 22.6, 14.1 (CH_3). MS m/z (%): 258 (M^+, 4), 159 (33), 145 (75), 129 (14), 85 (23), 70 (36), 69 (100), 61 (47), 57 (24), 56 (43), 55 (65).

(RS)-*n*-Decylthio trifluoromethyl carbinol 7a. IR: 3457, 2925, 2854, 1272, 1166, 1127, 1102 cm^{-1}. ^1H NMR δ: 4.02 (m, 1H, C*H*OH), 3.09 (d J=4.5 Hz, 1H, CHO*H*), 2.90 (dd J=14.4 J'=3.3 Hz, 1H, CH_aH_bCHOH), 2.72 (dd J=14.1 J'=9.6 Hz, 1H, CH_aH_bCHOH), 2.56 (t J=7.2 Hz, 2H, CH_2S), 1.61 (m, 2H, CH_2CH_2S), 1.44-1.18 (c, 10H, $5CH_2$), 0.88 (t J=6.6 Hz, 3H, CH_3). ^{19}F NMR δ: -79.44 (d J=6.2 Hz, CF_3). ^{13}C NMR δ: 124.3 (q J=282 Hz, CF_3),

68.6 (q J=31.0 Hz, *C*HOH), 32.5 (q J=1.6 Hz, $CH_2CHOHCF_3$), 32.4, 31.8, 29.49, 29.44, 29.38, 29.25, 29.11, 28.7, 22.6, 14.0 (CH_3). MS m/z (%): 286 (M^+, 4), 187 (29), 173 (100), 97 (24), 84 (16), 83 (56), 70 (42), 69 (66), 61 (50), 57 (40), 56 (43), 55 (91). Elemental Analysis: Calculated for $C_{13}H_{25}OF_3S$: C, 54.51; H, 8.79; F, 19.90; S, 11.19. Found: C, 54.41; H, 8.88; F, 19.67; S, 11.02.

Lipase-catalysed acylation of carbinols 1a-7a and 1c-2c. Synthesis of (R)-(+)-2a and (S)-(-)-2a as representative procedure. In an erlenmeyer-flask was placed a solution of racemic alcohol (*RS*)-**2a** (31 mg) in 2 ml of hexane. To the solution was added 107 µl (10 equiv.) of vinyl acetate and 62 mg of *Candida antarctica* lipase. The erlenmeyer-flask was capped, placed in a thermostatized bath at 37°C and shaken at 80 U/min. The reaction was monitored by GC, and when the transformation was ca. 50% (45 h) the mixture was filtered off and the enzyme washed with ether. The solvent was stripped off and the resulting crude purified by column chromatography on silica gel, eluting with mixtures of hexane:ether, to afford acetate **(S)-(-)-2b** (16 mg, 44%) and alcohol **(R)-(+)-2a** (15 mg, 48%). Acetate **(S)-2b** was dissolved in 2 ml of methanol and to the solution was added 150 µl of 10% NaOH soln. The mixture was stirred for 2 h at room temperature, the solvent removed and the residue extracted with ether. Usual work-up yielded alcohol **(S)-(-)-2a** (12 mg, 40% overall yield from racemic **2a**). The specific rotations of alcohols **1a-7a** and **1c-2c** are the following: **(R)-(+)-1a:** $[\alpha]_D^{24}$= +14.5 (c=1.6, $CHCl_3$). **(S)-(-)-1a**: $[\alpha]_D^{24}$= -16.2 (c=0.5, $CHCl_3$). **(R)-(+)-2a**: $[\alpha]_D^{24}$= +14.8 (c=0.66, $CHCl_3$). **(S)-(-)-2a**: $[\alpha]_D^{24}$= -16.5 (c=0.57, $CHCl_3$). **(R)-(+)-3a**: $[\alpha]_D^{24}$= +10.8° (c=2.97, $CHCl_3$). **(S)-(-)-3a**: $[\alpha]_D^{24}$= -11.9 (c=0.75, $CHCl_3$). **(R)-(+)-4a:** $[\alpha]_D^{24}$= +15.5 (c=1.9, $CHCl_3$). **(S)-(-)-4a**: $[\alpha]_D^{24}$= -16.1 (c=1.6, $CHCl_3$). **(R)-(+)-5a:** $[\alpha]_D^{24}$= +31.9 (c=2.27, $CHCl_3$). **(S)-(-)-5a**: $[\alpha]_D^{24}$= -40.5 (c=1.22, $CHCl_3$). **(R)-(+)-6a:** $[\alpha]_D^{24}$= +27.2 (c=2.96, $CHCl_3$). **(S)-(-)-6a**: $[\alpha]_D^{24}$= -36.5 (c=2.17, $CHCl_3$). **(R)-(+)-7a:** $[\alpha]_D^{24}$= +27.7 (c=1.26, $CHCl_3$). **(S)-(-)-7a**: $[\alpha]_D^{24}$= -37.3 (c=1.93, $CHCl_3$). **(S)-(+)-1c:** $[\alpha]_D^{24}$= +6.3 (c=4.54, $CHCl_3$). **(R)-(-)-1c**: $[\alpha]_D^{24}$= -6.3 (c=4.17, $CHCl_3$). **(S)-(+)-2c:** $[\alpha]_D^{24}$= +5.6 (c=2.53, $CHCl_3$). **(R)-(-)-2c**: $[\alpha]_D^{24}$= -3.8 (c=2.79, $CHCl_3$).

Determination of the enantiomeric excess of alcohols 1a-7a and 1c-2c. (*R*)-(+)-α-Methoxy-(trifluoromethyl)phenylacetic acid (MTPA) was converted into the acid chloride as previously described[14]. Determination of the e.e. of **(R)-3a** is given as a typical example. A mixture of 7.6 mg of alcohol **(R)-3a**, 49 µl of anh. Et_3N, 0.52 ml of a 0.1M soln. of MTPA chloride in anh. CH_2Cl_2 and one crystal of DMAP was stirred for 2 h at room temperature. After this time, no starting material was detected on TLC. Direct ^{19}F NMR spectrum of the crude diastereomeric ester allowed calculation of the e.e. by integration of the CF_3 signals: ^{19}F NMR δ: **R,R**: -71.96 (s, CF_3C), -76.89 (d J=6.5 Hz, CF_3CH); **R,S**: -72.38 (s, CF_3C), -77.20 (d J=6.2 Hz, CF_3CH). The calculated e.e. of the alcohols were the following: **(R)-(+)-1a:** 66% (63% on Cydex-B GC chiral capillary column); **(S)-(-)-1a:** >95% (>98% on Cydex-B GC chiral capillary column). **(R)-(+)-2a**: 86%; **(S)-(-)-2a**: >95%. **(R)-(+)-3a**: 68%; **(S)-(-)-3a**: 92%; **(R)-(+)-4a:** 84%; **(S)-(-)-4a**: >95%; **(R)-(+)-5a:** 68% (73% on SPB-5 capillary column of the diastereomeric Mosher ester); **(S)-(-)-5a**: >95% (98% on SPB-5 capillary column of the diastereomeric Mosher ester and ≥99% on Cydex-B GC chiral capillary column); **(R)-(+)-6a:** 80%. **(S)-(-)-6a**: >95%. **(R)-(+)-7a:** 70% (75% on SPB-5

capillary column of the diastereomeric Mosher ester); **(S)-(-)-7a**: >95% (>98% on SPB-5 capillary column of the diastereomeric Mosher ester); **(R)-(+)-1c:** >95%; **(S)-(-)-1c**: 92%; **(R)-(+)-2c:** >95%; **(S)-(-)-2c**: 86%.

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