Crystal structure analysis data for **1**: $C_{40}H_{50}N_2O_2ClFe$, $M_r = 682.12$, triclinic, $P\bar{1}$, $a = 10.738(1)$, $b = 13.195(1)$, $c = 14.061(1)$ Å, $\alpha = 75.19(1)$, $\beta = 79.71(1)$, $\gamma = 77.80(1)^\circ$, $V = 1866.1(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.214$ Mg m^{-3}; $\mu(Mo_{K\alpha}) = 0.511$ mm^{-1}, $F(000) = 726$; 18080 reflections collected at 100(2) K; 9891 independent reflections; GOF = 0.990; $R = 0.0508$; $wR2 = 0.1059$. Crystal structure analysis data for **2**: $C_{40}H_{50}N_2O_2BrFe$, $M_r = 726.58$, triclinic, $P\bar{1}$, $a = 10.4544(9)$, $b = 14.737(1)$, $c = 24.387(2)$ Å, $\alpha = 86.88(2)$, $\beta = 84.89(2)$, $\gamma = 87.58(2)^\circ$, $V = 3734.0(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.292$ Mg m^{-3}; $\mu(Mo_{K\alpha}) = 1.509$ mm^{-1}, $F(000) = 1524$; 29363 reflections collected at 100(2) K; 12766 independent reflections; GOF = 0.949; $R = 0.0552$; $wR2 = 0.1030$. Crystal structure data analysis for **3**: $C_{40}H_{50}N_2O_2IFe$, $M_r = 773.57$, monoclinic, $P2_1/c$, $a = 13.497(1)$, $b = 26.326(2)$, $c = 11.672(1)$ Å, $\beta = 112.99(2)^\circ$, $V = 3817.9(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.346$ Mg m^{-3}; $\mu(Mo_{K\alpha}) = 1.238$ mm^{-1}, $F(000) = 1596$; 38047 reflections collected at 100(2) K; 12090 independent reflections; GOF = 1.007; $R = 0.039$; $wR2 = 0.072$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-159894 (**1**), CCDC-159895 (**2**), and CCDC-159896 (**3**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[1] a) S. Koch, R. H. Holm, R. B. Frankel, *J. Am. Chem. Soc.* **1975**, *97*, 6714; b) D. P. Riley, D. H. Busch, *Inorg. Chem.* **1984**, *23*, 3235; c) K. L. Kostka, B. G. Fox, M. P. Hendrich, T. J. Collins, C. E. F. Rickard, L. J. Wright, E. Münck, *J. Am. Chem. Soc.* **1993**, *115*, 6746; d) H. Keutel, I. Käpplinger, E.-G. Jäger, M. Grodzicki, V. Schünemann, A. X. Trautwein, *Inorg. Chem.* **1999**, *38*, 2320; e) E.-G. Jäger, H. Keutel, *Inorg. Chem.* **1997**, *36*, 3512; f) D. Nicarchos, A. Kostikas, A. Simopoulos, D. Coucouvanis, D. Piltingsrud, R. E. Coffman, *J. Chem. Phys.* **1978**, *69*, 4411.

[2] a) M. D. Snodin, L. Ould-Moussa, U. Wallmann, S. Lecomte, V. Bachler, E. Bill, H. Hummel, T. Weyhermüller, P. Hildebrandt, K. Wieghardt, *Chem. Eur. J.* **1999**, *5*, 2554; b) R. M. Buchanan, S. L. Kessel, H. H. Downs, C. G. Pierpont, D. N. Hendrickson, *J. Am. Chem. Soc.* **1978**, *100*, 7894; c) W. O. Koch, V. Schünemann, M. Gerdan, A. X. Trautwein, H.-J. Krüger, *Chem. Eur. J.* **1998**, *4*, 1255.

[3] a) P. Chaudhuri, C. N. Verani, E. Bill, E. Bothe, T. Weyhermüller, K. Wieghardt, *J. Am. Chem. Soc.* **2001**, *123*, 2213; b) H. Chun, C. N. Verani, P. Chaudhuri, E. Bothe, E. Bill, T. Weyhermüller, K. Wieghardt, *Inorg. Chem.*, in press.

[4] C. N. Verani, S. Gallert, E. Bill, T. Weyhermüller, K. Wieghardt, P. Chaudhuri, *Chem. Commun.* **1999**, 1747.

[5] We have also recorded the Mössbauer spectrum of **3** at 298 K; a single quadrupole doublet is observed ($\delta = 0.22$ mm s^{-1}, $|\Delta E_Q| = 2.21$ mm s^{-1}). This clearly establishes that the increasing magnetic moment at temperatures > 100 K for **3** (Figure 2) is *not* due to a spin crossover $S_t = \frac{1}{2} \rightarrow S_t = \frac{3}{2}$.

[6] D. Sellmann, S. Emig, F. W. Heinemann, *Angew. Chem.* **1997**, *109*, 1808; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1734.

[7] C. K. Jörgensen, *Struct. Bonding (Berlin)* **1966**, *1*, 234.

Separation of Enantiomers by Extraction Based on Lipase-Catalyzed Enantiomer-Selective Fluorous-Phase Labeling**

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Lipase-mediated kinetic resolution of racemic alcohols and their esters by esterification or hydrolysis, respectively, is a well-established method for the preparation of enantiomerically pure or enriched building blocks.[1] Lipases are cheap biocatalysts; the reactions can be run with standard equipment and are highly selective in many cases. However, there is one major drawback of this type of biotransformation, which affords one of the enantiomers as an alcohol and the other one as the corresponding carboxylate: The products must be separated by chromatography. This separation step may not be a serious problem on the laboratory scale. However, on a large scale in the pharmaceutical industry, a chromatographic step might be the reason this method is not considered to be a useful access to enantiomerically pure intermediates. Until now, there has been no general solution to overcome this disadvantage.

On the other hand, remarkable progress has been made for the extractive separation of homogeneous catalysts,[2] reagents, and products[3] equipped with perfluorinated auxiliary groups. This methodology is based on partitioning between the organic and fluorous phases in order to improve the recovery of the homogeneous catalyst and the isolation of products from the reaction mixture.

From the progress made in performing reactions in fluorous media and/or improving workup procedures by the introduction of a fluorous phase,[4] the following question arises: Is it possible to apply a highly fluorinated acyl donor to a lipase-catalyzed kinetic resolution of a racemic alcohol? Such an acyl donor should promote lipase-mediated enantiomer-selective acyl transfer onto the faster-reacting enantiomer and, thereby, simultaneously label it. This labeled enantiomer with a "teflon ponytail"[2b] could then be recognized selectively by a fluorous phase, to allow the extractive separation of the fluorinated and nonfluorinated enantiomers between a fluorous and an organic solvent.

For a successful realization of this principle a suitable acyl donor is required. This reagent should be accepted by the lipase forming the reactive acyl enzyme, that subsequently reacts in an enantiomer-selective manner with a racemic alcohol. Furthermore, the transferred acyl residue should have a sufficient fluorine content to allow selective separation of the fluorinated ester from the nonfluori-

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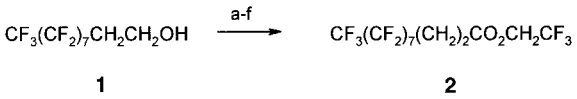
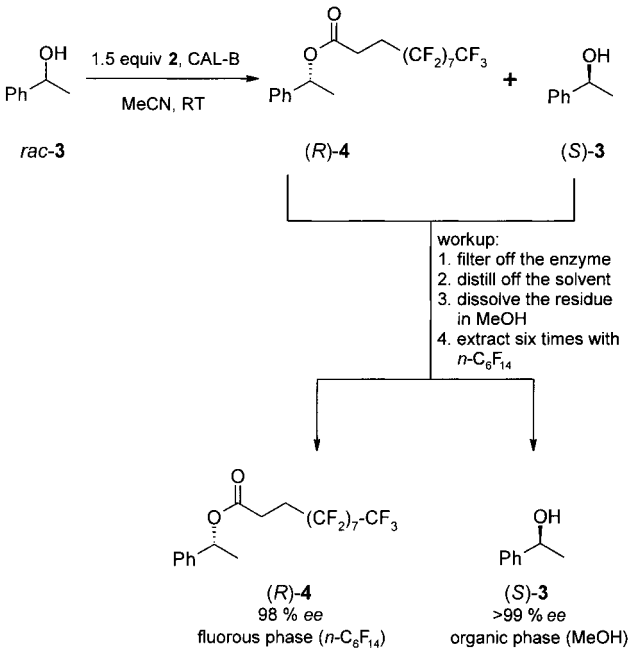
nated alcohol in an appropriate biphasic organic/fluorous system.

Esters of the structure $CF_3(CF_2)_n(CH_2)_mCOOR$ (where R = vinyl or 2,2,2-trifluoroethyl, for example) were designed as suitable irreversible or quasi-irreversible acyl donors.[1c] A spacer of one or two methylene groups ($m = 1$ or 2) should be necessary to exclude a nonselective chemical acylation of the alcohol. The commercially available alcohol **1**[5] was selected as a useful starting material for the synthesis of the ester **2**,[6] envisaged as a potential acyl donor and synthesized in high yield by the method shown in Scheme 1.



Scheme 1. Synthesis of the highly fluorinated acyl donor **2**. a) 4-$CH_3C_6H_4SO_2Cl$, b) LiBr, c) Mg, d) CO_2, e) PCl_5, f) CF_3CH_2OH, pyridine.

In order to demonstrate the feasibility of the principle, we chose 1-phenylethanol (*rac*-**3**) as the alcohol to be resolved. After screening of lipases and solvents, lipase B from *Candida antarctica* (CAL-B) in acetonitrile turned out to be a useful biocatalytic system with ester **2** as the acylating agent; the resolution of the enantiomers of *rac*-**3** into (*R*)-**4** and (*S*)-**3** proceeded with high efficacy within 19 hours (Scheme 2). The corresponding ester with one less CH_2 group ($m = 1$) was not suitable as an acyl donor.



Scheme 2. Lipase-catalyzed kinetic resolution of *rac*-**3** and subsequent extractive separation of the products with a biphasic fluorous/organic solvent system.

In order to determine the yields and enantiomeric excesses (*ee*)[7] of the products, the reaction mixture was worked up conventionally with purification by flash column chromatography to yield (*R*)-**4** (46% yield, *ee* > 99%) and (*S*)-**3** (41% yield, *ee* > 99%). In comparison, the resolution of *rac*-**3** with vinyl acetate in *tert*-butyl methyl ether in the presence of *Pseudomonas* sp. lipase reached 50% conversion after 44 hours to yield the corresponding (*R*)-acetate and (*S*)-**3** with *ee* values of > 99 and 93%, respectively.[8] This demonstrates that the reactivity of perfluoroester **2** is, at least, in the same range as that of vinyl acetate.

In the next step, we looked for a suitable biphasic fluorous/organic solvent system to separate ester (*R*)-**4** from alcohol (*S*)-**3** whilst avoiding chromatography. Screening of organic solvents immiscible with *n*-perfluorohexane such as cyclohexane, toluene, THF, and methanol showed that the biphasic mixture methanol/*n*-perfluorohexane was the system of choice and allowed a very efficient separation of the compounds *rac*-**3** and *rac*-**4**, which were used as model substances. When an equimolar mixture of *rac*-**3** and *rac*-**4** was extracted at least five times with *n*-perfluorohexane, *rac*-**3** remained in the organic phase and *rac*-**4** moved into the fluorous phase. The organic phase was contaminated with less than 1% of *rac*-**4** and the fluorous phase contained less than 1% of *rac*-**3**.

After identification of the appropriate fluorous/organic biphasic system for the separation of (*R*)-**4** and (*S*)-**3**, the reaction mixture was worked up as follows (Scheme 2): The enzyme was filtered off, the solvent was removed under reduced pressure, and the products were separated by partition between methanol and *n*-perfluorohexane. This method yielded (*S*)-**3** with an *ee* value of 99% in the organic phase and (*R*)-**4** with an *ee* value of 98% in the fluorous phase, which also contained the excess of the acylating agent **2**.

Comparison of the results obtained by conventional chromatographic separation and extractive separation shows that there is almost no difference between both procedures regarding the purity and the yield of the products. After the extractive workup (*S*)-**3** was contaminated with a trace (not more than 1%) of (*R*)-**4**.[9] The *ee* value of 98% determined after saponification of (*R*)-**4** to (*R*)-**3**, represents an impurity of not more than 1% of (*S*)-**3** in the fluorous phase. In addition, saponification of the mixture of (*R*)-**4** and **2** to yield (*R*)-**3** allows the almost quantitative recovery of the fluorinated carboxylic acid in solid form as the lithium salt.

This newly developed methodology for the separation of enantiomers, which combines a lipase-catalyzed kinetic resolution with fluorous-phase labeling and separation of the products in a biphasic fluorous/organic solvent system, should also be applicable for the enantiomer-selective hydrolysis or alcoholysis of fluorous-phase labeled esters of racemic alcohols and for the enantiomer-selective alcoholysis of esters of racemic carboxylic acids with highly fluorinated alcohols.[10] We are currently investigating further applications of this newly developed strategy.

Experimental Section

A solution of *rac*-**3** (1.22 g, 10 mmol) in MeCN (65 mL) was treated with ester **2** (8.61 g, 15 mmol) and CAL-B (Chirazyme L-2, c.-f., lyo., Roche Diagnostics, Mannheim; 2.00 g). The reaction mixture was stirred at ambient temperature until the conversion reached approximately 50% (19 h). The enzyme was filtered off and the solid residue was washed with acetone (2 × 40 mL). The combined filtrates were evaporated under reduced pressure and the residue was dissolved in MeOH (25 mL). The

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resulting solution was extracted with n-C_6F_{14} (6×25 mL). The organic phase was concentrated to dryness to yield (*S*)-**3** (0.59 g, 48 % yield, 99 % *ee*) with approximately 1 % of (*R*)-**4**. From the fluorous phase a mixture of (*R*)-**4** (*ee* 98 %) and the excess of **2** (8.50 g) was isolated.

Saponification of (*R*)-**4**: The mixture of (*R*)-**4** and **2** was dissolved in THF and water (1/1, 40 mL) together with LiOH (0.64 g, 26.7 mmol), and the mixture was heated to reflux for 3 h. Subsequently, the reaction mixture was diluted with cyclohexane (100 mL), cooled to 0 °C, and filtered. The filter cake was washed with a mixture of cyclohexane (100 mL) and *tert*-butyl methyl ether (30 mL). The filtrate was concentrated to dryness to yield (*R*)-**3** (0.57 g, 47 %, 98 % *ee*). The remaining solid filter cake (7.35 g, 98 %) consists of the lithium salt of the perfluorinated carboxylic acid.

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[1] a) C.-S. Chen, C.-J. Sih, *Angew. Chem.* **1989**, *101*, 711 – 724; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 695 – 707; b) W. Boland, C. Frößl, M. Lorenz, *Synthesis* **1991**, 1049 – 1072; c) K. Faber, S. Riva, *Synthesis* **1992**, 895 – 910; d) E. Santaniello, P. Ferraboschi, P. Grisenti, *Enzyme Microb. Technol.* **1993**, *15*, 367 – 382; e) F. Theil, *Chem. Rev.* **1995**, *95*, 2203 – 2227; f) U. T. Bornscheuer, R. J. Kazlauskas, *Hydrolases in Organic Synthesis*, Wiley-VCH, Weinheim, **1999**; g) G. Carrea, S. Riva, *Angew. Chem.* **2000**, *112*, 2312 – 2341; *Angew. Chem. Int. Ed.* **2000**, *39*, 2226 – 2254.

[2] a) I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72 – 75; b) J. A. Gladysz, *Science* **1994**, *266*, 55 – 56; c) B. Cornils, *Angew. Chem.* **1997**, *109*, 2147 – 2149; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2057 – 2059; d) B. Betzemeier, M. Cavazini, S. Quici, P. Knochel, *Tetrahedron Lett.* **2000**, *41*, 4343 – 4346.

[3] a) D. P. Curran, M. Hoshino, *J. Org. Chem.* **1996**, *61*, 6480 – 6481; b) P. Wipf, J. T. Reeves, *Tetrahedron Lett.* **1999**, *40*, 4649 – 4652; c) S. Röver, P. Wipf, *Tetrahedron Lett.* **1999**, *40*, 5667 – 5670.

[4] a) D. P. Curran, *Angew. Chem.* **1998**, *110*, 1231 – 1255; *Angew. Chem. Int. Ed.* **1998**, *37*, 1174 – 1196; b) U. Diederichsen, *Nachr. Chem. Tech. Lab.* **1999**, *47*, 805 – 809.

[5] One can expect that the currently very high price of the alcohol (104.10 € for 50 g, Avocado/ABCR) should go down significantly if there is a need for bulk quantities.

[6] B.p. 57 °C (1×10^{-3} mbar); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.52$ (tt, $^1J = 8.4$, $^2J = 8.0$ Hz, 2H), 2.76 (t, $J = 8.4$ Hz, 2H), 4.42 (q, $J = 8.4$ Hz, 2H).

[7] Before determination of the *ee* value, (*R*)-**4** was saponified to the corresponding alcohol (*R*)-**3**. The *ee* values of the enantiomeric alcohols (*R*)- and (*S*)-**3** were determined by HPLC on a Chiralcel OJ column (250×4.6 mm; eluent: *n*-heptane/*n*-propanol 95/5; flow rate: 1 mL min^{-1}; UV detection at 254 nm). The absolute configurations of the enantiomeric alcohols were assigned by comparison with commercially available authentic samples.

[8] K. Laumen, D. Breitgoff, M. P. Schneider, *J. Chem. Soc. Chem. Commun.* **1988**, 1459 – 1461.

[9] Extraction was carried out in an ordinary separation funnel. The residual 1 % of alcohol (*S*)-**3** left in the fluorous phase could either be caused by contamination of the glassware (for example, a stopcock) or by incomplete separation of the phases. However, a reextraction of the fluorous phase with methanol should remove the trace of (*S*)-**3**.

[10] We have not tested whether esterases or proteases will also accept long-chain fluoroesters.

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