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A versatile approach to optically active primary 2-fluoro-2-phenylalkanols through lipase-catalyzed transformations

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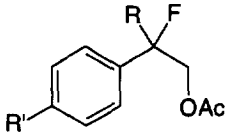
Abstract: Kinetic resolutions of (±)-1-acetoxy-2-fluoro-2-phenylalkanes **1** by enzymatic hydrolysis and of (±)-2-fluoro-2-phenylpropanol **2a** by lipase-catalyzed acetylation are described for the first time. Hydrolysis of (±)-**1** with lipase Amano PS *(Pseudomonas cepacia)* provided both the optically active acetates (−)-**1** and the corresponding primary alcohols (−)-**2** with high enantiomeric excess. (*R*)-enantiopreference was observed for the acetylation of (±)-2-fluoro-2-phenylpropanol **2a** which occurred with higher enantioselectivity and faster conversion compared to the unfluorinated parent compound (±)-2-phenylpropanol **3**. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Widespread utilization of optically active fluoroorganic compounds in biological and medicinal chemistry[1] and their potential application for optoelectronic substances such as liquid crystals[2] continues to expand and requires the development of synthetic methods with high stereoselectivity. Particularly enantiopure vicinal fluorohydrins gained actual interest due to their versatility as useful intermediates[3] and potent building blocks in the synthesis of polyfunctional bioactive molecules.[4] Besides conventional methodologies[5] and catalytic transformations,[6] employment of biocatalysts in preparative organic chemistry has become important over the past few years. In particular, enantiopure secondary β-fluoroalcohols have been prepared via asymmetric reduction of the corresponding ketones applying baker's yeast,[3] or resolution by lipase-catalyzed hydrolysis.[7] Recently, enzymatic esterification in organic media has also been found to be an effective approach[8] and confirmed the superiority of enzymes for the purpose of kinetic resolution compared to classical methods.[9]



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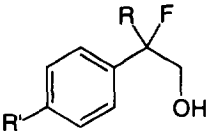

2

compound	a	b	c	d	e
R	Me	Et	*n*-Pr	*n*-Bu	Me
R'	H	H	H	H	*i*-Bu

Despite this rapid progress, to the best of our knowledge, nothing is known about the enzyme mediated synthesis of optically active 2-fluoro-2-phenylalcohols **2a–e**, bearing a terminal hydroxyl functionality and their corresponding acetates **1a–e**, respectively. Such compounds are of special interest as useful chiral precursors for the synthesis of enantiomerically pure 2-fluoro-2-phenylalkanoic acids, which were found to be effective chiral derivatising agents for ee-determination of enantiomerically enriched alcohols and amines by ^{19}F NMR spectroscopy.[10] As an extension of our recently published investigations toward the synthesis of monofluorinated analogues of anti-inflammatory agents[11] the synthesis of optically active 1-acetoxy-2-fluoro-2-(4-isobutylphenyl)propane **1e** and the corresponding alcohol **2e** as precursors for enantiomerically pure monofluorinated analogue of 'ibuprofen' is also of interest. Oxidation of enantiomerically pure alcohols **2** could be considered as a new promising

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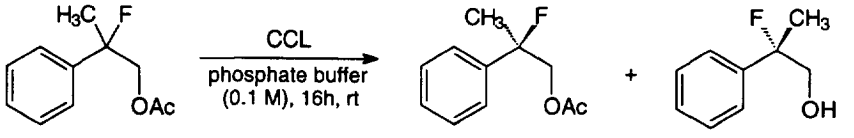
approach to fluorinated phenylalkanoic acids besides the classical enantiomer separation by fractional crystallization of diastereomeric derivatives[10] or resolution of the fluorinated carboxylates.[12]

Results and discussion

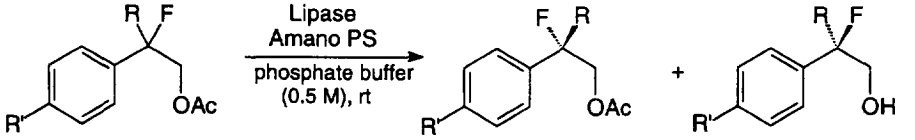
As previously described in our recent paper[13] racemic 2-fluoro-2-phenylalkanols **2** have been generated either by oxirane-ring opening using triethylamine trishydrofluoride of the corresponding styrene oxides or by saponification of the acetates **1**. These compounds can be obtained by nucleophilic substitution of bromine with acetate of the corresponding bromo fluorides.[13] Lipase-catalyzed hydrolysis of the acetates **1** should yield optically active fluorohydrins **2** without an additional reaction step. Furthermore we were interested whether the enantiomeric excess would be affected by the enlarged distance between the stereogenic center and the acetate or hydroxyl groups to be transformed by the lipase.

Our first trial in hydrolysis, employing lipase from *Candida cylindracea* (CCL, E.C. 3.1.1.3) and 1-acetoxy-2-fluoro-2-phenylpropane **1a** as substrate showed a conversion of 46% after stirring at room temperature for 16 h. Separation of the components and subsequent determination of the enantiomeric excess by ^{1}H NMR shift experiment (using necessarily 2 equivalents of Eu(hfc)$_3$) showed 27% ee for the fluoroacetate (+)-**1a**. For (+)-2-fluoro-2-phenylpropanol (+)-**2a** 37% ee was detected by chiral GC.



(±)-**1a** (+)-**1a** 27% (27% ee) (+)-**2a** 30% (37% ee)

This relatively low enantioselectivity prompted us to utilize lipase from *Pseudomonas cepacia* (Amano PS) which is known to be very selective to substrates with a small sterical demand.[14] Surprisingly, a 46% conversion of (±)-**1a** was observed after a very short reaction time (0.5 h). Moreover, higher enantiomeric excess has been detected for both the acetate (−)-**1a** (83% ee) and the alcohol (−)-**2a** (64% ee), however, with reverse specific rotation relative to the CCL catalyzed hydrolysis (Table 1, entry 1). Applying these reaction conditions to the next homologue **1b**, enantiomerically pure butylacetate (−)-**1b** (>98% ee) was formed along with the alcohol (−)-**2b** (91% ee) after 4.5 h. Hydrolysis of the pentyl and hexyl derivatives **1c** and **1d** (Table 1, entries 5 and 6) also gave good ee-values for both components. These results indicate that elongation of the alkyl side chain by one methylene group compared to (±)-**1a** improves chiral recognition of compound (−)-**1b**. Moreover, the hydrolysis of **1c** and **1d** gives rise to assume that the flexible alkyl side chains possess the structural features for good 'induced fit'.



(±)-**1a-e** (-)-**1a-e** (-)-**2a-e**

In order to increase the enantioselectivity of the hydrolysis of (±)-**1a** we diminished the enzyme/substrate ratio (Table 1, entries 2 and 3). Using 14 mg lipase per mmol of (±)-**1** the ee for the alcohol (−)-**2a** was increased up to 79% ee, whereas the enantiomeric excess of the acetate (−)-**1a** was increased up to 88% ee. Variation of other reaction parameters (temperature, pH, buffer concentration)[15] did not improve the enantioselectivity.

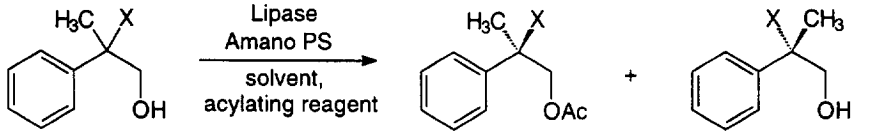
Unfortunately para-substitution of the phenyl ring by an isobutyl group dramatically decreased the ee-values for both compounds (−)-**1e** and (−)-**2e** (39% and 38% ee), respectively.

Furthermore, we investigated the enzymatic esterification of the racemic fluorohydrin (±)-**2a** using

Table 1. Kinetic resolution of 1-acetoxy-2-fluoro-2-phenylalkanes **1a–d** and 1-acetoxy-2-fluoro-2-(4-isobutylphenyl)propane **1e** with lipase from *Pseudomonas cepacia* (Amano PS)

Entry	R	R'	mg enzyme/ mmol (±)-**1**	time (h)	conversion (%)	product	yield (%)	ee (%)
1	CH_3	H	61	0.5	46	(-)-**1a** (-)-**2a**	34 35	83 64
2	CH_3	H	20	1.25	45	(-)-**1a** (-)-**2a**	31 26	89 70
3	CH_3	H	14	1.75	42	(-)-**1a** (-)-**2a**	27 19	88 79
4	C_2H_5	H	61	4.5	48	(-)-**1b** (-)-**2b**	27 35	>98 91
5	n-C_3H_7	H	61	8.0	43	(-)-**1c** (-)-**2c**	34 29	92 86
6	n-C_4H_9	H	61	8.5	46	(-)-**1d** (-)-**2d**	33 31	96 88
7	CH_3	i-C_4H_9	10	2.5	45	(-)-**1e** (-)-**2e**	32 27	39 38

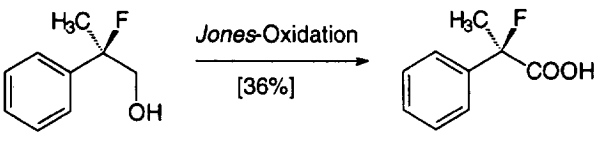
both pure and immobilized[16] lipase Amano PS with vinylacetate or acetic anhydride as acylating agents in cyclohexane or toluene, respectively. Determination of ee-values for the acetate (+)-**1a** was obtained by chiral GC after hydrolysis to the corresponding alcohol (−)-**2a**. As expected, both the acetate (+)-**1a** and the alcohol (+)-**2a** showed reverse specific rotation compared to the products provided by hydrolysis of (±)-**1a**.



X = F (±)-**2a** (*R*)-(+)-**1a** (*S*)-(+)-**2a**
X = H (±)-**3** (*S*)-(-)-**4** (*R*)-(+)-**3**

As indicated in Table 2 utilization of immobilized lipase Amano PS and vinylacetate in toluene (entry 10) gave the highest enantiomeric excesses for the fluoroacetate (+)-**1a** (95% ee) at 46% conversion. Compared to the respective enzymatic hydrolysis of (±)-**1a** (Table 1, entry 3) the optical purity of the fluoroacetate (+)-**1a** was enhanced by 7%, whereas the ee-value for the alcohol (+)-**2a** was diminished by 9%.

Although the absolute stereochemistry of the fluorohydrin (−)-**2a** could not be established by X-ray crystallography of several solid derivatives because of the lack of good crystals,[17] we determined the absolute configuration after *Jones* oxidation of the fluorohydrin (−)-**2a**, which gave the known (*R*)-(−)-2-fluoro-2-phenylpropionic acid (*R*)-(−)-**5**.[18]



(*R*)-(-)-**2a** (71% ee) (*R*)-(-)-**5** (71% ee)

Thus, we assume the (*R*)-enantiopreference for the lipase Amano PS for esterification of chiral vicinal monofluorinated primary alcohols. This is in good agreement with an empirical rule, proposed by Kazlauskas et al.[19] that predicts (*S*)-selectivity of lipase Amano PS in enzymatic esterifications and

Table 2. Enzymatic esterification of (±)-2-fluoro-2-phenylpropan-1-ol **1a** and (±)-2-phenylpropanol **3** with lipase from *Pseudomonas cepacia* (Amano PS)

Entry	substrate	enzyme Amano PS	acylating reagent	solvent	time (h)	conversion (%)	product	yield (%)	ee (%)
8	(±)-**2a**	pure	vinylacetate	cyclohexane	18	63	(*R*)-(+)-**1a**	33	75
							(*S*)-(+)-**2a**	12	78
9	(±)-**2a**	immob.	vinylacetate	cyclohexane	12	47	(*R*)-(+)-**1a**	24	84
							(*S*)-(+)-**2a**	26	60
10	(±)-**2a**	immob.	vinylacetate	toluene	18	46	(*R*)-(+)-**1a**	26	95
							(*S*)-(+)-**2a**	31	70
11	(±)-**2a**	immob.	Ac_2O	toluene	3	37	(*R*)-(+)-**1a**	12	80
							(*S*)-(+)-**2a**	38	46
12	(±)-**3**	pure	vinylacetate	cyclohexane	17	53	(*S*)-(-)-**4**	30	48
							(*R*)-(+)-**3**	20	70
13	(±)-**3**[16]	immob.	Ac_2O	benzene	1	60	(*S*)-(-)-**4**	50	8
							(*R*)-(+)-**3**	34	28

a) b)

Figure 1. (a) Empirical Kazlauskas rule for the enantiopreference of lipase Amano PS toward primary alcohols.[19] (b) Proposed enantiopreference of lipase Amano PS towards (±)-**2a**.

hydrolyses of nonfluorinated primary alcohols with a tertiary stereocenter. The formal substitution of H with F changes the priority of the substituents determining the (*R*)- or (*S*)-description according to the CIP system.

According to the model of Kazlauskas[19] (Figure 1a) we can accept, that the lipase cannot distinguish between the hydrogen and fluorine atom which are supposed to be sterically similar. Thus all substituents at the stereocenters of (−)-**2a** and (−)-**3** can be placed into the same pockets of the active site without significant differences in sterical demand. We repeated the experiment by Bianchi et al.[16] using vinyl acetate instead of acetic anhydride and obtained an increase of enantioselectivity (Table 2, entries 12 and 13) furnishing the (*R*)-(+)-2-phenylpropan-1-ol **3** (70% ee) and the (*S*)-(−)-1-acetoxy-2-phenylpropane **4** (48% ee), using lipase Amano PS and vinylacetate in cyclohexane. Comparison of the rate of esterification of **2a** and 2-phenylpropan-1-ol **3** showed an unexpected high rate for the fluorohydrin **2a** relative to the nonfluorinated alcohol **3** (Figure 2).

In contrast to the enzymatic esterification we[20] recently observed, that the chemical esterification of vicinal fluorohydrins was not nearly as fast. Different interaction between the alcohols **2a** and **3** and the active site of the lipase should be responsible for the observed reactivities. Insertion of fluorine into a molecule can change the acidity and basicity of neighbor groups as well as the preferred conformation. On the one hand additional hydrogen bonding near the catalytic center could decrease the energy of activation of the 'induced fit'[21] and on the other hand intramolecular hydrogen bonding of **2a** stabilizes the conformer shown in Figure 1b which causes a better fit into the enzyme's pocket. Based on the flexibility along the C(1)–C(2) bond of **3** the enzyme has to discriminate between several possible conformations and maybe the energy of activation of the enzymatic esterification is enhanced compared to the fluorohydrin **2a**.

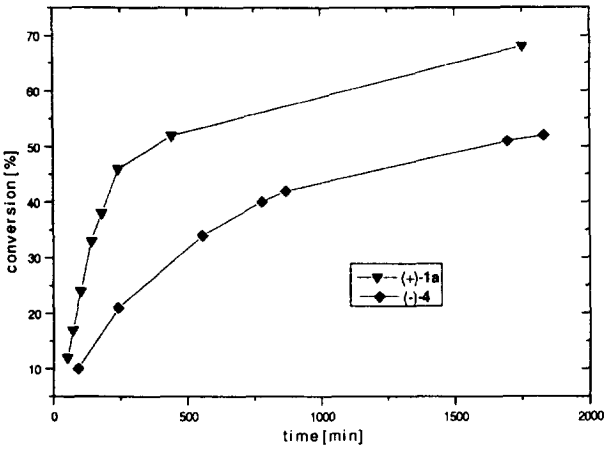


Figure 2. Conversion/time plot of the enzymatic acetylation of **2a** and **3** with pure enzyme and vinylacetate in cyclohexane.

Experimental

General (see ref.13)

Mass spectra (electron-impact ionisation, 70 eV): GC/MS coupling: Varian GC 3400/MAT and data system of Finnigan/MAT. — GC: Hewlett–Packard 5890 II gas chromatograph, quartz capillary column 0.33 mm × 25 m, 0.52 μm HP-1 (Hewlett–Packard) and quartz capillary column 0.2 mm × 25 m, 0.11 μm HP-5 (Hewlett–Packard), nitrogen as carrier gas, and FID. Conversion of the substrates during the enzymatic reactions was determined by GC. Tables 1 and 2 present corrected values of conversion. — Optical rotations: Perkin–Elmer 241 polarimeter (Na–D-line: λ=589 nm). — Enantiomeric excess: by ^{1}H NMR shift experiment (compound **1a**) [addition of 2 eq. Eu(hfc)$_3$; integration of resonance signals for the α-methyl group[22]]; by chiral GC [column 1: FS-Hydrodex β-PM (50 m, Ø 0.25 mm, *Macherey and Nagel*; column 2: FS-Lipodex E (25 m, Ø 0.25 mm, *Macherey and Nagel*; column 3: Beta-Dex® 120 (30 m, Ø 0.25 mm, 0.25 μm film thickness), *Supelco*]; for compound **5** by ^{1}H,^{19}F decoupled ^{19}F NMR derivatisation experiment [using menthol as derivatising agent (see ref. 10b), integration of resonance signals for the two diastereomeric signals]. — Thin-layer chromatography: Merck silica gel DC 60 F254. — Column chromatography: Silica gel (Merck 60, 70–230 mesh). Lipase from *candida cylindracea* (CCL) was purchased from *Sigma* and Lipase Amano PS was a gift from *Amano Pharmaceuticals Co.* All applied reagents were obtained from *Fluka* or *Janssen*. Phosphate buffer (0.5 M, pH=7.0) was prepared from K_2HPO_4 and KH_2PO_4. Cyclohexane, ethyl acetate and toluene were purified by distillation prior to use.

*Enzymatic hydrolysis of (±)-1-acetoxy-2-fluoro-2-phenylpropane (±)-**1a** with lipase from* Candida cylindracea *(CCL)*

140 mg (0.7 mmol) of (±)-**1a** are suspended in 15 mL phosphate buffer (0.1 M, pH=7.0) and 10 mg of lipase from *Candida cylindracea* is added. After stirring for 16 hours at ambient temperature the reaction mixture is extracted with diethylether (5 × 15 mL). The combined organic phases are dried ($MgSO_4$), filtered and the solvent is removed in vacuum. Subsequent GC analysis of the colorless residue shows a conversion of 46%. Separation by column chromatography (cyclohexane/ethyl acetate 5:1 (v/v)) provides the pure compounds.

*(+)-1-Acetoxy-2-fluoro-2-phenylpropane (+)-**1a***

Yield: 37 mg (27%) — $[\alpha]_D^{20}$: +1.3 (c=1.80, methanol), 27% ee [^{1}H NMR, 2 eq. Eu(hfc)$_3$ or chiral GC (column 2, 65°C, 1.2 bar N_2)]. The difference between both methods is <1%. —All spectroscopic data agree with those published for racemic **1a**.[13]

*(+)-2-Fluoro-2-phenylpropanol (+)-**2a***

Yield: 37 mg (30%) — $[\alpha]_D^{20}$: +1.8 (c=1.90, methanol), 37% ee [chiral GC (column 3, 135°C, 0.5 bar N_2)]. —All spectroscopic data agree with those published for racemic **2a**.[13]

General procedure for the enzymatic hydrolysis of 1-acetoxy-2-aryl-2-fluoroalkanes with lipase from Pseudomonas cepacia *(Amano PS)*

1 mmol fluoroacetate is suspended in 34 ml phosphate buffer (0.5 M, pH=6.8) and 60 mg lipase Amano PS are added in portions and the suspension is stirred at room temperature as indicated in Table 1. The reaction is quenched by adding a spatula sodium chloride, 60 ml ethyl acetate and 2 spatulas Celite®. After filtration of the mixture using a short path column of Celite® the layers are separated. The aqueous phase is extracted with ethyl acetate (4×30 mL) and the combined extracts are dried ($MgSO_4$). After filtration with suction and removal of the solvent in vacuum, the residue is subjected to GC analysis to determine the uncorrected ratio of acetate and alcohol. These values must be corrected, because a 1:1 mixture (mol/mol) shows a 53:47 ratio in GC.[15] Separation was carried out by column chromatography (cyclohexane/ethyl acetate 5:1 (v/v)). Determination of the enantiomeric excess was performed as indicated below.

*Hydrolysis of (±)-1-acetoxy-2-fluoro-2-phenylpropane (±)-**1a***

According to the general procedure 198 mg (1 mmol) (±)-**1a** are treated with lipase Amano PS. After 0.5 h GC analysis shows a conversion of 43% and the compounds are separated by column chromatography.

*(−)-1-Acetoxy-2-fluoro-2-phenylpropane (−)-**1a***

Yield: 34 mg (27%) — $[\alpha]_D^{20}$: −4.1 (c=0.90, methanol), 83% ee [chiral GC (column 2, 65°C, 1.2 bar N_2)].

*(−)-2-Fluoro-2-phenylpropanol (−)-**2a***

Yield: 54 mg (35%) — $[\alpha]_D^{20}$: −8.5 (c=0.80, methanol), 64% ee [chiral GC (column 1, 130°C, 1.0 bar N_2)].

*Hydrolysis of (±)-1-acetoxy-2-fluoro-2-phenylbutane (±)-**1b***

According to the general procedure 217 mg (1 mmol) (±)-**1b** are treated with lipase Amano PS. After 4.5 h GC analysis shows a conversion of 48% and the compounds are separated by column chromatography.

*(−)-1-Acetoxy-2-fluoro-2-phenylbutane (−)-**1b***

Yield: 59 mg (27%) — $[\alpha]_D^{20}$: −14.4 (c=0.90, methanol), >98% ee [chiral GC (column 1, 100°C, 2.0 bar N_2)]. —All spectroscopic data agree with those published for racemic **1b**.

*(−)-2-Fluoro-2-phenylbutanol (−)-**2b***

Yield: 61 mg (35%) — $[\alpha]_D^{20}$: −3.8 (c=0.90, methanol), 91% ee [chiral GC (column 1, 115°C, 2.0 bar N_2)]. −All spectroscopic data agree with those published for racemic **2b**.

*Hydrolysis of (±)-1-acetoxy-2-fluoro-2-phenylpentane (±)-**1c***

According to the general procedure 225 mg (1 mmol) (±)-**1c** are treated with lipase Amano PS. After 8 h GC analysis shows a conversion of 43% and the compounds are separated by column chromatography.

*(−)-1-Acetoxy-2-fluoro-2-phenylpentane (−)-**1c***

Yield: 78 mg (35%) — $[\alpha]_D^{20}$: −8.3 (c=1.00, methanol), 92% ee [chiral GC (column 1, 105°C, 1.0 bar N_2)]. — All spectroscopic data agree with those published for racemic **1c**.[13]

*(−)-2-Fluoro-2-phenylpentanol (−)-**2c***

Yield: 53 mg (30%) — $[\alpha]_D^{20}$: −8.0 (c=1.00, methanol), 86% ee [chiral GC (column 1, 120°C, 1.0 bar N_2)]. — All spectroscopic data agree with those published for racemic **2c**.[13]

*Hydrolysis of (±)-1-acetoxy-2-fluoro-2-phenylhexane (±)-**1d***

According to the general procedure 168 mg (0.7 mmol) (±)-**1d** are treated with lipase Amano PS. After 8.5 h GC analysis shows a conversion of 46% and the compounds are separated by column chromatography.

*(−)-1-Acetoxy-2-fluoro-2-phenylhexane (−)-**1d***

Yield: 56 mg (33%) — $[\alpha]_D^{20}$: −14.4 (c=0.90, methanol), 96% ee [chiral GC (column 2, 105°C, 1.2 bar N_2)]. — All spectroscopic data agree with those published for racemic **1d**.[13]

*(−)-2-Fluoro-2-phenylhexanol (−)-**2d***

Yield: 44 mg (31%) — $[\alpha]_D^{20}$: −1.2 (c=0.80, methanol), 88% ee [chiral GC (column 2, 105°C, 1.2 bar N_2)]. — All spectroscopic data agree with those published for racemic **2d**.[13]

Optimization of the enantiomeric excess by variation of enzyme/substrate ratio

Trial A (Table 1, entry 2)

As described above 147 mg (0.75 mmol) (±)-1-acetoxy-2-fluoro-2-phenylpropane (±)-**1a** is treated with 15 mg lipase Amano PS in 22 mL phosphate buffer. After 1.25 h GC analysis shows a 45% conversion and purification by column chromatography yields acetate (−)-**1a** (45 mg, 31%) with 89% ee and alcohol (−)-**2a** (31 mg, 26%) with 70% ee (GC).

Trial B (Table 1, entry 3)

As described above 213 mg (1.1 mmol) (±)-1-acetoxy-2-fluoro-2-phenylpropane (±)-**1a** were treated with 15 mg lipase Amano PS in 33 mL phosphate buffer. After 1.75 h GC analysis indicates a 42% conversion. Purification by column chromatography yields (−)-**1a** (58 mg, 27%) with 88% ee and (−)-**2a** (32 mg, 19%) with 79% ee.

*Hydrolysis of (±)-1-acetoxy-2-fluoro-2-(4-isobutylphenyl)propane (±)-**1e***

Utilizing the optimized condition (trial B) 385 mg (1.52 mmol) (±)-**1e** are treated with 15 mg lipase Amano PS in 45 mL phosphate buffer. After 2.25 h GC analysis indicates a conversion of 45% and the components are separated by column chromatography.

*(−)-1-Acetoxy-2-fluoro-2-(4-isobutylphenyl)propane (−)-**1e***

Yield: 121 mg (32%) — $[\alpha]_D^{20}$: −1.5 (c=0.80, methanol), 39% ee [^{1}H NMR, 2 eq. Eu(hfc)$_3$]. — All spectroscopic data agree with those published for racemic **1e**.[11]

(−)-2-Fluoro-2-(4-isobutylphenyl)propanol (−)-2e

Yield: 86 mg (27%) — $[\alpha]_D^{20}$: −1.2 (c=0.50, methanol), 38% ee [after acetylation, ^{1}H NMR, 2 eq. Eu(hfc)$_3$]. — All spectroscopic data agree with those published for racemic **2e**.[11]

General procedure for enzymatic esterification of (±)-2-fluoro-2-phenylpropan-1-ol (±)-2a with lipase from Pseudomonas cepacia *(Amano PS)*

1 mmol fluorohydrin (±)-**2a** and 1 mmol of the acylating reagent are dissolved in 5 mL of the dried organic solvent. After addition of lipase Amano PS the resulting suspension is magnetically stirred at room temperature and the conversion is determined by GC analysis. After filtration of the reaction mixture using a short path column of Celite® the solvent is evaporated in vacuum. Separation was carried out by column chromatography (cyclohexane/ethyl acetate 5:1 (v/v)). Before determination of the enantiomeric excess by chiral GC the fluoroacetate (+)-**1a** is converted into the corresponding fluorohydrin (−)-**2a** by saponification.[13]

Entry 8

As described above 155 mg (1 mmol) (±)-2-fluoro-2-phenylpropan-1-ol (±)-**2a** and 86 mg (1 mmol) vinyl acetate are dissolved in 5 mL cyclohexane. The mixture is treated with 10 mg lipase Amano PS. After 18 h GC analysis shows a 63% conversion and purification by column chromatography yields alcohol (+)-**2a** (19.2 mg, 12%), $[\alpha]_D^{20}$: +10.2 (c=0.26, methanol), with 78% ee and acetate (+)-**1a** (64.4 mg, 33%), $[\alpha]_D^{20}$: +3.9 (c=0.50, methanol), with 75% ee (GC after saponification, column 3, 135°C, 0.5 bar N_2).

Entry 9

As described above (±)-**2a** (155 mg, 1 mmol) and vinyl acetate (86 mg, 1 mmol) is treated with 74 mg immobilized[16] lipase Amano PS (corresponds to 14.8 mg pure lipase) in 5 mL cyclohexane. After 12 h GC analysis shows a 47% conversion and purification by column chromatography yields alcohol (+)-**2a** (40 mg, 26%), $[\alpha]_D^{20}$: +8.7 (c=1.09, methanol), with 60% ee and acetate (+)-**1a** (46.5 mg, 24%), $[\alpha]_D^{20}$: +4.7 (c=0.98, methanol), with 84% ee (GC).

Entry 10

As described in entry 9 (±)-**2a** and vinyl acetate are dissolved in 5 mL toluene. The mixture is treated with 74 mg immobilized lipase Amano PS. After 18 h GC analysis shows a 46% conversion and purification by column chromatography yields alcohol (+)-**2a** (47.4 mg, 31%), $[\alpha]_D^{20}$: +9.1 (c=1.09, methanol), with 70% ee and acetate (+)-**1a** (50.3 mg, 26%), $[\alpha]_D^{20}$: +5.1 (c=1.0, methanol), with 95% ee (GC, after saponification).

Entry 11

As described in entry 9 (±)-**2a** and 102 mg (1 mmol) acetic anhydride are dissolved in 5 mL toluene. The mixture is treated with 74 mg immobilized lipase Amano PS. After 3 h GC analysis shows a 37% conversion. Purification by column chromatography yields alcohol (+)-**2a** (29 mg, 38%), $[\alpha]_D^{20}$: +4.5 (c=2.0, methanol), with 46% ee and acetate (+)-**1a** (24 mg, 12%), $[\alpha]_D^{20}$: +4.1 (c=1.03, methanol), with 80% ee (GC, after saponification).

Enzymatic esterification of (±)-2-phenylpropan-1-ol (±)-3 with lipase from Pseudomonas cepacia *(Amano PS) (entry 12)*

As described in entry 9 137 mg (1 mmol) (±)-2-phenylpropan-1-ol (±)-**3** and 86 mg (1 mmol) vinylacetate are dissolved in 5 mL cyclohexane. The mixture is treated with 10 mg lipase Amano PS. After 17 h the reaction is quenched and purified by column chromatography (cyclohexane/ethyl acetate 5:1 (v/v)).

(+)-2-Phenylpropan-1-ol (+)-3

Yield: 27.8 mg (20%) — $[\alpha]_D^{20}$: +10.2 (c=0.87, methanol), with 70% ee [chiral GC (column 3, 105°C, 1.2 bar N_2)]. — All other spectroscopic data agree with those published for racemic **3**.[23]

(−)-1-Acetoxy-2-phenylpropane (−)-4

Yield: 41.1 mg (30%) — $[\alpha]_D^{20}$: −2.4 (c=1.13, methanol), with 48% ee [GC, after saponification (column 3, 105°C, 1.2 bar N_2)] — All other spectroscopic data agree with those published for racemic **4**.[24]

(R)-(−)-2-Fluoro-2-phenylpropionic acid (−)-5

This procedure is carried out as described in one of our recent papers.[13] All spectroscopic data agree with those published for racemic **5**[13]: yield: 36% $[\alpha]_D^{20}$:−24.4 (c=1.3, methanol), 71% ee (^{19}F NMR).

A comparison of the reaction rates of the enzymatic esterification of (±)-2a and (±)-3

In a parallel treatment a solution of 155 mg (1 mmol) (±)-**2a** or 137 mg (1 mmol) (±)-**3**, respectively, and 86 mg (1 mmol) vinylacetate in 5 ml cyclohexane 10 mg lipase Amano PS is added. The resulting suspension are magnetically stirred at room temperature and the conversion is observed by GC analysis. The results are shown in Figure 2.

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