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Preparation of novel phenylfuran-based cyanohydrin esters: lipase-catalysed kinetic and dynamic resolution

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Abstract—A series of novel (*R*)-5-phenylfuran-2-yl cyanomethyl butanoates were prepared by *Pseudomonas cepacia* lipase-catalysed dynamic kinetic resolution in toluene. The method exploits a basic resin both for the racemization and formation of phenylfuran-based cyanohydrins and for the decomposition of acetone cyanohydrin in one-pot with enzymatic enantioselective acylation using vinyl butanoate. The lipase-catalysed methanolysis of racemic 5-phenylfuran-2-yl cyanomethyl butanoates in toluene with $E \gg 100$ was shown to be usable when the corresponding (*S*)-butanoates are needed. *Candida antarctica* lipase A provided racemic cyanohydrin butanoates with quantitative chemical yields under mild conditions.

1. Introduction

Phenylfuran-based structures are important units for the synthesis of various kinds of biologically active molecules. When a phenylfuran-based structure is attached to a stereogenic centre in a molecule the preparation of enantiomers will be required. For that purpose biocatalysts where enantioselectivity is introduced by the homochirality of an enzyme, are becoming increasingly attractive tools for synthetic chemistry.[1] The value of biocatalysis is now more relevant than ever for environmental reasons in addition to the demand for high enantioselectivities.

Optically active cyanohydrins are versatile intermediates for organic synthesis, since cyanohydrin enantiomers can be easily converted to other optically active compounds. Two main biocatalytic methods are known for the preparation of optically active cyanohydrins.[2,3] The (*R*)- and (*S*)-oxynitrilase-catalysed enantioface addition of hydrogen cyanide to an aldehyde or ketone offers highly enantiopure products in almost quantitative chemical yields. In these reactions, both isolated highly optimised enzymes[4–6] and unisolated enzymes such as economical defatted meals[7,8] and dechlorophylled shoots[7] have served as asymmetric catalysts.[2] Enzymatic kinetic resolution is another effective biocatalytic approach to optically active cyanohydrins. This has been previously accomplished by the acylation of racemic cyanohydrins and by the lysis of the acylated counterparts in the presence of a suitable lipase[9,10] or by the oxynitrilase-catalysed enantioselective decomposition of racemic cyanohydrins.[11–13] The main disadvantage of the traditional resolution method is, however, the maximum 50% theoretical yield of one enantiomer and the dependence of enantiomeric excess (ee) on the conversion of a reaction. These disadvantages are overcome in dynamic kinetic resolution, where a racemic mixture is transformed to one of the enantiomers by racemizing the less reactive enantiomer in situ in the course of the process. This principle was previously exploited for lipase-catalysed enantioselective acylations with isopropenyl acetate using an efficient one-pot synthesis of cyanohydrin esters in the presence of a basic resin.[10,14,15] A modification of this method previously allowed the preparation of (*R*)-furylbenzotiazol-based cyanohydrin acetates.[16]

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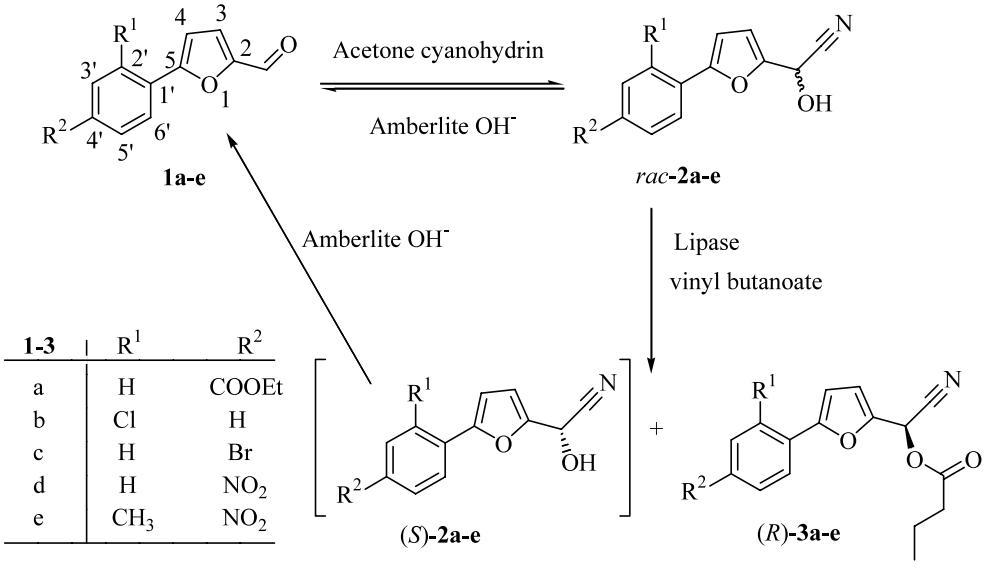
In this work, enzymatic possibilities for the preparation of highly enantiopure hydroxy-(5-phenylfuran-2-yl)-acetonitriles were investigated. At the early stage of the studies it was shown that our model aldehyde **1c** was not a substrate for (*R*)-oxynitrilase in almond meal and attention was focused on lipase-catalysed reactions. We now report the preparation of novel (*R*)-cyanohydrin butanoates **3a**–**e** from the corresponding aldehydes **1a**–**e** and acetone cyanohydrin (source of HCN) by the lipase-catalysed dynamic kinetic resolution of cyanohydrins **2a**–**e** with vinyl butanoate in the presence of Amberlite IRA-904 basic resin in non-aqueous media (Scheme 1). Vinyl butanoate was used as an acyl donor because the resulting butanoates **3a**–**e** were easily separated by the chiral HPLC method, whereas the enantiomers of the corresponding acetates were unseparable. Traditional kinetic resolution provides the enantioselectivity basis for successful dynamic kinetic resolution. Accordingly, reaction conditions were first optimized for the lipase-catalysed acylation of novel cyanohydrins **2a**–**e** (Scheme 2). In order to supply the need for (*S*)-cyanohydrin esters, the lipase-mediated alcoholysis of racemic butanoates **3a**–**e** was studied (Scheme 3). Moreover, chemical and lipase-catalysed methods for the preparation of racemic esters **3a**–**e** for analytical and substrate purposes are described.

2. Results and discussion

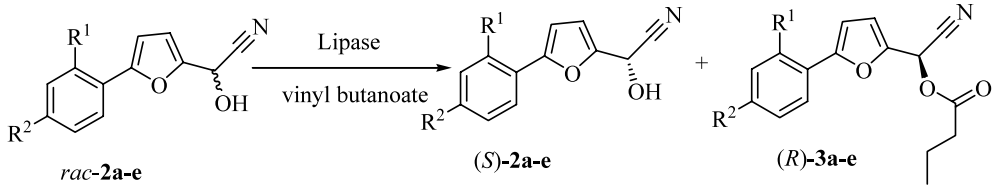
2.1. Kinetic enzymatic resolution by acylation

A large number of commercially available lipases exhibit a high degree of substrate tolerance, leading to products with various degrees of enantioselectivity. Potential lipases were screened for the enantioselective acylation of cyanohydrin *rac*-**2c** as a model substrate with vinyl butanoate as an irreversible acyl donor using diisopropyl ether as solvent (Scheme 2). The behaviour of lipases greatly differs. While lipases AK and F are

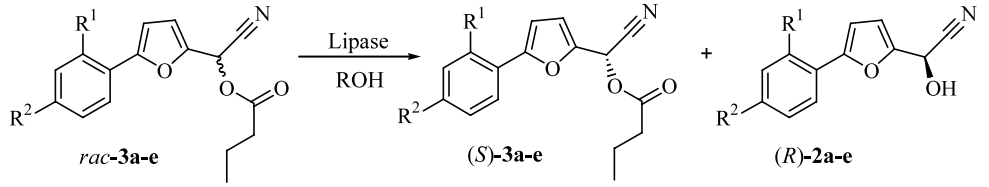


1-3	R^1	R^2
a	H	COOEt
b	Cl	H
c	H	Br
d	H	NO_2
e	CH_3	NO_2

Scheme 1. One pot synthesis of (*R*)-(+)-**3a**–**e** by dynamic kinetic resolution.



Scheme 2. Kinetic resolution of racemic cyanohydrins **2a**–**e**.



Scheme 3. Kinetic resolution of racemic cyanohydrin esters **3a**–**e**.

catalytically inactive, lipase PS ($E=15\pm2$) and CAL-B ($E=10\pm0.3$) enantioselectively catalyse the reaction. In the case of CAL-A, a fast reaction leads to the formation of racemic butanoate **3c** with almost quantitative chemical yields. Since the best selectivity was observed with lipase PS, this enzyme was used for further studies. It is worth emphasizing that for catalytic activity of lipase PS it is essential that immobilized enzyme is involved. Thus, no reaction between **2c** and vinyl butanoate was observed in the presence of a native enzyme in toluene within 2 weeks, whereas the initial rate $v_o=0.19$ μmol mg^{-1} h^{-1} was observed when the present enzyme preparation (the enzyme adsorbed on Celite in the presence of sucrose)[17] was used. Effects of other immobilization methods on reactivity were not investigated in this work.

In order to enhance enantioselectivity (E values), the lipase PS-catalysed acylation of cyanohydrin *rac*-**2c** with vinyl butanoate was carried out in different solvents (Table 1). The cost of the high enantioselectivity in acetonitrile and dichloromethane is a significant drop in reactivity (conversion reached after the certain time, entries 1 and 2). Vinyl butanoate and toluene proved to be the best solvents for the present acylation (entries 7 and 8). Due to the low solubility of cyanohydrin esters **3a**, **3d** and **3e** in vinyl butanoate and for economic reasons, toluene was chosen for further investigations.

Table 1. Solvent effects on the acylation of cyanohydrin *rac*-**2c** with vinyl butanoate by lipase PS preparation (10 mg ml^{-1})

Entry	Solvent	E	Time (h)	Conv. (%)
1	Acetonitrile	$\gg100$	168	7
2	Dichloromethane	$\gg100$	168	16
3	Diisopropyl ether	15 ± 2	96	45
4	*t*-Butanol	–	168	0
5	Tetrahydrofuran	–	168	0
6	*t*-Butyl methyl ether	9 ± 0.2	144	35
7	Toluene	82 ± 12	96	46
8	Vinyl butanoate	70 ± 10	96	47

Lipase PS shows different reactivity and selectivity in the acylation of racemic cyanohydrins **2a**–**e** with vinyl butanoate in toluene (Table 2). While conversion in 4 days is only slightly influenced by the position and properties of the substituents R^1 and R^2 in **2b**–**e** (entries 2–5), a considerably lower reactivity is evident for substrate **2a** (entry 1). Strongly electron withdrawing substituents R^2 (CO_2Et and NO_2) seem to result in low enzymatic enantioselectivities for **2a** and **2d** (entries 1 and 4), whereas the presence of electron donating methyl substituent R^1 in **2e** leads to improved enantioselectivity when compared to that observed for **2d** (entries 5 and 4, respectively).

Table 2. Acylation of cyanohydrins **2a**–**e** with vinyl butanoate in toluene by lipase PS preparation (10 mg ml^{-1})

Entry	Resolution products	E	Time (h)	Conv. (%)
1	(*S*)-**2a**, (*R*)-**3a**	13 ± 0.2	168	26
2	(*S*)-**2b**, (*R*)-**3b**	84 ± 15	96	47
3	(*S*)-**2c**, (*R*)-**3c**	82 ± 12	96	46
4	(*S*)-**2d**, (*R*)-**3d**	25 ± 1	96	43
5	(*S*)-**2e**, (*R*)-**3e**	144 ± 23	96	39

2.2. Dynamic kinetic resolution and the preparation of (*R*)-cyanohydrin esters

As a general requirement for enzymatic dynamic kinetic resolution, the enzyme must stay active throughout the reaction and the less reactive enantiomer must be rapidly racemized under the conditions where the product of an enzyme-catalysed reaction is stable. Under such conditions, the starting material is always racemic, allowing the maxim enantiopurity (determined by the E value for the corresponding kinetic resolution) at the theoretical zero conversion to the more reactive enantiomer to be maintained throughout the reaction. This is extremely important for an enzymatic reaction proceeding enantioselectively since ee of the product enantiomer tends to decrease with increasing conversion of kinetic resolution especially at E values less than 100.

For the production of (*R*)-cyanohydrin butanoates **3a**–**e** (Scheme 1), a fast equilibrium between a cyanohydrin and the corresponding aldehyde (and acetone) and hydrogen cyanide in the presence of a base is essential for the present method. In order to show that cyanohydrins are smoothly produced at high enough amounts, the mixture of aldehyde **1c** (0.15 mmol) and acetone cyanohydrin (0.325 mmol) in the presence of the Amberlite IRA-904 basic resin (5 mg ml^{-1}; 0.65 mmol ml^{-1}) were studied in toluene at room temperature. The equilibrium value [**2c**]/[**1c**] = 6 was reached in less than 3 h clearly satisfying the requirement. In order to verify the enantiomeric stability of the products, the effect of the basic resin (5 mg ml^{-1}; 0.65 mmol ml^{-1}) was investigated on the product mixture [(*S*)-**2a**–**e** and (*R*)-**3a**–**e**] of the above-described kinetic resolution (Scheme 2). Free (*S*)-cyanohydrins **2a**–**e** were racemized within less than 2 h while the enantiopurity of (*R*)-cyanohydrin esters **3a**–**e** was still unchanged after 7 days.

The amount of the basic resin is critical for the dynamic kinetic resolution as previously pointed out in the case of mandelonitrile as a substrate.[15] When the amount is too low it can be neutralized by the formation of butanoic acid that is liberated from the achiral acyl donor by the lipase-catalysed action of the water in the formally dry enzyme preparation and by the presence of hydrogen cyanide. That the basic resin still is active at the end of the dynamic kinetic resolution of **2c** was shown by adding a new proportion of acetone cyanohydrin. The dark brown color appeared immediately, indicating that the base-catalysed decomposition of ace-

tone cyanohydrin had produced hydrogen cyanide the formation of which was followed by its base-catalysed polymerization.[18] The dark brown color was also introduced when 10 mg ml^{-1} (1.3 mmol ml^{-1}) of the resin in the dynamic kinetic resolution mixture was used instead of 5 mg ml^{-1}, the high base content totally preventing the enzymatic acylation.

In the present one-pot synthesis of (*R*)-cyanohydrin butanoates **3a–e** by lipase PS (Table 3), the observed ee values are in accordance with the theoretical values that can be calculated by the equation of Chen et al.[19] using the *E* values in Table 2 and extrapolating ee to zero conversion. Finally, gram-scale reactions stopped at high conversions, indicating that the aldehydes can be almost totally converted to the corresponding (*R*)-cyanohydrin butanoates. The products were also isolated in high chemical yields. As is shown in Table 3, reaction times are strongly affected by the enzyme content and temperature, these variables not having an effect on the high enantiopurities. This allows the choice between using low amounts of the expensive enzyme or to save time under otherwise less economical conditions.

2.3. Kinetic enzymatic resolution by alcoholysis

For the preparation of cyanohydrin enantiomers by kinetic resolution, it is advantageous to select a reaction which gives the desired enantiomer as a less reactive acylated counterpart because the separation of the resolution products (one enantiomer as a free cyanohydrin and the other as an acylated counterpart) often leads to considerable decomposition and racemization of the free cyanohydrin. Accordingly, racemic cyanohydrin esters **3a–e** were subjected to the lipase PS-catalysed alcoholysis with methanol and propanol in toluene in order to prepare (*S*)-cyanohydrin esters (Scheme 3; Table 4). Highly enantioselective reactions tended to stop at 50% conversion, affording the two enantiomers simultaneously in the resolution mixture.

2.4. Preparation of racemic cyanohydrin esters

The above enzyme screening proved CAL-A to be an excellent, fast and environmentally benign catalyst for the preparation of racemic ester **3c**. Encouraged by this, cyanohydrins **2a–e** were subjected to acylation with vinyl butanoate in toluene in the presence of CAL-A.

Table 3. Dynamic kinetic resolution of cyanohydrins **2a–e** with vinyl butanoate in toluene by lipase PS preparation

Entry	Product	Conv. (%)	Yield (%)	Time (h)	Ee (%)	Theoretical ee (%)	$[\alpha]_D$[a]
1	(*R*)-**3a**[b]	75	69	168	80	85	+4.4
2	(*R*)-**3a**[c]	81	72	120	80	85	+4.4
3	(*R*)-**3a**[d]	86	73	72	79	–	+4.4
4	(*R*)-**3b**[b]	86	79	168	97	98	+9.0
5	(*R*)-**3b**[c]	>99	93	96	96	98	+8.8
6	(*R*)-**3b**[d]	>99	94	36	96	–	+8.8
7	(*R*)-**3c**[b]	91	93	168	95	97	+3.2
8	(*R*)-**3c**[c]	>99	92	96	95	97	+3.2
9	(*R*)-**3c**[d]	>99	92	36	95	–	+3.1
10	(*R*)-**3d**[b]	87	82	168	91	92	+11.1
11	(*R*)-**3d**[c]	>99	91	96	91	92	+11.1
12	(*R*)-**3d**[d]	>99	92	36	91	–	+11.0
13	(*R*)-**3e**[b]	95	88	168	98	98	+4.8
14	(*R*)-**3e**[c]	>99	91	96	96	98	+4.7
15	(*R*)-**3e**[d]	>99	93	36	96	–	+4.7

[a] $t = 25°C$, (*c* 1, $CHCl_3$).
[b] 10 mg ml^{-1} of the enzyme preparation, 22–23°C.
[c] 50 mg ml^{-1} of the enzyme preparation, 22–23°C.
[d] 50 mg ml^{-1} of the enzyme preparation, 45°C.

Table 4. Alcoholysis of cyanohydrin esters **3a–e** with an alcohol in toluene by lipase PS preparation (10 mg ml^{-1})

Entry	Substrate	ROH (M)	Time (h)	Conv. (%)	$Ee_{(S)\text{-}3}$ (%)	$Ee_{(R)\text{-}2}$ (%)	*E*
1	*rac*-**3a**	Methanol (0.8 M)	144	47	82	93	70±2
2	*rac*-**3b**	Methanol (0.8 M)	48	50	>99	>99	≫100[a]
3	*rac*-**3c**	Methanol (0.8 M)	48	50	>99	>99	≫100[a]
4	*rac*-**3c**	Methanol (0.4 M)	48	49	91	95	131±5
5	*rac*-**3c**	Propanol (0.8 M)	48	49	90	94	93±2
6	*rac*-**3c**	Propanol (0.4 M)	48	51	98	92	120±8
7	*rac*-**3d**	Methanol (0.8 M)	48	50	>99	>99	≫100[a]
8	*rac*-**3e**	Methanol (0.8 M)	48	50	>99	>99	≫100[a]

[a] Only one enantiomer was detected by the HPLC method.

In 2 h the substrates were totally transformed to the butanoate esters **3a**–**e** (method A; Table 5). For the chemical acylation of the cyanohydrins **2a**–**e** with butanoic anhydride (method B), the presence of 4-*N*,*N*-dimethylaminopyridine in pyridine and triethylamine is necessary. The chemical reactions are accompanied by the formation of several unidentified by-products in addition to the related aldehydes **1a**–**e** and lead to moderate chemical yields for **3a**–**e**. Accordingly, the enzymatic method A is clearly better than the chemical method B which suffers from the lability of cyanohydrins.

Table 5. Enzymatic (method A) and chemical (method B) synthesis of racemic **3a**–**e**

Product	Method A			Method B
	Conv. (%)	Yield (%)[a]	Time (h)	Yield (%)[a]
rac-**3a**	>99	95	2	66
rac-**3b**	>99	96	2	71
rac-**3c**	>99	95	2	68
rac-**3d**	>99	94	2	70
rac-**3e**	>99	94	2	67

[a] Isolated yield.

3. Conclusion

The present work describes the predictability of dynamic kinetic resolution for the preparation of novel cyanohydrin butanoates (*R*)-**3a**–**e** (Table 3). The method combines the base-catalysed in situ formation of racemic cyanohydrins **2a**–**e** from the corresponding aldehydes **1a**–**e** and hydrogen cyanide to the in situ lipase-catalysed kinetic resolution and to the base-catalysed in situ racemization of the less reactive (*S*)-**2a**–**e** (Scheme 1). In most cases, more than 99% of an aldehyde was easily transformed to the corresponding (*R*)-**3** with high enantiopurity, the efficiency of the method depending on the amount of the enzyme and temperature. As an advantage of the present method the separate preparation and purification of relatively labile cyanohydrins is not necessary. As another benefit, the handling of hydrogen cyanide is avoided by making use of the base-lability of acetone cyanohydrin. In addition, an effective and fast enzymatic method for the preparation of racemic **3a**–**e** from the corresponding cyanohydrin with vinyl butanoate in the presence of CAL-A in toluene is described.

The lipase PS-catalysed alcoholysis of racemic **3a**–**e** with methanol in toluene proved to be a convenient method for the preparation of (*S*)-cyanohydrin butanoates **3a**–**e** through traditional kinetic resolution proceeding at high enantioselectivity ($E \gg 100$).

4. Experimental

4.1. Materials and methods

4.1.1. Analytical methods. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Jeol Lambda 400 spectrometer operating at 399.78 and 100.54 MHz, respectively. ^{1}H spectra were referenced internally to the solvent signal ($C\underline{H}Cl_3$, 7.24 ppm); ^{13}C spectra to the solvent signal ($\underline{C}DCl_3$, 77.00 ppm). The correct assignment of the chemical shifts was confirmed by use of standard ^{13}C, ^{1}H correlation measurements. Either f1-decoupled heteronuclear correlation spectroscopy method (CHSHF) or heteronuclear multiple-quantum correlation spectroscopy method preceding a bilinear rotation decoupling pulse sequence (HMQC-BIRD) was used for tracking the direct connectivity between the ^{13}C and ^{1}H nuclei (methods optimized to 145 Hz $^{1}J_{CH}$ coupling). For tracking the connectivity over multiple-bonds, either correlation via long-range coupling spectroscopy method (COLOC) or heteronuclear multiple-bond correlation spectroscopy method preceding a bilinear rotation decoupling pulse sequence (HMBC-BIRD) was used (methods optimized to $^{n}J_{CH}$ couplings of 4 or 8 Hz). Mass spectra (MS) were taken on a VG 7070E mass spectrometer.

High performance liquid chromatography (HPLC) analyses were conducted with a HP 1090 instrument using a CHIRACEL OD column (0.46×25 cm) and elution with the mixture of hexane and isopropyl alcohol (9:1). Baseline enantiomeric separation of all chiral substances **2a**–**e**, **3a**–**e** was performed. For quantitative chromatographic determination, molar abortion constants (ε) were used. UV spectra were taken with a Helios Lambda spectrofotometer. Thin layer chromatography (TLC) was carried out using Merck Kieselgel $60F_{254}$ sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdic acid solution and heating. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (0.063–0.200 μm). Melting points were determined by a hot plate method and are uncorrected. Optical rotations (*c* 1, $CHCl_3$) were determined on a Perkin Elmer 241 polarimeter. Elemental analyses of **2a**–**c** (lability of **2d** and **2e** prevented the determination) and **3a**–**e** were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyser. The determination of E was based on equation $E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$.[19] Using linear regression E is achieved as the slope of a line. All enzymatic reactions were performed at room temperature (23–24°C).

4.1.2. Reagents and solvents. Anilines, furfural, vinyl butanoate, trimethylsilyl cyanide, $CuCl_2$ and ZnI_2 were products of Aldrich or Fluka. All solvents were purified and dried by standard methods as required.[20] Amberlite IRA 904 was purchase from Acros and it was conditioned as previously described.[14]

4.1.3. Biocatalyst. Lipases from *Pseudomonas fluorescence* (lipase AK), *Pseudomonas cepacia* (lipase PS) and *Rhizopus oryzae* (lipase F) were from Amano Europe, England. Lipase A (CAL-A) and lipase B (CAL-B, Chirazyme L2) from *Candida antarctica* were purchased from Boehringer-Mannheim. Before use CAL-A and lipases AK and PS were adsorbed on Celite (4.0 g) by dissolving the enzyme and sucrose (0.24 g) in Tris–HCl buffer (pH 7.9) and thereafter left to dry at room temperature.[17] The

final lipase content in the enzyme preparation was 20% (w/w).

4.2. Synthesis of aldehydes 1a–e

5-Phenylfuran-2-carbaldehydes were prepared using the Meerwein method.[21] To a solution of one of the diazonium salts $R^1R^2PhN_2^+Cl^-$ (ca. 0.1 mol) in water (100 ml) furan-2-carbaldehyde (9.6 g, 8.28 ml, 0.1 mol) and cuprous chloride (9.9 g, 0.1 mol) were added at 0–5°C and the reaction mass was stirred at room temperature for 48 h. The product **1a–e** was filtered, washed with water (4×50 ml), dried, purified by column chromatography on silica gel with dichloromethane and recrystallized from hexane **1a**,**b** or ethanol **1c–e**.

4.2.1. 5-(4-Carboxyethylphenyl)furan-2-carbaldehyde 1a. Yield: 73%; mp: 125°C (lit. 124.5–126°C)[22]; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 7.83×10^4 (270), 11.24×10^4 (330); HRMS M$^+$ found (M$^+$ calculated for $C_{14}H_{12}O_4$): 244.07408 (244.07356); MS: m/z (relative intensity) = 246 (2), 245 (12), 244 (81) [M]$^+$, 243 (2), 217 (3), 215 (24), 214 (6), 201 (2), 200 (16), 199 (100), 172 (3), 171 (6), 160 (1), 159 (9), 116 (3), 115 (29), 114 (14), 113 (6); ^{1}H NMR ($CDCl_3$, 25°C): $\delta = 1.37$ (t, $J = 7.2$ Hz, 3H, C(4′)-COOCH$_2$C$\underline{\text{H}}_3$), 4.36 (q, $J = 7.2$ Hz, 2H, C(4′)-COOC$\underline{\text{H}}_2$CH$_3$), 6.92 (d, $J = 4$ Hz, 1H, C(4)-H), 7.30 (d, $J = 4$ Hz, 1H, C (3)-H), 7.83 (d, $J = 8.52$ Hz, 2H, C(2′)-H, C(6′)-H), 8.06 (d, $J = 8.52$ Hz, 2H, C(3′)-H, C(5′)-H), 9.64 (s, 1H, C(2)-C$\underline{\text{H}}$O); ^{13}C NMR ($CDCl_3$, 25°C): $\delta = 14.24$ (C(4′)-COOCH$_2$$\underline{\text{C}}H_3$), 61.17 (C(4′)-COO$\underline{\text{C}}H_2CH_3$), 109.27 (C(4)), 123.09 (C(3)), 124.92 (C(2′), C(6′)), 130.09 (C(3′), C(5′)), 131.02 (C(4′)), 132.62 (C(1′)), 152.44 (C(2)), 157.88 (C(5)), 165.81 (C(4′)-$\underline{\text{C}}$OOCH$_2$CH$_3$), 177.37 (C(2)-$\underline{\text{C}}$HO); anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.86; H, 4.89%.

4.2.2. 5-(2-Chlorophenyl)furan-2-carbaldehyde 1b. Yield: 67%; mp: 77°C (lit. 76.5–77°C)[23]; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 1.82×10^4 (265), 7.29×10^4 (323); HRMS M$^+$ found (M$^+$ calculated for $C_{11}H_7ClO_2$): 206.013140 (206.013457); MS: m/z (relative intensity) = 209 (4), 208 (32), 207 (20), 206 (100) [M]$^+$, 205 (27), 204 (3), 180 (2), 179 (1), 178 (6), 152 (2), 151 (18), 150 (6), 149 (56), 116 (2), 115 (17), 114 (17), 113 (10); ^{1}H NMR ($CDCl_3$, 25°C): $\delta = 7.24$ (m, $J = 4.1$ Hz, 2H, C(4)-H, C(4′)-H), 7.27 (d, $J = 3.8$ Hz, 1H, C(3)-H), 7.30 (ddd, $J = 7.4$ Hz, $J = 1.4$ Hz, 1H, C(5′)-H), 7.40 (dd, $J = 7.9$ Hz, $J = 1.5$ Hz, 1H, C(3′)-H), 7.93 (dd, $J = 7.68$ Hz, $J = 1.92$ Hz, 1H, C (11)-H), 9.62 (s, 1H, C(2)-C$\underline{\text{H}}$O); ^{13}C NMR ($CDCl_3$, 25°C): $\delta = 113.14$ (C(4)), 122.84 (C(3)), 127.12 (C(5′)), 127.54 (C(1′)), 129.07 (C(3′)), 130.11 (C(4′)), 130.89 (C(6′)), 131.47 (C(2′)), 151.49 (C(2)), 155.35 (C(5)), 177.43 (C(2)-$\underline{\text{C}}$HO); anal. calcd for $C_{11}H_7ClO_2$: C, 63.94; H, 3.41; Cl, 17.16. Found: C, 63.86; H, 3.43; Cl, 17.25%.

4.2.3. 5-(4-Bromophenyl)furan-2-carbaldehyde 1c. Yield: 75%; mp: 153°C (lit. 153.5–154°C)[24]; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 9.83×10^4 (270), 11.98×10^4 (329); HRMS M$^+$ found (M$^+$ calculated for $C_{11}H_7BrO_2$): 249.96283 (249.96294); MS: m/z (relative intensity) = 253 (11), 252 (95), 251 (29), 250 (100) [M]$^+$, 249 (18), 222 (6), 196 (4), 195 (37), 194 (4), 193 (38), 157 (2), 155 (2), 116 (3), 115 (29), 114 (37), 113 (15); ^{1}H NMR ($CDCl_3$, 25°C): $\delta = 6.80$ (d, $J = 3.64$ Hz, 1H, C(4)-H), 7.28 (d, $J = 3.64$ Hz, 1H, C(3)-H), 7.53 (d, $J = 8.56$ Hz, 2H, C(3′)-H, C(5′)-H), 7.64 (d, $J = 8.56$ Hz, 2H, C(2′)-H, C(6′)-H), 9.62 (s, 1H, C(2)-C$\underline{\text{H}}$O); ^{13}C NMR ($CDCl_3$, 25°C): $\delta = 108.04$ (C(4)), 123.40 (C(3)), 123.87 (C(4′)), 126.63 (C(2′), C(6′)), 127.81 C(1′), 132.14 ((C(3′), C(5′)), 152.09 (C(2)), 158.14 (C(5)), 177.2 C(2)-$\underline{\text{C}}$HO; anal. calcd for $C_{11}H_7BrO_2$: C, 52.62; H, 2.81; Br, 31.82. Found: C, 52.66; H, 2.84; Br, 31.85%.

4.2.4. 5-(4-Nitrophenyl)furan-2-carbaldehyde 1d. Yield: 62%; mp: 203°C (lit. 203–204°C)[25]; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 5.08×10^4 (271), 7.36×10^4 (330); HRMS M$^+$ found (M$^+$ calculated for $C_{11}H_7NO_4$): 217.03725 (217.03751); MS: m/z (relative intensity) = 218 (12), 217 (100) [M]$^+$, 216 (6), 188 (3), 187 (19), 172 (1), 171 (6), 170 (2), 160 (2), 159 (6), 143 (2), 142 (4), 131 (4), 117 (2), 116 (3), 115 (32), 114 (22), 113 (8); ^{1}H NMR ($CDCl_3$, 25°C): $\delta = 7.02$ (d, $J = 3.7$ Hz, 1H, C (4)-H), 7.35 (d, $J = 3.7$ Hz, 1H, C(3)-H), 7.96 (dd, $J = 8.97$ Hz, $J = 2.2$ Hz, 2H, C(2′)-H, C(6′)-H), 8.29 (dd, $J = 8.97$ Hz, $J = 2.2$ Hz, 2H, C(3′)-H, C(5′)-H), 9.71 (s, 1H, C(2)-C$\underline{\text{H}}$O); ^{13}C NMR ($CDCl_3$, 25°C): $\delta = 110.6$ (C(4)), 122.8 (C(3)), 124.4 (C(3′), C(5′)), 125.8 (C(2′), C(6′)), 134.6 (C(1′)), 147.9 (C(4′)), 153.0 (C(2)), 156.3 (C(5)), 177.6, (C(2)-$\underline{\text{C}}$HO); anal. calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.86; H, 3.34; N, 6.52%.

4.2.5. 5-(2-Methyl-4-nitrophenyl)furan-2-carbaldehyde 1e. Yield: 65%; mp: 143°C; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 2.53×10^4 (272), 3.54×10^4 (318); HRMS M$^+$ found (M$^+$ calculated for $C_{12}H_9NO_4$): 231.05333 (231.05316); MS: m/z (relative intensity) = 232 (2), 231 (14) [M]$^+$, 203 (1), 202 (12), 201 (100), 158 (4), 146 (7), 145 (4), 144 (6), 132 (2), 131 (7), 130 (50), 129 (9), 128 (31), 127 (19), 126 (7), 119 (4), 118 (12), 117 (2), 116 (9), 115 (20); ^{1}H NMR ($CDCl_3$, 25°C): $\delta = 2.44$ (s, 3H, C(2′)-C$\underline{\text{H}}_3$), 6.71 (d, $J = 3.84$ Hz, 1H, C(4)-H), 7.27 (d, $J = 3.84$ Hz, 1H, C(3)-H), 7.43 (d, $J = 8.12$ Hz, 1H, C(6′)-H), 7.59 (s, 1H, C(3′)-H), 7.68 (d, $J = 8.12$ Hz, 1H, C(5′)-H), 9.63 (s, 1H, C(2)-C$\underline{\text{H}}$O); ^{13}C NMR ($CDCl_3$, 25°C): $\delta = 21.08$ C(2′)-$\underline{\text{C}}$H$_3$, 111.51 (C(4)), 120.1 (C(1′)), 122.1 (C(3)), 124.62 (C(3′)), 129.82 (C(5′)), 133.05 (C(6′)), 141.42 (C(2′)), 147.78 (C(4′)), 152.65 (C(2)), 153.68 (C(5)), 177.56, C(2)-$\underline{\text{C}}$HO; anal. calcd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.36; H, 3.88; N, 6.12%.

4.3. Synthesis of racemic cyanohydrins 2a–e

Using a known method,[26] a catalytic amount of ZnI_2 (3.2 mg, 10 μmol) and trimethylsilyl cyanide (119 mg, 150 μl, 1.2 mmol) were added to a stirred solution of one of the aldehydes **1a–e** (1 mmol) in dry dichloromethane (10 ml) and the resulting mixture was stirred at room temperature until the entire quantity of an aldehyde was transformed. The solvent was evaporated and the crude product redissolved in 10 ml acetonitrile. The formed trimethylsilyl cyanohydrin decomposed when HCl (3 M, 2 ml) was added. The reaction mass was evaporated to the final volume of 2 ml and water (3 ml) and dichloromethane (6 ml) were

added. The aqueous layer was extracted with dichloromethane (6 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed. The resulted crude cyanohydrins were purified by recrystallization from hexane *rac*-**2a**–**c** or hexane–ethyl acetate *rac*-**2d**,**e**.

4.3.1. Hydroxy-[5-(4-carboxyethylphenyl)-furan-2-yl]-acetonitrile *rac*-2a. Yield: 92%; mp: 78–80°C; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 6.59×10^3 (276), 4.16×10^4 (321); HRMS M$^+$ found (M$^+$ calculated for $C_{15}H_{13}NO_4$): 271.08466 (271.08446); MS: m/z (relative intensity) = 271 (2) [M]$^+$, 255 (1), 254 (1), 246 (3), 245 (28), 244 (88), 217 (6), 216 (44), 215 (12), 201 (4), 200 (34), 199 (100), 188 (2), 172 (5), 171 (10), 160 (2), 159 (14), 143 (4), 142 (6), 131 (4), 117 (3), 116 (4), 115 (39), 114 (21), 113 (9); ^{1}H NMR ($CDCl_3$, 25°C): δ = 1.38 (t, J = 6.8 Hz, 3H, C(4′)-COOCH$_2$C$\underline{H}_3$), 4.35 (q, J = 6.8 Hz, 2H, C(4′)-COOC$\underline{H}_2$CH$_3$), 5.60 (s 1H, C(2)-C$\underline{H}$(OH)CN), 6.65 (d, J = 3.4 Hz, 1H, C(4)-H), 6.67 (1H, d, J = 3.4 Hz, 1H, C(3)-H), 7.60 (d, J = 8.4 Hz, 2H, C(2′)-H, C(6′)-H), 7.95 (d, J = 8.4 Hz, 2H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 25°C): δ = 14.21 (C(4′)-COOCH$_2$$\underline{C}H_3$), 57.11 (C(2)-$\underline{C}$H(OH)CN), 61.39 (C(4′)-COO$\underline{C}$H$_2$CH$_3$), 107.88 (C(4)), 112.15 (C(3)), 116.82 (C(2)-CH(OH)$\underline{C}$N), 123.66 (C(2′), C(6′)), 129.28 (C(4′)), 130.01 (C(3′), C(5′)), 133.58 (C(1′)), 148.15 (C(2)), 154.42 (C(5)), 166.70 (C(4′)-$\underline{C}$OOCH$_2$CH$_3$); HPLC (CHIRACEL OD, 1 ml/min): $t_R(S)$ 27.3 min, $t_R(R)$: 34.3 min; anal. calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.36; H, 4.74; N, 5.22%.

4.3.2. Hydroxy-[5-(2-chlorophenyl)-furan-2-yl]acetonitrile *rac*-2b. Yield: 90%; mp: 88–89°C; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 1.53×10^4 (299); HRMS M$^+$ found (M$^+$ calculated for $C_{12}H_8ClNO_2$): 233.02361 (233.02436); MS: m/z (relative intensity) = 236 (1), 235 (8), 234 (4), 233 (26) [M]$^+$, 231 (1), 219 (2), 218 (13), 217 (5), 216 (39), 209 (4), 208 (32), 207 (23), 206 (100), 205 (27), 204 (3), 180 (3), 179 (1), 178 (7), 153 (5), 152 (5), 151 (21), 150 (7), 149 (67), 140 (2), 139 (1), 138 (5), 123 (2), 116 (3), 115 (24), 114 (24), 113 (15); ^{1}H NMR ($CDCl_3$, 25°C): δ = 5.61 (s 1H, C(2)-C$\underline{H}$(OH)CN), 6.71 (d, J = 3.4 Hz, 1H, C(3)-H)), 7.10 (d, J = 3.4 Hz, 1H, C(4)-H)), 7.24 (ddd, J = 7.7 Hz, J = 1.4 Hz, 1H, C(4′)-H), 7.32 (dd, J = 7.4 Hz, 1H, C(5′)-H), 7.44 (d, J = 7.92 Hz, 1H, C(3′)-H), 7.84 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 25°C): δ = 57.09 (C(2)-$\underline{C}$H(OH)CN), 111.67 (C(4)), 112.10 (C(3)), 116.73 (C(2)-CH(OH)$\underline{C}$N), 126.97 (C(5′)), 128.17 (C(1′)), 128.96 (C(3′)), 130.5 (C(2′)), 130.7 (C(6′)), 130.74 (C(4′)), 146.70 (C(2)), 152.04 (C(5)); HPLC (CHIRACEL OD, 1 ml/min): $t_R(S)$ 12.5 min, $t_R(R)$ 16.4 min; anal. calcd for $C_{12}H_8ClNO_2$: C, 61.69; H, 3.45; Cl; 15.17; N, 5.99. Found: C, 61.65; H, 3.47; Cl, 15.23; N, 6.03%.

4.3.3. Hydroxy-[5-(4-bromophenyl)-furan-2-yl]acetonitrile *rac*-2c. Yield: 88%; mp: 94–95°C; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 3.65×10^4 (299), 3.70×10^4 (308); HRMS M$^+$ found (M$^+$ calculated for $C_{12}H_8BrNO_2$): 276.97409 (276.97384); MS: m/z (relative intensity) = 279 (2), 277 (2) [M]$^+$, 254 (1), 253 (12), 252 (99), 251 (32), 250 (100), 249 (20), 223 (1), 222 (7), 195 (33), 194 (4), 193 (33), 155 (2), 116 (2), 115 (20), 114 (25), 113 (10); ^{1}H NMR ($CDCl_3$, 25°C): δ = 5.57 (s, 1H, C(2)-C$\underline{H}$(OH)CN), 6.62 (d, J = 3.4 Hz, 1H, C(4)-H)), 6.65 (1H, d, J = 3.4 Hz, 1H, C(3)-H)), 7.47–7.52 (m, 4H, C(2′)-H), C(3′)-H, C(5′)-H, C(6′)-H)); ^{13}C NMR ($CDCl_3$, 25°C): δ = 57.10 (C(2)-$\underline{C}$H(OH)CN), 106.35 (C(4)), 112.38 (C(3)), 116.68 (C(2)-CH(OH)$\underline{C}$N), 122.26 (C(4′)), 125.59 (C(2′), C(6′)), 128.5 (C(1′)), 131.9 (C(3′), C(5′)), 147.04 (C(2)), 154.84 (C(5)); HPLC (CHIRACEL OD, 1 ml/min): $t_R(S)$ 31.1 min, $t_R(R)$ 38.9 min; anal. calcd for $C_{12}H_8BrNO_2$: C, 51.83; H, 2.90; Br, 28.73; N, 5.04. Found: C, 51.83; H, 2.93; Br, 28.83 N, 5.13%.

4.3.4. Hydroxy-[5-(4-nitrophenyl)-furan-2-yl]acetonitrile *rac*-2d. Yield: 93%; mp: 115–118°C; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 3.95×10^4 (270), 5.25×10^4 (347); HRMS M$^+$ found (M$^+$ calculated for $C_{12}H_8N_2O_4$): 244.04854 (244.04841); MS: m/z (relative intensity) = 244 (1) [M]$^+$, 227 (1), 219 (2), 218 (18), 217 (100), 216 (9), 188 (3), 187 (26), 171 (7), 170 (5), 160 (3), 159 (9), 131 (5), 130 (2), 117 (2), 116 (3), 115 (37), 114 (23), 113 (9); ^{1}H NMR ($CDCl_3$, 25°C): δ = 5.63 (s 1H, C (2)-C$\underline{H}$ (OH) CN), 6.74 (dd, J = 3.4 Hz, J = 0.7 Hz, 1H, C (3)-H)), 6.86 (1H, d, J = 3.7 Hz, 1H, C(4)-H)), 7.80 (ddd, J = 9.0 Hz, J = 2.2 Hz, 2H, C(2′)-H, C(6′)-H), 8.25 (d, J = 9.0 Hz, J = 2.2 Hz, 2H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 25°C): δ = 57.1 (C(2)-$\underline{C}$H(OH)CN), 109.5 (C(4)), 112.6 (C(3)), 116.42 (C(2)-CH(OH)$\underline{C}$N), 124.4 (C(3′), C(5′)), 124.5 (C(2′), C(6′)), 135.2 (C(1′)), 147.1 (C(4′)), 148.9 (C2)), 153.43 (C(5)); HPLC (CHIRACEL OD, 1.5 ml/min): $t_R(S)$ 42.4 min, $t_R(R)$ 51.6 min.

4.3.5. Hydroxy-[5-(2-methyl-4-nitrophenyl)-furan-2-yl]acetonitrile *rac*-2e. Semisolid; yield: 81%; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 6.47×10^3 (281), 7.41×10^3 (296); HRMS M$^+$ found (M$^+$ calculated for $C_{13}H_{10}N_2O_4$): 258.06433 (258.06406); MS: m/z (relative intensity) = 258 (2) [M]$^+$, 232 (2), 231 (10), 203 (12), 202 (100), 186 (2), 146 (6), 145 (3), 144 (5), 130 (5), 129 (40), 128 (21), 127 (13), 126 (4), 118 (8), 117 (2), 116 (6), 115 (13); ^{1}H NMR ($CDCl_3$, 25°C): δ = 2.41 (s, 3H, C(2′)-C$\underline{H}_3$), 5.56 (s, C(2)-C$\underline{H}$(OH)CN), 6.56 (d, J = 3.4 Hz, 1H, C(4)-H)), 6.65 (d, J = 3.6 Hz, 1H, C(3)-H)), 7.37 (d, J = 7.8 Hz, 1H, C(6′)-H)), 7.53 (s, 1H, C(3′)-H)), 7.55 (d, J = 7.8 Hz, 1H, C(5′)-H)); ^{13}C NMR ($CDCl_3$, 25°C): δ = 20.94 (C7-$\underline{C}$H$_3$), 56.87 (C(2)-$\underline{C}$H(OH)CN), 109.98 (C(4)), 111.91 (C(3)), 116.65 (C(2)-CH(OH)$\underline{C}$N), 120.64 (C(1′)), 124.41 (C(3′)), 129.2 (C(5′)), 133.0 (C(6′)), 140.2 (C(2′)), 147.30 (C(4′)), 148.41 (C(2)), 150.27 (C(5)); HPLC (CHIRACEL OD, 1 ml/min): $t_R(S)$ 32.3 min, $t_R(R)$ 35.7 min.

4.4. Chemical acylation of racemic cyanohydrins 2a–e with butanoic anhydride (Method A)

To a solution of one of the cyanohydrins *rac*-**2a**–**e** (0.5 mmol) in dichloromethane (5 ml) butanoic anhydride (79 mg, 81.8 μl, 0.5 mmol), a catalytic amount of 4-*N*,*N*-dimethylaminopyridine in pyridine (5 μl; 1% solution) and triethylamine (50.5 mg, 69.2 μl, 0.5 mmol) were added. After stirring 15 min at room temperature the solvent was evaporated in vacuum and the crude product was purified by column chromatography using dichloromethane as eluent. Yields for *rac*-**3a**–**e** are shown in Table 5.

4.4.1. [5-(4-Carboxyethylphenyl)-furan-2-yl]-cyanomethyl butanoate *rac*-3a. Semisolid; ε ([mol^{-1} dm^3 cm^{-1} dm^3 cm^{-1}], λ [nm]): 1.32×10^3 (274), 5.48×10^3 (318); HRMS M$^+$ found (M$^+$ calculated for $C_{19}H_{19}NO_5$): 341.12637 (341.12632); MS: m/z (relative intensity) = 343 (1), 342 (9), 341 (42) [M]$^+$, 297 (2), 296 (12), 272 (3), 271 (19), 270 (1), 261 (1), 260 (4), 256 (2), 255 (17), 254 (100), 253 (40), 228 (1), 227 (5), 226 (28), 225 (11), 210 (4), 209 (11), 208 (25), 207 (2), 199 (2), 198 (2), 197 (2), 182 (4), 181 (22), 180 (5), 159 (2), 154 (2), 153 (5), 152 (2), 148 (2), 127 (6), 126 (4), 115 (3), 114 (4); ^{1}H NMR ($CDCl_3$, 25°C): δ = 0.95 (t, J = 7.6 Hz, 3H, C(2)-CH(CN)OC-OCH$_2$CH$_2$CH$_3$), 1.38 (t, J = 7.2 Hz, 3H, C(4′)-COOC-H$_2$CH$_3$), 1.69 (qt, J = 7.6 Hz, 2H, C(2)-CH(CN)OC-OCH$_2$CH$_2$CH$_3$), 2.40 (td, J = 7.4 Hz, J = 2.2 Hz, 2H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 4.37 (q, J = 7.2 Hz, 2H, C(4′)-COOCH$_2$CH$_3$), 6.53 (s, 1H, C(2)-CH(CN)-OCOCH$_2$CH$_2$CH$_3$), 6.76 (d, J = 3.2 Hz, 1H, C(4)-H)), 6.77 (d, J = 3.2 Hz, 1H, C(3)-H)), 7.71 (d, J = 8 Hz, 2H, C(2′)-H), C(6′)-H)), 8.05 (d, J = 8 Hz, 2H, C(3′)-H), C(5′)-H)); ^{13}C NMR ($CDCl_3$, 25°C): δ = 13.39 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 14.27 (C(4′)-COOCH$_2$-CH$_3$), 18.10 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 35.36 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 55.60 (C(2)-CH-(CN)OCO-CH$_2$CH$_2$CH$_3$), 61.07 (C(4′)-COOCH$_2$CH$_3$), 107.87 (C(4)), 114.05 (C(2)-CH(CN)OCOCH$_2$-CH$_2$CH$_3$), 114.57 (C(3)), 123.86 (C(2′), C(6′)), 130.01 (C(4′)), 130.06 (C(3′), C(5′)), 133.26 (C(1′)), 144.36 (C(2)), 155.26 (C(5)), 166.01 (C(4′)-COOCH$_2$CH$_3$), 171.41 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$); HPLC (CHIRACEL OD, 1 ml/min): $t_R(R)$ 15.0 min, $t_R(S)$ 16.4 min; anal. calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.83; H, 5.62; N, 4.13%.

4.4.2. [5-(2-Chlorophenyl)furan-2-yl]-cyanomethyl butanoate *rac*-3b. Semisolid; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 1.35×10^4 (282), 2.47×10^4 (298); HRMS M$^+$ found (M$^+$ calculated for $C_{16}H_{14}ClNO_3$): 303.06619 (303.06622); MS: m/z (relative intensity) = 306 (2), 305 (11), 304 (6), 303 (31) [M]$^+$, 292 (2), 235 (7), 234 (3), 233 (20), 224 (10), 223 (4), 222 (30), 219 (5), 218 (32), 217 (28), 216 (100), 215 (45), 194 (4), 193 (2), 189 (7), 188 (2), 187 (14), 181 (5), 180 (34), 159 (5), 154 (3), 153 (18), 152 (13), 151 (6), 150 (2), 149 (13), 141 (6), 140 (2), 139 (16), 136 (3), 127 (2), 126 (5), 125 (4), 114 (4), 113 (7), 112 (7); ^{1}H NMR ($CDCl_3$, 25°C): δ = 0.95 (t, J = 7.24 Hz, 3H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 1.69 (qt, J = 7.24 Hz, 2H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 2.40 (td, J = 7.4 Hz, J = 2.4 Hz, 2H, C(2)-CH(CN)OCO-CH$_2$CH$_2$CH$_3$), 6.55 (s, 1H, C(2)-CH(CN)OCOCH$_2$-CH$_2$CH$_3$), 6.77 (d, J = 3.6 Hz, 1H, C(3)-H)), 7.12 (d, J = 3.6 Hz, 1H, C(4)-H)), 7.24 (ddd, J = 7.7 Hz, J = 1.7 Hz, 1H, C(4′)-H)), 7.32 (dd, J = 7.6 Hz, 1H, C(5′)-H)), 7.43 (dd, J = 8.0 Hz, J = 1.2 Hz, 1H, C(3′)-H)), 7.83 (dd, J = 7.9 Hz, J = 1.7 Hz, 1H, C(6′)-H)); ^{13}C NMR ($CDCl_3$, 25°C): δ = 13.42 (C(2)-CH(CN)OCO-CH$_2$CH$_2$CH$_3$), 18.12 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 35.38 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 55.59 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 111.74 (C(4)), 114.13 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 114.2 (C(3), 126.99 (C(5′)), 128.00 (C(1′)), 128.26 (C(3′)), 129.10 (C(4′)), 130.60 (C(2′)), 130.76 (C(6′)), 143.42 (C(2)), 152.57 (C(5)), 171.42 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$); HPLC (CHIRACEL OD, 1 ml/min): $t_R(R)$ 9.0 min, $t_R(S)$ 11.8 min; anal. calcd for $C_{16}H_{14}ClNO_3$: C, 63.27; H, 4.65; Cl, 11.67; N, 4.61. Found: C, 63.33; H, 4.67; N, 4.62%.

4.4.3. [5-(4-Bromophenyl)furan-2-yl]-cyanomethyl butanoate *rac*-3c. Semisolid; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 2.81×10^4 (273), 1.99×10^4 (318); HRMS M$^+$ found (M$^+$ calculated for $C_{16}H_{14}BrNO_3$): 347.01550 (347.01571); MS: m/z (relative intensity) = 350 (5), 349 (31), 348 (5), 347 (31) [M]$^+$, 280 (2), 279 (11), 278 (2), 277 (11), 267 (10), 266 (10), 263 (14), 262 (98), 261 (49), 260 (100), 259 (36), 233 (6), 231 (6), 195 (6), 193 (6), 185 (8), 183 (9), 182 (4), 181 (11), 180 (34), 157 (7), 155 (8), 154 (5), 153 (35), 152 (12), 131 (4), 130 (2), 127 (4), 126 (10), 125 (3), 115 (5), 114 (10), 113 (6); ^{1}H NMR ($CDCl_3$, 25°C): δ = 0.95 (t, J = 7.4 Hz, 3H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 1.69 (qt, J = 7.4 Hz, 2H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 2.39 (td, J = 7.3 Hz, J = 3.5 Hz, 2H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 6.52 (s, 1H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 6.65 (d, J = 3.4 Hz, 1H, C(4)-H), 6.73 (dd, J = 3.4 Hz, J = 0.5 Hz, 1H, C(3)-H), 7.51 (m, 2H, C(2′)-H, C(6′)-H), 7.53 (m, 2H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 25°C): δ = 13.44 (C(2)-CH(CN)OCO-CH$_2$CH$_2$CH$_3$), 18.15 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 35.42 (C(2)-CH(CN)OCO CH$_2$CH$_2$CH$_3$), 55.62 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 106.45 (C(4)), 114.12 (C(2)-CH(CN)OCOCH$_2$CH$_2$-CH$_3$), 114.57 (C(3)), 122.47 (C(4′)), 125.73 (C(2′), C(6′)), 128.5 (C(1′)), 131.99 (C(3′), C(5′)), 143.74 (C(2)), 155.37 (C(5)), 171.48 (C(2)-CH(CN)OCOCH$_2$-CH$_2$CH$_3$); HPLC (CHIRACEL OD, 1 ml/min): $t_R(R)$ 17.2 min, $t_R(S)$ 18.5 min; anal. calcd for $C_{16}H_{14}BrNO_3$: C, 55.19; H, 4.05; Br, 22.95; N, 4.02. Found: C, 55.23; H, 4.07; Br, 22.99, N, 4.10%.

4.4.4. [5-(4-Nitrophenyl)-furan-2-yl]-cyanomethyl butanoate *rac*-3d. Semisolid; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 1.83×10^4 (270), 3.41×10^4 (338); HRMS M$^+$ found (M$^+$ calculated for $C_{16}H_{14}N_2O_5$): 314.09061 (314.09027); MS: m/z (relative intensity) = 315 (6), 314 (33) [M]$^+$, 245 (6), 244 (45), 229 (2), 228 (16), 227 (100), 226 (91), 215 (4), 211 (1), 210 (2), 209 (3), 198 (6), 197 (5), 196 (4), 182 (5), 181 (33), 180 (19), 179 (2), 171 (1), 170 (3), 169 (12), 168 (4), 154 (2), 153 (15), 152 (11), 151 (2), 150 (4), 141 (2), 140 (10), 130 (2), 128 (1), 127 (6), 126 (12), 125 (3), 117 (1), 116 (1), 115 (5), 114 (10), 113 (4); ^{1}H NMR ($CDCl_3$, 25°C): δ = 0.95 (t, J = 7.5 Hz 3H, C(2)-CH(CN)OCO CH$_2$CH$_2$CH$_3$), 1.69 (qt, J = 7.5 Hz, 2H, C(2)-CH(CN) OCOCH$_2$CH$_2$CH$_3$), 2.41 (td, J = 7.4 Hz, J = 2.6 Hz, 2H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 6.55 (s, 1H, C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 6.80 (d, J = 3.64 Hz, 1H, C(3)-H), 6.87 (d, J = 3.64 Hz, 1H, C(4)-H), 7.81 (d, J = 8.8 Hz, 2H, C(2′)-H, C(6′)-H), 8.24 (d, J = 8.8 Hz, 2H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 25°C): δ = 13.39 (C(2)-CH(CN)OCOCH$_2$CH$_2$-CH$_3$), 18.09 (C(2)-CH(CN)OCO-CH$_2$CH$_2$CH$_3$), 35.33 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 55.50 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 109.56 (C(4)), 113.87 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$), 114.76 (C(3)), 124.30 (C(3′), C(5′)), 124.58 (C(2′), C(6′)), 135.03 (C(1′)), 145.42 (C(2)), 147.15 (C(4′)), 153.84 (C(5)),

171.34 (C(2)-CH(CN)OCOCH$_2$CH$_2$CH$_3$); HPLC (CHIRACEL OD, 1.5 ml/min): $t_R(R)$ 25.3 min, $t_R(S)$ 30.2 min; anal. calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.13; H, 4.52; N, 8.92%.

4.4.5. [5-(2-Methyl-4-nitrophenyl)-furan-2-yl]-cyanomethyl butanoate *rac*-3e. Semisolid; ε ([mol^{-1} dm^3 cm^{-1}], λ [nm]): 2.45×10^4 (271), 1.12×10^4 (330); HRMS M$^+$ found (M$^+$ calculated for $C_{17}H_{16}N_2O_5$): 328.10608 (328.10592); MS: m/z (relative intensity) = 328 (6) [M]$^+$, 242 (4), 241 (30), 240 (9), 204 (1), 203 (8), 202 (70), 196 (1), 195 (3), 194 (2), 187 (12), 186 (100), 184 (2), 183 (2), 182 (2), 175 (2), 174 (1), 169 (1), 168 (3), 167 (6), 166 (13), 159 (2), 158 (6), 155 (2), 154 (2), 148 (4), 147 (4), 146 (4), 141 (8), 140 (3), 139 (10), 138 (6), 132 (2), 131 (5), 130 (35), 129 (3), 128 (9), 126 (6), 118 (2), 117 (10), 116 (5), 115 (2), 114 (8); ^{1}H NMR ($CDCl_3$, 25°C): δ = 0.94 (t, J = 7.48 Hz, 3H, C(2)-CH(CN)-OCOCH$_2$CH$_2$C$\underline{H}_3$), 1.68 (qt, J = 7.48 Hz, 2H, C(2)-CH(CN)OCO-CH$_2$C$\underline{H}_2$CH$_3$), 2.39 (t, J = 7.48 Hz, 2H, C(2)-CH(CN)OCOC$\underline{H}_2$CH$_2$CH$_3$), 2.43 (s, 3H, C(2′)-C$\underline{H}_3$), 6.48 (s, 1H, C(2)-C$\underline{H}$(CN)OCOCH$_2$CH$_2$CH$_3$), 6.58 (d, J = 3.4 Hz, 1H, C(4)-H), 6.74 (dd, J = 3.5 Hz, J = 0.5 Hz, 1H, C(3)-H), 7.40 (m, J = 8.1 Hz, 1H, C(6′)-H), 7.55 (s, 1H, C(3′)-H), 7.57 (d, J = 7.88 Hz, 1H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 25°C): δ = 13.40 (C(2)CH(CN)OCO CH$_2$CH$_2$C$\underline{H}_3$), 18.05 (C(2)-CH-(CN)OCOCH$_2$C$\underline{H}_2$CH$_3$), 20.97 (C(2′)-C$\underline{H}_3$), 35.31 (C(2)CH(CN)OCO C$\underline{H}_2$CH$_2$CH$_3$), 55.44 (C(2)-C$\underline{H}$-(CN)OCOCH$_2$CH$_2$CH$_3$), 110.05 (C(4)), 113.96 (C(2)-CH(C$\underline{N}$)OCOCH$_2$CH$_2$CH$_3$), 114.09 (C(3)), 120.42 (C(1′)), 124.45 (C(3′)), 129.24 (C(5′)), 132.87 (C(6′)), 140.36 (C(2′)), 144.77 (C(2)), 147.55 (C(4′)), 150.91 (C(5)), 171.36 (C(2)-CH(CN)O$\underline{C}$OCH$_2$CH$_2$CH$_3$); HPLC (CHIRACEL OD, 1 ml/min): $t_R(R)$ 22.1 min, $t_R(S)$ 25.9 min; anal. calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.21; H, 4.89; N, 8.57%.

4.5. Enzymatic acylation of racemic cyanohydrins 2a–e with vinyl butanoate (Method B)

To a solution of one of the cyanohydrins *rac*-**2a**–**e** (0.5 mmol) in anhydrous toluene (1 ml) vinyl butanoate (171 mg, 190 μl, 1.5 mmol) and CAL-A preparation (20 mg, corresponding to 2 mg of the enzyme) were added and the mixture was stirred at room temperature for 3 h. The enzyme was filtered off and washed with toluene (2×0.5 ml). Solvents were distilled off from the filtrate and the residue was purified as above. Yields for *rac*-**3a**–**e** are shown in Table 5.

4.6. Kinetic resolution of racemic cyanohydrins 2a–e

In a typical small scale experiment, one of the cyanohydrins *rac*-**2a**–**e** (0.05 mmol) and vinyl butanoate (17.1 mg, 19 μl, 0.125 mmol) were dissolved in a dry organic solvent (1 ml). Lipase PS preparation (10 mg, corresponding to 2 mg of the enzyme) was added. Samples (5 μl) were taken after 6, 12, 24, 48, 72, 96, 120, 144, 168 h and diluted with hexane:isopropyl alcohol (9:1, 80 μl).

4.7. One-pot synthesis of cyanohydrin esters (*R*)-(+)-3a–e

One of the aldehydes **1a**–**e** (0.15 mmol), acetone cyanohydrin (28 mg, 30 μl, 0.325 mmol) and vinyl butanoate (51.3 mg, 57 μl, 0.45 mmol) were added in dry toluene (3 ml). To this solution Amberlite IRA 904 ($^-$OH form, 5 mg/0.008 equiv.) and lipase PS preparation (10 or 50 mg ml^{-1}) were added. The reaction mixture was stirred at room temperature for 168 h. The enzyme and the resin were filtered off and washed with toluene (2×0.5 ml). Solvents were distilled off from the filtrate and the residue was purified by column chromatography on silica gel with dichloromethane yielding (*R*)-(+)-**3a**–**e** (Table 3).

4.8. Kinetic resolution of racemic cyanohydrin esters 3a–e

In a typical small scale experiment, one of the cyanohydrin esters *rac*-**3a**–**e** (0.05 mmol) and methanol (12.8 mg, 16.4 μl, 0.4 mmol) were dissolved in dry toluene (1 ml). Lipase PS preparation (10 mg, corresponding to 2 mg of the enzyme) was added. Samples (5 μl) were taken after 4, 8, 12, 24, 36, 48, 72, 96, 120, 144 h and diluted with the same solvent (80 μl) as the mobile phase for HPLC (Table 4).

4.9. Absolute configurations

In order to determine which enantiomer reacts faster in the present lipase PS-catalysed reactions, the lipase PS-mediated kinetic resolution of furan-2-yl-hydroxyacetonitrile with vinyl butanoate and vinyl acetate in toluene were studied. The corresponding (*R*)-(+)-butanoic and (*R*)-(+)-acetic acid esters with $[\alpha]_D^{25}$ = +9.9 (*c* 1, $CHCl_3$) (ee >98%) and $[\alpha]_D^{25}$ = +22.9 (*c* 1.5, $CHCl_3$) (ee 95%) were obtained, respectively. The latter value of $[\alpha]_D^{25}$ is in full accordance with the value of $[\alpha]_D^{20}$ = +24.3 (*c* 1.6, $CHCl_3$) (ee = 98%) reported for the (*R*)-(+)-acetic ester.[27]

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