Enantioselective Synthesis of Protected Cyanohydrins

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A straightforward process for the preparation of optically active protected cyanohydrins, important building blocks for the synthesis of drugs and agrochemicals, has been established. Lipase B from *Candida Antarctica* (CAL-B) catalysed the kinetic resolution of racemic cyanohydrin acetates under mild conditions. The resulting labile cyanohydrins were re-protected either by an enzyme-catalysed route involving the addition of vinyl butyrate, or chemically after removal of the enzyme from the reaction mixture. This process gave access to both enantiomers in pure form and in good yields, while considerably reducing the risks due to HCN. A variety of different protection groups have also been introduced.

Introduction

Cyanohydrins are versatile building blocks in organic synthesis.[1−6] They can readily be converted into a wide range of compounds, such as α-hydroxy acids,[7] α-hydroxy esters,[8] α-hydroxy ketones,[9] α-hydroxy aldehydes,[10] and β-hydroxy amines.[11] Indeed, they have been utilised for the synthesis of, for example, (*R*)-salbutamol,[12] (*R*)-terbutaline[12], (*S*)-amphetamines (a family of drugs commonly referred to as Ecstasy[13]), as well as the Williamson glycine template.[14] In addition, they are crucial components in the synthesis of pyrethroid insecticides.

Despite the fact that the first enantioselective hydroxynitrile lyase catalysed synthesis of cyanohydrins was described as early as 1908,[15] and also their major role in the "synthon approach",[16] they are still not utilised to the extend that one might expect. We therefore set out to develop a straightforward, enantioselective process for the synthesis of protected, and hence stable, cyanohydrins.

The kinetic resolution of cyanohydrin acetates has been investigated with a range of lipases.[17−20] Recently, the readily available *Candida antarctica* lipase B (CAL-B, "Novozyme 435" or chirazyme L-2, c.-f., C2, Lyo, immobilised on a macroporous acrylic resin) has been used in the enantioselective deacylation of mandelonitrile acetate (*R*,*S*)-**1a** to give (*R*)-mandelonitrile acetate (*R*)-**1a** and (*S*)-mandelonitrile cyanohydrin (*S*)-**2a**.[21] This procedure has been optimised for the kinetic resolution of a wide range of aromatic cyanohydrin acetates, with excellent results.[22] However, the resulting (*S*)-cyanohydrins are relatively unstable. To avoid this problem, the kinetic resolution should ideally be coupled with a chemical or enzymatic protection reaction. This would yield both enantiomers of the cyanohydrin, protected as two different, and therefore readily separable, derivatives.

The TBDMS group and the pivaloyl group were chosen as protection groups that could be introduced under basic conditions. Both are known as versatile protecting groups in cyanohydrin chemistry, and the TBDMS group can be introduced without significant racemisation.[23] THP ethers were the obvious choice for a protection group that could be introduced under acidic conditions.[14]

By using the same enzyme (CAL-B) to protect the (*S*)-cyanohydrins directly after kinetic resolution with a suitable acylating agent in a true one-pot reaction, esters can be formed under neutral conditions. This procedure should give access to a wide range of potentially interesting esters.

By the approaches described above, stable, protected and enantiopure cyanohydrin acetates may be obtained. Since the racemic cyanohydrin acetates can be prepared by straightforward treatment of the appropriate aldehyde with sodium cyanide and acetic anhydride,[24] any risk of releasing HCN is minimised and the remaining cyanide ions can be destroyed by standard procedures.[25]

Results and Discussion

For kinetic resolution of the racemic cyanohydrin acetates, the conditions described earlier were applied.[22] However, since the protection reaction had to be performed with the mixture obtained from the kinetic resolution, these conditions had to be reassessed. For the protection of (*S*)-**2a**−**d** as TBDMS ethers, several sets of conditions were explored. TBDMS triflate in the presence of lutidine[26] gave higher

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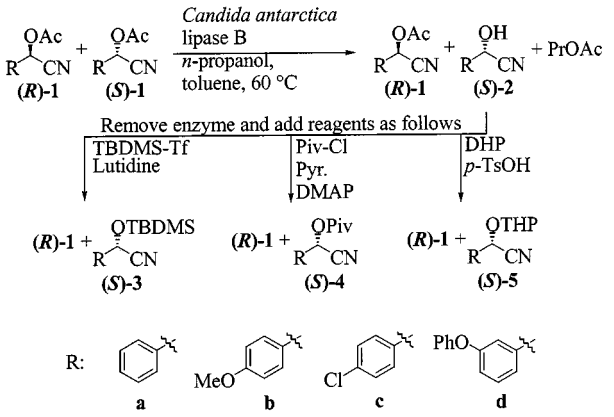
yields than when Hünig's base[27] was employed. TBDMS-Cl in combination with imidazole[23] gave less favourable results, possibly due to solubility problems of imidazole in toluene. Pivaloate was readily introduced as pivaloyl chloride in the presence of pyridine and DMAP,[28] and the THP ethers were also formed with great ease under standard conditions (Scheme 1). Introduction of methoxyisopropyl and benzyl ethers (under acidic[29] and basic[30] conditions) failed, however.



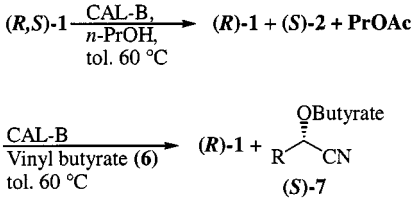
Scheme 1. Kinetic resolution of cyanohydrin acetates and protection of the formed (*S*)-cyanohydrins

Four cyanohydrin acetates (*R*,*S*)-**1a**−**d** were subjected to kinetic resolution followed by chemical protection of the newly formed (*S*)-cyanohydrins (*S*)-**2a**−**d**. All the desired products (*S*)-**3a**−**d**, (*S*)-**4a**−**d**, and (*S*)-**5a**−**d** were obtained in good yields and enantiomeric purities (Table 1, Scheme 1). Previous work in this group had indicated low selectivity for the kinetic resolution of aliphatic cyanohydrin acetates, and so this class of compounds was not included in this work.[32] However, if the kinetic resolution of aliphatic cyanohydrins should be desired, other lipases has been used with excellent results.[33,34]

In order to prevent any enzyme degradation, the protection reactions were performed after removal of the enzyme from the reaction mixture. In the case of the synthesis of the TBDMS and pivaloyl derivatives, straightforward column filtration gave the pure products. This was not the case for the THP ethers, since two diastereoisomers were formed and the THP ethers had polarities similar to those of the acetates. Conversions were therefore determined by ^{1}H NMR. However, these conversions corresponded to the isolated yields, within the margins of experimental error.

The results showed that the *ee* values of (*S*)-**3a**−**d** and (*S*)-**4a**−**d** were lower than those for (*S*)-**5a**−**d**. This might be due to the instability of cyanohydrins under basic conditions (a base being used for the silylation and the esterification), under which they slowly racemise. In contrast to that of (*S*)-**3a**−**d** and (*S*)-**4a**−**d**, the formation of (*S*)-**5a**−**d** takes place under acidic reaction conditions. The racemisation was therefore suppressed, and the *ee* values were therefore higher. However, when the kinetic resolution was performed without coupling to a protection reaction[22] the *ee* values of (*S*)-**2a**−**d** were even higher than those of (*S*)-**3a**−**d**, (*S*)-**4a**−**d**, or (*S*)-**5a**−**d**.

In order to increase the optical purity of the protected variants of (*S*)-**2a**−**d** to the level of the unprotected compounds, a different approach was explored. Instead of removing the enzyme and performing the protection chemically, the acylating agent vinyl butyrate (**6**) was added to the reaction mixture (Scheme 2).



Scheme 2. One-pot synthesis of (*S*)-**7a**−**d**

Under the same conditions as used for the kinetic resolution, (*S*)-**2a**−**d** was now acylated in the same pot by the same enzyme to give the (*S*)-cyanohydrin butyrates (*S*)-**7a**−**d** (Table 2). (*S*)-Cyanohydrin decanoates were prepared in the same way with similar results, but with reaction times of several days.

With this truly one-pot procedure, even better *ee* values could be obtained for the reprotected cyanohydrins (*S*)-**7a**−**d**. The separation was, again, a straightforward column filtration, giving access to the desired products in good yields and with great ease. However, the *ee* values of (*R*)-**1a**−**d** obtained from the enzymatic protection were lower

Table 1. Results of the kinetic resolution of cyanohydrin acetates and protection of the formed (*S*)-cyanohydrins

R	Yield[a] (*ee*) (*S*)-**3**	Yield (*ee*) (*R*)-**1**[b]	Yield (*ee*) (*S*)-**4**	Yield (*ee*) (*R*)-**1**[a]	Ratio (*ee*) (*S*)-**5**	Ratio (*ee*) (*R*)-**1**[d]	Ratio aldehyde[e]
a	88 (89)	93 (96)	99 (83)	98 (98)	96 (93)	100 (93)	4
b	79 (89)	90 (97)	81 (88)	90 (97)	84 (93)	100 (92)	16
c	78 (82)	96 (> 99)	76 (78)	85 (> 99)	86 (90)	99 (> 99)	16
d	89 (−)	94 (87)	71 (81)	89 (90)	86 (84)	100 (91)	14

[a] Yields are isolated yields (%). Enantiomeric excess (%) was determined by chiral HPLC. Ratios of **5**, **1** and the aldehyde in the reaction mixture were determined by NMR. [b] From protection as silyl ether. [c] From protection as pivaloyl ester. [d] From protection as THP ether. [e] Degradation product of cyanohydrin.

Table 2. Results of the kinetic resolution of cyanohydrin acetates and the enzymatic protection of the formed (*S*)-cyanohydrins in a one-pot reaction

R	Yield[a] (*ee*)[b] (*S*)-**7**	Yield[a] (*ee*)[b] (*R*)-**1**
a	85 (98)	93 (95)
b	80 (97)	81 (91)
c	73 (97)	93 (98)
d	67 (96)	92 (75)

[a] Yields are isolated yields (%). [b] Enantiomeric excess (%) was determined by chiral HPLC.

than those observed after the chemical protection. This can be explained by the presence of propyl acetate formed during the kinetic resolution, which can also act as an acylating agent, (albeit more slowly than **6**), to give (*S*)-**1a**−**d** instead of (*S*)-**7a**−**d**. As a consequence, the yields of (*S*)-**7a**−**d** and the *ee* values of (*R*)-**1a**−**d** would decrease. In addition, any racemisation of (*S*)-**2a**−**d**, which would give rise to lower *ee* values in the chemical protection reactions, would give lower yields for the enzyme protections, since (*R*)-**2a**−**d** is not a substrate for the enzyme.

Since (*R*)-**1a**−**d** and (*S*)-**7a**−**d** can both easily be racemised[31] and then once more be subjected to the kinetic resolution, it is possible to obtain either enantiomer in close to quantitative yields with excellent selectivities.

With this CAL-B-based kinetic resolution and protection sequence, protected aromatic cyanohydrins become readily available in high optical purity. In the case of aliphatic cyanohydrins, CAL-B is significantly less selective.[32] However, it is well known that Porcine pancreatic lipase and *Candida rugosa* lipase show excellent selectivity for these substrates.[33,34]

To examine the recyclability of CAL-B, the kinetic resolution of racemic (*R*,*S*)-**1c** followed by protection as a THP ether was repeated four times (Table 3). Even in the fifth run, no loss of activity or selectivity of the enzyme was observed. This confirms the great versatility of CAL-B for the enantioselective synthesis of protected cyanohydrins.

Table 3. Recycling experiment

Cycle	0	1	2	3	4
Ratio[a] (% *ee*)[b] (*R*)-**1c**	98 (99)	96 (99)	98 (97)	98 (98)	98 (98)
Ratio (% *ee*) (*S*)-**5c**	86 (90)	86 (90)	88 (93)	90 (93)	91 (93)
Ratio 4-chlorobenzaldehyde **8**	16	18	14	12	10

[a] The ratios between **1c**, **5c** and **8** were determined in the reaction mixture by ^{1}H NMR (no other products were observed). [b] Enantiomeric excess (%) was determined by chiral HPLC.

Conclusion

In summary, we have developed a straightforward, enzyme-based method to synthesise either enantiomer of differently protected cyanohydrins, in excellent yield and optical purities [(*R*): > 91% *ee*; (*S*): > 97% *ee*]. This should help in further establishing the cyanohydrins as versatile building blocks in organic synthesis.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR 400S (400 and 100 MHz, respectively) or a Varian Unity Inova 300 (300 MHz and 75 MHz, respectively) instrument. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane. Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). Mass spectra were determined with a VG 70 SE spectrometer working at 70 eV. Optical rotations were obtained with a Perkin−Elmer 241 polarimeter. Melting points are uncorrected. Column chromatography was carried out with silica gel (0.060−0.200 mm, pore diameter ca. 6 nm) and with mixtures of petroleum ether (PE) and ethyl acetate (EtOAc) as solvent. TLC was performed on 0.20 mm silica gel and developed in a vanillin bath [vanillin (15 g) in ethanol (250 mL) + concd. H_2SO_4 (2.5 mL)] in which all products containing a CN group gave orange spots, except for the THP ethers, which gave blue spots. Dry toluene and dry *n*-propanol were purchased from Aldrich. Racemic cyanohydrin acetates[24] and cyanohydrins[35] were synthesised according to literature procedures. Immobilised Lipase B from *Candida antarctica* (CAL-B, Chirazyme L-2, c.-f., C2, Lyo) was a generous gift from Roche Diagnostics Penzberg (W. Tischer). HPLC analysis: The optical purity was determined by HPLC using a 4.6 × 250 mm 10 μ Chiracel OD column with a Waters 510 pump, and a Waters 486 UV detector. The eluent and the retention times for the different products are given in Table 4. The flow was 0.8 mL·min^{-1}.

Table 4. Eluents and retention times for HPLC analysis

Compound	Eluent hexane/*i*PrOH	t_r (*R*) [min]	t_r (*S*) [min]
(*R*,*S*)-**1a**	98:2	13.87	15.49
(*R*,*S*)-**1b**	90:10	10.55	11.94
(*R*,*S*)-**1c**	90:10	10.22	12.14
(*R*,*S*)-**1d**	90:10	19.40	15.28
(*R*,*S*)-**3a**	99.5:0.5	8.38	6.62
(*R*,*S*)-**3b**	99.5:0.5	9.36	8.34
(*R*,*S*)-**3c**	99.75:0.25	10.78	10.19
(*R*,*S*)-**4a**	99.5:0.5	9.36	10.34
(*R*,*S*)-**4b**	99.5:0.5	14.97	16.11
(*R*,*S*)-**4c**	99.5:0.5	12.43	14.51
(*R*,*S*)-**4d**	90:10	11.59	8.11
(*R*,*S*)-**5a**	98:2	10.12	10.65
(*R*,*S*)-**5b**	90:10	8.16	8.73
(*R*,*S*)-**5c**	90:10	7.28	8.35
(*R*,*S*)-**5d**	90:10	8.74	12.73
(*R*,*S*)-**7a**	95:5	7.90	8.45
(*R*,*S*)-**7b**	95:5	10.04	11.11
(*R*,*S*)-**7c**	95:5	9.11	10.47
(*R*,*S*)-**7d**	95:5	18.21	15.96

Enzyme Activity Test: Tributyrin (1.47 mL, 5.02 mmol) was added to 48.5 mL of a 10 mM potassium phosphate buffer, pH = 7.0 [10 mM of potassium dihydrogen phosphate (100 mL) adjusted to pH = 7.0 with 10 mM of dipotassium hydrogen phosphate (ca. 100 mL)] in a thermostatted vessel at 25 °C, and the mixture was

stirred mechanically. The pH was maintained at 7.0 with an automatic burette, and when the pH had stabilised, immobilised Lipase B from *Candida antarctica* CAL-B (9 mg) was added. The consumption of 100 mM sodium hydroxide was monitored over 40 min and plotted against time. The specific activity was calculated from the base consumption at the linear part of the graph; 1 μmol of NaOH consumed per min corresponds to 1 unit (1 U) of activity. The activity was found to be 3.8 KU/g dry carrier.

General Procedure A. Kinetic Resolution: Immobilised Lipase B from *Candida antarctica* CAL-B (368 mg) was dried overnight over SiO_2 in a dessicator and added to a mechanically stirred solution of **1** (3.68 mmol) in dry toluene (36 mL) under N_2, at 25 °C. The reaction mixture was heated to 60 °C, and *n*-propanol (0.54 mL, 7.36 mmol) was then added. After stirring for 3 h, the reaction mixture was cooled to 0 °C and transferred through a thin cannula into a new reaction vessel. The residual immobilised enzyme was washed with dry toluene (7 mL) to ensure complete transfer. The liquid phase was then treated according to the following general procedures.

General Procedure B. Protection as TBDMS Ether: Lutidine (1.46 mL, 12.5 mmol) and TBDMS-Tf (2.11 mL, 9.2 mmol) were added to the liquid phase of General Procedure A and the mixture was stirred at ambient temperature under N_2 for 3 h. The reaction was quenched with water (10 mL). The organic phase was washed with 1 M HCl (25 mL) and satd. $NaHCO_3$ (25 mL) and dried with $MgSO_4$. The solvent was removed under vacuum, and the products were purified by column chromatography on silica gel; (*S*)-**3a**−**d** was eluted with PE/EtOAc (95:5), and (*R*)-**1a**−**d** with PE/EtOAc (90:10).

Racemic Cyanohydrins Protected as TBDMS Ethers: Racemic (*R*,*S*)-**3a**−**d** was prepared from racemic (*R*,*S*)-**2a**−**d** according to General Procedure B, with the modification that a solution of the cyanohydrin (1.84 mmol) in dry toluene (36 mL) and *n*-propanol (0.54 mL) was used in place of the filtrate from the kinetic resolution. The yields were: (*R*,*S*)-**3a**: 71%; (*R*,*S*)-**3b**: 78%; (*R*,*S*)-**3c**: 92%; (*R*,*S*)-**3d**: 98%. NMR as below.

(*S*)-(−)-α-[(*tert*-Butyldimethylsilyl)oxy]-α-(phenyl)acetonitrile [(*S*)-3a] and (*R*)-(+)-Cyano(phenyl)methyl Acetate [(*R*)-1a]: The title compounds were prepared from racemic (*R*,*S*)-**1a** according to General Procedure B.

Compound (*S*)-3a: Obtained as a pale yellow oil (399 mg, 88%, 89% *ee*): $[\alpha]_D^{25} = -17.5$ (*c* = 1.0, $CHCl_3$) {ref.[23] $[\alpha]_D^{25} = +17.0$ (*c* = 1.0, $CHCl_3$) for the (*R*) enantiomer with *ee* > 99%}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.15 (s, 3 H, CH_3Si), 0.23 (s, 3 H, CH_3Si), 0.94 [s, 9 H, $(CH_3)_3C$], 5.52 (s, 1 H, CHO), 7.36−7.50 (m, 5 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.2 (CH_3Si), −5.1 (CH_3Si), 18.2 [Si*C*$(CH_3)_3$], 25.5 [(*C*H_3)$_3$C], 64.0 (CHO), 119.3 (CN), 126.1 (C-2,6), 128.9 (C-3,5), 129.2 (C-4), 136.5 (C-1).

Compound (*R*)-1a: Obtained as a pale yellow oil (300 mg, 93%, 96% *ee*): $[\alpha]_D^{25} = +6.3$ (*c* = 1.0, $CHCl_3$) {ref.[36] $[\alpha]_D^{25} = -7.2$ (*c* = 2.3, $CHCl_3$) for the (*S*) enantiomer with > 99% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3CO), 6.40 (s, 1 H, CHO), 7.20−7.58 (m, 5 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5 (*C*H_3CO), 62.9 (CHO), 116.2 (CN), 127.9 (C-2,6), 129.3 (C-3,5), 130.4 (C-4), 131.8 (C-1), 169.94 (C=O).

(*S*)-(−)-α-[(*tert*-Butyldimethylsilyl)oxy]-α-(4-methoxyphenyl)acetonitrile [(*S*)-3b] and (*R*)-(−)-Cyano(4-methoxyphenyl)methyl Acetate [(*R*)-1b]: The title compounds were prepared from racemic (*R*,*S*)-**1b** according to General Procedure B.

Compound (*S*)-3b: Obtained as a pale yellow oil (404 mg, 79%, 89% *ee*): $[\alpha]_D^{25} = -11.6$ (*c* = 1.0, $CHCl_3$) {ref.[23] $[\alpha]_D^{20} = +16$ (*c* = 1.0, $CHCl_3$) for the (*R*) enantiomer with > 99% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, CH_3Si), 0.20 (s, 3 H, CH_3Si), 0.92 [s, 9 H, $(CH_3)_3C$], 3.82 (s, 3 H, OCH_3), 5.45 (s, 1 H, CHO), 6.92 (m, 2 H, 3,5-H), 7.38 (m, 2 H, 2,6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.1 [$(CH_3)_2Si$], 18.2 [Si*C*$(CH_3)_3$], 25.6 [(*C*H_3)$_3$C], 55.4 (OCH_3), 63.7 (CHO), 114.3 (C-3,5), 119.5 (CN), 127.7 (C-2,6), 128.7 (C-1), 160.3 (C-4).

Compound (*R*)-1b: Obtained as a pale yellow solid (343 mg, 90%, 97% *ee*): m.p. 58.2−58.4 °C. $[\alpha]_D^{25} = -20.0$ (*c* = 1.0, $CHCl_3$) {ref.[36] $[\alpha]_D^{20} = +19.0$ (*c* = 1.55, $CHCl_3$) for the (*S*) enantiomer with 95% *ee*}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3 H, CH_3CO), 3.82 (s, 3 H, OCH_3), 6.35 (s, 1 H, CHO), 6.94 (m, 2 H, aromatic), 7.44 (m, 2 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (*C*H_3CO), 55.4 (OCH_3), 62.6 (CH), 114.6 (C-3,5), 116.4 (CN), 123.9 (C-1), 129.7 (C-2,6), 161.2 (C-4), 169.0 (C=O).

(*S*)-(−)-α-[(*tert*-Butyldimethylsilyl)oxy]-α-(4-chlorophenyl)acetonitrile [(*S*)-3c] and (*R*)-(−)-Cyano(4-chlorophenyl)methyl Acetate [(*R*)-1c]: The title compounds were prepared from racemic (*R*,*S*)-**1c** according to General Procedure B.

Compound (*S*)-3c: Obtained as a pale yellow oil (405 mg, 78%, 82% *ee*): $[\alpha]_D^{25} = -11.6$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 3 H, CH_3Si), 0.23 (s, 3 H, CH_3Si), 0.94 [s, 9 H, $(CH_3)_3C$], 5.48 (s, 1 H, CHO), 7.4 (m, 4 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.2 (CH_3Si), −5.1 (CH_3Si), 18.2 [Si*C*$(CH_3)_3$], 25.5 [(*C*H_3)$_3$C], 63.4 (CHO), 118.9 (CN), 127.4 (C-2,5), 129.2 (C-3,6), 135.1, 135.3 (C-1,4).

Compound (*R*)-1c: Obtained as a pale yellow oil (370 mg, 96%, > 99% *ee*): $[\alpha]_D^{25} = -10.5$ (*c* = 1.0, $CHCl_3$) {ref.[37] $[\alpha]_D^{25} = +31.5$ (*c* = 1.17, benzene) for the (*S*) enantiomer with 84% *ee*}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3CO), 6.39 (s, 1 H, CHO), 7.4−7.5 (m, 4 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 (*C*H_3CO), 62.2 (CHO), 115.8 (CN), 129.3, 129.5 (C-2,3,5,6), 130.3 (C-1), 136.6 (C-4), 168.8 (C=O).

(*S*)-(−)-α-[(*tert*-Butyldimethylsilyl)oxy]-α-(3-phenoxyphenyl)-acetonitrile [(*S*)-3d] and (*R*)-(−)-Cyano(3-phenoxyphenyl)methyl Acetate [(*R*)-1d]: The title compounds were prepared from racemic (*R*,*S*)-**1d** according to General Procedure B.

Compound (*S*)-3d: Obtained as a pale yellow oil (555 mg, 89%): $[\alpha]_D^{25} = -18.0$ (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 3 H, CH_3Si), 0.21 (s, 3 H, CH_3Si), 0.90 [s, 9 H, $(CH_3)_3C$], 5.47 (s, 1 H, CHO), 6.98−7.40 (m, 9 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.3 (CH_3Si), −5.1 (CH_3Si), 18.1 [Si*C*$(CH_3)_3$], 25.5 [(*C*H_3)$_3$C], 63.5 (CHO), 115.8 (C-2′), 119.0 (CN), 119.1 (C-4′), 119.4 (C-2′′, 6′′), 120.3 (C-6′), 123.9 (C-4′′), 129.9 (C-3′′, 5′′), 130.3 (C-5′), 138.4 (C-1′), 156.4 (C-3′), 158.1 (C-1′′).

Compound (*R*)-1d: Obtained as a pale yellow oil (461 mg, 94%, 87% *ee*): $[\alpha]_D^{25} = -7.1$ (*c* = 1.0, $CHCl_3$) {ref.[36] $[\alpha]_D^{25} = +7.44$ (*c* = 0.75, $CHCl_3$) for the (*S*) enantiomer with 99% *ee*}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_3CO), 6.36 (s, 1 H, CHO), 7.0−7.42 (m, 9 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 (*C*H_3CO), 62.4 (CHO), 115.9 (CN), 117.7 (C-2′), 119.4 (C-2′′, 6′′), 120.1 (C-4′), 122.1 (C-6′), 124.1 (C-4′′), 130.0 (C-3′′, 5′′), 130.6 (C-5′), 133.5 (C-1), 156.2 (C-3′), 158.2 (C-1′′), 168.8 (C=O).

General Procedure C. Protection as Pivaloyl Ester: DMAP (5 mg, 0.04 mmol), pivaloyl chloride (1.36 mL, 11.04 mmol), and pyridine (0.71 mL, 8.83 mmol) were added to the filtrate of General Procedure A, and the mixture was stirred at ambient temperature under N_2 for 14 h. HCl (1 M, 25 mL) was added, and the organic phase

was washed with satd. $NaHCO_3$ (25 mL) and dried with $MgSO_4$. Solvents were removed under vacuum and the crude products were purified by column chromatography on silica gel (PE/EtOAc, 90:10).

Racemic Cyanohydrins Protected as Pivaloyl Esters: Racemic (*R*,*S*)-**4a**−**d** was prepared from racemic (*R*,*S*)-**2a**−**d** according to General Procedure C with the modification that a solution of the cyanohydrin (1.84 mmol) in dry toluene (36 mL) and *n*-propanol (0.54 mL) was used instead of the filtrate from the kinetic resolution. The yields were: (*R*,*S*)-**4a**: 76%; (*R*,*S*)-**4b**: 47%; (*R*,*S*)-**4c**: 84%; (*R*,*S*)-**4d**: 78%.

(*S*)-(−)-Cyano(phenyl)methyl Pivaloate [(*S*)-4a] and (*R*)-(+)-Cyano(phenyl)methyl Acetate [(*R*)-1a]: The title compounds were prepared from racemic (*R*,*S*)-**1a** according to General Procedure C.

Compound (*S*)-4a: Obtained as a pale yellow oil (395 mg, 99%, 83% *ee*): $[\alpha]_D^{25} = -5.9$ ($c = 1.0$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 [s, 9 H, $(CH_3)_3C$], 6.41 (s, 1 H, CH-O), 7.41−7.51 (m, 5 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9 [($CH_3)_3C$], 38.9 (*C*-CO), 62.8 (CHO), 116.3 (CN), 127.5 (C-2,6), 129.2 (C-3,5), 130.2 (C-4), 132.1 (C-1), 176.4 (C=O).

Compound (*R*)-1a: Obtained as a pale yellow oil (313 mg, 97%, 98% *ee*): $[\alpha]_D^{25} = +5.6$ ($c = 1.0$ $CHCl_3$). NMR spectroscopic data as above.

(*S*)-(+)-Cyano(4-methoxyphenyl)methyl Pivaloate [(*S*)-4b] and (*R*)-(+)-Cyano(4-methoxyphenyl)methyl Acetate [(*R*)-1b]: The title compounds were prepared from racemic (*R*,*S*)-**1b** according to General Procedure C.

Compound (*S*)-4b: Obtained as a pale yellow solid (371 mg, 81%, 88% *ee*): m.p. 40.2−41.4 °C. $[\alpha]_D^{25} = +0.4$ ($c = 1.0$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 [s, 9 H, $(CH_3)_3C$], 3.81 (s, 3 H, CH_3O), 6.35 (s, 1 H, CHO), 6.94 (m, 2 H, aromatic), 7.43 (m, 2 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.0 [($CH_3)_3C$], 39.0 (*C*CO), 55.5 (OCH_3), 62.8 (CHO), 114.7 (C-3,5), 116.7 (CN), 124.3 (C-1), 129.5 (C-2,5), 161.2 (C-4), 176.7 (C=O). MS: *m*/*z* (%) = 247 (43), 163 (14), 146 (100), 135 (33), 57 (64). $C_{14}H_{17}NO_3$ (247.12): calcd. C 68.00, H 6.93, N 5.66; found C 67.76, H 6.94, N 5.61. HRMS: calcd. 247.1208; found 247.1209.

Compound (*R*)-1b: Obtained as a pale yellow solid (340 mg, 90%, 88% *ee*): $[\alpha]_D^{25} = +13.6$ ($c = 1.0$, $CHCl_3$). NMR spectroscopic data as above.

(*S*)-(+)-Cyano(4-chlorophenyl)methyl Pivaloate [(*S*)-4c] and (*R*)-(−)-Cyano(4-chlorophenyl)methyl Acetate [(*R*)-1c]: The title compounds were prepared from racemic (*R*,*S*)-**1c** according to General Procedure C.

Compound (*S*)-4c: Obtained as a pale yellow oil (352 mg, 76%, 78% *ee*): $[\alpha]_D^{25} = +2.8$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 [s, 9 H, $(CH_3)_3C$], 6.38 (s, 1 H, CHO), 7.44 (m, 4 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6 [($CH_3)_3C$], 38.6 (*C*CO), 62.0 (CHO), 115.8 (CN), 128.8, 129.3 (C-2,3,5,6), 130.5 (C-1), 136.1 (C-4), 176.0 (C=O). MS: *m*/*z* (%) = 251 (28), 167 (13), 150 (50), 139 (90), 111 (60), 85 (25), 57 (100). $C_{13}H_{14}ClNO_2$ (251.07): calcd. C 62.03, H 5.61, N 5.56; found C 62.44. H 5.76, N 5.41. HRMS: calcd. 251.0713; found 251.0713.

Compound (*R*)-1c: Obtained as a pale yellow oil (328 mg, 85%, > 99% *ee*): $[\alpha]_D^{25} = -13.9$ ($c = 1.0$, $CHCl_3$). NMR spectroscopic data as above.

(*S*)-(+)-Cyano(3-phenoxyphenyl)methyl Pivaloate (*S*)-4d and (*R*)-(−)-Cyano(3-phenoxyphenyl)methyl Acetate (*R*)-1d: The title compounds were prepared from racemic (*R*,*S*)-**1d** according to General Procedure C.

Compound (*S*)-4d: Obtained as a pale yellow oil (419 mg, 73%, 81% *ee*): $[\alpha]_D^{25} = +0.2$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.23 [s, 9 H, $(CH_3)_3C$], 6.35 (s, 1 H, CHO), 7.0−7.2 (m, 9 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 [($CH_3)_3C$], 38.9 (*C*CO), 62.3 (CHO), 116.0 (CN), 117.0 (C-2′), 119.5 (C-2′′, 6′′), 119.9 (C-4′), 121.6 (C-6′), 124.1 (C-4′′), 130.0 (C-3′′, 5′′), 130.6 (C-5′), 133.8 (C-1), 156.2 (C-3′), 158.3 (C-1′′), 176.3 (C=O).

Compound (*R*)-1d: Obtained as a pale yellow oil (416 mg, 84%, 90% *ee*): $[\alpha]_D^{25} = -7.2$ ($c = 1.0$, $CHCl_3$). NMR spectroscopic data as above.

General Procedure D. Protection as THP Ether: *p*TsOH (5 mg, 0.028 mmol) was added to the filtrate of General Procedure A at 0 °C. DHP (0.75 mL, 8.24 mL) was then added dropwise over a period of 10 min. The reaction mixture was then stirred under N_2 for 2 h at ambient temperature and the reaction quenched with satd. $NaHCO_3$ (25 mL). The organic phase was dried with $MgSO_4$. Solvents were removed under vacuum and the crude products were analysed by ^1H NMR.

Racemic Cyanohydrins Protected as THP Ethers: Racemic (*R*,*S*)-**5a**−**d** was prepared from racemic (*R*,*S*)-**2a**−**d** according to General Procedure D, with the modification that a solution of the cyanohydrin (1.84 mmol) in dry toluene (36 mL) and *n*-propanol (0.54 mL) was used in place of the filtrate of the kinetic resolution. The products were purified by column chromatography on silica gel (PE/EtOAc, 90:10). The yields were: (*R*,*S*)-**5a**: 92%; (*R*,*S*)-**5b**: 96%; (*R*,*S*)-**5c**: 94%; (*R*,*S*)-**5d**: 92%.

(2*S*)-Phenyl[(tetrahydropyran-2-yloxy)]acetonitrile [(*S*)-5a] and (*R*)-(−)-Cyano(phenyl)methyl Acetate [(*R*)-1a]: The title compounds were prepared from racemic (*R*,*S*)-**1a** according to General Procedure D. The ratio of aromatic components in the reaction mixture was determined by ^1H NMR (300 MHz, $CDCl_3$): (*S*)-**5a**: 47% (δ = 5.42 and 5.59, CHO); (*R*)-**1a**: 51% (δ = 6.40, CHO); benzaldehyde: 2% (δ = 10.03, HC=O); (*S*)-**5a**: 93% *ee*; (*R*)-**1a**: 93% *ee*.

Characterisation of Racemic (*R*,*S*)-5a: ^1H NMR (300 MHz, $CDCl_3$): diastereoisomer A: δ = 1.44−1.95 (m, 6 H, THP), 3.63 (m, 1 H, OCH_2), 4.01 (m, 1 H, OCH_2), 4.74 (m, 1 H, OCHO), 5.42 (s, 1 H, CHO), 7.38−7.56 (m, 5 H, aromatic); diastereoisomer B: δ = 1.44−1.95 (m, 6 H, THP), 3.63 (m, 1 H, OCH_2), 3.79 (m, 1 H, OCH_2), 5.11 (m, 1 H, OCHO), 5.59 (s, 1 H, CHO), 7.38−7.56 (m, 5 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): diastereoisomer A: δ = 18.7, 25.1, 29.8 (THP), 62.4 (OCH_2), 65.8 (OCHO), 96.8 (CHO), 117.6 (CN), 127.4 (C-2, 6), 129.1 (C-3, 5), 129.8 (C-4), 133.9 (C-1); diastereoisomer B: δ = 18.2, 25.1, 29.8 (THP), 62.0 (OCH_2), 66.5 (OCHO), 97.5 (CHO), 118.3 (CN), 127.4 (C-2, 6), 129.0 (C-3, 5), 129.6 (C-4), 133.7 (C-1).

(2*S*)-(4-Methoxyphenyl)[(tetrahydropyran-2-yloxy)]acetonitrile [(*S*)-5b] and (*R*)-(−)-Cyano(4-methoxyphenyl)methyl Acetate [(*R*)-1b]: The title compounds were prepared from racemic (*R*,*S*)-**1b** according to General Procedure D. The ratio of aromatic components in the reaction mixture was determined by ^1H NMR (300 MHz, $CDCl_3$): (*S*)-**5b**: 42% (δ = 5.36 and 5.53, CHO); (*R*)-**1b**: 50% (δ = 6.35, CHO); anisaldehyde: 8% (δ = 9.89, HC=O); (*S*)-**5b**: 93% *ee*; (*R*)-**1b**: 92% *ee*. The reaction mixture was purified by column chromatography (PE/EtOAc, 90:10) to give diastereoisomer A as a pale yellow oil (218 mg, 48%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50−1.85 (m, 6 H, THP), 3.62 (m, 1 H, OCH_2), 3.78 (m, 1 H, OCH_2), 3.83 (s, 3 H, MeO), 5.08 (m, 1 H, OCHO), 5.53 (s, 1 H, CHO), 6.94 (m, 2 H, aromatic), 7.45 (m, 2 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 25.1, 29.8 (THP), 55.4 (MeO), 62.4

(OCH_2), 65.5 (OCHO), 96.8 (CHO), 114.4 (C-3, 5), 117.8 (CN), 125.8 (C-1), 129.0 (C-2, 6), 160.6 (C-4). A mixture of diastereoisomer B together with (*R*)-**1b** was also obtained, and was purified once more by column chromatography (toluene 100%) to give diastereoisomer B as a pale yellow solid (164 g, 36%): m.p. 56.2−56.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50−1.90 (m, 6 H, THP), 3.62 (m, 1 H, OCH_2), 4.00 (m, 1 H, OCH_2), 5.08 (m, 1 H, OCHO), 5.36 (s, 1 H, CHO), 6.94 (m, 2 H, aromatic), 7.40 (m, 2 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 25.2, 29.8 (THP), 55.4 (MeO), 62.0 (OCH_2), 66.0 (OCHO), 96.9 (CHO), 114.4 (C-3, 5), 118.5 (CN), 125.9 (C-1), 129.1 (C-2, 6), 160.7 (C-4). MS: *m*/*z* (%) = 247 (9), 205 (8), 163 (29), 146 (100), 107 (12), 85 (86), 55 (27). HRMS calcd. for $C_{14}H_{17}NO_3$: 247.1208; found 247.1216.

Compound (*R*)-1b: Obtained as a pale yellow solid (375 mg, 99%): $[\alpha]_D^{25}$ = +17.0 (*c* = 1.0, $CHCl_3$). NMR spectroscopic data as above.

(2*S*)-(4-Chlorophenyl)[(tetrahydropyran-2-yloxy)]acetonitrile [(*S*)-5c] and (*R*)-(−)-Cyano(4-chlorophenyl)methyl Acetate [(*R*)-1c]: The title compounds were prepared from racemic (*R*,*S*)-**1c** according to General Procedure D. The ratio of aromatic components in the reaction mixture was determined by ^{1}H NMR (300 MHz, $CDCl_3$): (*S*)-**5c**: 43% (δ = 5.39 and 5.57, CHO); (*R*)-**1c**: 49% (δ = 6.38, CHO); 4-chlorobenzaldehyde: 8% (δ = 9.98, HC=O); (*S*)-**5c**: 90% *ee*; (*R*)-**1c**: > 99% *ee*. Characterisation of racemic (*R*,*S*)-**5c**: ^{1}H NMR (400 MHz, $CDCl_3$): diastereoisomer A: δ = 1.50−1.90 (m, 6 H, THP), 3.63 (m, 1 H, OCH_2), 4.00 (m, 1 H, OCH_2), 4.73 (m, 1 H, OCHO), 5.39 (s, 1 H, CHO), 7.39−7.49 (m, 4 H, aromatic); diastereoisomer B: δ = 1.50−1.90 (m, 6 H, THP), 3.63 (m, 1 H, OCH_2), 3.75 (m, 1 H, OCH_2), 5.09 (m, 1 H, OCHO), 5.57 (s, 1 H, CHO), 7.35−7.49 (m, 4 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): diastereoisomers A and B: δ = 18.2, 18.7, 25.0, 25.1, 29.7 (2 C) (THP), 62.1, 62.5 (OCH_2), 65.1, 65.8 (OCHO), 96.9, 97.6 (CHO), 117.2, 118.0 (CN), 128.8 (2 C), 129.2, 129.3 (C-2,6 or 3,5), 132.2, 132.4 (C-1), 135.7, 135.8 (C-4).

(2*S*)-(3-Phenoxyphenyl)[(tetrahydropyran-2-yloxy)]acetonitrile [(*S*)-5d] and (*R*)-(−)-Cyano(3-phenoxyphenyl)methyl Acetate [(*R*)-1d]: The title compounds were prepared from racemic (*R*,*S*)-**1d** according to General Procedure D. The ratio of aromatic components in the reaction mixture was determined by ^{1}H NMR (300 MHz, $CDCl_3$): (*S*)-**5d**: 43% (δ = 5.36 and 5.54, CHO); (*R*)-**1d**: 50% (δ = 6.36, CHO); 3-phenoxybenzaldehyde: 7% (δ = 9.95, HC=O); (*S*)-**5d**: 84% *ee*; (*R*)-**1d**: > 99% *ee*. Characterisation of racemic (*R*,*S*)-**5d**: ^{1}H NMR (300 MHz, $CDCl_3$): diastereoisomer A: δ = 1.40−1.90 (m, 6 H, THP), 3.60 (m, 1 H, OCH_2), 3.70 (m, 1 H, OCH_2), 5.08 (m, 1 H, OCHO), 5.54 (s, 1 H, CHO), 6.95−7.36 (m, 9 H, aromatic); diastereoisomer B: δ = 1.40−1.90 (m, 6 H, THP), 3.60 (m, 1 H, OCH_2), 3.95 (m, 1 H, OCH_2), 4.72 (m, 1 H, OCHO), 5.36 (s, 1 H, CHO), 6.95−7.36 (m, 9 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): diastereoisomer A: δ = 18.5, 25.0, 29.7 (THP), 62.2 (OCH_2), 65.3 (OCHO), 96.7 (CHO), 118.1 (CN), 119.2 (C-2′′,6′′), 119.3 (C-2′), 121.7 (C-4′), 123.8 (C-4′′), 129.9 (C-3′′,5′′), 130.3 (C-5′), 135.6 (C-1′), 156.4 (C-3′), 157.9 (C-1′′); diastereoisomer B: δ = 18.2, 25.1, 29.7 (THP), 62.0 (OCH_2), 66.1 (OCHO), 97.7 (CHO), 117.3 (CN), 119.2 (C-2′′,6′′), 119.4 (C-2′), 121.7 (C-4′), 123.8 (C-4′′), 129.9 (C-3′′,5′′), 130.4 (C-5′), 135.9 (C-1′), 156.4 (C-3′), 158.0 (C-1′′). MS: diastereoisomer A: *m*/*z* (%) = 309 (7), 225 (14), 198 (100), 169 (50), 141 (40), 115 (17), 85 (54). Diastereoisomer A: $C_{19}H_{19}NO_3$ (309.14): calcd. C 73.77, H 6.19, N 4.53; found C 73.54, H 6.26, N 4.32. HRMS: calcd. 309.1365; found 309.1374.

General Procedure E: Enzyme-Catalysed Protection as Butyryl Ester: The kinetic resolution was performed as in General Procedure A, but instead of the cooling of the reaction mixture and the separation of the enzyme from the reaction mixture, vinyl butyrate (**6**) (2.8 mL, 18.4 mmol) was added. After stirring at 60 °C overnight, the reaction mixture was filtered. HCl (1 M, 25 mL) was added to the filtrate and the organic phase was washed with satd. $NaHCO_3$ (25 mL) and dried with $MgSO_4$. Solvents were removed under vacuum and the crude products were purified by column chromatography on silica gel (PE/EtOAc, 95:5).

Racemic Cyanohydrins Protected as Butyryl Esters: Racemic (*R*,*S*)-**7a−d** was prepared from racemic (*R*,*S*)-**2a−d** according to General Procedure C, with the modifications that a solution of the cyanohydrin (1.84 mmol) in dry toluene (36 mL) and *n*-propanol (0.54 mL) was used instead of the filtrate from the kinetic resolution, and butyryl chloride (11.4 mmol) was used instead of pivaloyl chloride. The yields were: (*R*,*S*)-**7a**: 62%; (*R*,*S*)-**7b**: 84%; (*R*,*S*)-**7c**: 74%; (*R*,*S*)-**7d**: 84%.

(*S*)-(−)-Cyano(phenyl)methyl Butyrate [(*S*)-7a] and (*R*)-(+)-Cyano(phenyl)methyl Acetate [(*R*)-1a]: The title compounds were prepared from racemic (*R*,*S*)-**1a** according to General Procedure E.

Compound (*S*)-7a was obtained as a pale yellow oil (316 mg, 85%, 98% *ee*): $[\alpha]_D^{25}$ = −7.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.70 (tq, 2 H, *J* = 7.4 Hz, CH_2CH_3), 2.38 (dt, *J* = 2.8, 7.5 Hz, 2 H, CH_2CO), 6.44 (s, 1 H, CHO), 7.41−7.58 (m, 5 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 18.2 (CH_2CH_3), 35.6 (CH_2CO), 62.6 (CHO), 116.2 (CN), 127.8 (C-2,6), 129.2 (C-3,5), 130.3 (C-4), 131.9 (C-1), 171.6 (C=O).

Compound (*R*)-1a: Obtained as a pale yellow oil (302 mg, 93%, 95% *ee*): $[\alpha]_D^{25}$ = +5.9 (*c* = 1.0, $CHCl_3$). NMR spectroscopic data as above.

(*S*)-(+)-Cyano(4-methoxyphenyl)methyl Butyrate [(*S*)-7b] and (*R*)-(+)-Cyano(4-methoxyphenyl)methyl Acetate [(*R*)-1b]: The title compounds were prepared from racemic (*R*,*S*)-**1b** according to General Procedure E.

Compound (*S*)-7b: Obtained as a pale yellow oil (364 mg, 80%, 97% *ee*): $[\alpha]_D^{25}$ = +12.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, 3 H, *J* = 7.5, CH_3), 1.68 (tq, 2 H, *J* = 7.4, CH_2CH_3), 2.37 (dt, *J* = 2.9, 7.5 Hz, 2 H, CH_2CO), 3.83 (s, 3 H, CH_3O), 6.38 (s, 1 H, CH-O), 6.94 (m, 2 H, aromatic), 7.45 (m, 2 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (CH_3), 18.2 (CH_2CH_3), 35.6 (CH_2CO), 55.4 (OCH_3), 62.3 (CHO), 114.5 (C-3,5), 116.4 (CN), 124.03 (C-1), 129.6 (C-2,6), 161.1 (C-4), 171.7 (C=O). MS: *m*/*z* (%) = 233 (26), 163 (32), 146 (100), 135 (77), 77 (37). $C_{13}H_{15}NO_3$ (233.11): calcd. C 66.94, H6.48, N 6.00; found C 67.22, H 6.45, N 5.64. HRMS: calcd. 233.1052; found 233.1049.

Compound (*R*)-1b: Obtained as a pale yellow solid (306 mg, 81%, 91% *ee*): $[\alpha]_D^{25}$ = −17.5 (*c* = 1.0, $CHCl_3$). NMR spectroscopic data as above.

(*S*)-(+)-Cyano(4-chlorophenyl)methyl Butyrate [(*S*)-7c] and (*R*)-(−)-Cyano(4-chlorophenyl)methyl Acetate [(*R*)-1c]: The title compounds were prepared from racemic (*R*,*S*)-**1c** according to General Procedure E.

Compound (*S*)-7c: Obtained as a pale yellow oil (338 mg, 73%, 97% *ee*): $[\alpha]_D^{25}$ = +6.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, *J* = 7.4, CH_3), 1.68 (tq, 2 H, *J* = 7.4, CH_2CH_3), 2.39 (dt, *J* = 3.0, 7.4 Hz, 2 H, CH_2CO), 6.41 (s, 1 H, CHO), 7.40−7.49 (m, 4 H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5 (CH_3), 18.2 (CH_2CH_3), 35.5 (CH_2CO), 61.9 (CHO), 115.8 (CN), 129.2, 129.5 (C-2,6,3,5), 130.5 (C-4), 136.6 (C-1), 171.5 (C=O). MS: *m*/*z* (%) = 237 (16), 167 (45), 150 (76), 139 (26), 71 (100).

$C_{12}H_{12}ClNO_2$ (237.05): calcd. C 60.64, H 5.09, N 5.89; found C 60.89, H 5.16, N 5.80. HRMS: calcd. 237.0557; found 237.0558.

Compound (*R*)-1c: Obtained as a pale yellow oil (357 mg, 93%, 98% *ee*): $[\alpha]_D^{25} = -9.9$ (c = 1.0, $CHCl_3$). NMR spectroscopic data as above.

(*S*)-(+)-Cyano(3-phenoxyphenyl)methyl Butyrate [(*S*)-7d] and (*R*)-(−)-Cyano(3-phenoxyphenyl)methyl Acetate [(*R*)-1d]: The title compounds were prepared from racemic (*R*,*S*)-**1d** according to general procedure E.

Compound (*S*)-7d: Obtained as a pale yellow oil (388 mg, 67%, 96% *ee*): $[\alpha]_D^{25} = +4.2$ (c = 1.0 $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3 H, J = 7.4, CH_3), 1.68 (tq, 2 H, J = 7.4, CH_2CH_3), 2.39 (dt, 2 H, ^2J = 11.7, ^3J = 7.4 Hz, CH_2CO), 6.38 (s, 1 H, CHCN), 7.00−7.42 (m, 9 H, aromatic). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (CH_3), 18.2 (CH_2CH_3), 35.5 (CH_2CO), 62.2 (CHO), 115.9 (CN), 117.5 (C-2′), 119.4 (C-2′′,6′′), 120.1 (C-4′), 122.0 (C-6′), 124.1 (C-4′′), 130.0 (C-3′′,5′′), 130.6 (C-5′), 133.6 (C-1′), 156.2 (C-3′), 158.2 (C-1′′), 171.5 (C=O).

Compound (*R*)-1d: Obtained as a pale yellow oil (464 mg, 92%, 75% *ee*): $[\alpha]_D^{25} = -5.1$ (c = 1.0 $CHCl_3$). NMR spectroscopic data as above.

Recycling Experiment: The experiment yielding (*S*)-**5c** and (*R*)-**1c** was repeated four times using the same enzyme. The reactions were performed as described in General Procedure D with the following modifications. In the four repetitions the enzyme was not dried but directly used in the next cycle after it had been washed with dry toluene (7 mL). Toluene, *n*-propanol and racemic (*R*,*S*)-**1c** were then added to the enzyme. The ratio of aromatic components in the reaction mixture was determined by integration of the following ^{1}H NMR signals (300 MHz, $CDCl_3$): (*S*)-**5c** (δ = 5.39 and 5.57, CHO), (*R*)-**1c** (δ = 6.38, CHO), **8** (δ = 9.98, HC=O). Cycle 0: (*S*)-**5c** (49%, *ee* 99%), (*R*)-**1c** (43%, *ee* 90%), **8** (8%); cycle 1: (*S*)-**5c** (48%, *ee* 99%), (*R*)-**1c** (43%, *ee* 90%), **8** (9%); cycle 2: (*S*)-**5c** (49%, *ee* 97%), (*R*)-**1c** (44%, *ee* 93%), **8** (7%); cycle 3: (*S*)-**5c** (49%, *ee* 98%), (*R*)-**1c** (45%, *ee* 93%), **8** (6%); cycle 4: (*S*)-**5c** (49%, *ee* 98%), (*R*)-**1c** (45%, *ee* 93%), **8** (5%).

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