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Chemoenzymatic method for the preparation of γ-amino alcohols from phenylfuran-based aldehydes; lipase-catalyzed kinetic resolution of β-hydroxy nitriles

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ABSTRACT

The chemoenzymatic preparation of novel enantiopure phenylfuran-based γ-amino alcohols with *N*-Boc-protection starting from the corresponding aldehydes is described. Enantiopurity (ee 98–99%) is introduced using *Thermomyces lanuginosus* lipase as the IMMTLL-T1-1500 preparation with β-hydroxy nitriles in an acylation/alcoholysis sequence in *tert*-butylmethyl ether.

1. Introduction

Amino alcohol moieties with a certain stereochemistry infer interesting biological activities to organic molecules. Many naturally occurring molecules, synthetic pharmaceutically active intermediates, and chiral ligands and auxiliaries are amino alcohols. Compounds containing vicinal β-amino alcohol (1,2-amino alcohol) moieties have been thoroughly studied, and synthetic approaches to access such molecules by chemical and biocatalytic ways are abundant.[1] Compounds containing γ-amino alcohol (1,3-amino alcohol) moieties, 3-amino-1-arylpropan-1-ols in particular, are widely used for the treatment of psychiatric and metabolic disorders and an access to such molecules is described. Such compounds include fluoxetine (Prozac™, a selective serotonin reuptake inhibitor),[2,3] atomoxetine (Strattera™, a norepinephrine reuptake inhibitor),[4] and duloxetine (Cymbalta™, a serotonin–norepinephrine reuptake inhibitor).[5] Because the enantiomers of pharmaceutically active compounds often display different physiological properties and may have their own effects on drug–ligand interactions and metabolic behavior, the preparation of enantiopure molecules is of great importance. Reported chemocatalyzed synthesis strategies include the asymmetric hydrogenation of prochiral amino ketones[6,7] and the preparation of chiral 3-hydroxypropanenitriles (β-hydroxy nitriles)[8–11]as methods to introduce enantiopurity in the1,3-amino alcohol moiety.

Today, enzymes as green chemistry catalysts often replace chemocatalysts as enantiopurity-producing steps in chemoenzymatic synthesis. This is due to the enantio- and chemoselectivity of enzymes, allowing the preparation of highly enantiopure products under mild conditions and usually by small number of reaction steps. Potential enzymatic methods to the enantiomers of 3-amino-1-arylpropan-1-ols exploit asymmetric synthesis by the reduction of ketone precursors (Scheme 1, routes A and B) and the kinetic resolution of racemic alcohol precursors (routes C and D). The biocatalytic reduction of β-keto nitriles,[12,13] the lipase-catalyzed acylation of β-hydroxy nitriles,[14–18] and the lipase-catalyzed hydrolysis[19] and alcoholysis[18] of their racemic esters have been reported. On the other hand, the enzymatic reduction of 3-amino-1-arylpropan-1-one has not been described evidently due to potential imine formation between the functional groups. 1-Aryl-3-aminopropan-1-ols are not ideal substrates for lipase-catalyzed enantioselective acylation in spite of the fact that some lipases (e.g., *Burkholderia cepacia* lipase) are known to acylate the alcohol function of an amino alcohol in a highly chemoselective manner.[20–22] This is due to the chemical and/or enzyme-aided *O*→*N* acyl migration, leading to the mixture of mono- and diacylated products when the two functionalities are separated by 2–4 carbon atoms.

Our aim herein has been to study the chemoenzymatic synthesis of new enantiopure phenyl-furan-based 1,3-amino alcohols in *N*-Boc-protected forms **4a**–**e** starting from the corresponding commercial aldehydes **1a**–**e** (Scheme 2). High stability and enantioselectivity in addition to good availability have made lipases as the most commonly used biocatalysts in organic chemistry, producing both enantiomers (one as an alcohol and the other as an ester) in the highly enantioselective acylation of an initially racemic alcohol (or amine) or in the deacylation of the corresponding racemic ester. Herein, the enantioseparation step was chosen to be the lipase-catalyzed acylation of phenylfuran-based nitriles **2a**–**e**, allowing the separation of the unreacted (*S*)-**2a**–**e** from the resolved mixture. The lipase-catalyzed deacylation of the esters (*R*)-**3a**–**e** thereafter

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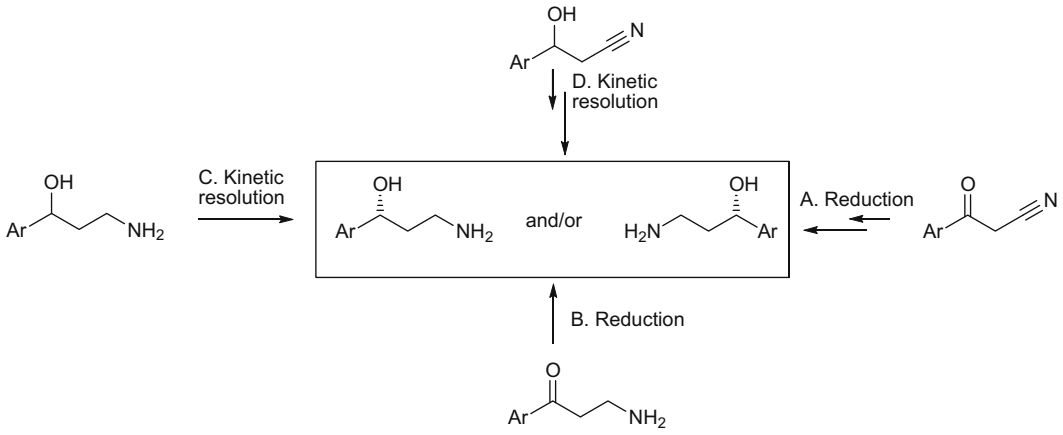
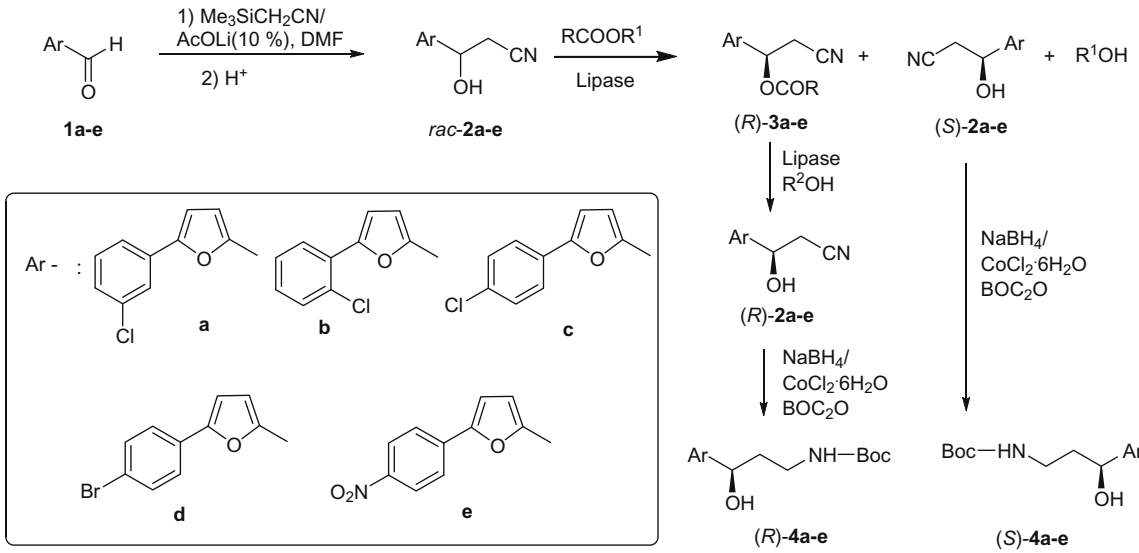


Scheme 1. Potential biocatalytic methods to introduce enantiopurity in 3-amino-1-arylpropan-1-ols.



Scheme 2. Chemoenzymatic route to enantiopure *N*-Boc-protected γ-amino alcohols.

allows the preparation of the corresponding (*R*)-alcohols. In the subsequent reduction step *N*-Boc-protected (*R*)- and (*S*)-**4a**–**e** are obtained.

2. Results and discussion

2.1. Preparation of racemates

Sulfur heterocyclic β-hydroxy nitriles have previously been prepared from sulfur-containing aldehydes and (trimethylsilyl)acetonitrile in the presence of lithium acetate as a Lewis base using a known method.[18,23] The same method was successfully exploited to obtain racemic β-hydroxy nitriles **2a**–**e** from commercial phenylfuran-based aldehydes **1a**–**e** with isolated yields within the range 78–83% (Scheme 2). The reaction between *rac*-**2a**–**e** and acetic anhydride in the presence of catalytic amounts of DMAP (1%)/Py produced the corresponding racemic acetate esters *rac*-**3a**–**e**. Racemic mixtures were needed for kinetic resolution studies and also to provide the analytical methods.

2.2. Lipase-catalyzed acylation

In continuation of our work with heterocyclic aromatic β-hydroxy nitriles,[18] we planned to use a lipase-catalyzed reaction consisting of an acylation/alcoholysis sequence for the production of both (*R*)- and (*S*)-**2a**–**e** as novel phenylfuran-based β-hydroxy nitriles (Scheme 2). This enzymatic sequence achieves the highest possible enantiopurities for both alcohol enantiomers with the minimal number of reaction steps even in the cases when the enantioselectivity for the kinetic resolution is not high enough to allow the enantioseparation at the theoretical 50% conversion.[24] To start the work, *rac*-**2a** was chosen as a model substrate. Unlike the case with previous sulfur heterocycles,[18] the lipase PS-D-catalyzed acylation of *rac*-**2a** (0.05 M) with vinyl acetate (0.1 M) in *tert*-butylmethyl ether (TBME) was barely enantioselective (Table 1, entry 1). Thus, lipase screening with potential lipases from *B. cepacia*, *Pseudomonas fluorescens*, *Thermomyces lanuginosus*, and *Candida antarctica* in various immobilized forms started the studies. Lipases from *T. lanuginosus* (lipozyme TL IM and lipase IMMTLL-T1-1500) gave the most promising enantioselectivities (entries 7 and 8). Because the acylation with lipozyme TL IM (on granulated silica material) practically stopped at 16% conversion (entry 7), the work continued with lipase IMMTLL-T1-1500 (on dry polypropylene beads with size <1500 μm, entry 8). The same enantiomer of *rac*-**2a** reacted faster with all the lipases tested. In accordance with the enantiopreference of lipase PS-D with previous sulfur heterocycles,[18] the (*R*)-enantiomer reacts faster also with the present substrates.

Table 1
Lipase screening (50 mg mL^{-1}) for the acylation of *rac*-**2a** (0.05 M) with vinyl acetate (0.1 M) in TBME

Entry	Enzyme preparation	Time (h)	ee$^{(S)\text{-}\mathbf{2a}}$ (%)	ee$^{(R)\text{-}\mathbf{3a}}$ (%)	Conversion (%)	*E*
1	Lipase PS-D	0.25	10	47	18	3 ± 1
2	Lipase PS-C II	0.25	11	43	20	3 ± 1
3	Lipase AK	3	50	93	35	50 ± 3
4	Lipase IMMAPF-T2-150	3	22	97	19	60 ± 5
5	CAL-A	3	51	41	55	5 ± 1
6	CAL-B	3	14	93	13	30 ± 2
7	Lipozyme TL IM[a]	0.5	14	99	13	≫200
8	Lipase IMMTLL-T1-1500	3	87	93	48	79 ± 3
9	Lipase IMMTLL-T2-150	3	16	99	14	50 ± 5

[a] Acylation stopped at 16% conversion after 1 h.

In order to make kinetic resolution attractive in a preparative sense, the concentrations of *rac*-**2a** and vinyl acetate were doubled for further optimization. Thus, the acylation of *rac*-**2a** (0.1 M) with vinyl acetate (0.2 M) and lipase IMMTLL-T1-1500 (50 mg mL^{-1}) was tested in three commonly used solvents, namely in TBME, diisopropyl ether (DIPE), and toluene. When the acylation was performed in DIPE (E = 64 ± 2) and in toluene (E = 47 ± 2) the enantioselectivity was low compared to the reaction in TBME (E = 79 ± 3). For the reaction in toluene, the conversion rate was also considerably reduced (33% conversion in 3 h) compared to the reactions in TBME and DIPE with 50–51% conversions in 3 h. When the acylation was performed in neat isopropyl acetate (a solvent and an acyl donor) the reaction was extremely slow (1% conversion in 1 day). In terms of enantioselectivity, the acylation with vinyl acetate was favorable compared to that with isopropenyl acetate (E = 67 ± 1), another commonly used irreversible acyl donor in TBME. For economic reasons, the lipase IMMTLL-T1-1500 content 50 mg mL^{-1} was finally chosen for the acylation of *rac*-**2a** (0.1 M) with vinyl acetate (0.2 M) in TBME after it was shown that the further increase of the catalyst content had just a negligible effect on conversion with time (Fig. 1).

Finally, the acylation of all the substrates *rac*-**2a**–**e** was performed under the above optimized conditions. The results in Table 2 indicate clear effects of the substrate structure on both reactivity and enantioselectivity. Electron-withdrawing substituents lead to reduced electron density at the aromatic system. As

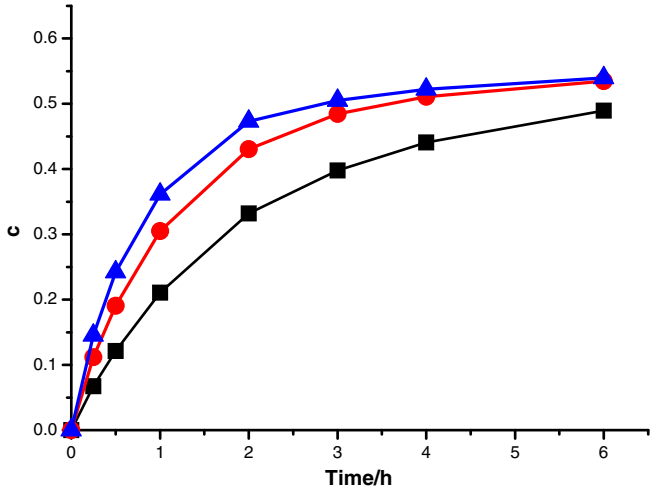


Figure 1. Progression curves for the acylation of *rac*-**2a** in TBME with different amounts of lipase IMMTLL-T1-1500 (25 mg mL^{-1}, 50 mg mL^{-1}, 75 mg mL^{-1}).

Table 2
Acylation of *rac*-**2a**–**e** (0.1 M) with vinyl acetate (0.2 M) in the presence of lipase IMMTLL-T1-1500 (50 mg mL^{-1}) in TBME

Entry	*rac*-**2**	Time (h)	ee$^{(R)\text{-}\mathbf{3a\text{–}e}}$ (%)	Conversion (%)	*E*	Conversion[a] (%)
1	**a**	0.5	97	19	79 ± 3	51–53
2	**b**	0.25	98	17	120 ± 5	50–52
3	**c**	0.25	98	26	115 ± 11	50–52
4	**d**	0.25	95	25	96 ± 7	51–52
5	**e**[b]	2	95	40	46 ± 12	53–55

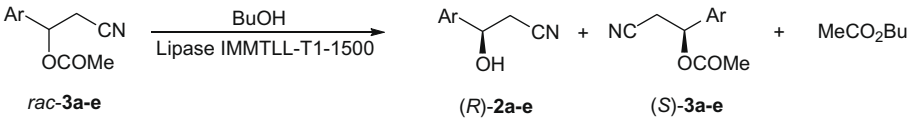
[a] Theoretical conversion calculated from E-producing ee$^{(S)\text{-}\mathbf{2a\text{–}e}}$over the range (95–99)%.
[b] TBME/acetone (9/1) as a solvent.

a consequence, for instance enhanced π–π–interactions may improve substrate binding at the active site. Indeed, the electron-withdrawing halogen atoms at *ortho*- and *para*-positions (entries 2–4) are favorable compared to the electron-donating *meta*-chlorine (entry 1). However, the lowest reactivity and enantioselectivity were recorded for the acylation of *rac*-**2e** with the strongly electron-withdrawing *para*-nitro group (Table 2, entry 5). This result can be explained by the use of acetone as a co-solvent (1 part) to make the compound soluble in TBME. As a conclusion, the conditions optimized for the acylation of *rac*-**2a** are suitable for the kinetic resolution of all the substrates *rac*-**2a**–**e**. In order to plan the second alcoholysis step of the acylation/alcoholysis sequence (Scheme 2), the theoretical conversions (50–55%) to reach ee$^{(S)\text{-}\mathbf{2a\text{–}e}}$ 95–99% for the unreacted substrates were calculated based on the observed E values and are given in Table 2 (column at the right).

2.3. Lipase-catalyzed alcoholysis

Naturally, the same enantiopreference is observed in the acylation and deacylation (alcoholysis, hydrolysis, and so on) directions with a certain lipase. Alcoholysis was preferred in the present work due to the low solubility of compounds **2** and **3** in aqueous environments. Lipase IMMTLL-T1-1500-mediated alcoholysis was investigated primarily aiming to deacylate the (*R*)-esters **3a**–**e** obtained through the preparative-scale kinetic resolution of *rac*-**2a**–**e**. In addition, we wanted to know how enantioselectively the alcoholysis proceeds. Alcohols are known to be competitive inhibitors of lipases,[25,26] and accordingly low alcohol contents were favored.

Each of the esters *rac*-**3a**–**e** (0.1 M) was subjected to alcoholysis (Scheme 3) with butan-1-ol (0.3 M) in TBME in the presence of lipase IMMTLL-T1-1500 (50 mg mL^{-1}), and the results are shown in Table 3. Reactions proceeded slowly although in highly enantioselective fashion compared to the corresponding acylation reactions (Table 2). Both the unreacted (*S*)-**3a**–**d** and the produced (*R*)-**2a**–**d** were furnished in enantiopure forms at close to 50% conversion (entries 1–4) while the alcoholysis of *rac*-**3e** was slow and the enantioselectivity was low (entry 5) the presence of acetone being again an evident reason. The reactivity with **3a** in 3 h was improved from 26% conversion with 50 mg mL^{-1} of lipase IMMTLL-T1-1500 to 46% conversion with 100 mg mL^{-1} of the enzyme. On the other hand, 0.2 M (conversion 29% in 3 h) and 0.3 M (conversion 26% in 3 h) butan-1-ol concentrations gave practically the same reactivity in the presence of lipase IMMTLL-T1-1500 (50 mg mL^{-1}) while higher alcohol contents caused dramatic rate retardations. Accordingly, the highly enantioselective alcoholysis with butan-1-ol proved to be an excellent second step in the two-step acylation/deacylation protocol, improving the enantiopurity of the reactive (*R*)-enantiomer at the same time. In spite of excellent enantioselectivity, alcoholysis is not the choice for kinetic resolution due to the fact that the unreacted ester enantiomers then cannot be transformed into the corresponding alcohol enantiomers by lipase catalysis under mild conditions.



Scheme 3. Kinetic resolution of *rac*-**3a–e** with butan-1-ol.

Table 3
Alcoholysis of *rac*-**3a–e** (0.1 M) with butan-1-ol (0.3 M) and lipase IMMTLL-T1-1500 (50 mg mL^{-1}) in TBME

Entry	*rac*-**3**	Time (h)	ee$^{(R)\text{-}\mathbf{2a-e}}$ (%)	ee$^{(S)\text{-}\mathbf{3a-e}}$ (%)	Conversion (%)	*E*
1	**a**	24	96	97	50	>200
2	**b**	24	95	98	51	162 ± 16
3	**c**	24	96	98	51	>200
4	**d**	24	94	99	51	>200
5	**e**[a]	24	97	52	35	72 ± 19

[a] TBME/acetone (4/1) as a solvent.

2.4. Chemoenzymatic preparation of (*R*)- and (*S*)-4a–e

Finally the preparative-scale kinetic resolution of *rac*-**2a–e** was performed under optimized conditions of the substrate (0.1 M), vinyl acetate (0.2 M), and lipase IMMTLL-T1-1500 (50 mg mL^{-1}) in TBME, affording unreacted (*S*)-**2a–e** enantiopure at 83–97% isolated yields when the reactions were stopped at 51–53% conversions. After purification by column chromatography, the isolated (*R*)-**3a–e** ester products were subjected to alcoholysis with butan-1-ol (0.2 M) in TBME in the presence of lipase IMMTLL-T1-1500 (50 mg mL^{-1}), affording (*R*)-**2a–e** at 71–92% isolated yields also enantiopure. For the kinetic resolution of *rac*-**2e** and for the deprotection of (*R*)-**3e** acetone served as a co-solvent due to solubility problems. The outcome of the enzymatic preparative work is given in Table 4.

Table 4
Enantiopure **2a–e** prepared by lipase IMMTLL-T1-1500-catalyzed kinetic resolution: the *R*-enantiomers obtained through acylation/alcoholysis sequence and the *S*-enantiomers through acylation

	(*R*)-**2**			(*S*)-**2**		
	ee (%)	Yield[a] (%)	Specific rotation[b]	ee (%)	Yield[c] (%)	Specific rotation[b]
a	99	71	+46.7	98	83	−46.3
b	99	92	+44.7	99	97	−43.8
c	99	88	+45.5	99	91	−48.2
d	99	89	+39.4	99	89	−36.2
e	99	74	+55.4	97	95	−56.6

[a] Overall yields from the enzymatic acylation/deacylation sequence.
[b] (*c* 1, $CHCl_3$).
[c] Isolated yields based on the conversion of enzymatic acylation.

With the enantiomers of β-hydroxy nitriles at hands, the reduction of the nitrile group finished the chemoenzymatic synthesis (Scheme 2). Sodium borohydride as a mild and easy-to-handle reagent was used in the presence of $CoCl_2{\cdot}6H_2O$ for the reductions. $CoCl_2{\cdot}6H_2O$ was present because transition metal salts have been reported to allow the fine-tuning of the reactivity of the metal hydride.[27] The reduction of (*R*)- and/or (*S*)-**2a–d** was achieved with 57–70% isolated yields without any significant depletion of the original enantiopurity (Table 5). The primary amine products obtained by reduction were trapped with di-*tert*-butyl dicarbonate (Boc_2O) in situ in order to prevent the dimerization of the amine produced with an imine intermediate.[28] Reduction of *rac*-**2e** was not completed because the nitro group was primarily reduced by $NaBH_4$ as reported also in the literature.[28]

Table 5
Prepared enantiopure γ-amino alcohols **4a–d**

γ-Amino alcohol	ee (%)	Specific rotation[a]	Yield[b] (%)
(*S*)-**4a**	99	+1.4[c]	59
(*S*)-**4b**	98	+0.2	68
(*R*)-**4b**	99	−0.2	70
(*S*)-**4c**	99	+1.9	57
(*S*)-**4d**	95	+1.2	61
(*R*)-**4d**	94	−1.1	68

[a] (*c* 2, $CHCl_3$).
[b] Isolated yields for the reduction step.
[c] (*c* 1, $CHCl_3$).

3. Conclusion

Four new enantiopure phenylfuran-based 1,3-amino alcohols in *N*-Boc-protected forms **4a–d** were prepared chemoenzymatically starting from the corresponding commercial aldehydes **1a–d**. The lipase IMMTLL-T1-1500 (lipase from *T. lanuginosus*)-catalyzed reaction, consisting of an acylation/alcoholysis sequence, was successfully applied as an enantiopurity-producing step through kinetic resolution of β-hydroxy nitrile precursors. The products (*R*)- and (*S*)-**2a–e** were obtained at excellent enantiopurity (>98%) and in high isolated yields. Further transformation of the β-hydroxy nitriles into the corresponding *N*-Boc-protected γ-amino alcohols was achieved by reduction with $NaBH_4$ in the presence of $CoCl_2{\cdot}6H_2O$.

4. Experimental part

4.1. Materials and methods

All solvents were of the highest analytical grade and were dried by standard methods when necessary. Aldehydes **1a–e**, trimethylsilyl acetonitrile, lithium acetate, and vinyl acetate were purchased from Sigma–Aldrich. Vinyl butanoate was the product of Fluka and isopropenyl acetate of Merck. Lipase PS from *B. cepacia* on diatomaceous earth (lipase PS-D) and on ceramic particles (lipase PS-C II) and lipase AK powder from *P. fluorescens* were purchased from Amano Pharmaceuticals. *C. antarctica* lipase A (CAL-A) was the product of Roche. CAL-A and lipase AK were immobilized on Celite in the presence of sucrose as described before.[29] *C. antarctica* lipase B (CAL-B, Novozym 435) and Lipozyme TL IM were obtained from Novozymes. Lipase preparations IMMAPF-T2-150 from *P. fluorescens* and IMMTLL-T1-1500 and IMMTLL-T2-150 from *T. lanuginosus* were acquired from ChiralVision. The ^1H and ^{13}C NMR spectra were recorded at 25 °C on a Brucker Avance 500 spectrometer equipped with a BBO-5 mm-Zgrad probe operating at 500.13 and 125.77 MHz, respectively, with tetramethylsilane (TMS) as an internal standard. HRMS were recorded with a ZabSpec-oaTof instrument. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel $60F_{254}$ sheets. Preparative chromatographic separations were performed using column chromatography on Merck Kieselgel 60 (0.063–0.200 μm). Optical rotations were measured with a Perkin–Elmer 341 Polarimeter using the sodium D line, and the $[\alpha]_D^{25}$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were measured with a Gallenkamp apparatus and

are uncorrected. The determination of E was based on the equation $E = \ln[(1-c)(1-ee_S)]/\ln[(1-c)(1+ee_S)]$ using linear regression {E as the slope of the line $\ln[(1-c)(1-ee_S)]$ versus $\ln[(1-c)(1+ee_S)]$}.[30] For enzymatic acylation conversion was obtained using equation $c = ee_S/(ee_S + ee_P)$. For enzymatic alcoholysis conversion was obtained using benzil for (*R*)-**3a**, acetophenone for (*R*)-**3b**, and 1,4-dimethoxybenzene for (*R*)-**3c–e** as external standards. The enzymatic reactions were performed at room temperature (23–24 °C) unless otherwise stated.

4.2. Preparation of *rac*-2a–e

4.2.1. 3-[5-(3-Chlorophenyl)furan-2-yl]-3-hydroxypropanenitrile *rac*-2a

Racemates **2a–e** were all prepared according to the known method.[18,23] (Trimethylsilyl)acetonitrile (1.53 g, 13.51 mmol, 1.85 mL) was added to the combined solution of lithium acetate (10% molar) in DMF (17 mL) and 5-(3-chlorophenyl)furan-2-carbaldehyde (2.00 g, 9.68 mmol) in DMF (40 mL) at 0 °C. The mixture was allowed to warm slowly to room temperature, and thereafter the stirring was continued for 3 h. The reaction was quenched with HCl (1 M, 8 mL) and MeOH (40 mL). Distilled water (200 mL) was added and the mixture was extracted with diethyl ether (3 × 120 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The crude product was purified by passing through a silica gel column with ethyl acetate/hexane (3/7) as an eluent to obtain *rac*-**2a** as light yellow solid (1.98 g, 7.99 mmol, mp 76–78 °C) in 83% yield. HRMS M^+ found (M^+ calculated for $C_{13}H_{10}ClNO_2$): 247.03900 (247.04001); MS: *m*/*z* (relative intensity) = 115(15), 149 (8), 207(100), 247(18); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.71 (d, J = 5.0 Hz, 1H, OH), 2.92–3.01 (dd, J = 6.0 Hz, J = 2.0 Hz, 2H, C(2)-CH(OH)CH_2CN), 5.10 (q, J = 6.0 Hz, 1H, C(2)-CH(OH)CH_2CN), 6.49 (dd, J = 3.5 Hz, J = 0.5 Hz, 1H, C(3)-H), 6.64 (d, J = 3.5 Hz, 1H, C(4)-H), 7.23–7.25 (m, 1H, C(4′)-H), 7.31 (t, J = 8.0 Hz, 1H, C(5′)-H), 7.52 (dt, J = 8.0 Hz, J = 1.5 Hz, 1H, C(6′)-H), 7.62 (t, J = 2.0 Hz, 1H, C(2′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm) 25.05 (C(2)-CH(OH)CH_2CN), 63.96 (C(2)-CH(OH)CH_2CN), 106.80 (C(3)), 109.74 (C(4)), 116.72 (CN), 121.97 (C(6′), 123.89 (C(2′)), 127.81 (C(4′)), 130.09 (C(5′)), 131.79 (C(1′)), 134.82 (C(3′)), 152.81 (C(5)), 152.95 (C(2)).

4.2.2. 3-[5-(2-Chlorophenyl)furan-2-yl]-3-hydroxypropanenitrile *rac*-2b

Yellow solid (mp 60–61 °C) in 81% yield. HRMS M^+ found (M^+ calculated for $C_{13}H_{10}ClNO_2$): 247.03990 (247.04001); MS: *m*/*z* (relative intensity) = 247 (20), 207 (100), 149 (7), 115 (15), 84 (18), 49 (20); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.74 (d, J = 5.0 Hz, 1H, OH), 2.96 (dd, J = 6.2 Hz, J = 2.2 Hz, 2H, C(2)-CH(OH)CH_2CN), 5.11 (q, J = 5.5 Hz, 1H, C(2)-CH(OH)CH_2CN), 6.52 (dd, J = 3.5 Hz, J = 0.5 Hz, 1H, C(3)-H), 7.07 (d, J = 3.5 Hz, 1H, C(4)-H), 7.22 (td, J = 7.5 Hz, J = 1.5 Hz, 1H, C(4′)-H), 7.32 (td, J = 7.5 Hz, J = 1.5 Hz, 1H, C(5′)-H), 7.43 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, C(3′)-H), 7.81 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm): 25.05 (C(2)-CH(OH)CH_2CN), 63.95 (C(2)-CH(OH)CH_2CN), 109.54 (C(3)), 115.59 (C(4)), 116.79 (CN), 126.96 (C(5′)), 128.00 (C(6′)), 128.59 (C(3′)), 130.36 (C(4′)), 130.79 (C(2′), C(1′)), 150.67 (C(5)), 152.29 (C(2)).

4.2.3. 3-[5-(4-Chlorophenyl)furan-2-yl]-3-hydroxypropanenitrile *rac*-2c

Light yellow solid (mp 96–97 °C) in 79% yield. HRMS M^+ found (M^+ calculated for $C_{13}H_{10}ClNO_2$): 247.04080 (247.04001); MS: *m*/*z* (relative intensity) = 247 (18), 207 (100), 149 (8), 115 (12), 84 (26), 49 (29); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.59 (d, J = 5.0 Hz, 1H, OH), 2.96 (dd, J = 6.0 Hz, J = 2.5 Hz, 2H, C(2)-CH(OH)CH_2CN), 5.10 (q, J = 5.5 Hz, 1H, C(2)-CH(OH)CH_2CN), 6.48 (dd, J = 3.5 Hz, J = 0.5 Hz, 1H, C(3)-H), 6.60 (d, J = 3.5 Hz, 1H, C(4)-H), 7.35 (dt, J = 8.5 Hz, J = 2.5 Hz, 1H, (C(3′)-H, C(5′)-H), 7.57 (dt, J = 8.5 Hz, J = 2.5 Hz, 1H, C(2′)-H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm): 25.03 (C(2)-CH(OH)CH_2CN), 63.96 (C(2)-CH(OH)CH_2CN), 106.16 (C(3)), 109.74 (C(4)), 116.71 (CN), 125.15 (C(2′), C(6′)), 128.63 (C(1′)), 129.01 (C(3′)), C(5′)), 133.63 (C(4′)), 152.48 (C(5)), 153.42 (C(2)).

4.2.4. 3-[5-(4-Bromophenyl)furan-2-yl]-3-hydroxypropanenitrile *rac*-2d

Light yellow solid (mp 111–112 °C) in 78% yield. HRMS M^+ found (M^+ calculated for $C_{13}H_{10}BrNO_2$): 290.98860 (290.98949); MS: *m*/*z* (relative intensity) = 291 (18), 251 (100), 172 (9), 144 (7), 115 (17); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.67 (d, J = 5.5 Hz, 1H, OH), 2.96 (dd, J = 6.0 Hz, J = 2.5 Hz, 2H, C(2)-CH(OH)CH_2CN), 5.09 (q, J = 5.5 Hz, 1H, C(2)-CH(OH)CH_2CN), 6.48 (d, J = 3.5 Hz, 1H, C(3)-H), 6.61 (d, J = 3.5 Hz, 1H, C(4)-H), 7.51 (s, 4H, C(2′)-H, C(3′)-H, C(5′)-H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm): 25.03 (C(2)-CH(OH)CH_2CN), 63.95 (C(2)-CH(OH)CH_2CN), 106.27 (C(3)), 109.77 (C(4)), 116.73 (CN), 121.74 (C(4′)), 125.39 (C(2′), C(6′)), 129.06 (C(1′)), 131.93 (C(3′), C(5′)), 152.56 (C(5)), 153.41 (C(2)).

4.2.5. 3-Hydroxy-3-[5-(4-nitrophenyl)furan-2-yl]-propanenitrile *rac*-2e

Orange solid (mp 111–112 °C) in 81% yield. HRMS M^+ found (M^+ calculated for $C_{13}H_{10}N_2O_4$): 258.06500 (258.06500); MS: *m*/*z* (relative intensity) = 258 (15), 240 (7), 218 (100), 178 (32), 115 (13); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.67 (s, 1H, OH); 3.00 (t, J = 6.5 Hz, 2H, C(2)-CH(OH)CH_2CN), 5.16 (t, J = 6.0 Hz, 1H, C(2)-CH(OH)CH_2CN), 6.58 (dd, J = 3.5 Hz, J = 0.5 Hz, C(3)-H), 6.85 (d, J = 3.5 Hz, 1H, C(4)-H), 7.78 (dt, J = 9.0 Hz, J = 2.5 Hz, 2H, C(2′)-H, C(6′)-H), 8.25 (dt, J = 9.0 Hz, J = 2.5 Hz, 2H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm): 25.11 (C(2)-CH(OH)CH_2CN), 63.95 (C(2)-CH(OH)CH_2CN), 109.63 (C(4)), 110.26 (C(3)), 116.50 (CN), 124.15 (C(3′), C(5′)), 124.39 (C(2′), C(6′)), 135.72 (C(1′)), 146.76 (C(4′)), 152.10 (C(5)), 154.47 (C(2)).

4.3. Lipase-catalyzed acylation of *rac*-2a–e

In a typical small-scale experiment, one of the lipases (typically 50 mg mL^{-1}) was added to the solution of one of the substrates *rac*-**2a–e** (0.05 or 0.1 M) and an acyl donor (2 equiv) in an organic solvent. The reaction mixture was shaken at room temperature. The progress of the reaction was followed by taking samples (10 μL) at intervals. After derivatization the samples were analyzed by HP 1090 Liquid Chromatograph equipped with Daicel Chiralcel (0.46 × 25 cm) OD-H column. Derivatization with butanoic anhydride for *rac*-**2c–d** and with propanoic anhydride for *rac*-**2e** in the presence of catalytic amounts of DMAP (1%)/Py was needed to achieve base-line separation of both the substrate and product enantiomers.

4.4. Preparative-scale kinetic resolution of *rac*-2a–e

4.4.1. Kinetic resolution of *rac*-2a

The general procedure is described for *rac*-**2a** as a model compound. Lipase IMMTLL-T1-1500 (2.02 g) was added to the solution of *rac*-**2a** (1.00 g, 4.04 mmol) and vinyl acetate (0.69 g, 8.08 mmol, 0.74 mL) in TBME (40 mL), and the mixture was shaken at room temperature. The reaction was stopped by filtering off the enzyme after 4 h at 52% conversion. The enzyme was washed twice with TBME (2 × 10 mL). After evaporation of the solvent, the unreacted (*S*)-**2a** and the produced (*R*)-**3a** were separated on silica gel by elution with ethyl acetate/hexane (1/4). Compound (*S*)-**2a** was obtained as a light yellow solid in 83% yield {mp 90–91 °C, ee = 98%),

$[\alpha]_D^{25} = -46.3$ (c 1, $CHCl_3$)}. Compound (*R*)-**3a** was obtained as a yellow oil in 82% yield {ee = 89%, $[\alpha]_D^{25} = +181.6$ (c 1, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{15}H_{12}ClNO_3$): 289.05057 (289.05060); MS: *m*/*z* (relative intensity) = 289 (26), 230 (25), 207 (100), 149 (9), 43 (24); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.15 (s, 3H, $OCOCH_3$), 3.08 (dd, J = 7.5 Hz, J = 6.5 Hz, 2H, $CH(OCOCH_3)CH_2CN$), 6.09 (t, J = 6.5 Hz, 1H, $CH(OCOCH_3)CH_2CN$), 6.57 (d, J = 3.5 Hz, 1H, C(3)-H), 6.65 (d, J = 3.5 Hz, 1H, C(4)-H), 7.25–7.27 (ddd, J = 8.0 Hz, J = 2.0 Hz, J = 1.0 Hz, 1H, C(4′)-H), 7.32 (t, J = 8.0 Hz, 1H, C(5′)-H), 7.54 (dt, J = 7.5 Hz, J = 1.5 Hz, 1 H, C(6′)-H), 7.64 (t, J = 2.0 Hz, 1 H, C(2′)-H); ^{13}C NMR ($CDCl_3$, 500 MHz), δ (ppm): 20.84 ($OCOCH_3$), 22.15 ($CH(OCOCH_3)CH_2CN$), 63.72 ($CH(OCOCH_3)CH_2CN$), 106.83 (C(3)), 112.27 (C(4)), 115.69 (CN), 122.12 (C(6′)), 124.02 (C(2′)), 127.98 (C(4′)), 130.09 (C(5′)), 131.65 (C(1′)), 134.82 (C(3′)), 148.84 (C(5)), 153.40 (C(2)), 169.59 ($OCOCH_3$).

4.4.2. Kinetic resolution of *rac*-2b

The reaction for *rac*-**2b** was stopped after 4 h at 53% conversion, yielding (*S*)-**2b** as an orange solid in 97% yield {mp 43 °C, ee = 99%, $[\alpha]_D^{25} = -43.8$ (c 1, $CHCl_3$)}. Compound (*R*)-**3b** was obtained as a yellow solid in 97% yield {mp 41 °C, ee = 88%, $[\alpha]_D^{25} = +171.0$ (c 1, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{15}H_{12}ClNO_3$): 289.05060 (289.05057); MS: *m*/*z* (relative intensity) = 289 (27), 230 (25), 207 (100), 149 (11), 43 (26); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.15 (s, 3H, $OCOCH_3$), 3.09 (dd, J = 6.5 Hz, J = 6.0 Hz, 2H, $CH(OCOCH_3)CH_2CN$), 6.12 (t, J = 6.5 Hz, 1H, $CH(OCOCH_3)CH_2CN$), 6.61 (d, J = 3.5 Hz, 1H, C(3)-H), 7.08 (d, J = 3.5 Hz, 1H, C(4)-H), 7.23 (ddd, J = 9.0 Hz, J = 7.5 Hz, J = 1.5 Hz, 1H, C(4′)-H), 7.33 (td, J = 8.0 Hz, J = 1.0 Hz, 1H, C(5′)-H), 7.44 (dd, J = 8.0 Hz, J = 1.5 Hz, 1 H, C(3′)-H), 7.83 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 500 MHz), δ (ppm): 20.84 ($OCOCH_3$), 22.17 ($CH(OCOCH_3)CH_2CN$), 63.68 ($CH(OCOCH_3)CH_2CN$), 111.60 (C(3)), 111.99 (C(4)), 115.74 (CN), 126.99 (C(4′)), 128.15 (C(6′)), 128.48 (C(2′)), 128.75 (C(5′)), 130.49 (C(1′)), 130.81 (C(3′)), 148.35 (C(5)), 151.14 (C(2)), 169.61 ($OCOCH_3$).

4.4.3. Kinetic resolution of *rac*-2c

The reaction for *rac*-**2c** was stopped after 2.5 h at 53% conversion, yielding (*S*)-**2c** as a yellow solid in 91% yield {mp 93–94 °C, ee = 99%, $[\alpha]_D^{25} = -48.2$ (c 1, $CHCl_3$)}. Compound **(*R*)-3c** was obtained as a light yellow solid in 91% yield {mp 108–109 °C, ee = 93%, $[\alpha]_D^{25} = +198.8$ (c 1, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{15}H_{12}ClNO_3$): 289.05090 (289.05057); MS: *m*/*z* (relative intensity) = 289 (30), 230 (28), 207 (100), 149 (12), 43 (21); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.15 (s, 3H, $OCOCH_3$), 3.08 (dd, J = 6.5 Hz, J = 3.5 Hz, 2H, $CH(OCOCH_3)CH_2CN$), 6.09 (t, J = 6.5 Hz, 1H, $CH(OCOCH_3)CH_2CN$), 6.56 (d, J = 3.5 Hz, 1H, C(3)-H), 6.61 (d, J = 3.5 Hz, 1H, C(4)-H), 7.36 (dt, J = 8.5 Hz, J = 2.5 Hz, 2H, C(3′)-H, C(5′)-H), 7.59 (td, J = 8.5 Hz, J = 2.5 Hz, 2H, C(2′)-H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 500 MHz), δ (ppm): 20.85 ($OCOCH_3$), 22.16 ($CH(OCOCH_3)CH_2CN$), 63.71 ($CH(OCOCH_3)CH_2CN$), 106.19 (C(4)), 112.27 (C(3)), 115.72 (CN), 125.29 (C(2′), C(6′)), 128.53 (C(1′)), 129.02 (C(3′), C(5′)), 133.80 (C(4′)), 148.58 (C(5)), 153.85 (C(2)), 169.60 ($OCOCH_3$).

4.4.4. Kinetic resolution of *rac*-2d

The reaction for *rac*-**2d** was stopped after 2 h at 52% conversion, yielding (*S*)-**2d** as a yellow solid in 89% yield {mp 109–110 °C, ee = 99%, $[\alpha]_D^{25} = -36.2$ (c 1, $CHCl_3$)}. Compound (*R*)-**3d** was obtained as a light yellow solid in 96% yield {mp 128–129 °C, ee = 82%, $[\alpha]_D^{25} = +167.4$ (c 1, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{15}H_{12}BrNO_3$): 334.99790 (334.99800); MS: *m*/*z* (relative intensity) = 333 (34), 274 (24), 251 (100), 195 (12), 172 (10), 114 (10), 43 (50); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.15 (s, 3H, $OCOCH_3$), 3.08 (dd, J = 6.0 Hz, J = 4.0 Hz, 2H, $CH(OCOCH_3)CH_2CN$), 6.09 (t, J = 6.5 Hz, 1H, $CH(OCOCH_3)CH_2CN$), 6.56 (d, J = 3.5 Hz, 1H, C(3)-H), 6.63 (d, J = 3.5 Hz, 1H, C(4)-H), 7.52 (s, 4H, C(2′)-H, C(3′)-H, C(5′)-H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 500 MHz), δ (ppm): 20.85 ($OCOCH_3$), 22.15 ($CH(OCOCH_3)CH_2CN$), 63.70 ($CH(OCOCH_3)CH_2CN$), 106.30 (C(3)), 112.28 (C(4)), 115.72 (CN), 121.94 (C(4′)), 125.53 (C(2′), C(6′)), 128.93 (C(1′)), 131.94 (C(3′), C(5′)), 148.62 (C(5)), 153.85 (C(2)), 169.60 ($OCOCH_3$).

4.4.5. Kinetic resolution of *rac*-2e

The reaction for *rac*-**2e** was stopped after 7 h, at 51% conversion, yielding (*S*)-**2e** as an orange solid in 95% yield {mp 112–113 °C, ee = 97%, $[\alpha]_D^{25} = -56.6$ (c 1, $CHCl_3$)}. Compound (*R*)-**3e** was obtained as an orange solid in 89% yield {mp 106–107 °C, ee = 93%, $[\alpha]_D^{25} = +221.9$ (c 1, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{15}H_{12}N_2O_5$): 300.07570 (300.07462); MS: *m*/*z* (relative intensity) = 300 (23), 241 (20), 218 (100), 195 (9), 172 (11), 139 (4), 115 (8), 43 (31); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 2.17 (s, 3H, $OCOCH_3$), 3.10 (d, J = 6.0 Hz, 2H, $CH(OCOCH_3)CH_2CN$), 6.12 (t, J = 6.0 Hz, 1H, $CH(OCOCH_3)CH_2CN$), 6.65 (d, J = 3.5 Hz, 1H, C(3)-H), 6.86 (d, J = 3.5 Hz, 1H, C(4)-H), 7.80 (dt, J = 9.0 Hz, J = 2.0 Hz, 2H, C(2′)-H, C(6′)-H), 8.26 (dt, J = 9.0 Hz, J = 2.0 Hz, 2H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 500 MHz), δ (ppm): 20.81 ($OCOCH_3$), 22.22 ($CH(OCOCH_3)CH_2CN$), 63.61 ($CH(OCOCH_3)CH_2CN$), 109.55 (C(4)), 112.62 (C(3)), 115.52 (CN), 124.34 (C(3′), C(5′)), 124.39 (C(2′), C(6′)), 135.56 (C(1′)), 146.92 (C(4′)), 150.48 (C(5)), 152.52 (C(2)), 169.52 ($OCOCH_3$).

4.5. Lipase-catalyzed deprotection of (*R*)-3a–e

General procedure is described for (*R*)-**3a** as a model compound. Lipase IMMTLL-T1-1500 (0.34 g) and butan-1-ol (0.13 mL) were added to the solution of (*R*)-**3a** (0.20 g, 0.69 mmol, ee 89%) in TBME (6.90 mL), and the mixture was shaken at room temperature for 48 h to reach 91% conversion. The reaction was stopped by filtering off the enzyme. The produced (*R*)-**2a** was purified in 84% yield as a light yellow solid {mp 90–91.5 °C, ee = 99%, $[\alpha]_D^{25} = +46.7$ (c 1, $CHCl_3$)} by silica gel column chromatography with ethyl acetate/hexane (3/7) as an eluent.

Compound (*R*)-**2b** was obtained as an orange solid in 95% yield {mp 46–47 °C, ee = 99%, $[\alpha]_D^{25} = +44.7$ (c 1, $CHCl_3$)}.

Compound (*R*)-**2c** was obtained as a light yellow solid in 92% yield {mp 95–96 °C, ee = 99%, $[\alpha]_D^{25} = +45.5$ (c 1, $CHCl_3$)}.

Compound (*R*)-**2d** was obtained as a yellow solid in 90% yield {mp 109–110 °C, ee = 99%, $[\alpha]_D^{25} = +39.4$ (c 1, $CHCl_3$)}.

Compound (*R*)-**2e** was obtained as an orange solid in 82% yield {mp 115–116 °C, ee = 99%, $[\alpha]_D^{25} = +55.4$ (c 1, $CHCl_3$)}.

4.6. Preparation of the enantiomers of 4a–d

After derivatization with butanoic anhydride for **4a**–**b** and **4d** and with acetic anhydride for **4c** the values of ee were determined with HP 1090 Liquid Chromatograph equipped with a Daicel Chiralcel (0.46 × 25 cm) OD-H column using hexane/isopropyl alcohol as an eluent.

The preparation of (*S*)-**4a** is used to illustrate the general procedure. Boc_2O (0.88 g, 4.03 mmol) and $CoCl_2{\cdot}6H_2O$ (0.48 g, 2.02 mmol) were introduced into a round-bottomed flask in methanol (75 mL) under argon atmosphere, at 0 °C, and (*S*)-**2a** (0.50 g, 2.02 mmol) was added. $NaBH_4$ (0.53 g, 14.01 mmol) was added with caution in small portions. The mixture was stirred at room temperature for 2 h before methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and the solution was saturated with $NaHCO_3$ (50 mL). The mixture was filtered and the organic layer was separated and washed once with ethyl acetate (100 mL). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4 before the

solvent was evaporated. The crude product was purified by column chromatography with ethyl acetate/hexane (3/7) as an eluent to yield (*S*)-**4a** as a yellow solid {0.47 g, 1.33 mmol, yield 59%, mp 79–80 °C, ee = 99%, $[\alpha]_D^{25} = +1.4$ (*c* 1, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{18}H_{22}ClNO_4$): 351.12320 (351.12373); MS: *m*/*z* (relative intensity) = 351 (4), 295 (29), 277 (22), 260 (16), 250 (20), 234 (28), 221 (48), 207 (100), 191 (7), 116 (15); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.45 (s, 9H, C(C*H*$_3$)$_3$), 2.02 (q, *J* = 6.0 Hz, 2H, CH(OH)C*H*$_2$CH$_2$NH), 3.20–3.26 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 3.52–3.56 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 3.62 (s, 1H, OH), 4.81 (t, *J* = 7.0 Hz, 1H, C(2)C*H*(OH)), 4.88 (b, 1H, NH), 6.35 (d, *J* = 3.5 Hz, 1H, C(3)-H), 6.60 (d, *J* = 3.5 Hz, 1H, C(4)-H), 7.20 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H, C(4′)-H), 7.28 (t, *J* = 8.0 Hz, 1H, C(5′)-H), 7.50 (dt, *J* = 7.5 Hz, *J* = 1.5 Hz, 1H, C(6′)-H), 7.63 (t, *J* = 2.0 Hz, 1H, C(2′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm): 28.39 (C(*C*H$_3$)$_3$), 36.17 (CH(OH)*C*H$_2$CH$_2$NH), 36.95 (CH(OH)CH$_2$*C*H$_2$NH), 65.15 (C(2)*C*H(OH)), 79.85 (*C*(CH$_3$)), 106.74 (C(4)), 108.06 (C(3)), 121.74 (C(6′)), 123.67 (C(2′)), 127.16 (C(4′)), 129.91 (C(5′)), 132.42 (C(1′)), 134.67 (C(3′)), 151.79 (C(5)), 156.63 (C(2)), 157.11 (NH*C*OOC(CH$_3$)$_3$).

Compound (*S*)-**4b** was obtained as a yellow oil in 68% yield {ee = 98%, $[\alpha]_D^{25} = +0.2$ (*c* 2, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{18}H_{22}ClNO_4$): 351.12360 (351.12373); MS: *m*/*z* (relative intensity) = 351 (4), 295 (23), 277 (16), 250 (18), 56 (221), 207 (100), 191 (11), 115 (18); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.44 (s, 9H, C(C*H*$_3$)$_3$), 2.03 (q, *J* = 6.0 Hz, 2H, CH(OH)C*H*$_2$CH$_2$NH), 3.22–3.27 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 3.51–3.55 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 4.83 (t, *J* = 7.0 Hz, 1H, C(2)C*H*(OH)), 4.89 (b, 1H, NH), 6.39 (d, *J* = 3.5 Hz, 1H, C(3)-H), 7.05 (d, *J* = 3.5 Hz, 1H, C(4)-H), 7.17 (td, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, C(4′)-H), 7.29 (td, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H, C(5′)-H), 7.41 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H, C(3′)-H), 7.33 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 1H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ (ppm): 28.39 (C(*C*H$_3$)$_3$), 36.12 (CH(OH)*C*H$_2$CH$_2$NH), 36.99 (CH(OH)CH$_2$*C*H$_2$NH), 65.24 (C(2)*C*H(OH)), 79.79 (*C*(CH$_3$)), 107.95 (C(3)), 111.64 (C(4)), 126.79 (C(5′)), 127.84 (C(4′)), 127.95 (C(6′)), 129.11 (C(1′)), 130.01 (C(3′)), 130.67 (C(2′)), 149.46 (C(5)), 156.03 (C(2)), 157.03 (NH*C*OOC(CH$_3$)$_3$).

Compound (*R*)-**4b** was obtained as a light yellow oil in 70% yield {ee = 99%, $[\alpha]_D^{25} = -0.2$ (*c* 2, $CHCl_3$)}.

Compound (*S*)-**4c** was obtained as a light yellow solid in 57% yield {mp 89.5–90.5 °C, ee = 99%, $[\alpha]_D^{25} = +1.9$ (*c* 2, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{18}H_{22}ClNO_4$): 351.12510 (351.12373); MS: *m*/*z* (relative intensity) = 351 (10), 295 (32), 277 (9), 250 (20), 221 (45), 191 (6), 116 (15); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.45 (s, 9H, C(C*H*$_3$)$_3$), 2.01 (q, *J* = 6.5 Hz, 2H, CH(OH)C*H*$_2$CH$_2$NH), 3.20–3.26 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 3.51–3.57 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 4.80 (t, *J* = 6.5 Hz, 1H, C(2)C*H*(OH)), 4.88 (b, 1H, NH), 6.33 (dd, *J* = 3.5 Hz, *J* = 0.5 Hz, 1H, C(3)-H), 6.56 (d, *J* = 3.5 Hz, 1H, C(4)-H), 7.32 (dt, *J* = 8.5 Hz, *J* = 2.0 Hz, 2H, C(2′)-H, C(6′)-H), 7.56 (dt, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H, C(3′)-H, C(5′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ(ppm): 28.39 (C(*C*H$_3$)$_3$), 36.12 (CH(OH)*C*H$_2$CH$_2$NH), 36.98 (CH(OH)CH$_2$*C*H$_2$NH), 65.15 (C(2)*C*H(OH)), 79.82 (*C*(CH$_3$)), 106.08 (C(3)), 108.04 (C(4)), 124.93 (C(2′), C(6′)), 128.83(C(3′), C(5′)), 129.27 (C(1′)), 132.90 (C(4′)), 152.24 (C(5)), 156.31 (C(2)), 157.06 (NH*C*OOC(CH$_3$)$_3$).

Compound (*S*)-**4d** was obtained as a yellow oil in 68% yield {ee = 95%, $[\alpha]_D^{25} = +1.2$ (*c* 2, $CHCl_3$)}. HRMS M^+ found (M^+ calculated for $C_{18}H_{22}BrNO_4$): 395.07350 (395.07322); MS: *m*/*z* (relative intensity) = 395 (10), 339 (33), 323 (12), 304 (14), 294 (26), 265 (46), 251 (100), 193 (14), 116 (26); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.45 (s, 9H, C(C*H*$_3$)$_3$), 2.01 (q, *J* = 6.5 Hz, 2H, CH(OH)C*H*$_2$CH$_2$NH), 3.20–3.26 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 3.51–3.56 (m, 1H, CH(OH)CH$_2$C*H*$_2$NH), 4.80 (t, *J* = 6.5 Hz, 1H, C(2)C*H*(OH)), 4.87 (b, 1H, NH), 6.34 (dd, *J* = 3.5 Hz, *J* = 0.5 Hz, 1H, C(3)-H), 6.58 (d, *J* = 3.5 Hz, 1H, C(4)-H), 7.46–7.52 (m, 4H, C(2′)-H, C(3′)-H, C(5′)-H, C(6′)-H); ^{13}C NMR ($CDCl_3$, 126 MHz), δ(ppm): 28.39 (C(*C*H$_3$)$_3$), 36.14 (CH(OH)*C*H$_2$CH$_2$NH), 36.97 (CH(OH)CH$_2$*C*H$_2$NH), 65.15 (C(2)*C*H(OH)), 79.84 (*C*(CH$_3$)), 106.20 (C(3)), 108.09 (C(4)), 121.00 (C(4′)), 125.21 (C(2′), C(6′)), 129.68 (C(1′)), 131.75 (C(3′), C(5′)), 152.25 (C(5)), 156.37 (C(2)), 157.06 (NH*C*OOC(CH$_3$)$_3$).

Compound (*R*)-**4d** was prepared as a light brown solid in 61% yield {mp 76–77 °C, ee = 94%, $[\alpha]_D^{25} = -1.1$ (*c* 2, $CHCl_3$)}.

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