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Stereoselective Chemoenzymatic Synthesis of Enantiopure 1-(Heteroaryl)ethanamines by Lipase-Catalysed Kinetic Resolutions

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The efficient chemical synthesis and enzymatic kinetic resolution of a family of 1-(heteroaryl)ethanamines have been performed with lipases responsible for the preparation of nitrogenated compounds in high optical purity. Thus, *Candida antarctica* lipase type B has been identified as an excellent biocatalyst for the stereoselective production of the corresponding enantiomerically enriched (*R*)-acetamides and (*S*)-amines. A similar effect of the heteroatom in the cyclic ring has been observed in terms of reactivity and enantioselectivity, with benzoxazole, benzothiazole and benzimidazole derivatives being obtained with excellent enantiopurities after one day of reaction.

Introduction

Optically active amines are an important set of compounds because of their practical applications as chiral building blocks in the preparation of more complex structures. In particular, enantiomerically pure heteroarylamines are employed in medicinal chemistry,[1] agriculture[2] or asymmetric organocatalysis, in some cases being a part of metal complexes commonly used for the catalytic hydrogenation of aromatic ketones.[3]

Although a wide range of synthetic procedures have been adapted for industry, the convenient synthesis of suitable enantiomerically pure amines by traditional chemical methods is sometimes associated with several protection and deprotection steps, which present serious drawbacks such as low isolated yields, use of air-sensitive catalysts or extremely long reaction times. Biocatalysis has presented itself as a practical alternative for asymmetric synthesis in the last two decades,[4] attracting the attention of industry as a result of the mild and environmentally friendly conditions employed in the production of enantiopure compounds.[5] Lipase-mediated kinetic resolution processes are the most common approach to the synthesis of enantiopure compounds[6] even though just a few of these studies involve the preparation of optically active 1-(heteroaryl)ethanamines,[7] in contrast to the vast number of chemoenzymatic syntheses described for 1-(heteroaryl)ethanol analogues.[8]

Therefore, as part of our ongoing project devoted towards the stereoselective preparation of heterocyclic molecules of biological interest, we report herein the chemical preparation of three racemic heteroarylethanamines and a comparison of their reactivity towards different enzymatic preparations such as *Candida antarctica* lipase (CAL-B) and *Pseudomonas cepacia* lipase (PSL-C I) in their enzymatic kinetic resolution. In addition, non-activating esters have traditionally been used as resolving agents in the preparation of optically active amines. In this manner, parameters that influence the enzymatic catalysis have been exhaustively studied, looking for the best conditions to isolate the desired chiral targets.

Results and Discussion

In this study, we first explored different chemical routes to the suitable production of a family of racemic heterocyclic compounds based on the presence of a benzene ring fused to a heterocycle. Hence, we describe the chemoenzymatic synthesis of three compounds with potential biological interest, as occurs with their alcohol-derived analogues: 1-(benzo[*d*]imidazol-2-yl)ethanamine (**1a**), 1-(benzo[*d*]thiazol-2-yl)ethanamine (**1b**) and 1-(benz[*d*]oxazol-2-yl)ethanamine (**1c**). The chemical synthesis of all of these compounds has been studied starting from commercially available low-cost compounds.

Our first target compound was the benzimidazole derivative **1a** because of the importance of the benzimidazole ring as a pharmacophore in modern drug discovery.[9] Thus, we prepared 1-(benzo[*d*]imidazol-2-yl)ethanamine (**1a**) by modifying a previously reported process,[10] subjecting 1,2-phenylendiamine (**2a**) to a direct acidic condensation with D,L-alanine (**3**) at reflux in an aqueous solution of 6 N HCl. A long reaction time was required due to the low kinetics of the process and the desired heterocyclic compound was

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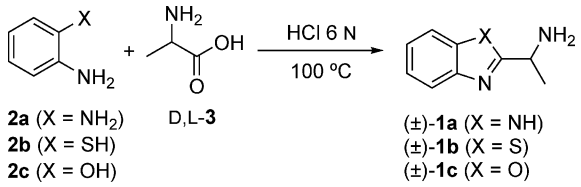
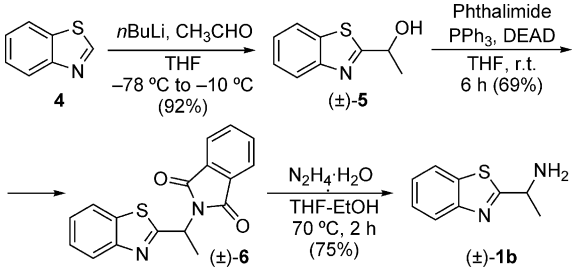
finally isolated in 63% yield after 144 h in a straightforward manner (Scheme 1). The reaction was next carried out with commercially available L-alanine, isolating the (*S*)-amine **1a** in enantiopure form as previously observed by Zang and Chow.[11]



Scheme 1. Initial attempts at the chemical synthesis of amines **1a**–**c**.

Then, encouraged by the ease of preparation of the benzimidazole derivative **1a**, we decided to synthesize the racemic heteroarylamines (±)-**1b**,**c** by the same methodology. Thus, 2-mercaptoaniline (**2b**) and 2-aminophenol (**2c**) were treated with D,L-alanine at reflux in an aqueous solution of 6 N HCl. Unfortunately, no reaction was observed with either of the reactants, even though the reaction times were extended to several days. Therefore we decided to search for new synthetic methods starting from other commercial reagents.

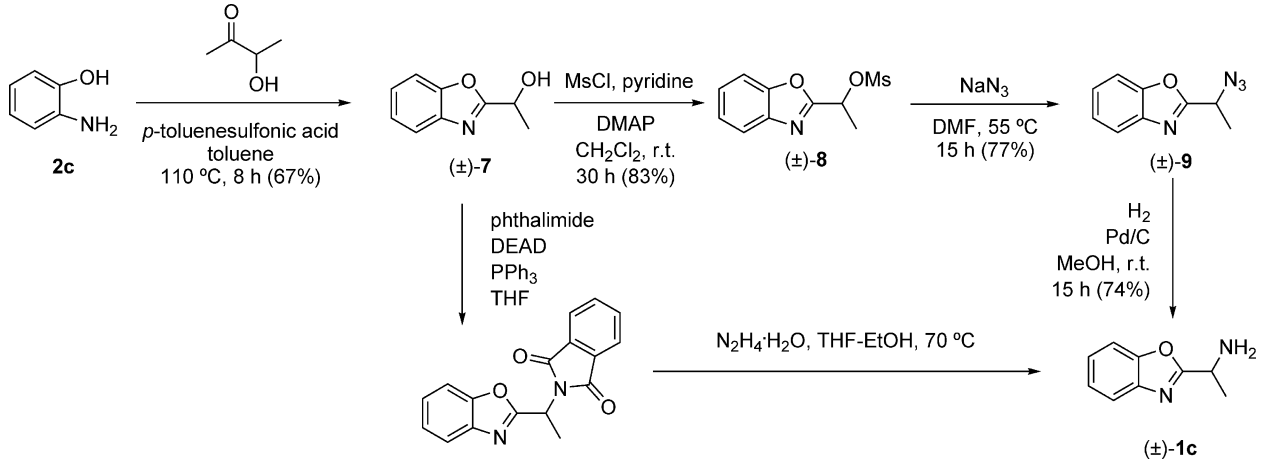
Racemic 1-(benzo[*d*]thiazol-2-yl)ethanamine (**1b**) was prepared through a three-step route starting from benzothiazole (**4**), as described in Scheme 2. First, benzothiazole was acylated by using *n*BuLi and acetaldehyde following the method previously described by Poppe and co-workers[8c] to give the alcohol **5**, which was then subjected to a nucleophilic substitution reaction under Mitsunobu conditions with phthalimide, triphenylphosphane (PPh_3) and diethyl azodicarboxylate (DEAD) in dry THF at room temperature. After 6 h, racemic compound **6** was isolated in 69% yield after flash chromatography. Next, deprotection of the phthalimide using hydrazine monohydrate in a mixture of THF/EtOH at 70 °C afforded the amine (±)-**1b** in 75% yield after 2 h.



Scheme 2. Chemical synthesis of 1-(benzo[*d*]thiazol-2-yl)ethanamine (**1b**).

Following the same approach, the synthesis of 1-(benz[*d*]oxazol-2-yl)ethanamine (**1c**) was attempted, but poor reactivity in the Mitsunobu reaction of the corresponding alcohol, in conjunction with several problems encountered in the isolation of both the phthalimide and the deprotection product, led us to develop an alternative method. 2-Aminophenol (**2c**) was treated with lactic acid, employing *p*-toluenesulfonic acid monohydrate as the catalyst in a Dean–Stark apparatus and toluene as the solvent, to obtain the racemic alcohol **7** after 8 h in 67% isolated yield (Scheme 3). Next, Mitsunobu reaction with phthalimide and deprotection with hydrazine monohydrate allowed the preparation of racemic 1-(benz[*d*]oxazol-2-yl)ethanamine (**1c**). However, low yields and several problems in both purification steps led us to search for another synthetic route.

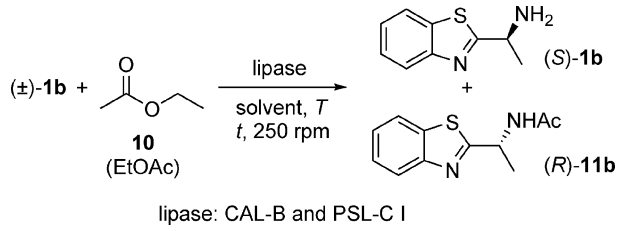
To establish the optimal conditions for the preparation of (±)-**1c**, the racemic alcohol **7** was subjected to an activation step with mesyl chloride in the presence of pyridine and DMAP in dry dichloromethane (CH_2Cl_2) as the solvent at room temperature. The mesylated alcohol **8** was then converted into the azide **9** by using sodium azide and *N*,*N*-dimethylformamide (DMF) as solvent at 55 °C, isolated by flash chromatography in 77% yield. Finally, the azide was transformed into the benzoxazolylamine **1c** by hydrogenation using Pd over activated carbon in deoxygenated MeOH at room temperature. Thus, after 15 h the



Scheme 3. Chemical synthesis of 1-(benzo[*d*]oxazol-2-yl)ethanamine (**1c**).

desired racemic amine was finally recovered in a 74% isolated yield.

With the three desired substrates in hand, we undertook the enzymatic studies. We decided to use the two lipases CAL-B and PSL-C I due to their well-documented capacity to produce chiral nitrogenated compounds such as amines and amides.[12] A non-activated ester such as ethyl acetate (EtOAc, **10**) was selected as the resolving agent, which additionally offers may behave as an acyl donor and solvent at the same time. Various reaction parameters that could influence the enzymatic catalysis were then studied with **1b** as the model substrate (Scheme 4). The reaction data are summarized in Table 1.

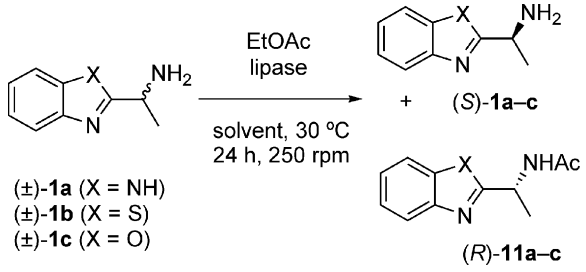


Scheme 4. Lipase-mediated resolution of benzothiazolylethanamine **1b**.

The use of the acyl donor as both reactant and solvent was first studied at 0.15 M substrate concentration, both biocatalysts displaying high activity towards the formation of the acetamide (*R*)-**11b** in high enantiomeric excess after 24 h (Table 1, entries 1 and 2). Although the lipases showed excellent stereopreference, our main goal was not accomplished because conversion values over 50% were attained. To isolate both the amine and the amide in enantiopure form, we next decided to perform the enzymatic kinetic resolutions using different solvents such as tetrahydrofuran (THF) or *tert*-butyl methyl ether (TBME) and only 2 or 3 equiv. of the acyl donor (entries 3–6). Both CAL-B and PSL-C I showed good enantioselectivity, higher activity being observed with a combination of CAL-B and TBME (entry 5). The reactions in THF presented lower reaction rates, the drop being more noticeable with PSL-C I.

After the solvent had been chosen, we focused our efforts on improving both the conversion and the reaction rates, increasing the reaction times of the enzymatic processes, but using low temperatures to avoid a decrease in enantioselectivity. However, the latter was observed, maybe because of a reduction in enzyme activity at times over 24 h (entries 7 and 8). Because the solubility of the substrate maybe an important factor in the kinetics of the reaction, the concentration of **1b** was decreased to 0.1 M (entries 9 and 10). Again CAL-B showed the best results and, although the enantiomeric excesses of (*R*)-**11b** fell to 97%, the enantioselectivity was still excellent and the total conversion reached 50%, also yielding the substrate in a nearly enantiopure form (entry 9).

Once we had established a methodology for the resolution of benzothiazole **1b**, we extended the study to the enzymatic resolution of racemic amines **1a** and **1c** using the same successful experimental conditions (Scheme 5). The reaction data are summarized in Table 2. First we tested the benzimidazole derivative **1a**, but it was poorly soluble in TBME, so we decided to explore the possibilities of using THF as solvent for the enzymatic kinetic resolution of **1a** (entries 3 and 4). As was observed with **1b**, CAL-B gave the best results in the stereoselective preparation of the acetamide (*R*)-**11a** and the amine (*S*)-**1a**, yielding >99 and 98% *ee*, respectively, after 24 h and 51% conversion (entry 3). On the other hand, PSL-C I showed a lower reaction rate, reaching 29% conversion in the same reaction time and allowing isolation of the amide in enantiopure form (entry 4).



Scheme 5. Enzymatic kinetic resolution of racemic amines **1a** and **1c**.

The benzoxazole derivative (±)-**1c** showed similar behaviour to **1b**. Both CAL-B and PSL-C I showed an excellent enantiopreference for the acetylation of the (*R*)-amine enantiomer, the kinetics of the CAL-B process being much

Table 1. Lipase-mediated kinetic resolution of **1b** using EtOAc as the acyl donor at 250 r.p.m. in the production of acetamide (*R*)-**11b** and amine (*S*)-**1b**.

Entry	Enzyme	Solvent	EtOAc [equiv.]	*T* [°C]	[Substrate] [M]	*t* [h]	ee_S [%][a]	ee_P [%][a]	Conv. [%][b]	*E*[c]
1	CAL-B	EtOAc	69	30	0.15	24	98	82	55	45
2	PSL-C I	EtOAc	69	30	0.15	24	95	90	51	70
3	CAL-B	THF	2	30	0.15	24	64	>99	39	>200
4	PSL-C I	THF	2	30	0.15	24	10	>99	9	>200
5	CAL-B	TBME	3	30	0.15	24	91	>99	48	>200
6	PSL-C I	TBME	3	30	0.15	24	78	>99	44	>200
7	CAL-B	TBME	3	20	0.15	48	85	96	47	118
8	PSL-C I	TBME	3	20	0.15	48	50	98	34	168
9	CAL-B	TBME	3	30	0.1	24	97	97	50	>200
10	PSL-C I	TBME	3	30	0.1	24	58	>99	37	>200

[a] Measured by HPLC, see details in the Supporting Information. [b] $c = ee_S/(ee_S + ee_P)$. [c] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.

Table 2. Enzymatic kinetic resolution of racemic amines **1a**–**c** using CAL-B or PSL-C I as the biocatalyst and 3 equiv. of EtOAc as the acyl donor over 24 h at 30 °C and 250 r.p.m. The starting amine was used at a concentration of 0.1 M.

Entry	X	Enzyme	Solvent	% ee_S[a]	% ee_P[a]	% Conv.[b]	E[c]
1	S (**1b**)	CAL-B	TBME	97	97	50	>200
2	S (**1b**)	PSL-C I	TBME	58	>99	37	>200
3	N (**1a**)	CAL-B	THF	>99	98	51	>200
4	N (**1a**)	PSL-C I	THF	39	>99	29	>200
5	O (**1c**)	CAL-B	TBME	97	>99	49	>200
6	O (**1c**)	PSL-C I	TBME	72	>99	42	>200

[a] Measured by HPLC, see details in the Supporting Information. [b] $c = ee_S/(ee_S + ee_P)$. [c] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.

higher than the PSL-C I process. The amine was completely soluble in TBME and after 24 h, 49% conversion was attained, affording the (*R*)-acetamide **11c** in enantiopure form.

To demonstrate the stereopreference shown by lipases, we designed a simple synthetic methodology to obtain compounds of known stereochemistry and we compared the signal of their optical rotations with those obtained by the lipase-mediated kinetic resolution of racemic amines. First, we performed the CAL-B kinetic resolution of the racemic alcohol **5**, as described elsewhere.[8c] Once this enantiopure alcohol (*S*)-**5** had been isolated, it was subjected to the Mitsunobu inversion reaction with PPh_3, phthalimide and DEAD in THF followed by deprotection with N_2H_4 in a mixture of THF and EtOH, which gave the (*R*)-(+)-amine **1b**. This amine showed an optical rotation sign opposite to that observed for the amine obtained directly from the kinetic resolution of the racemic amine catalysed by CAL-B {$[\alpha]_D^{20}$ = +10.3 (*c* = 0.98, MeOH) for 98% *ee* of (*R*)-**1b** and $[\alpha]_D^{20}$ = –9.3 (*c* = 0.88, MeOH) for 95% *ee* of (*S*)-**1b**}. The opposite sign was the result of the Mitsunobu inversion in the synthesis of the nitrogenated compound, so the lipases act with the same stereopreference for these amine and alcohol derivatives.

Similarly, it has recently been reported that lipases such as CAL-B or PSL have successfully catalysed the acetylation of the (*R*)-alcohol of the corresponding benzimidazole derivative, structurally analogous to the amino compound **1a** object of our enzymatic study.[8b]

Thus, CAL-B and PSL-C I have made possible the resolution of a family of 1-(heteroaryl)amines under very mild reaction conditions, allowing in all cases the recovery of the (*R*)-acetamides and the (*S*)-amines with excellent enantiopurities. The appropriate choice of biocatalyst and organic solvent is highly important for the success of the enzymatic synthetic method.

Conclusions

We have chemically synthesized a family of racemic heteroarylamines by using the most suitable approach in each case for the isolation of the benzimidazole, benzothiazole or benzoxazole derivatives. The enzymatic kinetic resolution reactions of these substrates have been exhaustively tested using ethyl acetate as the acyl donor and different lipases, obtaining optically enriched (*R*)-acetamides and (*S*)-amines in high-to-excellent yields. CAL-B was found to be the best enzyme for the preparation of enantiomerically pure compounds with TBME or THF as solvent, depending on the solubility properties of each starting material.

Experimental Section

General: *Candida antarctica* lipase type B (CAL-B, Novozyme 435, 7300 PLU/g) was a gift from Novo Nordisk Co. *Pseudomonas cepacia* lipase was acquired from Sigma–Aldrich as Amano Lipase PSL-C I immobilized on ceramic (1061 U/g). All other reagents were purchased from different commercial sources (Acros, Fluka or Sigma–Aldrich) and used without further purification. Solvents were distilled from a suitable desiccant under nitrogen. Flash chromatography was performed using silica gel 60 (230–240 mesh). Melting points were measured on samples in open capillary tubes and are uncorrected. IR spectra were recorded by using NaCl plates or KBr pellets with a Perkin–Elmer 1720-X F7 spectrometer. ^1H and ^{13}C NMR, DEPT and ^1H-^{13}C heteronuclear experiments were performed with a Bruker AC-300 (^1H: 300.13 MHz; ^{13}C: 75.5 MHz), DPX-300 (^1H: 300.13 MHz; ^{13}C: 75.5 MHz) or AV-400 (^1H: 400.13 MHz; ^{13}C: 100.6 MHz) spectrometer. The chemical shifts are given in delta (δ) values and the coupling constants (*J*) in Hertz (Hz). Mass spectra in $APCI^+$, EI^+ and ESI^+ modes were recorded with a HP1100 chromatograph mass detector. High-resolution mass spectra were obtained with a Bruker Microtof-Q spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. High-performance liquid chromatography (HPLC) was performed with a Hewlett–Packard 1100 chromatograph with a UV detector at 210 nm using a Daicel CHIRALCEL OD, CHIRALPAK IC or CHIRALPAK IA column (25 cm × 4.6 mm i.d.), varying the conditions depending on the specific substrate. Conditions and retention times are given in the Supporting Information.

Procedure for the Synthesis of Racemic 1-(1*H*-Benzimidazol-2-yl)-ethanamine (1a): *o*-Phenylenediamine (**2a**; 432 mg, 4.0 mmol) and an aqueous solution of 6 N HCl (4 mL) were mixed and stirred in a round-bottomed flask. After a solution had formed, D,L-alanine (534 mg, 6.0 mmol) was added and the mixture heated at reflux for 144 h, when a considerable proportion of the product was detected by TLC (70% EtOAc/MeOH). The reaction was quenched by adding a saturated aqueous solution of NH_3 until the pH of the mixture turned slightly basic (pH 8–9) and then it was extracted with EtOAc (6 × 5 mL). The organic phases were combined and dried with Na_2SO_4 and the solvent was evaporated under reduced pressure to give a crude product that was purified by flash chromatography (100% CH_2Cl_2 to 5% MeOH/CH_2Cl_2). Racemic amine **1a** was finally recovered as a pale-yellow solid (409 mg, 63% isolated yield). R_f (5% MeOH/CH_2Cl_2) = 0.21. IR (NaCl): $\tilde{\nu}$ = 3367, 3050, 2974, 2890, 2733, 1932, 1889, 1772, 1622, 1590, 1457, 1419, 1309, 1273, 1221, 1061, 1020, 991, 933, 850, 769, 751 cm^{-1}. ^1H NMR (MeOD, 300.13 MHz): δ = 7.60 (m, 2 H_{arom}), 7.20 (m, 2 H_{arom}), 4.31 (q, *J* = 6.6 Hz, 1 H, CH), 1.59 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (MeOD, 75.5 MHz): δ = 23.3 (CH_3), 47.4 (CH-NH_2), 112.2 (CH_{arom}), 121.0 (CH_{arom}), 126.1 (CH_{arom}), 126.8 (CH_{arom}), 142.3 (C_{arom}), 152.6 (C_{arom}), 160.9 (NCN) ppm. HRMS (ESI^+): calcd. for $[M + H]^+$ 162.1031; found 162.1026.

Procedure for the Synthesis of Racemic 1-(1,3-Benzothiazol-2-yl)ethanol (5): Ethanol **5** was prepared from benzothiazole (**4**) following the same approach described by Poppe and co-workers.[8c]

Procedure for the Synthesis of 2-[1-(1,3-Benzothiazol-2-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (6): PPh_3 (179 mg, 0.68 mmol) and phthalimide (83 mg, 0.57 mmol) were successively added to a solution of racemic alcohol **5** (100 mg, 0.57 mmol) in dry THF (3 mL) under nitrogen. The resulting solution was cooled to 0 °C and DEAD (124 μL, 0.68 mmol) dissolved in dry THF (0.9 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 6 h; no starting material was detected after this time by TLC analysis (90% CH_2Cl_2/MeOH). The organic solvent was evaporated under reduced pressure and the crude purified by flash chromatography (eluent gradient 50% CH_2Cl_2/hexane to 5% MeOH/CH_2Cl_2), isolating **6** as a pale-yellow oil (121 mg, 69% isolated yield). R_f (5% MeOH/CH_2Cl_2) = 0.85. IR (NaCl): $\tilde{\nu}$ = 3057, 2984, 2940, 1995, 1778, 1718, 1612, 1520, 1469, 1437, 1383, 1352, 1335, 1265, 1208, 1127, 1030, 898, 880 cm^{-1}. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 7.98 (d, J = 8.2 Hz, 1 H_{arom}), 7.86 (m, 2 H_{arom}), 7.80 (d, J = 8.5 Hz, 1 H_{arom}), 7.72 (m, 2 H_{arom}), 7.43 (t, J = 7.0 Hz, 1 H_{arom}), 7.33 (t, J = 7.0 Hz, 1 H_{arom}), 5.92 (q, J = 7.2 Hz, 1 H, CH), 2.09 (d, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 17.6 (CH_3), 48.3 (CH), 121.5 (CH_{arom}), 123.2 (CH_{arom}), 123.4 (2 CH_{arom}), 125.1 (CH_{arom}), 126.0 (CH_{arom}), 131.8 (2 C_{arom}), 134.1 (2 C_{arom}), 152.8 (CH_{arom}), 167.4 (2 CO), 170.0 (NCS) ppm. MS (ESI^+): m/z (%) = 331 (100) $[M + Na]^+$, 309 (10) $[M + H]^+$.

Procedure for the Synthesis of Racemic 1-(1,3-Benzothiazol-2-yl)-ethanamine (1b): Hydrazine monohydrate (137 μL, 2.9 mmol) was added to a solution of **6** (120 mg, 0.39 mmol) in THF (5.6 mL) and EtOH (0.9 mL) and the mixture was stirred at 70 °C for 2 h. The white suspension formed after this time was filtered off and washed with THF. The organic solvents were evaporated under reduced pressure to give a crude that was purified by flash chromatography (gradient eluent 100% CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to give the corresponding racemic amine **1b** as a yellowish oil (52 mg, 75% isolated yield). R_f (5% MeOH/CH_2Cl_2) = 0.34. IR (NaCl): $\tilde{\nu}$ = 3366, 3297, 2967, 2915, 2863, 2351, 1650, 1590, 1512, 1433, 1308, 756, 726 cm^{-1}. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 7.95 (d, J = 7.9 Hz, 1 H_{arom}), 7.85 (d, J = 7.9 Hz, 1 H_{arom}), 7.43 (t, J = 7.5 Hz, 1 H_{arom}), 7.33 (t, J = 7.3 Hz, 1 H_{arom}), 4.50 (br. d, 1 H, CH), 2.46 (br. s, NH_2), 1.60 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 24.3 (CH_3), 50.2 (CH), 121.6 (CH_{arom}), 122.6 (CH_{arom}), 124.6 (CH_{arom}), 125.8 (CH_{arom}), 134.1 (C_{arom}), 153.3 (C_{arom}), 178.8 (NCS) ppm. MS (EI^+): m/z (%) = 178 (90) $[M]^+$, 136 (100) $[M - C_2H_4N]^+$.

Procedure for the Synthesis of Racemic 1-(1,3-Benzoxazol-2-yl)ethanol (7): Lactic acid (5 mL, 55 mmol) and *p*-toluenesulfonic acid (570 mg, 5.5 mmol) were successively added to a solution of *o*-aminophenol (**2c**; 6 g, 55 mmol) in toluene (25 mL) and the suspension formed was heated at reflux in a Dean–Stark apparatus for 8 h. After this time, the two phases were separated and the aqueous layer was extracted with EtOAc (4 × 10 mL). Subsequently, the organic layers were combined and dried with Na_2SO_4 and, after that, the solvents were evaporated. The crude was purified by flash chromatography (20–40% EtOAc/hexane) to give the alcohol **7** (6.04 g, 67% isolated yield) as a brownish solid. R_f (50% EtOAc/hexane) = 0.37; m.p. 29–31 °C. IR (KBr): $\tilde{\nu}$ = 3421, 3284, 2986, 2931, 2871, 1649, 1593, 1512, 1460, 1431, 1365, 1275, 1240, 1185, 1139, 1099, 1028, 1015, 771, 714 cm^{-1}. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 7.67 (m, 1 H_{arom}), 7.46 (m, 1 H_{arom}), 7.29 (m, 2 H_{arom}), 5.17 (q, J = 6.6 Hz, 1 H, CH), 1.72 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 21.1 (CH_3), 63.8 (CH), 110.5 (CH_{arom}), 119.6 (CH_{arom}), 124.3 (CH_{arom}), 125.0 (CH_{arom}), 140.1 (CH_{arom}), 150.5 (CH_{arom}), 168.5 (NCO) ppm. HRMS (ESI^+): calcd. for $[M + H]^+$ 164.0712; found 164.0706.

Procedure for the Synthesis of Racemic 1-(1,3-Benzoxazol-2-yl)ethyl Methanesulfonate (8): Pyridine (370 μL, 4.6 mmol) and DMAP (38.0 mg, 0.30 mmol) were added to a solution of racemic alcohol **7** (250 mg, 1.5 mmol) in dry CH_2Cl_2 (19.1 mL) under nitrogen and the resulting mixture was cooled to 0 °C. Then mesyl chloride (665 μL, 9 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 30 h; no starting material was detected after this time by TLC analysis (50% EtOAc/hexane). The organic solvent was evaporated under reduced pressure and the crude purified by flash chromatography (30–50% EtOAc/hexane), isolating compound **8** as a pale-yellow oil (301 mg, 83% isolated yield). R_f (50% EtOAc/hexane) = 0.37. IR (NaCl): $\tilde{\nu}$ = 3001, 2992, 2941, 2358, 2340, 1615, 1575, 1477, 1455, 1415, 1351, 1241, 1175, 1106, 1077, 973, 918, 813, 766, 751 cm^{-1}. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 7.73 (d, J = 8.4 Hz, 1 H_{arom}), 7.55 (d, J = 8.5 Hz, 1 H_{arom}), 7.37 (m, 2 H_{arom}), 5.92 (q, J = 6.8 Hz, 1 H, CH), 3.10 [s, 3 H, $(SO_2)CH_3$], 1.90 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 19.3 (CH_3), 37.3 (CH_3), 71.8 (CH), 110.9 (CH_{arom}), 120.6 (CH_{arom}), 124.8 (CH_{arom}), 126.0 (CH_{arom}), 140.3 (C_{arom}), 150.6 (C_{arom}), 161.7 (NCO) ppm. MS (EI^+): m/z (%) = 241 (60) $[M]^+$, 162 (100) $[M - CH_3SO_2]^+$.

Procedure for the Preparation of the Azide 9: Sodium azide (175 mg, 2.7 mmol) was added to a solution of **8** (433 mg, 1.8 mmol) in DMF (7.2 mL) and the mixture was heated at reflux at 55 °C overnight. After no more starting material was detected by TLC (50% EtOAc/hexane), water (5 mL) was added to the mixture and then extracted with Et_2O (3 × 5 mL). The organic layers were combined, dried with Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography (10% EtOAc/hexane), isolating the azide **9** as a colourless oil (262 mg, 77% isolated yield). R_f (50% EtOAc/hexane) = 0.60. IR (NaCl): $\tilde{\nu}$ = 3336, 3057, 2991, 2939, 2475, 2112, 1617, 1569, 1475, 1455, 1241, 1074, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 7.75 (m, 1 H_{arom}), 7.56 (m, 1 H_{arom}), 7.37 (m, 2 H_{arom}), 4.79 (q, J = 7.0 Hz, 1 H, CH), 1.77 (d, J = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 17.6 (CH_3), 53.9 (CH), 110.7 (CH_{arom}), 120.3 (CH_{arom}), 124.6 (CH_{arom}), 125.5 (CH_{arom}), 140.5 (C_{arom}), 150.7 (C_{arom}), 163.8 (NCO) ppm. MS (EI^+): m/z (%) = 188 (50) $[M]^+$, 146 (100) $[M - N_3]^+$.

Procedure for the Preparation of the Racemic 1-(1,3-Benzoxazol-2-yl)ethanamine (1c): The azide **9** (265 mg, 1.4 mmol) and activated Pd/C (105 mg, 0.14 mmol) were placed in a round-bottom flask under vacuum. The mixture was dissolved in deoxygenated MeOH (5.6 mL) injecting at the same time a H_2 balloon. The suspension formed was stirred vigorously overnight, then filtered through Celite and concentrated under reduced pressure. The crude was purified by flash chromatography (5–10% MeOH/EtOAc), isolating the racemic amine **1c** as a yellow oil (169 mg, 74% isolated yield). R_f (10% MeOH/EtOAc) = 0.32. IR (NaCl): $\tilde{\nu}$ = 3336, 3290, 2972, 2929, 1611, 1562, 1452, 1058, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 300.13 MHz): δ = 7.68 (m, 1 H_{arom}), 7.59 (m, 1 H_{arom}), 7.36 (m, 2 H_{arom}), 4.31 (q, J = 7.0 Hz, 1 H, CH), 1.60 (d, J = 6.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 21.9 (CH_3), 47.2 (CH), 112.2 (CH_{arom}), 121.0 (CH_{arom}), 126.1 (CH_{arom}), 126.8 (CH_{arom}), 142.3 (C_{arom}), 152.6 (C_{arom}), 171.8 (NCO) ppm. HRMS (ESI): calcd. for $[M + H]^+$ 163.0871; found 163.0866.

General Procedure for the Enzymatic Acylation Reactions: The appropriate dry solvent (2 mL; TBME for X = S or O; THF for X = NH) and EtOAc (59 μL, 0.60 mmol) were added to a suspension of racemic amine **1a**–**c** (0.20 mmol) and the enzyme (ratio 2:1 of enzyme/substrate by weight) under nitrogen. The reaction mixture was placed in an orbital shaker (250 rpm) for 24 h at 30 °C and

250 r.p.m., and after this time the enzyme was filtered off, the solvent evaporated under reduced pressure and the crude purified by flash chromatography (10% MeOH/EtOAc for **1b**,**c** or 30–50% MeOH/EtOAc for **1a**). The amide formed was then directly injected into the chiral HPLC apparatus {optical rotation values: $[a]_D^{20}$ = +99.5 (*c* = 0.99, MeOH) for 98% *ee* of (*R*)-**11a**, $[a]_D^{20}$ = +119.6 (*c* = 0.96, MeOH) for 99% *ee* of (*R*)-**11b** and $[a]_D^{20}$ = +145.5 (*c* = 0.98, CH_2Cl_2) for >99% *ee* of (*R*)-**11c**} and the enantiopure amines were subjected to a derivatization procedure to determine their enantiomeric excesses by HPLC. The optical rotations for the enantiomerically enriched amines are: $[a]_D^{20}$ = –8.6 (*c* = 0.98, MeOH) for >99% *ee* of (*S*)-**1a**, $[a]_D^{20}$ = –9.3 (*c* = 0.88, MeOH) for 95% *ee* of (*S*)-**1b** and $[a]_D^{20}$ = –12.2 (*c* = 0.59, MeOH) for 96% *ee* of (*S*)-**1c**.

General Procedure for the Chemical Acetylation of Racemic or Optically Active Amines 1a–c: Acetyl chloride (6.7 mmol, 478 μL) was added to a solution of the corresponding amine (1.7 mmol) in dry CH_2Cl_2 (2.5 mL) and pyridine (4.2 mmol, 340 μL) at 0 °C. The resulting mixture was stirred at room temperature until no more amine was detected by TLC. After that time, the solvent was evaporated under reduced pressure and the residue purified by flash chromatography using different proportions of MeOH/EtOAc as eluent to give the corresponding amides **11a**–**c**.

***N*-[1-(1*H*-Benzimidazol-2-yl)ethyl]acetamide (11a):** R_f (30% MeOH/EtOAc) = 0.65; m.p. 245–247 °C. IR (KBr): $\tilde{\nu}$ = 3172, 2296, 2968, 2848, 2303, 2269, 1651, 1568, 1456, 1440, 1375, 1319, 1276, 1147, 833, 746, 737 cm^{-1}. ^1H NMR (MeOD, 300.13 MHz): δ = 7.56 (m, 2 H_{arom}), 7.23 (m, 2 H_{arom}), 5.30 (q, *J* = 7.1 Hz, 1 H, CH), 2.07 [s, 3 H, $(CO)CH_3$], 1.66 (d, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (MeOD, 100.6 MHz): δ = 20.2 (CH_3), 23.1 [$(CO)CH_3$], 45.8 (CH), 116.2 (2 CH_{arom}), 124.0 (2 CH_{arom}), 139.8 (C_{arom}), 140.0 (C_{arom}), 157.8 (NCN), 173.6 (CO) ppm. HRMS (ESI^+): calcd. for $[M + H]^+$ 204.1137; found 204.1131.

***N*-[1-(1,3-Benzothiazol-2-yl)ethyl]acetamide (11b):** R_f (30% MeOH/EtOAc) = 0.63; m.p. 139–141 °C. IR (KBr): $\tilde{\nu}$ = 3283, 3109, 3042, 2976, 2939, 2426, 1624, 1569, 1472, 1435, 1378, 1156, 1203, 942, 825, 743, 715 cm^{-1}. ^1H NMR (MeOD, 300.13 MHz): δ = 7.98 (d, *J* = 8.1 Hz, H_{arom}), 7.85 (d, *J* = 7.7 Hz, H_{arom}), 7.48 (t, *J* = 7.4 Hz, H_{arom}), 7.37 (d, *J* = 7.4 Hz, H_{arom}), 6.63 (br. s, NH), 5.49 (q, *J* = 7.1 Hz, 1 H, CH), 2.07 [s, 3 H, $(CO)CH_3$], 1.67 (d, *J* = 7.0 Hz, 3 H, CH_3) ppm. ^{13}C NMR (MeOD, 100.6 MHz): δ = 21.8 (CH_3), 23.2 [$(CO)CH_3$], 47.7 (CH), 121.7 (CH_{arom}), 122.7 (CH_{arom}), 125.2 (CH_{arom}), 126.2 (CH_{arom}), 134.1 (C_{arom}), 152.5 (C_{arom}), 169.4 (NCS), 172.9 (CO) ppm. MS ($APCI^+$): *m*/*z* (%) = 222 (10) $[M + 2H]^+$, 221 (100) $[M + H]^+$.

***N*-[1-(1,3-Benzoxazol-2-yl)ethyl]acetamide (11c):** R_f (10% MeOH/EtOAc) = 0.51; m.p. 126–128 °C. IR (KBr): $\tilde{\nu}$ = 3278, 3096, 3042, 2985, 2979, 2932, 2426, 1611, 1572, 1472, 1458, 1378, 1245, 1168, 1113, 942, 825, 764, 753 cm^{-1}. ^1H NMR (MeOD, 300.13 MHz): δ = 7.69 (m, H_{arom}), 7.62 (m, 1 H_{arom}), 7.40 (m, 2 H_{arom}), 5.32 (q, *J* = 7.1 Hz, 1 H, CH), 2.07 [s, 3 H, $(CO)CH_3$], 1.66 (d, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (MeOD, 100.6 MHz): δ = 19.3 (CH_3), 22.9 [$(CO)CH_3$], 45.6 (CH), 112.3 (CH_{arom}), 121.0 (CH_{arom}), 126.3 (CH_{arom}), 127.0 (CH_{arom}), 142.3 (C_{arom}), 152.6 (C_{arom}), 169.1 (NCO), 173.4 (CO) ppm. HRMS (ESI^+): calcd. for $[M + H]^+$ 205.0977; found 205.0972.

Supporting Information (see also the footnote on the first page of this article): Conditions for chiral high-performance liquid chromatography (HPLC).

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