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Asymmetric synthesis of azolium-based 1,2,3,4-tetrahydronaphthalen-2-ols through lipase-catalyzed resolutions

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ABSTRACT

A series of racemic *trans*-1,2,3,4-tetrahydronaphthalen-2-ols bearing an azole nucleus at the C-1 or C-3 position has been synthesized by ring opening reactions of the corresponding epoxides using imidazole or 1,2,4-triazole. The kinetic resolutions of these racemates were undertaken through transesterification processes, finding good levels of activities and high to excellent enantiodiscrimination values for the *Pseudomonas cepacia* lipase immobilized on a ceramic carrier. Investigations into the optimum reaction conditions were carried out by consideration of different organic solvents, temperatures, enzyme loadings, and reaction times. With the best conditions in hand, the experiments were later carried out toward the resolution of the related racemic *cis*-alcohols, which were previously obtained through a Mitsunobu and deprotection chemical sequence from the *trans*-stereoisomers.

1. Introduction

The development of asymmetric synthetic routes toward chiral 1,2-amino alcohols, also known as β-amino alcohols, is an attractive task because of the versatility of this motif that is present in numerous biologically active compounds.[1] In addition, enantiopure 1,2-amino alcohols are versatile organic compounds in coordination chemistry and organocatalysis, playing an important role as chiral auxiliaries and as ligands in multiple asymmetric transformations.[2] Biocatalysis represents an elegant and sustainable strategy for the preparation of optically active amino alcohol derivatives,[3] as lipases offering significant advantages in the resolution of racemic *N*-substituted-2-amino-cycloalkanols by means of O-acetylation protocols[4] or complementary hydrolytic procedures.[5]

The presence of an azole subunit imparts remarkable properties, offering a myriad of possibilities in both organocatalysis[6] and medicinal chemistry.[7] A large list of azole drugs such as econazole, fluconazole, ketoconazole, miconazole, ravuconazole and voriconazole are currently commercialized for the treatment of human diseases. On the other hand, novel imidazole-based dihydronaphthalenes and indenes have been used as building blocks for the synthesis of potential inhibitors of aldosterone synthases with applications in the treatment of congestive heart failure and myocardial fibrosis.[8] Recently racemic cycloalkyl azoles have been described as potent antileishmanial agents.[9] In this context, lipase-catalyzed resolutions of pyrazole-,[10] imidazole-,[11] and triazole-cycloalkanols[12] have been studied in depth over the last two decades. The application of this class of hydrolytic enzymes provides an efficient access to alcohol and ester derivatives with high stereodiscrimination.

Herein, we have focused on the synthesis of a novel family of racemic azole derivatives, studying their lipase-catalyzed kinetic resolutions through transesterification reactions. The influence of the azole subunit and the spatial disposition of the substituents have been analyzed.

2. Results and discussion

2.1. Chemical synthesis and lipase-catalyzed resolution of *trans*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol

The synthesis of racemic *trans*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol **2** was performed from commercially available naphthalene. Following an already described pathway involving the Birch reduction of naphthalene to 1,4-dihydronaphthalene using sodium in THF,[13] and later transformation to the corresponding epoxide **1** using *meta*-chloroperbenzoic acid in dichloromethane for a global 36% isolated yield.[14] Epoxide **1** was reacted with a slight excess of imidazole (1.2 equiv) at 120 °C, obtaining exclusively the alcohol (±)-*trans*-**2** in good yield (Scheme in Table 1). Then, a vast number of lipases were tested using 3 equiv of vinyl acetate **3** as acyl donor in THF as solvent, which was the one that provided the best solubility of the alcohol.

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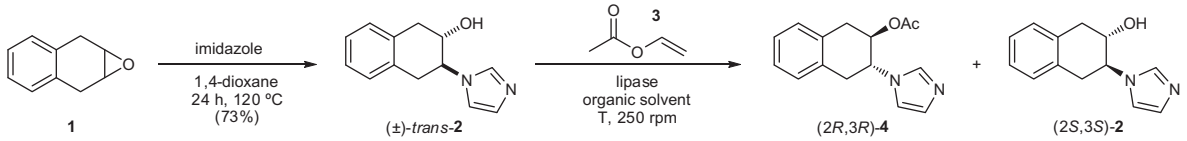
Table 1
Synthesis and kinetic resolution of alcohol (±)-*trans*-**2** (0.1 M) using different PSL preparations and 3 equiv of vinyl acetate **3** as the acyl donor and 250 rpm



Entry	Enzyme[a]	Solvent	T (°C)	t (h)	ee$_P$[b] (%)	ee$_S$[b] (%)	c[c] (%)	E[d]
1	PSL IM (1:1)	THF	30	38	97	18	16	79
2	PSL IM II (1:1)	THF	30	48	99	11	10	>200
3	PSL IM II (1:1)	THF	45	48	95	25	20	50
4	PSL-C I (1:1)	THF	30	48	95	83	46	102
5	PSL-C I (2:1)	THF	30	48	95	82	46	99
6	PSL-C I (1:1)	MTBE	30	48	94	8	8	35

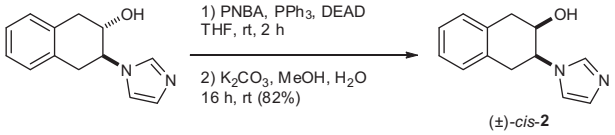
[a] Amount of enzyme in parentheses (ratio of enzyme:alcohol in weight).
[b] Enantiomeric excess of product and substrate calculated by HPLC using a chiral column (see further details in Section 4).
[c] Conversion: $c = ee_S/(ee_S + ee_P)$.
[d] Enantiomeric ratio: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1-c) \times (1 + ee_P)]$.[15]

Unfortunately, no reaction was observed with *Candida antarctica* lipase type B (CAL-B), *Candida antarctica* lipase type A (CAL-A), lipase AK from *Pseudomonas fluorescens*, lipase from *Rhizomucor miehei* (RML), porcine pancreatic lipase (PPL), *Candida rugosa* lipase (CRL), and lipase from *Thermomyces lanuginosus* (TLL). Only *Pseudomonas cepacia* lipase (PSL), currently known as *Burkholderia cepacia* lipase, catalyzed the reaction to an appreciable degree and in general with good selectivities. Various types of commercially available PSL were tested such as PSL IM (entry 1) and PSL IM II (entries 2 and 3), both supported on diatomite and only differing in the units per gram of solid (see Section 4 for further details) and PSL-C I that is immobilized onto a ceramic carrier (entries 4–6). Both PSL IM and PSL IM II provided a high stereodiscrimination in the acetylation of the (2*R*,3*R*)-alcohol although with low conversion values (entries 1 and 2), while an increase in the temperature resulted in an appreciable loss of the selectivity (entry 3).

Significantly, a 46% conversion and a high enantioselectivity were achieved with PSL-C I at 30 °C (entry 4), without observing appreciable improvements at higher enzyme loadings (entry 5). Finally, other solvents were tested in the resolution of (±)-*trans*-**2**, although the results did not improve upon the previous ones obtained with THF. The more environmentally friendly 2-methyltetrahydrofuran (2-Me-THF) did not solubilize the alcohol so the reaction did not proceed in any extension, while methyl *tert*-butyl ether (MTBE) led to lower conversion and selectivity values (entry 6). The absolute configurations were assigned as (2*S*,3*S*) for the *trans*-alcohol **2** and (2*R*,3*R*) for the *trans*-acetate **4** by comparison with previous investigations carried out in the lipase-catalyzed resolution of *N*-substituted-2-aminocyclohexanols.[4c,h,11a,12]

2.2. Chemical synthesis and lipase-catalyzed resolution of *cis*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol

In order to explore the reactivity of racemic *cis*-**2**, this alcohol was prepared following a Mitsunobu and deprotection sequence as depicted in Scheme 1. For this purpose, *para*-nitrobenzoic acid (PNBA), triphenylphosphine (PPh_3), and diethyl azodicarboxylate (DEAD) were used in combination with THF as solvent, leading to the total inversion of the C-2 position. Without isolation of the ester intermediate, its deprotection in basic media was carried out with potassium carbonate (K_2CO_3) in a mixture of water and methanol, obtaining the alcohol (±)-*cis*-**2** in an overall 82% isolated yield. Then, the enzymatic resolution was attempted using different PSL preparations and CAL-B, although only PSL displayed a



Scheme 1. Transformation of racemic alcohol *trans*-**2** into *cis*-**2** following a Mitsunobu and deprotection sequence.

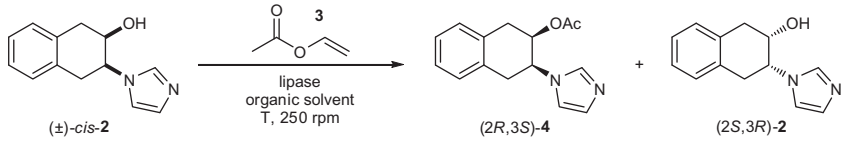
significant activity. All the reactions were carried out in THF to assure a proper solubilization of the alcohol and 3 equiv of **3** as acyl donor. The results are summarized in Table 2.

Both PSL supported on diatomite displayed good selectivities in the formation of the (2*R*,3*S*)-acetate **4** although with low conversions (entries 1 and 2), decreasing the enantiopurity of the product with longer reaction times. A better reactivity was observed with PSL-C I in THF, achieving a 32% conversion for a 97% ee of the acetate (entry 3). Trying to explore the possibilities of other reaction media, MTBE was tested but although the stereodiscrimination was higher the conversion became lower (entry 4). At this point, the loading of the enzyme was doubled trying to obtain a conversion close to 50% but a loss of selectivity was observed at shorter reaction times (entry 5). Finally, higher temperatures led to an increase in the conversion, although at 60 °C the conversion surpassed 50%, favouring at this point the acetylation of the undesired enantiomer (entries 6 and 7). The absolute configurations were assigned (2*S*,3*R*) for the *cis*-alcohol **2** and as (2*R*,3*S*) for the *cis*-acetate **4** by comparison with previous investigations carried out in the lipase-catalyzed resolution of *cis*-*N*-substituted-2-aminocyclohexanols.[4a,h,11b,12]

2.3. Chemical synthesis and lipase-catalyzed resolution of *trans*- and *cis*-3-(1*H*-1,2,4-triazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ols

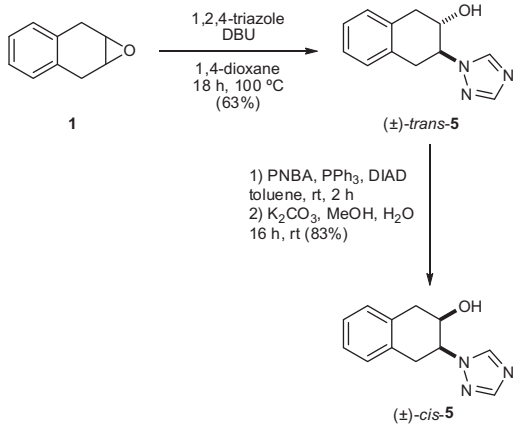
Once that the reactivity of *cis*- and *trans*-imidazolium-based 1,2,3,4-tetrahydronaphthalen-2-ols had been studied, we decided to focus on derivatives with the triazole nucleus (Scheme 2). Epoxide **1** was reacted with an equimolecular amount of 1,2,4-triazole in the presence of 2 equiv of 1,8-diazabicycloundec-7-ene (DBU) as the base using previously optimized reactions for the opening of cyclopentene and cyclohexene oxides.[12] Thus, the formation of the undesired 1,3,4-triazole derivative was minimized, and the racemic alcohol *trans*-**5** was finally isolated in 63% yield after column chromatography on silica gel. For the formation of

Table 2
PSL-catalyzed acetylation of (±)-*cis*-**2** (0.1 M) using 3 equiv of vinyl acetate **3** as the acyl donor and 250 rpm



Entry	Enzyme[a]	Solvent	T (°C)	t (h)	ee$_P$[b] (%)	ee$_S$[b] (%)	c[c] (%)	E[d]
1	PSL IM (1:1)	THF	30	48	95	15	14	45
2	PSL IM II (1:1)	THF	30	48	99	7	7	>200
3	PSL-C I (1:1)	THF	30	48	97	45	32	102
4	PSL-C I (1:1)	MTBE	30	48	99	9	8	>200
5	PSL-C I (2:1)	THF	30	24	86	54	39	22
6	PSL-C I (2:1)	THF	45	24	95	71	43	83
7	PSL-C I (2:1)	THF	60	24	86	94	53	47

[a] Amount of enzyme in parentheses (ratio of enzyme:alcohol in weight).
[b] Enantiomeric excess of product and substrate calculated by HPLC using a chiral column (see further details in Section 4).
[c] Conversion: $c = ee_S/(ee_S + ee_P)$.
[d] Enantiomeric ratio: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.[15]



Scheme 2. Chemical synthesis of racemic triazoles *trans*- and *cis*-**5**.

the racemic alcohol *cis*-**5**, identical conditions to those previously used with imidazole **2** were attempted, achieving a 78% yield. A slight improvement in the synthetic methodology was attained by employing toluene and diisopropyl azodicarboxylate (DIAD) instead of THF and DEAD, respectively, isolating alcohol *cis*-**5** in 83% after subsequent basic hydrolysis in the presence of K_2CO_3.

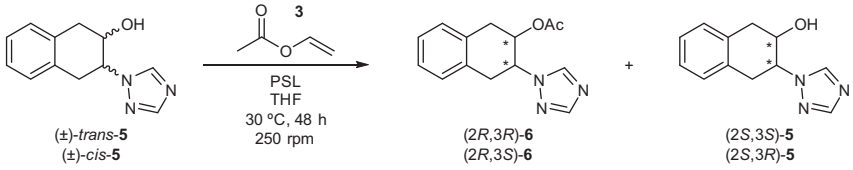
The lipase-catalyzed resolutions of racemic *trans*- and *cis*-alcohols **5** were studied under similar conditions to those previously described for **2**, that is, 3 equiv of vinyl acetate, THF as solvent for a 100 mM substrate concentration, 30 °C, and a ratio 1:1 of lipase/alcohol in weight (Table 3).

In all cases, excellent selectivities were observed, improving the results obtained with the imidazole ring, that is, the presence of an extra nitrogen atom provides a beneficial effect in the PSL action. Remarkably, alcohol *trans*-**5** was efficiently resolved with 48% conversion when PSL-C I was used (entry 3), displaying a higher activity in comparison with other PSL preparations (entries 1 and 2). Similarly, but with a more modest conversion, the same enzyme exclusively catalyzed the acetylation of the *cis*-(2*R*,3*S*)-**5** isomer (entries 4 and 5).

2.4. Chemical synthesis and lipase-catalyzed resolution of *trans*-1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol

Based on the exceptional antileishmanial properties reported for tetrahydronaphthylazoles, the synthesis of racemic *trans*-1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol **8** was performed opening epoxide **7** with imidazole in refluxing ethanol (Scheme in Table 4).[9] The synthesis of alcohol *cis*-**8** was developed following the Mitsunobu and deprotection inversion previously described for triazole **5**, that is, the use of PNBA, PPh_3, DIAD in

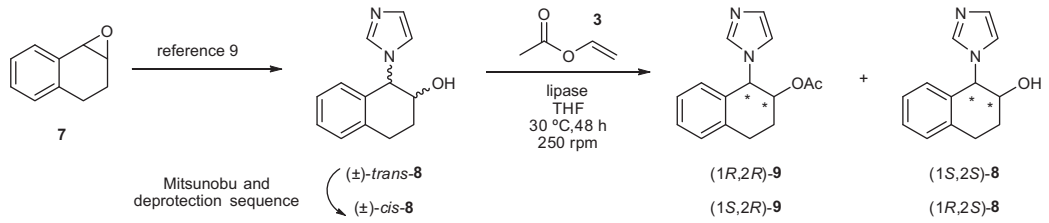
Table 3
PSL-catalyzed acetylation of (±)-*trans*- and (±)-*cis*-**5** using 3 equiv of vinyl acetate **3** in THF (0.1 M) at 30 °C and 250 rpm



Entry	(±)-**5**	Enzyme	ee$_P$[a] (%)	ee$_S$[a] (%)	c[b] (%)	E[c]
1	*trans*	PSL IM	98	35	28	140
2	*trans*	PSL IM II	99	19	19	>200
3	*trans*	PSL-C I	99	93	48	>200
4	*cis*	PSL IM II	99	7	7	>200
5	*cis*	PSL-C I	>99	29	23	>200

[a] Enantiomeric excess of product and substrate calculated by HPLC using a chiral column (see further details in Section 4).
[b] Conversion: $c = ee_S/(ee_S + ee_P)$.
[c] Enantiomeric ratio: $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.[15]

Table 4
Lipase-catalyzed acetylation of alcohol (±)-**8** using 3 equiv of **3** as the acyl donor in THF (0.1 M) at 30 °C and 250 rpm



Entry	(±)-**8**	Enzyme	ee_P[a] (%)	ee_S[a] (%)	c[b] (%)	E[c]
1	*trans*	PSL IM	>99	<3	<3	>200
2	*trans*	PSL-C I	96	85	43	133
3	*trans*	CAL-B	>99	41	30	>200
4	*cis*	PSL IM	—	—	—	—
5	*cis*	PSL-C I	98	98	50	>200
6	*cis*	CAL-B	—	—	—	—

[a] Enantiomeric excess of product and substrate calculated by HPLC using a chiral column (see further details in Section 4).
[b] Conversion: $c = ee_S/(ee_S + ee_P)$.
[c] Enantiomeric ratio: $E = \ln[(1-c) \times (1-ee_P)]/\ln[(1-c) \times (1 + ee_P)]$.[15]

toluene, and later deprotection of the resulting ester in a basic medium (Scheme in Table 4). Using both stereoisomers, PSL and CAL-B were tested as enzyme sources for the acetylation of the C-2 position (Table 4), finding the best results for the PSL-C I (entries 2 and 5), which acted with excellent stereodiscrimination for both the *trans*-alcohol (43% conversion) and the *cis*-alcohol (50% conversion) after 48 h at 30 °C. Remarkably, the CAL-B seems to exclusively recognize the alcohol *trans*-(1*R*,2*R*)-**8**, while the *cis*-stereoisomer was not acylated in any extension (entries 3 and 6).

The absolute configurations were assigned as (1*S*,2*S*) for the *trans*-alcohol **8** and (1*R*,2*R*) for the *trans*-acetate **9** by comparison with previous investigations carried out in the resolution of *N*-substituted-1-aminoindan-2-ols by means of PSL-catalyzed acetylation reactions.[4b]

3. Conclusions

In conclusion, the high stereodiscrimination of *Pseudomonas cepacia* lipase (PSL) has been demonstrated in the classical kinetic resolution of *trans*- and *cis*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol. Depending on the type of immobilization, the best results were found with the PSL supported onto ceramics rather than in diatomite, but in all cases PSL displayed better activities in comparison with other tested lipases. This methodology was successfully extended to other families of substrates such as 3-(1*H*-1,2,4-triazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol and 1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol both with *trans*- or *cis*-relative disposition of the substituents.

4. Experimental section

4.1. General

Chemical reagents were purchased from different commercial sources (Sigma–Aldrich, Acros and Fluka) and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. *Candida antarctica* lipase type B (CAL-B, 7300 PLU/g) immobilized by adsorption in Lewatit E, *Rhizomucor miehei* lipase (RML, 150 IUN/g) and *Thermomyces lanuginosus* lipase (TLL, 250 IUN/g) were kindly donated by Novozymes. *Pseudomonas cepacia* lipase immobilized over ceramic particles (PSL-C I, 1950 U/g), lipase AK from *Pseudomonas fluorescens* (22,100 U/g) and *Candida rugosa* lipase (CRL, 965 U/mg) were purchased from Sigma–Aldrich, while the ones immobilized on diatomite PSL IM (943 U/g) and PSL IM II (816 U/g) were provided by Amano Europe Pharmaceutical Company. The pancreatic porcine lipase (PPL, 46 U/mg) was purchased from Sigma. The *Candida antarctica* lipase type A (CAL-A, 2.6 U/mg) was provided by Codexis.

Flash chromatography was performed using silica gel 60 (230–240 mesh). Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded using KBr pellets. ^{1}H, ^{13}C NMR, and DEPT were obtained using Bruker AV-300 (^{1}H, 300.13 MHz; ^{13}C, 75.5 MHz) and Bruker DPX-300 spectrometers (^{1}H, 300.13 MHz, ^{13}C, 75.5 MHz). Chemical shifts are given in delta values (δ, ppm) and the coupling constants (J) in Hertz (Hz). APCI$^+$ experiments were carried out using a liquid chromatograph mass detector to record mass spectra (MS). High resolution mass experiments (HRMS) were measured by ESI$^+$ and carried out with a Bruker Micro TofQ.

High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph using the following chiral columns Chiralpak IC (25 × 4.6 mm D.I.), Chiralcel OD-H, (25 × 4.6 mm D.I.), and Chiralcel OJ-H, (25 × 4.6 mm D.I.) at 40 °C. Mixtures of hexane/2-propanol were employed as mobile phases (see later further details for each individual compound). A UV detector at 210 y 215 nm was used for the detection of the alcohols and acetates.

4.2. Synthesis of (±)-*trans*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (±)-*trans*-2

A solution of imidazole (227 mg, 3.23 mmol) and epoxide **1** (403 mg, 2.77 mmol) in 1,4-dioxane (1.4 mL) was placed in a sealed tube and stirred at 120 °C until the complete disappearance of the epoxide (24 h). The solvent was then evaporated and the resulting crude purifies by column chromatography on silica gel (2–6% MeOH/CH_2Cl_2), yielding the alcohol (±)-*trans*-**2** as a white solid (73% isolated yield). Mp: 169–171 °C. R_f (10% MeOH/CH_2Cl_2): 0.47; IR (KBr): ν 3496, 3115, 2987, 1073, 745 cm^{-1}; ^{1}H NMR (MeOD, 300.13 MHz): δ 2.82 (1H, dd, $^3J_{HH}$ = 16.6 Hz; $^3J_{HH}$ = 9.4 Hz), 3.11 (1H, dd, $^3J_{HH}$ = 16.6 Hz; $^3J_{HH}$ = 5.7 Hz), 3.16–3.23 (2H, m), 4.09 (1H, td, $^3J_{HH}$ = 9.4 Hz; $^3J_{HH}$ = 5.7 Hz), 4.20–4.31 (1H, m), 6.91 (1H, s), 7.01–7.07 (4H, m), 7.13 (1H, s), 7.65 (1H, s); ^{13}C NMR (MeOD, 75.5 MHz): δ 36.6 (CH_2), 38.7 (CH_2), 61.2 (CH), 70.6 (CH), 118.8 (CH), 127.4 (CH), 127.6 (CH), 128.9 (CH), 129.3 (CH), 129.8 (CH), 134.6 (C), 135.0 (C), 138.1 (CH); MS (APCI$^+$, m/z): 215 [(M+H)$^+$];

HRMS (ESI$^+$, m/z) calcd for $C_{13}H_{15}N_2O$ (M+H)$^+$: 215.1179 found: 215.1194.

4.3. Synthesis of racemic *trans*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl acetate (±)-*trans*-4

The synthesis of racemic *trans*-acetate **4** was performed just for analytical purposes in order to calculate the enantiomeric excess of the product in the lipase-catalyzed resolutions.

To a solution of alcohol (±)-*trans*-**2** (30 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL), Et_3N (59 μL, 0.42 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (26 μL, 0.28 mmol) were successively added under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h until the complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2), to yield the acetate (±)-*trans*-**4** as a pale yellow solid (97% isolated yield). Mp: 91–93 °C. R_f (10% MeOH/CH_2Cl_2): 0.81; IR (KBr): ν 3112, 2984, 1733, 1265, 1071, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.93 (3H, s), 2.98 (1H, dd, $^3J_{HH}$ = 16.7 Hz; $^3J_{HH}$ = 8.8 Hz), 3.23–3.41 (3H, m), 4.47–4.55 (1H, m), 5.33–5.41 (1H, m), 6.97 (1H, s), 7.08–7.15 (3H, m), 7.18–7.23 (2H, m), 7.57 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.1 (CH_3), 34.4 (CH_2), 35.2 (CH_2), 56.6 (CH), 71.6 (CH), 127.2 (CH), 127.4 (CH), 128.8 (2CH), 129.4 (2CH), 130.0 (CH), 132.6 (C), 132.7 (C), 170.4 (C); MS (APCI$^+$, m/z): 257 [(M+H)$^+$]; HRMS (ESI$^+$, m/z) calcd for $C_{15}H_{17}N_2O_2$ (M+H)$^+$: 257.1285, found: 257.1292.

4.4. General procedure for the lipase-catalyzed resolution of the alcohol (±)-*trans*-2

To a suspension of alcohol (±)-*trans*-**2** (30 mg, 0.14 mmol) and PSL (30 mg) in dry THF (1.4 mL), vinyl acetate (39 μL, 0.42 mmol) was added under a nitrogen atmosphere. The reaction was shaken for the appropriate time at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and stopped at 38 or 48 h. The enzyme was filtered off using CH_2Cl_2 (3 × 5 mL), the solvent evaporated under reduce pressure and the reaction crude purified by *flash* chromatography on silica gel (2–10% MeOH/CH_2Cl_2), affording the corresponding optically enriched acetate (2*R*,3*R*)-**4** and the alcohol (2*S*,3*S*)-**2** (see Table 1). Alcohol: $[\alpha]_D^{20}$ = +26.0 (*c* 1.0, MeOH) for 83% ee (Chiralcel OD-H; 50% Hexane/2-Propanol; 0.7 mL/min flow). Acetate: $[\alpha]_D^{20}$ = −4.5 (*c* 1.0, MeOH) for 99% ee (Chiralcel OD-H; 50% Hexane/2-Propanol; 0.7 mL/min flow).

4.5. Synthesis of racemic *cis*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (±)-*cis*-2

The synthesis was based on a Mitsunobu inversion reaction followed by the deprotection of the resulting ester group, and it is as follows.

4.5.1. Mitsunobu reaction

To a solution of alcohol (±)-*trans*-**2** (359 mg, 1.68 mmol) in dry THF (25.3 mL), *p*-nitrobenzoic acid (625 mg, 3.73 mmol), PPh_3 (981 mg, 3.73 mmol), and DEAD (683 μL, 3.73 mmol) were successively added under nitrogen atmosphere. The mixture was stirred for 2 h at room temperature, until complete consumption of the starting alcohol by TLC analysis (5% MeOH/CH_2Cl_2). The organic solvent was evaporated under reduced pressure to afford a reaction crude that was immediately used for the deprotection step.

4.5.2. Deprotection step

To a solution of the Mitsunobu reaction crude in MeOH (3.1 mL), K_2CO_3 (514 mg, 3.73 mmol) and H_2O (3.1 mL) were added. The mixture was stirred for 16 h and then MeOH was evaporated under reduced pressure. The resulting suspension was dissolved in H_2O (15 mL), after which brine (5 mL) was added, and then the resulting mixture was extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. Finally, the reaction crude was purified by column chromatography on silica gel (2–6% MeOH/CH_2Cl_2), yielding the alcohol (±)-*cis*-**2** as a white solid (82% isolated yield). Mp: 166–168 °C. R_f (10% MeOH/CH_2Cl_2): 0.37; IR (KBr): ν 3415, 3023, 2971, 1015, 846 cm^{-1}; ^{1}H NMR (MeOD, 300.13 MHz): δ 2.69–2.76 (2H, m), 3.00–3.21 (2H, m), 3.30–3.42 (1H, m), 4.10–4.25 (1H, m), 4.40–4.55 (1H, m), 6.85 (1H, s), 7.00–7.15 (5H, m), 7.66 (1H, s); ^{13}C NMR (MeOD, 75.5 MHz): δ 32.8 (CH_2), 37.5 (CH_2), 58.7 (CH), 69.1 (CH), 120.5 (CH), 127.6 (CH), 127.9 (CH), 128.5 (CH), 129.9 (CH), 130.8 (CH), 134.5 (C), 134.8 (C), 138.1 (CH); MS (APCI$^+$, m/z): 215 [(M+H)$^+$]; HRMS (ESI$^+$, m/z) calcd for $C_{13}H_{15}N_2O$ (M+H)$^+$: 215.1179, found: 215.1184.

4.6. Synthesis of racemic *cis*-3-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl acetate (±)-*cis*-4

The synthesis of racemic *cis*-acetate **4** was performed just for analytical purposes in order to calculate the enantiomeric excess of the product in the lipase-catalyzed resolutions.

To a solution of alcohol (±)-*cis*-**2** (30 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL), Et_3N (59 μL, 0.42 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (26 μL, 0.28 mmol) were successively added under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h until the complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2), yielding the acetate (±)-*cis*-**4** as a pale yellow solid (97% isolated yield). Mp: 136–138 °C. R_f (10% MeOH/CH_2Cl_2): 0.70; IR (KBr): ν 3022, 2971, 1735, 1266, 1020, 849 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.06 (3H, s), 2.97 (1H, dd, $^3J_{HH}$ = 17.5 Hz; $^2J_{HH}$ = 6.3 Hz), 3.19 (1H, dd, $^3J_{HH}$ = 17.5 Hz; $^2J_{HH}$ = 4.7 Hz), 3.36 (1H, dd, $^3J_{HH}$ = 16.8 Hz; $^2J_{HH}$ = 5.7 Hz), 3.51 (1H, dd, $^3J_{HH}$ = 16.8 Hz; $^2J_{HH}$ = 8.0 Hz), 4.64–4.70 (1H, m), 5.35–5.39 (1H, m), 6.91 (1H, s), 6.96 (1H, s), 7.04 (1H, s), 7.01–7.13 (1H, m), 7.16–7.25 (3H, m) 7.54 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.0 (CH_3), 32.0 (CH_2), 32.1 (CH_2), 54.4 (CH), 70.5 (CH), 118.1 (CH), 126.7 (CH), 126.8 (CH), 128.5 (CH), 129.0 (CH), 129.2 (CH), 131.7 (C), 132.0 (C), 136.4 (CH), 170.0 (C); MS (APCI$^+$, m/z): 257 [(M+H)$^+$], HRMS (ESI$^+$, m/z) calcd for $C_{15}H_{17}N_2O_2$ (M+H)$^+$: 257.1285, found: 257.1299.

4.7. General procedure for the lipase-catalyzed resolution of the alcohol (±)-*cis*-2

To a suspension of alcohol (±)-*cis*-**2** (30 mg, 0.14 mmol) and PSL (30 mg) in dry THF (1.4 mL), vinyl acetate (39 μL, 0.42 mmol) was added under nitrogen atmosphere. The reaction was shaken for the appropriate time at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and stopped at 24 or 48 h. The enzyme was filtered off using CH_2Cl_2 (3 × 5 mL), the solvent evaporated under reduce pressure and the reaction crude purified by *flash* chromatography on silica gel (2–10% MeOH/CH_2Cl_2), affording the corresponding optically enriched acetate (2*R*,3*S*)-**4** and the alcohol (2*S*,3*R*)-**2** (see Table 2). Alcohol: $[\alpha]_D^{20}$ = +39.0 (*c* 1.0, MeOH) for 94% ee (Chiralpak IC; 60% Hexane/2-Propanol; 0.8 mL/min flow). Acetate: $[\alpha]_D^{20}$ = −14.4 (*c* 0.5, MeOH) for 99% ee (Chiralcel OJ-H; 80% Hexane/2-Propanol; 0.8 mL/min flow).

4.8. Synthesis of racemic *trans*-3-(1*H*-1,2,4-triazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (±)-*trans*-5

A DBU solution (0.42 mL, 2.76 mmol) in 1,4-dioxane (0.42 mL) was carefully added to a solution containing 1,2,4-triazole (96 mg, 1.38 mmol) and epoxide **1** (200 mg, 1.38 mmol) in

1,4-dioxane (1.8 mL). The reaction was stirred at 100 °C for 18 h and then the mixture was cooled to room temperature. After this time, the solvent was evaporated under reduced pressure and the resulting crude purified by flash chromatography on silica gel (2–10% MeOH/CH_2Cl_2), yielding the alcohol (±)-*trans*-**5** as a white solid (63% isolated yield). Mp: 149–151 °C. R_f (5% MeOH/CH_2Cl_2): 0.33; IR (KBr): ν 3494, 3107, 2984, 1078, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 3.02 (1H, dd, $^3J_{HH}$ = 16.5 Hz; $^2J_{HH}$ = 8.4 Hz), 3.31 (2H, m), 3.59 (1H, dd, $^3J_{HH}$ = 16.3 Hz; $^2J_{HH}$ = 9.6 Hz), 4.14 (1H, br s), 4.43–4.49 (2H, m), 7.13–7.23 (4H, m), 7.90 (1H, s), 8.17 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 34.5 (CH_2), 37.2 (CH_2), 62.6 (CH), 68.9 (CH), 126.6 (CH), 126.8 (CH), 128.4 (CH), 129.0 (CH), 132.6 (C), 133.4 (C), 143.6 (CH), 151.8 (C); MS (APCI$^+$, *m*/*z*): 216 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{12}H_{14}N_3O$ (M+H)$^+$: 216.1131, found: 216.1150.

4.9. Synthesis of racemic *trans*-3-(1*H*-1,2,4-triazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl acetate (±)-*trans*-6

The synthesis of racemic *trans*-acetate **6** was performed just for analytical purposes in order to calculate the enantiomeric excess of the product in the lipase-catalyzed resolutions.

To a solution of alcohol (±)-*trans*-**5** (30 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL), Et_3N (59 μL, 0.42 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (26 μL, 0.28 mmol) were successively added under nitrogen atmosphere. The reaction was stirred at room temperature for 2 h until the complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2), yielding the acetate (±)-*trans*-**6** as a yellow solid (97% isolated yield). Mp: 117–119 °C. R_f (5% MeOH/CH_2Cl_2): 0.66; IR (KBr): ν 3115, 2983, 1728, 1259, 1070, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 1.91 (3H, s), 2.97 (1H, dd, $^3J_{HH}$ = 16.5 Hz; $^2J_{HH}$ = 5.8. Hz), 3.31 (1H, d, $^3J_{HH}$ = 5.8 Hz), 3.37 (1H, d, $^3J_{HH}$ = 5.8 Hz), 3.65 (1H, dd, $^3J_{HH}$ = 16.7 Hz; $^2J_{HH}$ = 10.5 Hz), 4.71 (1H, td, $^3J_{HH}$ = 10.1 Hz; $^2J_{HH}$ = 5.8 Hz), 5.51 (1H, td, $^3J_{HH}$ = 9.3 Hz; $^2J_{HH}$ = 5.9 Hz), 7.10–7.21 (4H, m), 7.96 (1H, s), 8.13 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 20.7 (CH_3), 33.8 (CH_2), 34.1 (CH_2), 58.8 (CH), 70.8 (CH), 126.8 (CH), 126.9 (CH), 128.4 (CH), 128.9 (CH), 132.2 (2C), 143.2 (CH), 152.0 (CH), 169.7 (C); MS (APCI$^+$, *m*/*z*): 258 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{14}H_{16}N_3O_2$ (M+H)$^+$: 258.1237, found: 258.1239.

4.10. General procedure for the lipase-catalyzed resolution of the alcohol (±)-*trans*-5

To a suspension of alcohol (±)-*trans*-**5** (30 mg, 0.14 mmol) and PSL (30 mg) in dry THF (1.4 mL), vinyl acetate (39 μL, 0.42 mmol) was added under a nitrogen atmosphere. The reaction was shaken for the appropriate time at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and stopped at 48 h. The enzyme was filtered off using CH_2Cl_2 (3 × 5 mL), the solvent evaporated under reduce pressure, and the reaction crude purified by flash chromatography on silica gel (2–10% MeOH/CH_2Cl_2), affording the corresponding optically enriched acetate (2*R*,3*R*)-**6** and the alcohol (2*S*,3*S*)-**5** (see Table 3). Alcohol: $[\alpha]_D^{20}$ = +35.0 (*c* 1.0, MeOH) for 93% ee (Chiralcel OD-H; 60% Hexane/2-Propanol; 0.8 mL/min flow). Acetate: $[\alpha]_D^{20}$ = −28.6 (*c* 1.0, MeOH) for >99% ee (Chiralcel OD-H; 60% Hexane/2-Propanol; 0.8 mL/min flow).

4.11. Synthesis of racemic *cis*-3-(1*H*-1,2,4-triazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (±)-*cis*-5

The synthesis was based on a Mitsunobu inversion reaction followed by the deprotection of the resulting ester group, and it is as follows.

4.11.1. Mitsunobu reaction

To a suspension of the alcohol (±)-*trans*-**5** (101 mg, 0.47 mmol) in dry toluene (6.8 mL), *p*-nitrobenzoic acid (156 mg, 0.93 mmol) and PPh_3 (246 mg, 0.93 mmol) were successively added under a nitrogen atmosphere, and warmed until the complete solubility of the reagents. Next, DIAD (181 μL, 0.93 mmol) was added and the mixture stirred for 2 h, until the complete consumption of the starting alcohol by TLC analysis (2% MeOH/CH_2Cl_2). The organic solvent was evaporated under reduced pressure affording a reaction crude that was immediately used for the deprotection step.

4.11.2. Deprotection step

To a solution of the Mitsunobu reaction crude in MeOH (800 μL), K_2CO_3 (140 mg, 0.93 mmol) and H_2O (800 μL) were added. The mixture was stirred for 16 h and then MeOH was evaporated under reduced pressure. The resulting suspension was dissolved in H_2O (7 mL), after which brine (3 mL) was added, and then the resulting mixture was extracted with EtOAc (4 × 10 mL). The organic phases were combined, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Finally, the reaction crude was purified by column chromatography on silica gel (2–6% MeOH/CH_2Cl_2), yielding alcohol (±)-*cis*-**5** as a white solid (83% isolated yield). Mp: 104–106 °C. R_f (10% MeOH/CH_2Cl_2): 0.57; IR (KBr): ν 3411, 3055, 2971, 1022, 844 cm^{-1}; ^1H NMR (MeOD, 300.13 MHz): δ 2.95 (1H, dd, $^3J_{HH}$ = 17.3 Hz; $^2J_{HH}$ = 4.2 Hz), 3.17–3.26 (2H, m), 3.58 (1H, dd, $^3J_{HH}$ = 15.9 Hz; $^2J_{HH}$ = 10.8 Hz), 4.45–4.48 (1H, m), 4.74–4.80 (1H, m), 7.10–7.17 (4H, m), 7.99 (1H, s), 8.59 (1H, s); ^{13}C NMR (MeOD, 75.5 MHz): δ 29.5 (CH_2), 35.9 (CH_2), 59.9 (CH), 66.5 (CH), 125.8 (CH), 126.2 (CH), 128.3 (CH), 129.0 (CH), 132.6 (C), 132.9 (C), 142.6 (CH), 150.1 (C); MS (APCI$^+$, *m*/*z*): 216 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{12}H_{14}N_3O$ (M+H)$^+$: 216.1131, found: 216.1155.

4.12. Synthesis of racemic *cis*-3-(1*H*-1,2,4-triazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl acetate (±)-*cis*-6

The synthesis of racemic *cis*-acetate **6** was performed just for analytical purposes in order to calculate the enantiomeric excess of the product in the lipase-catalyzed resolutions.

To a solution of alcohol (±)-*cis*-**5** (30 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL), Et_3N (59 μL, 0.42 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (26 μL, 0.28 mmol) were successively added under nitrogen atmosphere. The reaction was stirred at room temperature for 2 h until the complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2), yielding the acetate (±)-*cis*-**6** as a yellow solid (96% isolated yield). Mp: 133–135 °C. R_f (10% MeOH/CH_2Cl_2): 0.65; IR (KBr): ν 3054, 2979, 1728 1264, 1074, 846 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): δ 2.00 (3H, s), 3.08 (1H, dd, $^3J_{HH}$ = 17.7 Hz; $^2J_{HH}$ = 4.8 Hz), 3.24 (1H, dd, $^3J_{HH}$ = 17.7 Hz; $^2J_{HH}$ = 4.3 Hz), 3.38 (1H, dd, $^3J_{HH}$ = 16.3 Hz; $^2J_{HH}$ = 5.7 Hz), 3.64 (1H, dd, $^3J_{HH}$ = 16.3 Hz; $^2J_{HH}$ = 9.8 Hz) 4.90–4.95 (1H, m), 5.52–5.58 (1H, m), 7.12–7.25 (4H, m), 7.94 (1H, s), 8.16 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.1 (CH_3), 30.6 (CH_2), 32.7 (CH_2), 57.5 (CH), 69.5 (CH), 126.8 (CH), 127.0 (CH), 128.7 (CH), 129.3 (CH), 131.6 (C), 132.0 (C) 141.8 (CH), 151.5 (CH), 170.1 (C); MS (APCI$^+$, *m*/*z*): 258 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{14}H_{16}N_3O_2$ (M+H)$^+$: 258.1237, found: 258.1245.

4.13. General procedure for the lipase-catalyzed resolution of the alcohol (±)-*cis*-5

To a suspension of alcohol (±)-*cis*-**5** (30 mg, 0.14 mmol) and PSL (30 mg) in dry THF (1.4 mL), vinyl acetate (39 μL, 0.42 mmol) was added under a nitrogen atmosphere. The reaction was shaken for the appropriate time at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and stopped at 48 h. The enzyme was filtered off

using CH_2Cl_2 (3 × 5 mL), the solvent was evaporated under reduce pressure and the reaction crude was purified by flash chromatography on silica gel (2–10% MeOH/CH_2Cl_2), affording the corresponding optically enriched acetate (*R*,*S*)-**6** and alcohol (*S*,*R*)-**5** (see Table 3). Alcohol: $[\alpha]_D^{20}$ = +4.0 (*c* 1.0, MeOH) for 29% ee (Chiralcel OD-H; 60% Hexane/2-Propanol; 0.8 mL/min flow). Acetate: $[\alpha]_D^{20}$ = −29.0 (*c* 1.0, MeOH) for >99% ee (Chiralcel OD-H; 60% Hexane/2-Propanol; 0.8 mL/min flow).

4.14. Synthesis of racemic *trans*-1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (±)-*trans*-8

The synthesis of alcohol (±)-*trans*-**8** was performed from 1a,2,3,7b-tetrahydronaphtho[1,2-*b*]oxirene **7** following the protocol as described by Marrapu et al.[9]

4.15. Synthesis of racemic *trans*-1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl acetate (±)-*trans*-9

The synthesis of racemic *trans*-acetate **9** was performed just for analytical purposes in order to calculate the enantiomeric excess of the product in the lipase-catalyzed resolutions.

To a solution of alcohol (±)-*trans*-**8** (30 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL), Et_3N (59 μL, 0.42 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (26 μL, 0.28 mmol) were successively added under nitrogen atmosphere. The reaction was stirred at room temperature for 2 h until the complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2), yielding the acetate (±)-*trans*-**9** as a yellow solid (89% isolated yield). Mp: 93–95 °C. R_f (10% MeOH/CH_2Cl_2): 0.57; IR (KBr): *ν* 3117, 2986, 1732, 1262, 1072, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): *δ* 1.93–2.06 (1H, m), 2.00 (3H, s), 2.17–2.26 (1H, m), 3.02–3.08 (2H, m), 5.20–5.27 (1H, m) 5.33 (1H, d, $^3J_{HH}$ = 7.8 Hz), 6.82–6.88 (2H, m), 7.08 (1H, s), 7.14–7.29 (3H, m), 7.55 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 21.5 (CH_3), 26.8 (CH_2), 27.2 (CH_2), 60.4 (CH), 73.9 (CH), 118.5 (CH), 127.3 (CH), 127.5 (CH), 128.9 (CH), 129.4 (CH), 130.5 (CH), 132.6 (C), 132.7 (C), 138.3 (CH), 170.6 (C); MS (APCI$^+$, *m*/*z*): 257 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{15}H_{17}N_2O_2$ (M+H)$^+$: 257.1285, found: 257.1292.

4.16. General procedure for the lipase-catalyzed resolution of the alcohol (±)-*trans*-8

To a suspension of alcohol (±)-*trans*-**8** (30 mg, 0.14 mmol) and PSL (30 mg) in dry THF (1.4 mL), vinyl acetate (39 μL, 0.42 mmol) was added under a nitrogen atmosphere. The reaction was shaken for the appropriate time at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and stopped at 48 h. The enzyme was filtered off using CH_2Cl_2 (3 × 5 mL), the solvent was evaporated under reduce pressure ,and the reaction crude was purified by flash chromatography on silica gel (2–10% MeOH/CH_2Cl_2), affording the corresponding optically enriched acetate (1*R*,2*R*)-**9** and the alcohol (1*S*,2*S*)-**8** (see Table 4). Alcohol: $[\alpha]_D^{20}$ = −2.1 (*c* 1.0, MeOH) for 85% ee (Chiralpak IC; 60% Hexane/2-Propanol; 0.8 mL/min flow). Acetate: $[\alpha]_D^{20}$ = +7.0 (*c* 1.0, MeOH) for 99% ee (Chiralpak IC; 60% Hexane/2-Propanol; 0.8 mL/min flow).

4.17. Synthesis of racemic *cis*-1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol (±)-*cis*-8

The synthesis was based on a Mitsunobu inversion reaction followed by the deprotection of the resulting ester group, and it is as follows.

4.17.1. Mitsunobu reaction

To a suspension of the alcohol (±)-*trans*-**8** (100 mg, 0.47 mmol) in dry toluene (6.8 mL), *p*-nitrobenzoic acid (156 mg, 0.93 mmol) and PPh_3 (246 mg, 0.93 mmol) were successively added under a nitrogen atmosphere, and warmed until complete solubility of the reagents. Then, DIAD (181 μL, 0.93 mmol) was added and the mixture stirred for 2 h, until complete consumption of the starting alcohol by TLC analysis (2% MeOH/CH_2Cl_2). The organic solvent was evaporated under reduced pressure affording a reaction crude that was immediately used for the deprotection step.

4.17.2. Deprotection step

To a solution of the Mitsunobu reaction crude in MeOH (800 μL), K_2CO_3 (140 mg, 0.93 mmol) and H_2O (800 μL) were added. The mixture was stirred for 16 h and then MeOH evaporated under reduced pressure. The resulting suspension was dissolved in H_2O (7 mL), brine (3 mL) was added, and then the resulting mixture was extracted with EtOAc (4 × 10 mL). Organic phases were combined, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. Finally, the reaction crude was purified by column chromatography on silica gel (2–6% MeOH/CH_2Cl_2), yielding the alcohol (±)-*cis*-**8** as a white solid (76% isolated yield). Mp: 202–204 °C; IR (KBr): 3411, 3023, 2971, 1018, 846 cm^{-1}; ^1H NMR (300 MHz, MeOD): *δ* 1.81–2.02 (2H, m), 2.86–2.97 (1H, m), 3.10–3.20 (1H, m), 4.18–4.22 (1H, m), 5.45–5.49 (1H, m), 6.89–6.95 (3H, m), 7.14–7.18 (1H, m), 7.23–7.31 (2H, m), 7.57 (1H, s); ^{13}C NMR (300 MHz, MeOD): *δ* 26.1 (CH_2), 26.2 (CH_2), 60.0 (CH), 68.0 (CH), 120.4 (CH), 126.2 (CH), 126.4 (CH), 128.1 (CH), 128.6 (CH), 129.1 (CH), 132.7 (C), 136.8 (C), 138.0 (CH); MS (APCI$^+$, *m*/*z*): 215 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{13}H_{15}N_2O$ (M+H)$^+$: 215.1179, found: 215.1178.

4.18. Synthesis of racemic *cis*-1-(1*H*-imidazol-1-yl)-1,2,3,4-tetrahydronaphthalen-2-yl acetate (±)-*cis*-9

The synthesis of racemic *cis*-acetate **9** was performed just for analytical purposes in order to calculate the enantiomeric excess of the product in the lipase-catalyzed resolutions.

To a solution of alcohol (±)-*cis*-**8** (30 mg, 0.14 mmol) in dry CH_2Cl_2 (1.4 mL), Et_3N (59 μL, 0.42 mmol), DMAP (5 mg, 0.04 mmol), and Ac_2O (26 μL, 0.28 mmol) were successively added under a nitrogen atmosphere. The reaction was stirred at room temperature for 2 h until the complete consumption of the starting material, and then the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (1–3% MeOH/CH_2Cl_2), yielding the acetate (±)-*cis*-**9** as a yellow solid (96% isolated yield). Mp: 83–85 °C. R_f (10% MeOH/CH_2Cl_2): 0.58; IR (KBr): *ν* 3022, 2974, 1737, 1265, 1018, 896 cm^{-1}; ^1H NMR ($CDCl_3$, 300.13 MHz): *δ* 1.99–2.09 (2H, m), 2.06 (3H, s), 2.91–3.15 (2H, m), 5.25–5.31 (1H, m), 5.55 (1H, d, $^3J_{HH}$ = 4.3 Hz), 6.72–6.75 (1H, m), 6.96–7.03 (2H, m), 7.15–7.23 (2H, m), 7.27–7.30 (1H, m), 7.40 (1H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz): *δ* 21.2 (CH_3), 23.7 (CH_2), 26.5 (CH_2), 57.3 (CH), 71.0 (CH), 119.9 (CH), 127.0 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.7 (CH), 131.7 (C), 136.2 (C) 138.0 (CH), 170.4 (C); MS (APCI$^+$, *m*/*z*): 257 [(M+H)$^+$]; HRMS (ESI$^+$, *m*/*z*) calcd for $C_{15}H_{17}N_2O_2$ (M+H)$^+$: 257.1285, found: 257.1282.

4.19. General procedure for the lipase-catalyzed resolution of the alcohol (±)-*cis*-8

To a suspension of alcohol (±)-*cis*-**8** (30 mg, 0.14 mmol) and PSL (30 mg) in dry THF (1.4 mL), vinyl acetate (39 μL, 0.42 mmol) was added under a nitrogen atmosphere. The reaction was shaken for the appropriate time at 30 °C and 250 rpm. Aliquots were regularly analyzed by HPLC and stopped at 48 h. The enzyme was filtered off using CH_2Cl_2 (3 × 5 mL), the solvent evaporated under reduce

pressure, and the reaction crude purified by *flash* chromatography on silica gel (2–10% MeOH/CH_2Cl_2), affording the corresponding optically enriched acetate (1*S*,2*R*)-**9** and the alcohol (1*R*,2*S*)-**8** (see Table 4). Alcohol: $[\alpha]_D^{20} = -3.2$ (*c* 1.0, MeOH) for 98% ee (Chiralpak IC; 60% Hexane/2-Propanol; 0.8 mL/min flow). Acetate: $[\alpha]_D^{20} = +16.7$ (*c* 1.0, MeOH) for 98% ee (Chiralpak IC; 60% Hexane/2-Propanol; 0.8 mL/min flow).

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