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Chemoenzymatic Synthesis of Optically Active *cis*- and *trans*-2-(1*H*-Imidazol-1-yl)cycloalkanamines

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The preparation of enantiopure 2-(1*H*-imidazol-1-yl)cycloalkanamines has been studied by independent chemoenzymatic approaches. We first explored a route involving the enzymatic resolution of racemic cycloalkanol analogs for the preparation of the corresponding optically active amines by diverse substitution methodologies including (a) the formation of a mesylated intermediate that could be later substituted by an amine group and (b) the combination of Mitsunobu inversion of the hydroxy group followed by a deprotection step. In order to overcome low isolated yields of the desired optically active amines, racemic-*trans*-2-(1*H*-imidazol-1-yl)cycloalkanamines were prepared, and their lipase-catalyzed enzymatic resolutions were studied. These efforts revealed that lipase from *Candida antarctica* type B was an efficient biocatalyst. A combination of both chemoenzymatic methodologies has allowed us to obtain the four different enantiopure *cis*- and *trans*-(1*H*-imidazol-1-yl)cycloalkanamine isomers.

Introduction

The 1,2-diamine subunit is present in several natural products and therapeutic agents that possess a wide variety of biological activities.[1] Additionally, this structural feature possesses multiple applications because of its presence in semiconducting materials,[2] ligands, and resolving agents used in organic synthesis.[3] Within the 1,2-diamine family, optically active cycloalkane-1,2-diamines are of remarkable importance because of their applications as catalysts and ligands in asymmetric synthesis.[4] Most work presented in the literature has focused on the production of nonracemic *trans*-cyclohexane-1,2-diamine derivatives because of their special properties as chiral molecular receptors,[5] as chiral shift reagents,[6] or because of their ability to form metal–diamine complexes.[7] However, the synthesis of *trans*-cyclopentane-1,2-diamine[8] and related *cis*-derivatives[9] remains a challenging task.

Recently, we described the chemoenzymatic synthesis of novel enantiopure salts and ionic liquids through the kinetic resolution of racemic *trans*- and *cis*-2-(1*H*-imidazol-1-yl)cycloalkanols using lipases.[10] These examples constitute an elegant approach for the synthesis of interesting chiral 1,2-amino alcohols, a group of organic compounds with important applications in asymmetric synthesis and one that is easily obtained from inexpensive cyclohexene oxide.[11] Continued interest in the production of optically active *N*,*N*-disubstituted-cycloalkane-1,2-diamines has led us to focus our attention on the synthesis of related enantiopure *cis*- and *trans*-2-(1*H*-imidazol-2-yl)cycloalkanamines containing five- and six-membered rings. Here we present the chemoenzymatic production of imidazolium cycloalkanamines and describe how different strategies have been considered for the effective asymmetric synthesis of enantiomers of both the *cis* and *trans* derivatives.

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Results and Discussion

Following a chemical method already described, racemic cyclohexanol **1a** was prepared from imidazole and cyclohexene oxide[12] and then used for the synthesis of racemic cycloalkanamine **3a** (Scheme 1). In a fashion similar to the synthesis of a family of (±)-*trans*-cyclohexandiamines,[13] (±)-*trans*-**1a** was treated with mesyl chloride and subsequently with aqueous ammonia, all in one pot, to generate racemic (±)-*trans*-**3a**. Unfortunately, we failed to observe formation of this adduct to any significant extent and instead detected only trace amounts of mesylate (±)-*trans*-**2**. These observations are perhaps best rationalized by competing formation of a labile aziridinium species leaving (±)-*trans*-**2** as a minor product. Surprisingly, significantly different results were obtained when starting from enantiopure (1*S*,2*S*)-*trans*-**1a** prepared by using previously known methodology.[10a] In this case, (1*S*,2*S*)-alcohol **1a** was treated with mesyl chloride (MsCl) in the presence of pyridine (Py) in dichloromethane (CH_2Cl_2), which afforded protected alcohol (1*S*,2*S*)-*trans*-**2** in moderate yield (58%). The protected alcohol was then treated with sodium azide (NaN_3) in *N*,*N*-dimethylformamide (DMF) to afford (1*R*,2*S*)-*cis*-azide **4**, which was subsequently hydrogenated by using pal-

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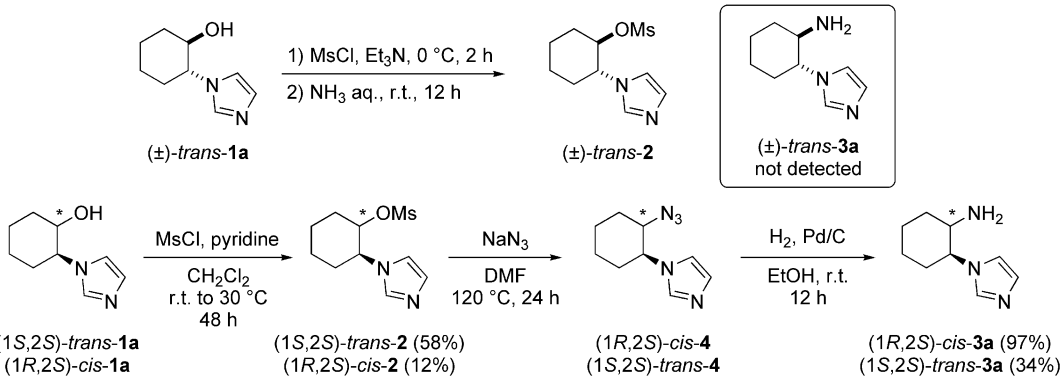
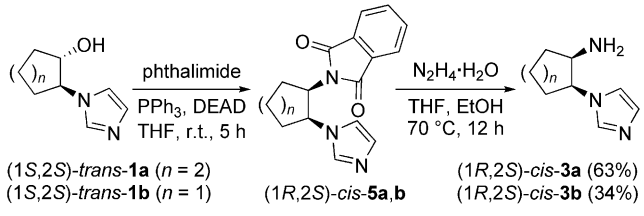


Scheme 1. Initial attempt to synthesize racemic and enantiopure amine *trans*-**3a** from mesylated derivative **2**.

ladium on activated carbon (Pd/C) in deoxygenated EtOH. In this manner, (1*R*,2*S*)-*cis*-cyclohexanamine **3a** was obtained in almost quantitative yield. Preparation of the corresponding *trans* enantiomer of **3a** by using a similar approach was marked by dramatically diminished yields; (1*S*,2*S*)-*trans*-**3a** was produced in only 4% overall yield. These results necessitated the development of a new synthetic approach to such compounds.

To better prepare these amine derivatives, we sought to exploit the synthetic usefulness of enantiopure alcohols (1*S*,2*S*)-**1a**,**b**, easily obtained by known chemoenzymatic methods.[10] Alcohols (1*S*,2*S*)-**1a**,**b** were employed as intermediates for the production of amines *cis*-(1*R*,2*S*)-**3a**,**b** and *trans*-(1*S*,2*S*)-**3a**,**b**. The corresponding *cis* derivatives were produced by using Mitsunobu chemistry to invert the stereochemistry at the hydroxy-bearing carbon atom. Enantiomerically pure (1*R*,2*S*)-*cis*-2-(1*H*-imidazol-1-yl)cycloalkanamines **3a**,**b** were obtained in moderate yields (34–63%, Scheme 2) following treatment of (1*S*,2*S*)-**1a**,**b** with phthalimide, triphenylphosphane (PPh_3), and diethyl azodicarboxylate (DEAD) in tetrahydrofuran (THF) and subsequent

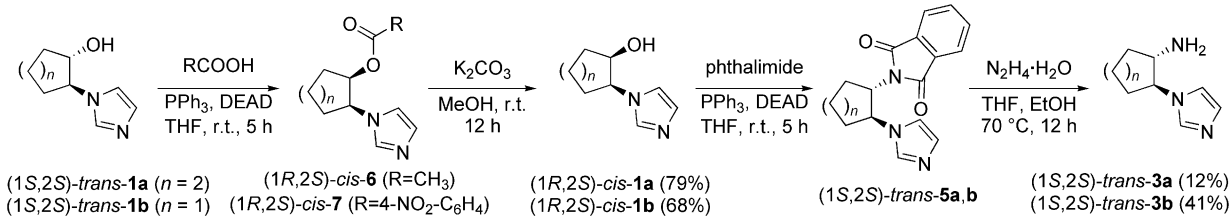


Scheme 2. Synthesis of enantiopure (1*R*,2*S*)-*cis*-cycloalkanamines **3a**,**b** by using a two–step sequence: Mitsunobu inversion and amine liberation following phthalimide cleavage.

cleavage of the phthalimide moiety with hydrazine monohydrate in refluxing THF/EtOH.

The synthesis of optically active *trans*-amines **3a**,**b** required a combination of (i) initial inversion of the hydroxy group configuration in (1*S*,2*S*)-*trans*-cycloalkanols **1a**,**b** followed by (ii) amino group installation by using Mitsunobu chemistry, and (iii) subsequent phthalimide cleavage to liberate the free amine (Scheme 3). Initial Mitsunobu reaction with either *p*-nitrobenzoic acid as the nucleophile for **1a** or acetic acid as the nucleophile for **1b** by employing conditions similar to those used in making **3a**,**b** resulted in the first of two stereochemical inversions. This produced *cis*-esters **6** and **7**, which were subsequently deprotected under alkaline conditions to afford (1*R*,2*S*)-*cis*-cycloalkanols **1a**,**b**.[10b] The *cis*-alcohols were then submitted to another Mitsunobu reaction in which each hydroxy moiety underwent replacement with the amine source phthalimide. The phthalimide moiety of each resulting intermediate (1*S*,2*S*)-*trans*-**5a**,**b** was then deprotected with hydrazine to provide the corresponding (1*S*,2*S*)-*trans*-cycloalkanamines **3a**,**b** in moderate to low yields (12–41%). It is notable that the overall yield for six-membered (1*S*,2*S*)-*cis*-**3a** was significantly lower than that for cyclopentanamine (1*S*,2*S*)-*cis*-**3b** (9 and 25% overall yield, respectively).

As noted with nucleophilic substitutions of the mesyl moiety, low reaction yields were obtained with both strategies used to prepare (1*S*,2*S*)-*trans*-cyclohexanamine **3a**. We attribute this observation to a structural feature that prevents the *cis* intermediate from undergoing nucleophilic attack with nucleophiles that differ in size; examples include ammonia, sodium azide, and phthalimide, which all have different stereoelectronic demands and capabilities. Conse-



Scheme 3. Synthesis of enantiopure (1*S*,2*S*)-*trans*-cycloalkanamines **3a**,**b**.

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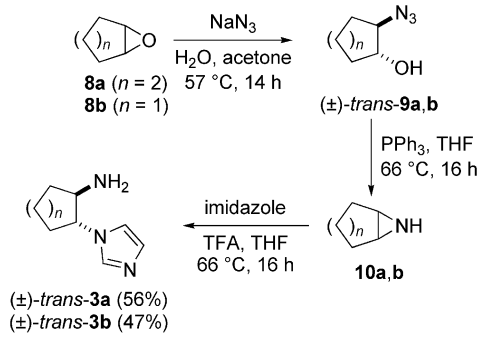
quently, we sought to overcome this limitation by preparing enantiopure *trans*-amines **3a**,**b** directly through the lipase-catalyzed kinetic resolution of their racemates. Thus, (±)-*trans*-cycloalkanamines **3a**,**b** were synthesized starting from corresponding cycloalkane oxides **8a**,**b**. Treatment of each epoxide with sodium azide (NaN_3) in a mixture of water and acetone afforded (±)-*trans*-**9a**,**b** (Scheme 4). Azido alcohols **9a**,**b** were later transformed into bicyclic aziridines **10a**,**b** under Staudinger reaction conditions with the addition of PPh_3 in THF at 66 °C. Aziridine intermediates **10a**,**b** were ultimately treated with imidazole and trifluoroacetic acid (TFA) in THF[14] to render ring-opened (±)-*trans*-cycloalkanamines **3a**,**b** in good overall yields (47–56%) over three steps.



Scheme 4. Preparation of (±)-*trans*-cycloalkanamines **3a**,**b**.

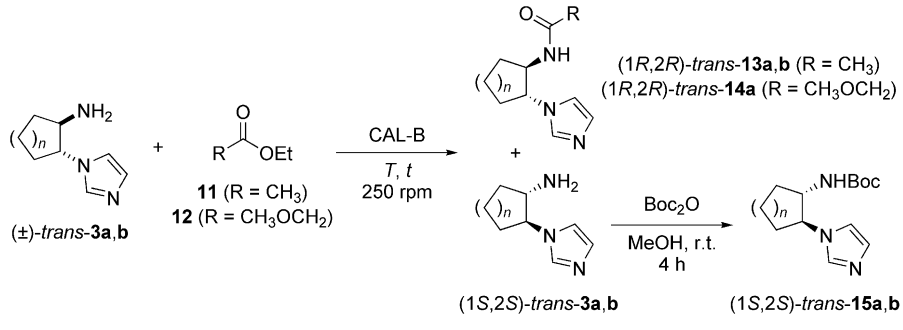
With racemic *trans*-amines **3a**,**b** in hand, we studied their amenability to enzymatic kinetic resolution by using *Candida antarctica* lipase B (CAL-B)-catalyzed acylation with ethyl acetate (**11**) or ethyl methoxyacetate (**12**); these non-activated esters are commonly used in stereoselective transformations of primary amines.[15] Esters **11** and **12** not only act as effective acyl donors but also serve as their own solvents in the biocatalyzed process.[13a,13b] As shown in Scheme 5, enzymatic kinetic resolution of *trans*-amines **3a**,**b** was attempted under different reaction conditions. Derivatization of the remaining *trans*-cycloalkanamines **3a**,**b** with di-*tert*-butyl dicarbonate (Boc_2O) was necessary to obtain carbamates **15a**,**b**. Production of **15a**,**b** allowed easy determination of their enantiomeric excess values by using chiral HPLC methods (Table 1).

Table 1. Enzymatic acylation of (±)-*trans*-cycloalkanamines **3a**,**b** after 24 h at 250 rpm. Reaction conditions: amine (0.15 M) in solvent (1.5 mL) using CAL-B/amine **3a**,**b** (1:1 in weight).

Entry	Amine	Ester	*T* [°C]	ee_S[a] [%]	ee_P[b] [%]	*c*[c] [%]	*E*[d]
1	**3a**	**11**	30	31	>99	24	>200
2	**3b**	**11**	30	36	>99	26	>200
3	**3a**	**12**	30	82	94	47	80
4	**3a**	**11**	45	92	>99	48	>200
5	**3b**	**11**	45	96	49	67	11

[a] Determined by HPLC by using carbamates **15a**,**b**. [b] Determined by HPLC. [c] $c = ee_S/(ee_S + ee_P)$. [d] $E = \ln[(1 - c) \times (1 - ee_P)]/\ln[(1 - c) \times (1 + ee_P)]$.

Initially, *Pseudomonas cepacia* lipase (PSL-C) and CAL-B were tested as possible stereoselective catalysts in the acetylation reaction with ethyl acetate (**11**) as solvent. Even though PSL-C did not display activity, CAL-B[16] showed excellent enantioselectivity, yielding enantiopure (1*R*,2*R*)-*trans*-acetamides **13a**,**b** with moderate conversions (Table 1, Entries 1 and 2). Unfortunately, longer reaction periods led to a loss of selectivity, perhaps due to partial enzyme inactivation (data not shown). To optimize the conversion values, we used a more highly activated ester, ethyl methoxyacetate (**12**), in the resolution of (±)-*trans*-**3a**. This provided a higher conversion to methoxyacetamide (1*R*,2*R*)-*trans*-**14a** but with an important decrease in selectivity (Table 1, Entry 3). Accordingly, we continued enzymatic studies by using ethyl acetate as the acyl donor instead of methoxyacetate and also raised the reaction temperature from 30 to 45 °C. These parameter alterations changed considerably between substrates. The best results were found by using six-membered (±)-*trans*-**3a**; about 50% conversion with excellent enantioselectivity was observed (Table 1, Entry 4). However, under the same experimental conditions using (±)-*trans*-**3b** as substrate, the enzyme suffered a dramatic decrease in enantioselectivity despite allowing (1*S*,2*S*)-*trans*-amine-**3b** to be isolated in 96%*ee* (Table 1, Entry 5). In short, CAL-B catalyzed the formation of both (1*S*,2*S*)-*trans*-amines **3a**,**b** with 92 and 96%*ee*, respectively, when the process was carried out at 45 °C. Additionally, (1*R*,2*R*)-*trans*-acetamide **13a** was isolated in enantiopure form at both 30 and 45 °C, and enantiopure five-membered (1*R*,2*R*)-*trans*-acetamide **13b** was obtained at 45 °C.



Scheme 5. Enzymatic kinetic resolution of racemic *trans*-cycloalkanamines **3a**,**b**.

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Conclusions

Complementary synthetic approaches have been developed for the production of enantiopure 2-(1*H*-imidazol-1-yl)cycloalkanamines from inexpensive commercially available starting materials. Lipase-catalyzed kinetic resolutions of these amines or the corresponding cycloalkanols have been shown to be remarkably important for the production of optically active imidazole derivatives. Meanwhile, access to (1*R*,2*S*)-*cis*-amines **3a**,**b** has been achieved in a straightforward manner from racemic alcohols **1a**,**b**, and CAL-B has proven to be an excellent biocatalyst in the stereoselective production of the (1*S*,2*S*)-*trans*-amines **3a**,**b**.

Experimental Section

General Methods: *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 PS/C I immobilized on ceramic (1061 U/g). All other reagents were purchased from different commercial sources (Acros, Fluka, and Sigma–Aldrich) and used without further purification. Solvents were distilled from an adequate desiccant under an atmosphere of nitrogen. Flash chromatography was performed by using silica gel 60 (230–240 mesh). Melting points were taken on samples in open capillary tubes. IR spectra were recorded b using NaCl plates or KBr pellets with a Perkin–Elmer 1720-X F7. ^{1}H NMR, ^{13}C NMR, DEPT, and ^{1}H–^{13}C heteronuclear experiments were obtained using AC-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) Bruker spectrometers. The chemical shifts are expressed in parts per million (ppm) using deuterated solvents as indicated for each compound. APCI+ and ESI+ using an HP1100 chromatograph mass detector were used to record mass spectra. High-resolution mass spectrometry was carried out by ESI+ with a Bruker MicroTofQ spectrometer or by EI+ with a VG autospec spectrometer. Measurement of the optical rotation was done with a Perkin–Elmer 241 polarimeter. High-performance liquid chromatography (HPLC) analyses were carried out with a Hewlett Packard 1100 chromatograph UV detector at 210 and 215 nm by using a Daicel CHIRALCEL OD, CHIRALCEL OD-H, or CHIRALPAK AS column (25 cm × 4.6 mm i.d.), varying the conditions depending on the specific substrate.

Experimental Procedure for Mesylation Reaction of (1*S*,2*S*)-*trans*-Cyclohexanol 1a: To a solution of (1*S*,2*S*)-*trans*-**1a** (100 mg, 0.6 mmol) in dry CH_2Cl_2 (7.5 mL) under an inert atmosphere was added pyridine (97 μL, 1.2 mmol). This mixture was kept at 0 °C and mesyl chloride (87 μL, 1.2 mmol) was added dropwise. During the course of reaction, up to 6 equiv. of the chloride was added (3 × 87 μL, 3.6 mmol). The solution was stirred at room temperature for 48 h until complete consumption of the starting material, as detected by TLC (10% MeOH/CH_2Cl_2). Product (1*S*,2*S*)-**2** (85 mg, 58% isolated yield) was obtained as a white solid. R_f (10% MeOH/CH_2Cl_2) = 0.55. M.p. 99–102 °C. IR (KBr): $\tilde{\nu}$ = 3428, 2943, 2868, 1646, 1501, 1347, 1236, 1174, 1085, 946, 884, 833, 749 cm^{-1}. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.36–1.51 (m, 2 H, 4-H), 1.60–1.73 (m, 1 H, 5-H), 1.80–1.90 (m, 3 H, 5-H, 2 6-H), 2.33 (s, 3 H, 14-H), 3.95–4.04 (m, 1 H, 1-H), 4.47–4.55 (m, 1 H, 2-H), 7.06 (d, J = 12.5 Hz, 2 H, 10-H, 11-H), 7.63 (s, 1 H, 8-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 23.7 (C-5), 24.2 (C-4), 32.0 (C-3), 33.2 (C-6), 36.7 (C-14), 59.6 (C-2), 83.7 (C-1), 116.8 (C-11), 129.4 (C-10), 136.9 (C_8) ppm. HRMS (ESI+): calcd. for [M + H]$^+$ 245.0954; found 245.0962.

Procedure for Synthesis of (1*R*,2*S*)-*cis*-Cycloalkanamine 3a by Formation of Azide Intermediate (1*R*,2*S*)-*cis*-4: To a solution of mesylated compound (1*S*,2*S*)-*trans*-**2** (30 mg, 0.12 mmol) in DMF (1.0 mL) was added sodium azide (24 mg, 0.37 mmol) under an inert atmosphere. The mixture was heated to 120 °C for 24 h. After this time no more starting material was detected by TLC (10% MeOH/CH_2Cl_2), and the solvent was evaporated under reduced pressure. The solid thus obtained was washed with Et_2O (5 × 3 mL), and the organic fractions were combined and dried with Na_2SO_4. Solids were filtered, and the solvent was evaporated under reduced pressure. The crude product was employed without further purification in the next step. Hence, this solid was treated with activated Pd/C (15 mg, 0.01 mmol) in a round-bottomed flask, which was closed hermetically with a septum and put under vacuum. To this mixture was added deoxygenated EtOH (1.0 mL). The reaction mixture was then blanketed with hydrogen by application of a hydrogen-filled balloon. The suspension was stirred vigorously for 12 h, then filtered over Celite, and the solvent was evaporated under reduced pressure. The crude material obtained was purified by flash chromatography (20% MeOH/CH_2Cl_2) to afford (1*R*,2*S*)-*cis*-**3a** as a yellowish oil (20 mg, 97% isolated yield).

Synthesis of (1*S*,2*S*)-*cis*-Cycloalkanamines-3a,b as a Representative Procedure for the Mitsunobu Reaction and Subsequent Deprotection of Alcohols (1*S*,2*S*)-*trans*-1a,b: To a solution of (1*S*,2*S*)-*trans*-**1a**,**b** (3.01 mmol) in dry THF (19.8 mL) was successively added PPh_3 (0.95 g, 3.61 mmol) and phthalimide (443 mg, 3.01 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DEAD (662 μL, 3.61 mmol) was added carefully dropwise. The mixture was warmed to room temperature and stirred for 4 h. After this time, no starting material was apparent as assessed by TLC (90% MeOH/CH_2Cl_2 for **1a**; 20% MeOH/CH_2Cl_2 for **1b**). The organic solvent was evaporated under reduced pressure, and crude product **5a**,**b** was used for the second step without further purification. Thus, to a solution of crude **5a** or **5b** (3.01 mmol) in THF (43.1 mL) and EtOH (7.1 mL) was added hydrazine monohydrate (703 μL, 22.6 mmol), and the mixture was stirred at 70 °C overnight. The white suspension formed during this time was filtered off and washed with THF, and the organic solvent was evaporated under reduce pressure, rendering a crude material that was purified by flash chromatography (10–50% MeOH/CH_2Cl_2) to afford (1*R*,2*S*)-*cis*-**3a** (313 mg, 63%, isolated yield) and (1*R*,2*S*)-*cis*-**3b** (155 mg, 34%, isolated yield) as yellowish oils. Data for (1*R*,2*S*)-*cis*-**3a**: R_f (20% MeOH/EtOAc) = 0.17. IR (NaCl): $\tilde{\nu}$ = 3374, 2939, 2359, 2166, 1644, 1500, 1452, 1296, 1112, 1086, 1034, 919, 820, 748 cm^{-1}. ^{1}H NMR (300.13 MHz, MeOD): δ = 1.50–1.68 (m, 3 H, 2 4-H, 5-H), 1.79–1.97 (m, 4 H, 3-H, 5-H, 2 6-H), 2.16–2.30 (m, 1 H, 3-H), 3.33 (q, J = 3.5 Hz, 1 H, 1-H), 4.32 (q, J = 3.6 Hz, 1 H, 2-H), 7.01 (s, 1 H, 11-H), 7.28 (s, 1 H, 10-H), 7.79 (s, 1 H, 8-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 20.8 (C-5), 25.5 (C-4), 27.1 (C-3), 30.1 (C-6), 53.5 (C-1), 58.5 (C-2), 120.3 (C-11), 129.7 (C-10), 137.9 (C-8) ppm. HRMS (ESI+): calcd. for [M + H]$^+$ 152.1182; found 152.1179. $[\alpha]_D^{20}$ = –59.9 (c = 1.0, MeOH) for the (1*R*,2*S*)-enantiomer with >99%*ee* by inversion of configuration. Data for (1*R*,2*S*)-*cis*-**3b**: R_f (20% MeOH/EtOAc) = 0.06. IR (NaCl): $\tilde{\nu}$ = 3362, 3106, 2966, 2350, 2170, 1990, 1644, 1567, 1504, 1236, 1111, 1086, 1018, 913, 823, 746 cm^{-1}. ^{1}H NMR (300.13 MHz, MeOD): δ = 1.61–1.73 (m, 1 H, 4-H), 1–77–1.88 (m, 1 H, 4-H), 2.01–2.38 (m, 4 H, 2 3-H, 2 5-H), 3.57 (q, J = 6.3 Hz, 1 H, 1-H), 4.64 (q, J = 6.6 Hz, 1 H, 2-H), 7.08 (s, 1 H, 10-H), 7.26 (s, 1 H, 9-H), 7.78 (s, 1 H, 7-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 21.9 (C-4), 24.6 (C-3), 32.2 (C-5), 56.5 (C-1), 62.7 (C-2), 120.8 (C-

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10), 129.8 (C-9), 138.8 (C-7) ppm. HRMS (ESI+): calcd. for $[M + H]^+$ 166.1339; found 166.1343. $[a]_D^{20}$ = –26.1 (*c* = 1.5, MeOH) for the (1*R*,2*S*)-enantiomer with >99% *ee* by inversion of configuration.

Procedure for the Preparation of (1*R*,2*S*)-*cis*-Cyclopentanol 1b by Mitsunobu Reaction and Subsequent Deprotection: To a solution of alcohol (1*S*,2*S*)-*trans*-**1b** (200 mg, 1.3 mmol) in dry THF (18 mL) was successively added acetic acid (141 μL, 2.6 mmol) and PPh_3 (682 mg, 2.6 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DEAD (477 μL, 2.6 mmol) was added slowly. The mixture was left to warm to room temperature and stirred for 2 h. After this time, no starting material could be observed by TLC analysis (90% CH_2Cl_2/MeOH). The organic solvent was evaporated under reduced pressure, and without further purification the crude reaction was used for the second step. The crude reaction mixture was dissolved in MeOH (2.2 mL), and to the solution was added K_2CO_3 (359 mg, 2.6 mmol) and H_2O (2.2 mL) to favor the solubility of the mixture. The reaction was stirred overnight, and after this time, the solvent was evaporated, and the resulting mixture was resuspended in H_2O (10 mL) and extracted with EtOAc (4 × 10 mL). The organic phases were combined and dried with Na_2SO_4. The solids were filtered and EtOAc was then evaporated, leaving a crude material that was purified by flash chromatography (2–10% MeOH/CH_2Cl_2) to render (1*R*,2*S*)-*cis*-**1b** as a white solid (136 mg, 68% isolated yield). Experimental data already published.[10b]

Procedure for the Synthesis of (1*S*,2*S*)-*trans*-Cyclopentanamine-3b: To a solution of alcohol (1*R*,2*S*)-*cis*-**1b** (135 mg, 0.9 mmol) in dry THF (6.0 mL) was added PPh_3 (279 mg, 1.1 mmol) and phthalimide (132 mg, 0.9 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DEAD (0.2 mL, 1.1 mmol) was added carefully. The mixture was left to warm to room temperature and stirred for 5 h. After this time, no starting material was apparent by TLC analysis (50% MeOH/AcOEt). The organic solvent was evaporated under reduced pressure, and the crude material was used for the second step without further purification. To the resulting mixture dissolved in THF (13 mL) and EtOH (2 mL) was added hydrazine monohydrate (210 μL, 6.8 mmol), and the clear solution was stirred at 70 °C overnight. The white suspension formed during this time was filtered and washed with THF (3 × 10 mL). The organic solvent was evaporated under reduced pressure to afford a crude material that was purified by flash chromatography (10–50% MeOH/CH_2Cl_2), rendering (1*S*,2*S*)-*trans*-**3b** as a yellowish oil (55 mg, 41% isolated yield). R_f (20% MeOH/CH_2Cl_2) = 0.07. IR (NaCl): $\tilde{\nu}$ = 3407, 2964, 1995, 1641, 1502, 1414, 1385, 1329, 1291, 1236, 1111, 1087, 921 cm^{-1}. ^1H NMR (300.13 MHz, MeOD): δ = 1.50–1.63 (m, 1 H, 4-H), 1.84–2.06 (m, 3 H, 2 5-H, 4-H), 2.11–2.22 (m, 1 H, 3-H), 2.25–2.36 (m, 1 H, 3-H), 3.38 (q, *J* = 8.4 Hz, 1 H, 1-H), 4.18 (q, *J* = 8.3 Hz, 1 H, 2-H), 7.05 (s, 1 H, 9-H), 7.26 (s, 1 H, 10-H), 7.78 (s, 1 H, 7-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 21.9 (C-4), 33.0 (C-3), 34.0 (C-5), 60.7 (C-1), 67.9 (C-2), 119.1 (C-10), 130.0 (C-9), 138.2 (C-7) ppm. HRMS (ESI+): calcd. for $[M + H]^+$ 152.1182; found 152.1186. $[a]_D^{20}$ = +51.8 (*c* = 1, MeOH) for the (1*S*,2*S*)-enantiomer with >99% *ee* by inversion of configuration.

Procedure for the Preparation of (1*R*,2*S*)-*cis*-Cyclohexanol 1a by Mitsunobu Reaction and Subsequent Deprotection: To a solution of alcohol (1*S*,2*S*)-*trans*-**1a** (500 mg, 3.0 mmol) in dry THF (41 mL) was added PPh_3 (1.57 g, 6.0 mmol) and *p*-nitrobenzoic acid (1.00 mg, 6.0 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DEAD (1.1 mL, 6.0 mmol) was carefully added dropwise. The mixture was allowed to warm to room temperature. and stirred for 6 h. After this time, no starting material was detected by TLC analysis (10% MeOH/CH_2Cl_2). The organic solvent was evaporated under reduced pressure, and the crude material was used without further purification for the second step. The crude material was dissolved in MeOH (5 mL), and to the solution was added K_2CO_3 (829.3 mg, 6.0 mmol) and H_2O (5 mL). The reaction was stirred overnight, and after this time the solvent was evaporated and the resulting mixture was resuspended in H_2O (10 mL) and extracted with EtOAc (4 × 10 mL). The organic layers were combined and dried with Na_2SO_4. Solids were then filtered and EtOAc was evaporated, rendering a crude material that was purified by flash chromatography (2 to 10% MeOH/CH_2Cl_2) to afford (1*R*,2*S*)-*cis*-**1a** as a white solid (395 mg, 79% isolated yield). Experimental data have been already described.[10b]

Procedure for the Synthesis of (1*S*,2*S*)-*trans*-Cyclohexanamine 3a: To a solution of (1*R*,2*S*)-*cis*-**1a** (200 mg, 1.2 mmol) in dry THF (6 mL) was added PPh_3 (378 mg, 1.4 mmol) and phthalimide (177 mg, 1.2 mmol) under a nitrogen atmosphere. The resulting solution was cooled to 0 °C and DEAD (257 μL, 1.4 mmol) dissolved in dry THF (1.9 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. After this time no starting material could be detected by TLC analysis (10% MeOH/CH_2Cl_2). The organic solvent was evaporated under reduced pressure, and the crude reaction was used for the second step without further purification. This mixture was dissolved in THF (17.2 mL) and EtOH (2.8 mL), and to this mixture was then added hydrazine monohydrate (280 μL, 9.0 mmol). The clear solution was stirred at 70 °C for 12 h. The white suspension formed during this time was filtered off and washed with THF (3 × 10 mL), and the organic solvent was evaporated under reduced pressure to afford a crude material that was purified by flash chromatography (10–50% MeOH/CH_2Cl_2). Product (1*S*,2*S*)-*trans*-**3a** was obtained as a yellowish oil (24 mg, 12% isolated yield). R_f (20% MeOH/CH_2Cl_2) = 0.08. IR (NaCl): $\tilde{\nu}$ = 3282, 2937, 2861, 2424, 1995, 1660, 1556, 1494, 1450, 1375, 1312, 1236, 1162, 1111, 1085, 1039, 993, 918, 750 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.31–1.41 (m, 1 H, 4-H), 1.46–1.54 (m, 2 H, 4-H, 5-H), 1.82–1.92 (m, 3 H, 3-H, 5-H, 6-H), 2.01–2.10 (m, 2 H, 3-H, 6-H), 2.92–3.01 (dt, *J* = 4.0 Hz, 1 H, 1-H), 3.73–3.82 (m, 1 H, 2-H), 7.06 (s, 1 H, 11-H), 7.26 (s, 1 H, 10-H), 7.77 (s, 1 H, 8-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 26.7 (C-4), 27.4 (C-5), 35.2 (C-3), 35.9 (C-6), 56.8 (C-1), 66.4 (C-2), 119.5 (C-11), 130.4 (C-10), 138.8 (C-8) ppm. HRMS (ESI+): calcd. for $[M + H]^+$ 166.1339; found 166.1345. $[a]_D^{20}$ = +16.0 (*c* = 0.8, MeOH) for the (1*S*,2*S*)-enantiomer with >99% *ee* by inversion of configuration.

Procedure for the Synthesis of Racemic *trans*-Cycloalkanamines 3a,b through an Aziridine Intermediate: To a solution of **8a**,**b** (11.9 mmol) in acetone (6.5 mL) and water (6.5 mL) was added sodium azide (1.9 mg, 29.8 mmol). The mixture was heated to reflux (57 °C) for 14 h, and the course of reaction was followed by TLC (10% MeOH/CH_2Cl_2). After 14 h the acetone was evaporated under reduced pressure, and the remaining aqueous mixture was extracted first with Et_2O (3 × 5 mL) and then with CH_2Cl_2 (3 × 5 mL). The organic layers were collected, washed with brine (2 × 5 mL), and evaporated under reduced pressure. The resulting crude material was dissolved in THF (6.1 mL) and PPh_3 (3.15 g, 11.9 mmol) was added. The solution was heated to reflux under an inert atmosphere for 16 h. After this time, the reaction mixture was cooled to room temperature, and to it was added trifluoroacetic acid (44.2 mL, 0.6 mmol) followed by imidazole (1.6 g, 23.8 mmol). This new reaction mixture was again heated to reflux for 16 h. Afterwards, the reaction was cooled to room temperature, the solvent was evaporated under reduced pressure, and the crude reaction

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products were purified by flash chromatography (40–80% MeOH/EtOAc). Chromatography afforded racemic *trans*-cycloalkanamines **3a**,**b** (1.10 g, 56% isolated yield for **3a**; 846 mg, 47% isolated yield for **3b**) as yellowish oils.

Procedure for the Chemical Synthesis of Racemic *trans*-Acetamides 13a,b and *trans*-Methoxyacetamides 14a: To a solution of *trans*-cycloalkanamine **3a**,**b** (0.19 mmol) in CH_2Cl_2 (280 μL) was added pyridine (38 μL, 0.48 mmol) under an inert atmosphere. The mixture was cooled to 0 °C and the respective chloride (acetyl chloride: 56 μL, 0.79 mmol; methoxyacetyl chloride: 52 μL, 0.73 mmol) was added carefully. Reactions were stirred at room temperature for 6 h at which point TLC analysis (60% MeOH/EtOAc) revealed the absence of starting materials. After this time, the solvent was evaporated under reduced pressure, and the crude reaction mixture was suspended in water (2 mL). Aqueous solutions were slightly alkalinized with 1 M NaOH and extracted with CH_2Cl_2 (3 × 3 mL). The organic fractions were combined, and the solvents were evaporated under reduced pressure. Flash chromatography (20–40% MeOH/EtOAc) afforded (±)-*trans*-**13a** (37 mg, 95% isolated yield), *trans*-**13b** (33 mg, 89% isolated yield), (±)-*trans*-**14a** (37 mg, 83% isolated yield), and (±)-*trans*-**14b** (23 mg, 55% isolated yield).

(±)-*N*-[*trans*-2-(1*H*-Imidazol-2-yl)cyclohexyl]acetamide (13a): Pale-yellow oil. R_f (60% MeOH/EtOAc) = 0.50. IR (NaCl): $\tilde{\nu}$ = 3405, 3282, 3114, 2900, 2861, 2374, 1317, 1640, 1562, 1505, 1454, 1376, 1279, 1112, 1041, 918, 734 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.47–1.56 (m, 3 H, 4-H, 2 5-H), 1.78 (s, 3 H, 13-H), 1.86–2.03 (m, 4 H, 3-H, 4-H, 2 6-H), 2.12–2.15 (m, 1 H, 3-H), 3.97–4.13 (m, 2 H, 1-H, 2-H), 6.96 (s, 1 H, 11-H), 7.20 (s, 1 H, 10-H), 7.73 (s, 1 H, 8-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 22.9 (C-13), 26.3 (C-5), 26.6 (C-4), 34.1 (C-3), 35.1 (C-6), 54.2 (C-1), 64.2 (C-2), 119.6 (C-11), 129.1 (C-10), 133.1 (C-8), 172.8 (C-12) ppm. HRMS (ESI+): calcd. for $[M + H]^+$ 208.1444; found 208.1444. HPLC (Chiralcel OD-H column, hexane/2-PrOH = 90:10, 0.8 mL/min, 30 °C): t_R = 16.3, 21.7 min.

(±)-*N*-[*trans*-2-(1*H*-Imidazol-2-yl)cyclopentyl]acetamide (13b): White semisolid. R_f (60% MeOH/EtOAc) = 0.45. IR (NaCl): $\tilde{\nu}$ = 3399, 3273, 3115, 2968, 2362, 1643, 1563, 1504, 1377, 1313, 1234, 1085, 1038, 918, 823, 736 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.62–1.75 (m, 1 H, 4-H), 1.91–2.07 (m, 3 H, 3-H, 4-H, 5-H), 1.93 (s, 3 H, 12-H), 2.15–2.26 (m, 1 H, 5-H), 2.29–2.40 (m, 1 H, 3-H) 4.36 (m, 2 H, 1-H, 2-H), 7.01 (s, 1 H, 10-H), 7.27 (s, 1 H, 9-H), 7.79 (s, 1 H, 7-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 22.1 (C-4), 23.1 (C-12), 31.4 (C-3), 32.4 (C-5), 58.1 (C-1), 84.7 (C-2), 119.5 (C-10), 129.6 (C-9), 138.2 (C-7), 173.6 (C-11) ppm. HRMS (ESI+): calcd. for $[M + H + Na]^+$ 216.1107; found 216.1107. HPLC (Chiralcel OD-H column, hexane/EtOH = 97:3, 1.0 mL/min, 30 °C): t_R = 37.0, 42.0 min.

(±)-*N*-[*trans*-2-(1*H*-Imidazol-2-yl)cyclohexyl]methoxyacetamide (14a): White semisolid. R_f (60% MeOH/EtOAc) = 0.43. IR (NaCl): $\tilde{\nu}$ = 3430, 3310, 2937, 2862, 1655, 1544, 1504, 1450, 1235, 1198, 1113, 921, 733 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.38–1.52 (m, 3 H, 2 4-H, 5-H), 1.71–1.91 (m, 3 H, 5-H, 2 6-H), 2.08–2.16 (m, 2 H, 2 3-H), 3.21 (s, 3 H, 15-H), 3.59 (d, J = 15.4 Hz, 1 H, 13-H), 3.76 (d, J = 15.1 Hz, 1 H, 13-H), 3.85–3.93 (m, 1 H, 1-H), 4.05–4.17 (m, 1 H, 2-H), 6.49 (d, J = 9.1 Hz, 1 H, NH), 6.99 (d, J = 10.8 Hz, 2 H, 10-H, 11-H), 7.47 (s, 1 H, 8-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 26.4 (C-4), 26.6 (C-5), 33.9 (C-3), 35.0 (C-6), 54.0 (C-1), 59.9 (C-2), 61.8 (C-15), 72.9 (C-13), 119.6 (C-11), 129.1 (C-10), 138.3 (C-8), 172.4 (C-12) ppm. MS (ESI+): m/z (%) = 260.1 $[M + Na]^+$ (100). HPLC (Chiralcel OD column, hexane/2-PrOH = 90:10, 0.8 mL/min, 20 °C): t_R = 28.2, 33.7min.

Procedure for the Preparation of Racemic Carbamates (±)-*trans*-15a,b: To a solution of amine (±)-*trans*-**3a**,**b** (0.19 mmol) dissolved in methanol (1.9 mL) was added Boc_2O (50 mg, 0.22 mmol) under an inert atmosphere, and the mixture was stirred at room temperature for 4 h. After this time, no evidence of starting material was detected by TLC (60% MeOH/EtOAc). The solvent was evaporated under reduced pressure, and the crude material was purified by flash chromatography (20% MeOH/EtOAc). Chromatography afforded (±)-*trans*-**15a** (51 mg, 98% isolated yield) as a white solid and (±)-*trans*-**15b** (47 mg, 98% isolated yield) as a colorless oil.

***tert*-Butyl (±)-*trans*-2-(1*H*-Imidazol-2-yl)cyclohexyl Carbamate (15a):** R_f (60% MeOH/EtOAc) = 0.65. M.p. 161–162 °C. IR (KBr): $\tilde{\nu}$ = 3404, 2938, 1695, 1504, 1421, 1366, 1316, 1237, 1171, 1136, 1048, 918 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, 15-H), 1.41–1.54 (m, 2 H, 2 5-H), 1.89–2.13 (m, 5 H, 2 3-H, 4-H, 2 6-H), 3.65–3.70 (m, 1 H, 1-H), 3.85–3.93 (m, 1 H, 2-H), 6.95 (s, 1 H, 11-H), 7.17 (s, 1 H, 10-H), 7.65 (s, 1 H, 8-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 26.5 (C-4), 26.7 (C-5), 29.1 (3C-15), 34.6 (C-3), 34.9 (C-6), 55.6 (C-1), 62.9 (C-2), 80.4 (C-14), 119.7 (C-11), 129.0 (C-10), 138.4 (C-8), 153.0 (C-12) ppm. HRMS (ESI+): calcd. for $[M + H]^+$ 266.1863; found 266.1861. HPLC (Chiralpak AS column, hexane/2-PrOH = 97:3, 0.8 mL/min, 40 °C): t_R = 28.0, 31.2 min.

***tert*-Butyl (±)-*trans*-2-(1*H*-Imidazol-2-yl)cyclopentyl Carbamate (15b):** R_f (60% MeOH/EtOAc) = 0.60. IR (NaCl): $\tilde{\nu}$ = 3425, 3055, 2978, 1699, 1501, 1418, 1367, 1266, 1169, 1079, 737 cm^{-1}. ^1H NMR (300.13 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, 14-H), 1.58–1.70 (m, 1 H, 4-H), 1.85–1.98 (m, 2 H, 4-H, 5-H), 2.00–2.08 (m, 1 H, 5-H), 2.12–2.20 (m, 1 H, 3-H), 2.23–2.35 (m, 1 H, 3-H), 4.07 (q, J = 6.3 Hz, 1 H, 1-H), 4.30–4.36 (m, 1 H, 2-H), 7.01 (s, 1 H, 10-H), 7.25 (s, 1 H, 9-H), 7.73 (s, 1 H, 7-H) ppm. ^{13}C NMR (75.5 MHz, MeOD): δ = 21.7 (C-4), 29.2 (3 C-14), 31.4 (C-3), 31.9 (C-5), 59.4 (C-1), 64.6 (C-2), 119.4 (C-10), 129.6 (C-9), 138.1 (C-7), 158.3 (C-11) ppm. HRMS (ESI+): calcd. for $[M + H]^+$ 252.1707; found 252.11708. HPLC (Chiralcel OD column, hexane/2-PrOH = 95:5, 0.8 mL/min, 20 °C): t_R = 24.3, 27.8 min.

Typical Procedure for the Enzymatic Kinetic Resolution of Racemic Amines *trans*-3a,b by Employing an Acylation Process: To a suspension of (±)-*trans*-**3a**,**b** and the enzyme (CAL-B or PSL-C I, 1:1 w/w ratio relative to substrate) was added the corresponding acylation agent [1.2 mL; ethyl acetate (**11**) or ethyl methoxyacetate (**12**)] under a nitrogen atmosphere. The resulting suspension was placed on an orbital shaker (250 rpm) for 24 h at either 30 or 45 °C. The enzyme was then filtered out of the reaction and washed with THF (3 × 5 mL). All organic solvents were then evaporated under reduced pressure, and the crude mixture of products was purified by flash chromatography (40–80%, MeOH, EtOAc). Acylated product **13a**,**b** or **14a** was subjected to HPLC analysis, and remaining amines were converted into carbamates **15a**,**b** to determine the enantiomeric excess values.

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