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Lipase-catalyzed desymmetrization of *meso*-1,2-diaryl-1,2-diaminoethanes

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Abstract—The synthesis and enzyme-catalyzed desymmetrization of *meso*-1,2-diaryl-1,2-diaminoethanes have been investigated. A family of aromatic *meso*-1,2-diamines, containing different substitution patterns in the aromatic ring, was firstly prepared and then enantioselectively desymmetrized using lipases as biocatalysts. Selective alkoxycarbonylation of one of the amino groups was achieved using allyl carbonates, isolating the corresponding allyl monocarbamates with moderate to high enantiomeric excess at 45 ºC. *Candida antarctica* lipase types A (CAL-A) and B (CAL-B) displayed the best activities and stereopreferences, a dramatic influence being observed depending on the diamine structure. Non substituted and *para*-substituted aryldiamines led to the formation of allyl carbamates with good enantiomeric excess, using CAL-A for the less hindered substrates and CAL-B for those more hindered. On the other hand *meta*- and *ortho*-derivatives afforded low or negligible conversions and selectivities, respectively.

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1. Introduction

Enantioselective desymmetrizations are highly attractive tasks in organic synthesis, consisting in the modification of one or more elements of symmetry in a target molecule. Thus, starting from a symmetric substrate such as a *meso*- or a prochiral compound, the isolation of a single enantiomer is possible in theoretically 100% yield. These processes clearly differ from dynamic kinetic resolutions or deracemization processes, where racemates are used as starting materials, but also in these cases more than one step is required for the transformation into pure enantiomers.[1]

The development of asymmetric enzymatic desymmetrization reactions has gained particular attention in recent years,[2] hydrolase-catalyzed processes using lipases or amidases being some of the most recent examples for this type of transformation.[3] Particularly, and due to the importance of the diamine scaffolds in synthetic, medicinal and coordination chemistry,[4] the desymmetrization of *meso*-diamines has recently attracted the attention of different research groups by means of non enzymatic or biocatalyzed methods. In this context, De and Seidel reported the first catalytic non enzymatic benzoylation of 1,2-diaryl-1,2-ethanediamines using the combination of an achiral nucleophilic catalyst and a chiral anion receptor,[5] while Berkessel and co-workers described the stereoselective alkoxycarbonylation of *cis*-1,2-diaminocyclohexane with diallyl carbonate and *Candida antarctica* lipase B (CAL-B) as biocatalyst in toluene.[6] In both cases excellent enantiomeric excess and high yields were achieved.

Based on the our experience in the field of enzyme-catalyzed desymmetrization of prochiral diamines,[7] we wish to report our latest results in the desymmetrization of 1,2-diaryl-1,2-ethanediamines using lipases as biocatalysts, where different variables affecting the enzyme catalytic action have been optimized, such as the source and amount of catalyst, temperature, resolving agent and the reaction time.

2. Results and discussion

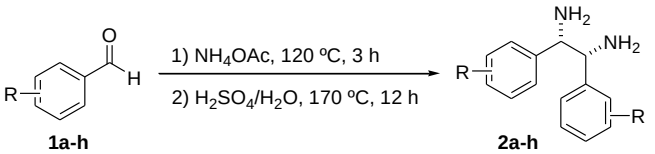
2.1. Chemical synthesis of meso-1,2-diaryl-1,2-ethanediamines.

The chemical synthesis of 1,2-diaryl-1,2-ethanediamines **2a**-**h** was performed in moderate to high yield (40-96%), reacting the corresponding benzaldehydes **1a**-**h** with a 3-fold molar excess of ammonium acetate (NH_4OAc) at 120 ºC, followed by acidic hydrolysis at 170 ºC (Table 1).[8] These eight diamines differ in the substitution pattern, bearing halogen atoms such as fluorine, chlorine or bromine, and also alkyl rests such as methyl, possessing some of them different rests in *ortho*, *meta* or *para*-positions of the aromatic ring.

2.2. Enzymatic desymmetrizatrion of meso-diamines

Once synthesized, the enantioselective enzymatic desymmetrization of *meso*-1,2-diamines **2a-h** was studied in several lipase-catalyzed alkoxycarbonylation reactions. For simplicity, the diamine **2a** was selected as model substrate because of its commercial availability. A broad panel of enzymes was used in this study including *Candida antarctica* lipase type A (CAL-A), *Candida antarctica* lipase type B (CAL-B), *Candida rugosa* lipase (CRL), lipase from porcine pancreas (PPL), *Pseudomonas cepacia* immobilized in diatomite (PSL-IM) or in a ceramic support (PSL-C I), lipase AK from *Pseudomonas fluorescens* and *Rhizomucor miehei* lipase (RML). Standard conditions previously optimized for prochiral diamines[7a] were used in an initial activity test, trying to find a suitable enzyme for the selective modification of one of the amino groups present in the diamine. Thus, 1,4-dioxane as organic solvent and a total concentration of 100 mM for **2a** were used in combination with one equivalent of commercially available diallyl carbonate (**3a**). Unfortunately none of the selected enzymes displayed activity at 30 ºC (Scheme 1).

Table 1. Chemical synthesis of *meso*-1,2-diamines **2a**-**h** from the corresponding benzaldehydes **1a**-**h**.

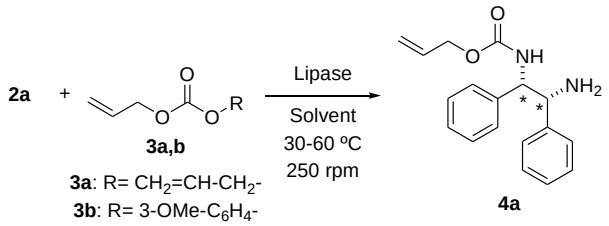


Entry	Aldehyde	R	Diamine **2a-h** (%)[a]
1	**1a**	H	71[b]
2	**1b**	4-F	90
5	**1c**	4-Cl	98
4	**1d**	4-Br	40
3	**1e**	4-Me	70
6	**1f**	3-Me	78
7	**1g**	3-Br	96
8	**1h**	2-Br	60

[a] Isolated yields after chromatography on silica gel.

[b] Diamine **2a** is commercially available but the chemical synthesis was also attempted from benzaldehyde (**1a**).

In order to increase the reactivity of the diamine **2a**, a more reactive carbonate such as allyl 3-methoxyphenyl carbonate (**3b**) was considered, which has allowed the efficient kinetic resolution of different secondary cyclic amines.[9] Using 2.5 equivalents of **3b**, the behaviour of different hydrolases was studied, finding after 38 h and 30 ºC, only a slight conversion (13% yield) with CAL-A, obtaining the monocarbamate **4a** with modest stereoselectivity (52%). It must be mentioned that the formation of the dicarbamate product was not observed. This fact is in agreement with the data obtained from the chemical reaction developed for the formation of racemic carbamates **4a**-**h** with allyl chloroformate in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), highlighting the difficulty in the modification of the amino groups of the diamines **2a-h**, probably because a stabilization of the monocarbamate by hydrogen bond interactions between the unreacted amino group and the carbonyl rest of the carbamate functionality (for more details see the Experimental section).

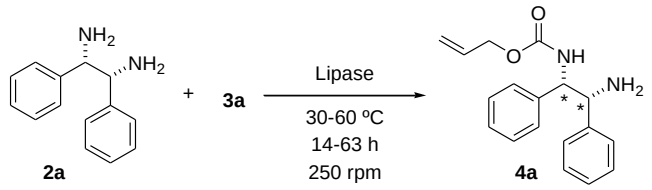


Scheme 1. Enzymatic desymmetrization of *meso*-diamine **2a** using different allyl carbonates (**3a**,**b**) in organic medium.

Trying to increase the diamine reactivity, the carbonate was employed as both alkoxycarbonylating agent and solvent, studying first the reactivity of the commercially available diallyl carbonate (**3a**). Only CAL-A displayed significant activity towards the formation of the monocarbamate **4a** (56% conversion after 62 h at 30 ºC), acting also with a good stereoselectivity (86% *ee*). On the other hand, slight activities were observed with CAL-B and CRL (<3% conversion), and finally with RML (5% conversion and 82% *ee*). Considering as a good starting point the

data obtained from the CAL-A catalyzed reaction, other parameters that have influence in biocatalytic processes were analyzed such as the temperature and the amount of enzyme. The experimental data are collected in Table 2.

Table 2. Enantioselective lipase-catalyzed desymmetrization of diamine **2a** with diallyl carbonate (100 mM) using CAL-A and RML at different temperatures and 250 rpm.



Entry	Enzyme[a]	T (ºC)	*t* (h)	*c* (%)[b]	*ee* (%)[c]
1	CAL-A (1:1)	30	63	56	86
2	CAL-A (1:1)	45	63	91	88
3	CAL-A (1:1)	60	14	70	78
4	CAL-A (2:1)	45	62	>97 (82)	88
5	RML (1:1)	30	62	5	82
6	RML (1:1)	60	38	11	51

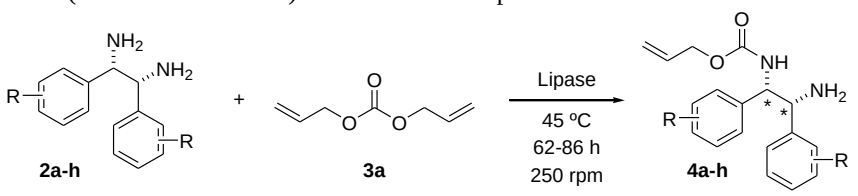
[a] Ratio enzyme: diamine **2a** in weight.
[b] Conversion value into the aminocarbamate **4a** calculated by ^{1}H NMR. Isolated yields in brackets after purification by chromatography on silica gel.
[c] Enantiomeric excess of **4a** calculated by HPLC.

An increase in the temperature to 45 ºC led to a significant improvement in the conversion value towards the monocarbamate **4a**, pleasingly maintaining the selectivity of the process (entry 2). However higher temperatures led to a decrease in the enantiomeric excess of the final product (entry 3). For that reason the loading of biocatalyst was doubled leading to **4a** as a unique product with 88% *ee* after 62 h (entry 4). On the other hand, RML was also used but the activity remained modest at both 30 and 60 ºC (entries 5 and 6).

Next, the study was extended to a panel of *meso*-diamines (**2b**-**h**), bearing different pattern substitution in the aromatic rings. The best conditions obtained for the desymmetrization of **2a** were used, which means the use of CAL-A (ratio 2:1 in weight with respect to the diamine) and allyl carbonate as solvent for 100 mM concentration of the diamine at 45 ºC (Table 3). In all cases, the conversion values were lower than for **2a** suggesting a strong influence of the aromatic substitution. Diamines with substituents in the *para*-position (**2b**-**e**, entries 2-5) led selectively to the monocarbamates with moderate to high conversions (44-88%), finding the best results in terms of selectivity for the diamine **2e** bearing methyl groups instead of halogen atoms (80% *ee*). However the best conversions were found for the halogenated substrates **2b**-**d**, and especially for the less hindered fluorinated substrate **2b**, which was recovered with 88% conversion. Interestingly a significant loss of activity and stereospecificity was attained with substrates bearing substitutions in the *meta*-position (diamines **2f**,**g** entries 6 and 7). This effect was also more dramatic for the *ortho*-bromo derivative **2h** (entry 8), which seems to be not recognized by *Candida antarctica* lipase type A.

With these results in hand, we decided to explore the possibilities of other lipases in the desymmetrization of the diamines that showed the poorest results. Initially we focused in the bulkier substrate **2d**, recovered in racemic form after the CAL-A catalyzed alkoxycarbonylation reaction. Biotransformations with CRL, PPL, RML and CAL-B (entries 9-12) were carried out, observing lower conversions in comparison with CAL-A, but a great improvement in the stereospecificity with RML (entry 11), and mainly with CAL-B (entry 12), leading in the latest to the allyl monocarbamate **4d** in a remarkable 91% *ee*.

Table 3. Enantioselctive desymmetrization of *meso*-diamines **2a**-**h** using different lipases (ratio 2:1 in weight with respect to the diamine) and diallyl carbonate (100 mM of diamine) at 45 ºC and 250 rpm.



Entry	Diamine	R	Enzyme	*t* (h)	*c* (%)[a]	*ee* (%)[b]
1	**2a**	H	CAL-A	62	>97 (82)	88
2	**2b**	4-F	CAL-A	62	88 (70)	70
3	**2c**	4-Cl	CAL-A	62	58 (42)	8
4	**2d**	4-Br	CAL-A	62	56 (38)	<3
5	**2e**	4-Me	CAL-A	62	44 (34)	80
6	**2f**	3-Me	CAL-A	62	29 (16)	18
7	**2g**	3-Br	CAL-A	86	34 (31)	14
8	**2h**	2-Br	CAL-A	62	<3	n.d.
9	**2d**	4-Br	CRL	62	6	<3
10	**2d**	4-Br	PPL	62	3	<3
11	**2d**	4-Br	RML	62	5	50
12	**2d**	4-Br	CAL-B	62	18 (14)	91
13	**2c**	4-Cl	CAL-B	62	17 (15)	88

[a] Conversion into the aminocarbamate **4a**-**h** calculated by ^{1}H NMR of the reaction crude. Isolated yields in brackets after purification on silica gel chromatography.
[b] Enantiomeric excesses of monocarbamates **4a**-**h** calculated by HPLC (n.d.: not determined).

Once we found with CAL-B these improvements in terms of activity and stereoselectivity, we decided to use this enzyme for the desymmetrization of diamines **2b**,**c**,**e-h**. However under the same reaction conditions only the *para*-chloro diamine **2c** was converted into the corresponding monocarbamate with 17% conversion and 88% *ee* (entry 13).

2.3. Absolute configuration determinations

Different attempts were made to obtain suitable crystals for X-ray diffraction analysis in order to assign the absolute configuration of the stereogenic centres for the so-obtained optically active aminocarbamates. With that purpose, the monocarbamate **4d** was selected as a possible candidate because of the presence of heavy bromine atoms in its structure, which could unequivocally allow us to determine the stereopreference of the enzyme. Once that crystalline structures were collected after a recristallyzation purification in acetonitrile, X-ray diffraction analyses were performed observing an (1*S*,2*R*)-configuration as shown in Figure 1.[10] Additional circular dichroism experiments were performed for those aminocarbamates isolated in good to high enantiomeric excess.[11] Thus *para*-halogenated derivatives **4c**,**d** resulting of enzymatic desymmetrization processes mediated by CAL-B, and also allyl carbamates **4a**,**b**,**e** obtained in CAL-A catalyzed reactions were considered. Based in the net positive intensity obtained for all of them as well as on the similarity of the electronic systems of these molecules, the formation of (1*S*,2*R*)-**4a-g** aminocarbamates is here described by chemoenzymatic methods taking also into account the unequivocally (1*S*,2*R*)-configuration assigned for **4d** using X-ray crystallographic studies.

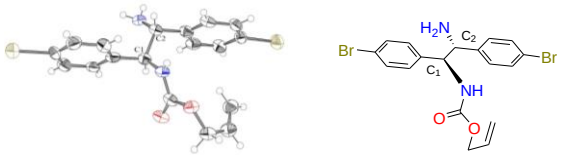


Figure 1. X-Ray structure of monoaminocarbamate (1*S*,2*R*)-**4d** obtained by enantioselective enzymatic desymmetrizatron of *meso*-1,2-diamine **2d** using diallyl carbonate (**3a**) as solvent and alkoxycarbonylating agent and CAL-B as biocatalyst.

3. Conclusions

In conclusion, a simple chemoenzymatic methodology has been developed for the asymmetric synthesis of a series of allyl monocarbamates derived from 1,2-diaryl-1,2-ethanediamines , and bearing different pattern substitutions in the aromatic rings. The crucial step based on the desymmetrization of the *meso*-diamines has been exhaustively analyzed, finding in all cases the monofunctionalization of the diamines. Moderate to good levels of selectivity were found for the *para*-substituted derivatives using either CAL-A (for methyl or fluorine substitutions) or CAL-B (for chlorine or bromine), attaining the best activity values for the non substituted diamine, which completely reacted towards the formation of the allyl (1*S*,2*R*)-aminocarbamate. On the other hand *meta*-substituted diamines led to low conversions and selectivities, while the studied *ortho*-substituted diamine seems to be not recognized by the enzyme.

4. Experimental section

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 and *Rhizomuccor miehei* lipase (RML, <15% in weight) were kindly donated by Novozymes. *Pseudomonas cepacia* lipase immobilized over ceramic particles (PSL-C-I, 1638 U/g) was purchased from Sigma-Aldrich, while the one immobilized on diatomite (PSL IM, 943 U/g) was given from Amano Europe Pharmaceutical Company. *Candida antarctica* lipase type A (CAL-A, 12 U/mg) was purchased from Codexis. *Candida rugosa* lipase (CRL, 965 U/mg), porcine pancreas lipase (PPL, 308 U/mg) and AK lipase from *Pseudomonas fluorescens* (AK, 22100 U/g) were purchased from Sigma.

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 Brüker AV-300 (^{1}H, 300.13 MHz,^{13}C, 75.5 MHz) and a Bruker DPX-300 spectrometers (^{1}H, 300.13 MHz, ^{13}C, 75.5 MHz). The chemical shifts are given in delta values (δ, ppm) and the coupling constants (*J*) in Hertz (Hz). ESI^{+} 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.) or Chiralcel OJ-H, (25 × 4.6 mm D.I.). Mixtures of hexane/2-propropanol 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 diamines and aminocarbamates.

*4.1. General procedure for the chemical synthesis of diamines **2a-h**.*

This is an adapted protocol of a previous research carried out by different authors.[8] A suspension of a previously distilled benzaldehyde **1a-h** (50 mmol) and ammonium acetate (150 mmol) was heated at 120 ºC, and stirred for 3 h. After this time, the reaction was cooled to room temperature, and the gummy residue was washed with hexane. The resulting crude was basified with an aqueous NaOH 4 N solution (pH>10) and extracted with Et_2O (4 x 20 mL). The organic phases were combined, dried and filtered, and the solvent was evaporated under reduced pressure. Without further purification, the resulting intermediate was suspended in an aqueous 50% H_2SO_4 solution (40 mL), and the mixture heated overnight at 170 ºC. Then the reaction was cooled down in an ice-bath with stirring, and H_2O (20 mL) was slowly added. The resulting solution was warmed till room temperature and extracted with Et_2O (4 x 60 mL). The aqueous phase was then neutralized with a concentrated aqueous ammonia solution, and then extracted with Et_2O (4 x 60 mL). The organic phases were combined, dried and filtered, and the solvent was evaporated

under reduced pressure, obtaining the corresponding *meso*-diamines **2a-h** as white, yellow or brown solids (40-98% isolated yield, Table 1).

***meso*-1,2-diphenyl-ethanediamine (2a)**: White solid (1.86 g, 70% isolated yield). R_f (60% MeOH/EtOAc): 0.45; Mp: 122-124 ºC; IR (KBr): ν_{max}/cm^{-1} 3347, 3028, 1590, 756 and 695; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.44 (brs, 4H,), 4.04 (s, 2H), 7.31-7.42 (m, 10H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 63.1 (2CH), 127.9 (6CH), 128.8 (4CH), 143.2 (2C); MS (ESI^+, *m/z*): 213.1 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{14}H_{17}N_2$ $(M+H)^+$: 213.1386 found: 213.1381.

***meso*-1,2-bis(4-fluorophenyl)-1,2-ethanediamine (2b)**: Brown solid (2.79 g, 90% isolated yield). R_f (60% MeOH/EtOAc): 0.41; Mp: 80-82 ºC; IR (KBr): ν_{max}/cm^{-1} 3219, 2914, 1602, 1219, 971, 750, and 837; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.60 (brs, 4H), 4.22 (s, 2H), 7.20-7.30 (m, 4H), 7.50-760 (m, 4H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 62.5 (2CH), 115.6 (d, $^2J_{CF}$ = 21.1 Hz, 4CH), 129.4 (d, $^3J_{CF}$ = 7.7 Hz, 4CH), 138.7 (d, $^4J_{CF}$ = 3.1 Hz, 2C), 162.6 (d, $^1J_{CF}$ = 245.7 Hz, 2C); MS (ESI^+, *m/z*): 249.1 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{14}H_{15}F_2N_2$ $(M+H)^+$: 249.1198 found: 249.1174.

***meso*-1,2-bis(4-clorophenyl)-1,2-ethanediamine (2c)**: Yellow solid (3.43 g, 98% isolated yield). R_f (60% MeOH/EtOAc): 0.47; Mp: 126-128 ºC; IR (KBr): ν_{max}/cm^{-1} 3380, 2950, 1202, 1600, 980, and 820; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.53 (brs, 4H), 4.00 (s, 2H), 7.27-7.34 (m, 8H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 62.0 (2CH), 128.5 (4CH), 128.9 (4CH), 133.4 (2C), 140.9 (2C); MS (ESI^+, *m/z*): 281.0 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{14}H_{15}Cl_2N_2$ $(M+H)^+$: 281.0607 found: 281.0592 (^{35}Cl,^{35}Cl), 283.0563 (^{35}Cl,^{37}Cl).

***meso*-1,2-bis(4-bromophenyl)-1,2-ethanediamine (2d)**: Yellow solid (1.84 g, 40% isolated yield). R_f (60% MeOH/EtOAc): 0.64; Mp: 122-124 ºC; IR (KBr): ν_{max}/cm^{-1} 3076, 2955, 1607, 1268, and 852; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.42 (brs, 4H), 3.98 (s, 2H), 7.21 (d, $^3J_{HH}$= 8.2 Hz, 4H), 7.47 (d, $^3J_{HH}$ = 8.2 Hz, 4H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 62.4 (2CH), 121.9 (2C), 129.7 (4CH), 131.9 (4CH), 141.9 (2C); MS (ESI^+, *m/z*): 370.9 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{14}H_{15}Br_2N_2$ $(M+H)^+$: 368.9597 found: 368.9570 (^{79}Br,^{79}Br), 370.9571 (^{79}Br,^{81}Br), 372.9562 (^{81}Br,^{81}Br).

***meso*-1,2-bis(4-methylphenyl)-1,2-ethanediamine (2e)**: White solid (2.11 g, 70% isolated yield). R_f (60% MeOH/EtOAc): 0.47; Mp: 76-78 ºC; IR (KBr): ν_{max}/cm^{-1} 3370, 2920, 1606, 1266, 1020, 890, 735; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 2.01 (brs, 4H), 2.76 (s, 6H), 4.38 (s, 2H), 7.57 (d, $^3J_{HH}$ = 7.9 Hz, 4H), 7.69 (d, $^3J_{HH}$ = 7.9 Hz, 4H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 21.4 ($2CH_3$), 62.0 (2CH), 127.8 (4CH), 129.4 (4CH), 137.5 (2C), 140.3 (2C); MS (ESI^+, *m/z*): 241.1 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{16}H_{21}N_2$ $(M+H)^+$: 241.1699 found: 241.1687.

***meso*-1,2-bis(3-methylphenyl)-1,2-ethanediamine (2f)**: White solid (2.34 g, 78% isolated yield). R_f (60% MeOH/EtOAc): 0.46; Mp: 135-137ºC; IR (KBr): ν_{max}/cm^{-1} 3052, 2855, 1603, 1265, 957, 789, and 740; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.37 (brs, 4H), 2.39 (s, 6H), 3.98 (s, 2H), 7.10-7.15 (m, 2H), 7.26-7.28 (m, 6H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 20.5 ($2CH_3$), 62.0 (2CH), 123.8 (2CH), 127.4-127.5 (6CH), 137.2 (2C), 142.0 (C); MS (ESI^+, *m/z*): 241.1 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{16}H_{21}N_2$ $(M+H)^+$: 241.1699 found: 241.1687.

***meso*-1,2-bis(3-bromophenyl)-1,2-ethanediamine (2g)**: White solid (4.42 g, 96% isolated yield,). R_f (60% MeOH/EtOAc): 0.64; Mp: 176-178ºC; IR (KBr): ν_{max}/cm^{-1} 3055, 2986, 1600, 1265, 894, 790, and 740; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.49 (brs, 4H), 3.99 (s, 2H), 7.23-7.28 (m, 4H), 7.44-7.46 (m, 2H), 7.55-7.57 (m, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 62.6 (2CH), 123.0 (2C), 126.7 (2CH), 130.3-130.9 (4CH), 131.2 (2CH), 145.3 (2C); MS (ESI^+, *m/z*): 370.9 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{14}H_{15}Br_2N_2$ $(M+H)^+$: 368.9597 found: 368.9572 (^{79}Br,^{79}Br), 370.9575 (^{79}Br,^{81}Br), 372.9566 (^{81}Br,^{81}Br).

***meso*-1,2-bis(2-bromophenyl)-1,2-ethanediamine (2h)**: White solid (2.76 g, 60% isolated yield). R_f (60% MeOH/EtOAc): 0.65; Mp: 148-150ºC; IR (KBr): ν_{max}/cm^{-1} 3055, 2985, 1265 and 740; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.59 (brs, 4H), 4.72 (s, 2H), 7.09-7.16 (m, 2H), 7.28-7.44 (m, 4H), 7.49-7.55 (m, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 59.5 (2CH), 125.1 (2C), 127.6 (2CH), 128.4 (2CH), 128.8 (2CH), 132.7 (2CH), 141.6 (2C); MS (ESI^+, *m/z*): 370.9 [$(M+H)^+$, 100%] HRMS (ESI^+, *m/z*) calcd for $C_{14}H_{15}Br_2N_2$ $(M+H)^+$: 368.9597 found: 368.9564 (^{79}Br,^{79}Br), 370.9566 (^{79}Br,^{81}Br), 372.9559 (^{81}Br,^{81}Br).

*4.2. General procedure for the chemical synthesis of racemic aminocarbamates **4a-h**.*

To a solution of the corresponding *meso*-diamine **2a-h** (0.47 mmol) in dry CH_2Cl_2 (4.72 mL, 0.1 M), first DMAP (63.5, 0.52 mmol) and next allyl chloroformate (55 μL, 0.52 mmol) were added under nitrogen atmosphere. The solution was magnetically stirred at room temperature till complete consumption of the starting material (24 h, TLC analysis 60% MeOH/EtOAc). Then the solvent was distilled under reduced pressure, and the resulting crude purified by chromatography on silica gel (30-70% EtOAc/hexane), yielding the corresponding racemic monocarbamte **4a-h** as a white solid (29-75% isolated yield).

(±)-*N*-(2-amino-1,2-diphenylethyl) allyl carbamate (4a): White solid (109 mg, 75% isolated yield). R_f (70% EtOAc/hexane): 0.40; Mp: 115-117 ºC; IR (KBr): ν_{max}/cm^{-1} 2936, 2269, 1694, 1604, 1572, 1446, 1266, 1159, 1090, 1026, 917 and 760; δ_H (300.13 MHz, MeOD, Me_4Si): 4.31 (d, $^3J_{HH}$= 8.7 Hz, 1H), 4.41-4.69 (m, 2H), 5.02 (brs, 1H), 5.13-5.31 (m, 2H), 5.82-6.01 (m, 1H), 7.38-7.65 (m, 10H); δ_C (75.5 MHz, MeOD, Me_4Si): 61.2 (CH), 62.7 (CH), 66.2 (CH), 117.2 (CH_2), 128.6 (2CH), 128.7 (2CH), 128.8 (2CH), 129.3 (2CH), 129.6 (2CH), 134.2 (CH), 141.5 (C), 143.1 (C), 157.6 (C): MS (ESI^+, *m/z*): 297.1 [$(M+H)^+$, 100%]; HRMS (ESI^+, *m/z*) calcd for $C_{18}H_{21}N_2O_2$ $(M+H)^+$: 297.1598 found: 297.1584.

(±)-*N*-[2-amino-1,2-bis(4-fluorophenyl)ethyl] allyl carbamate (4b): White solid (86 mg, 55% isolated yield,). R_f (70% EtOAc/hexane): 0.42; Mp: 123-125 ºC; IR (KBr): ν_{max}/cm^{-1} 2936, 2269, 1695, 1603, 1573, 1513, 1268, 1230, 1158, 923 and 841; δ_H (300.13 MHz, MeOD, Me_4Si): 4.28 (d, $^3J_{HH}$= 8.6 Hz, 1H), 4.44-4.61 (m, 2H), 4.98 (d, $^3J_{HH}$= 8.6 Hz, 1H), 5.19-5.33 (m, 2H), 5.88-6.07 (m, 1H), 7.15-7.38 (m, 4H), 7.49-7.64 (m, 4H); δ_C (75.5 MHz, MeOD, Me_4Si): 60.8 (CH), 62.4 (CH), 66.6 (CH_2), 116.1-116.7 [d, $^2J_{CF}$= 22 Hz, 2CH)+(d, $^2J_{CF}$= 22 Hz, 2CH)], 117.5 (CH_2), 130.7-131.0 [(d, $^3J_{CF}$= 8 Hz, 2CH)+(d, $^3J_{CF}$= 8 Hz, 2CH)], 134.5 (CH), 137.8 (C), 139.5 (C), 157.9 (C) 163.9-164.0 [(d, $^1J_{CF}$= 245 Hz, C)+(d, $^1J_{CF}$= 245 Hz, C)]; MS (ESI$^+$, *m/z*): 333.1 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{18}H_{19}F_2N_2O_2$ (M+H)$^+$: 333.1409; found: 333.1381.

(±)-*N*-[2-amino-1,2-bis(4-chlorophenyl)ethyl] allyl carbamate (4c): White solid (92 mg, 54% isolated yield). R_f (70% EtOAc/hexane): 0.52; Mp: 123-125 ºC; IR (KBr): ν_{max}/cm^{-1} 2900, 1694, 1536, 1491, 1410, 1250, 1090, 1012, 927 and 832; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 4.30 (d, $^3J_{HH}$= 8.6 Hz, 1H), 4.47-4.63 (m, 2H), 4.97 (d, $^3J_{HH}$= 8.6 Hz, 1H), 5.22-5.34 (m, 2H), 5.87-6.03 (m, 1H), 7.44-7.59 (m, 8H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 60.7 (CH), 62.3 (CH), 66.6 (CH_2), 117.6 (CH_2), 129.7-129.9 (4CH), 130.6-130.7 (4CH), 134.5-134.8 (2C+CH), 140.4 (C), 142.3 (C) 157.9 (C); MS (ESI$^+$, *m/z*): 365.0 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{18}H_{19}Cl_2N_2O_2$ (M+H)$^+$: 365.0818 found: 365.0812 (^{35}Cl,^{35}Cl), 367.0782 (^{35}Cl,^{37}Cl).

(±)-*N*-[2-amino-1,2-bis(4-bromophenyl)ethyl] allyl carbamate (4d): White solid (125 mg, 59% isolated yield). R_f (70% EtOAc/hexane): 0.41; Mp: 124-126 ºC; IR (KBr): ν_{max}/cm^{-1}2940, 2269, 1707, 1645, 1545, 1451, 1254, 1160, 1026, 1000, 932, 831 and 795; δ_H (300.13 MHz, MeOD, Me_4Si): 4.29 (d, $^3J_{HH}$= 8.6 Hz, 1H), 4.46-4.66 (m, 2H), 4.95 (d, $^3J_{HH}$= 8.6 Hz, 1H), 5.19-5.36 (m, 2H), 5.85-6.05 (m, 1H), 7.35-7.56 (m, 4H), 7.59-7.77 (m, 4H); δ_C (75.5 MHz, MeOD, Me_4Si): 60.8 (CH), 62.4 (CH), 66.6 (CH_2), 117.6 (CH_2), 122.6-122.9 (2C), 130.0-131.0 (4CH), 132.7-132.9 (4CH), 134.5 (CH), 140.9 (C), 142.7 (C), 157.9 (C); MS (ESI$^+$, *m/z*): 454.9 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{18}H_{19}Br_2N_2O_2$ (M+H)$^+$: 452.9822 found: 452.9822 (^{79}Br,^{79}Br), 454.9808 (^{79}Br,^{81}Br), 456.9787 (^{81}Br,^{81}Br).

(±)-*N*-[2-amino-1,2-bis(4-methylphenyl)ethyl] allyl carbamate (4e): White solid (44 mg, 29% isolated yield). R_f (70% EtOAc/hexane): 0.43; Mp: 116-118 ºC; IR (KBr): ν_{max}/cm^{-1} 2800, 2150, 1702, 1542, 1490, 1252, 1153, 1090, 920, 816, and 737; δ_H (300.13 MHz, MeOD, Me_4Si): 2.52 (s, 6H), 4.24 (d, $^3J_{HH}$= 8.7 Hz, 1H), 4.47-4.57 (m, 2H), 4.94 (d, $^3J_{HH}$= 8.7 Hz, 1H), 5.18-5.32 (m, 2H), 5.84-6.03 (m, 1H), 7.27-7.41 (m, 8H); δ_C (75.5 MHz, MeOD, Me_4Si): 21.5 ($2CH_3$), 61.2 (CH), 62.8 (CH), 66.5 (CH_2), 117.4 (CH_2), 128.9-129.0 (4CH), 130.2-130.5 (4CH), 134.6 (CH), 138.5-138.9 (2C), 140.3 (C), 141.7 (C), 157.9 (C); MS (ESI$^+$, *m/z*): 325.1 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{20}H_{25}N_2O_2$ (M+H)$^+$: 325.1911 found: 325.1910.

(±)-*N*-[2-amino-1,2-bis(3-methylphenyl)ethyl] allyl carbamate (4f): White solid (70 mg, 46% isolated yield). R_f (70% EtOAc/hexane): 0.53; Mp: 97-99 ºC; IR (KBr): ν_{max}/cm^{-1} 2924, 2490, 1697, 1536, 1495, 1451, 1251, 1042, 995, 922 and 785; δ_H (300.13 MHz, MeOD, Me_4Si): 2.52 (s, 6H), 4.23 (d, $^3J_{HH}$= 8.8 Hz, 1H), 4.42-4.61 (m, 2H), 4.94 (d, $^3J_{HH}$= 8.8 Hz, 1H), 5.16-5.32 (m, 2H), 5.83-6.00 (m, 1H), 7.21-7.47 (m, 8H); δ_C (75.5 MHz, MeOD, Me_4Si); 21.8 ($2CH_3$), 61.4 (CH), 63.0 (CH), 66.5 (CH_2), 117.4 (CH_2), 126.1 (2CH), 129.5-129.8 (6CH), 134.6 (CH), 139.2 (C), 139.6 (C) 141.8 (C), 143.3 (C) 157.9 (C); MS (ESI$^+$, *m/z*): 325.1 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{20}H_{25}N_2O_2$ (M+H)$^+$: 325.1911 found: 325.1908.

(±)-*N*-[2-amino-1,2-bis(3-bromophenyl)ethyl] allyl carbamate (4g): White solid (64 mg, 30% isolated yield). R_f (70% EtOAc/hexane): 0.57; Mp: 188-191 ºC; IR (KBr): ν_{max}/cm^{-1} 3047, 2487, 1682, 1604, 1554, 1454, 1251, 996, , 923 and 788; δ_H (300.13 MHz, MeOD, Me_4Si): 4.26 (d, $^3J_{HH}$= 8.8 Hz, 1H), 4.44-4.64 (m, 2H), 4.93 (d, $^3J_{HH}$= 8.8 Hz, 1H), 5.19-5.37 (m, 2H), 5.86-6.05 (m, 1H), 7.37-7.85 (m, 8H); δ_C (75.5 MHz, MeOD, Me_4Si): 60.9 (CH), 62.5 (CH), 66.7 (CH_2), 117.7 (CH_2), 123.6-123.8 (2C), 127.7-127.9 (2CH), 131.4-132.2 (6CH), 134.4 (CH), 142.3 (C), 146.1 (C), 157.8 (C); MS (ESI$^+$, *m/z*): 454.9 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{18}H_{19}Br_2N_2O_2$ (M+H)$^+$: 452.9822 found: 452.9818 (^{79}Br,^{79}Br), 454.9805 (^{79}Br,^{81}Br), 456.9782 (^{81}Br,^{81}Br).

(±)-*N*-[2-amino-1,2-bis(2-bromophenyl)ethyl] allyl carbamate (4h): Yellow oil (129 mg, 61% isolated yield). R_f (70% EtOAc/hexane): 0.56; Mp: 122-124 ºC; IR (KBr): ν_{max}/cm^{-1} 3005, 1703, 1504, 1468, 1454, 1241, 1023, 994, 931 and 737; δ_H (300.13 MHz, MeOD, Me_4Si): 4.54-4.69 (m, 2H), 4.96 (d, $^3J_{HH}$= 6.4 Hz, 1H), 5.23-5.43 (m, 2H), 5.80 (d, $^3J_{HH}$= 6.4 Hz, 1H), 5.92-6.11 (m, 1H), 7.29-7.74 (m, 8H); δ_C (75.5 MHz, MeOD, Me_4Si): 59.3 (CH), 59.5 (CH), 66.8 (CH_2), 117.9 (CH_2), 126.2-126.4 (2C), 129.0-129.1 (2CH), 130.0-130.6 (4CH), 134.1-134.2 (2CH), 134.5 (CH) 139.9 (C), 141.8 (C), 157.9 (C); MS (ESI$^+$, *m/z*): 454.9 [(M+H)$^+$, 100%]; HRMS (ESI$^+$, *m/z*) calcd for $C_{18}H_{19}Br_2N_2O_2$ (M+H)$^+$: 452.9822 found: 452.9815 (^{79}Br,^{79}Br), 454.9801 (^{79}Br,^{81}Br), 456.9780 (^{81}Br,^{81}Br).

*4.3. General procedure for the biocatalyzed desymmetrization of diamines **2a-h** using lipases and diallyl carbonate.*

A suspension of the corresponding diamine **2a-h** (0.2 mmol) and enzyme (ratio 2:1 of CAL-A or CAL-B respect to the diamine) in diallyl carbonate (**3a**, 2 mL) was shaken at 250 rpm for 62-86 h under nitrogen atmosphere. After this time, the reaction was filtered and the enzyme washed with MeOH (3 x 5 mL). The solvent was distilled under reduced pressure, and the resulting crude purified by chromatography on silica gel (30-70% EtOAc/hexane), yielding the corresponding optically active aminocarbamate **4a-h**. For further details see Tables 2 and 3.

*4.4. Analytical conditions and optical rotation values for optically active aminocarbamates **4a-h**.*

(1*S*,2*R*)-4a: $[\alpha]_D^{20}$ = +1.0 (*c* 0.5, EtOH) with 88% *ee*; Column Chiralcel OJ-H; Eluent (90% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 12.6 and 14.6 min (12.6

min for the major enantiomer in the enzymatic process); Diamine **2a**: 9.9 min.

(1*S*,2*R*)-4b: $[\alpha]_D^{20}$ = +1.8 (*c* 0.5, EtOH) with 70% *ee*; Column Chiralpak IC; Eluent (80% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 6.7 and 7.6 min (7.6 min for the major enantiomer in the enzymatic process); Diamine **2b**: 8.7 min.

(1*S*,2*R*)-4c: $[\alpha]_D^{20}$ = +1.0 (*c* 0.5, EtOH) with 88% *ee*; Column Chiralcel OJ-H; Eluent (95% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 32.2 and 38.9 min (32.2 min for the major enantiomer in the enzymatic process); Diamine **2c**: 26.7 min.

(1*S*,2*R*)-4d: $[\alpha]_D^{20}$ = -2.9 (*c* 0.5, EtOH) with 91% *ee*; Column Chiralpak IC; Eluent (90% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 12.9 and 13.6 min (12.9 min for the major enantiomer in the enzymatic process); Diamine **2d**: 18.2 min.

(1*S*,2*R*)-4e: $[\alpha]_D^{20}$ = +7.6 (*c* 0.5, EtOH) with 80% *ee*; Column Chiralpak IC; Eluent (90% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 23.1 and 33.4 min (33.4 min for the major enantiomer in the enzymatic process); Diamine **2e**: 26.2 min.

(1*S*,2*R*)-4f: $[\alpha]_D^{20}$ = +3.8 (c 0.5, EtOH) with 18% *ee*; Column Chiralpak IC; Eluent (70% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 7.2 and 10.8 min (10.8 min for the major enantiomer in the enzymatic process); Diamine **2g**: 8.6 min.

(1*S*,2*R*)-4g: $[\alpha]_D^{20}$ = +1.2 (c 0.5, EtOH) with 14% *ee*; Column Chiralcel OJ-H; Eluent (90% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 16.5 and 20.6 min (20.6 min for the major enantiomer in the enzymatic process); Diamine **2g**: 14.0 min.

4h: Column Chiralpak IC; Eluent (90% Hexane/2-propanol); Flow (0.8 mL/min); Retention times: 12.4 and 13.8 min; Diamine **2h**: 19.8 min.

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10. Data collection was made using the program CrysAlispro (Agilent Technologies). Crystal structure was solved by charge flipping methods using the program Superflip. Anisotropic least-squares refinement was carried out with SHELXL-97. Absolute configuration was determined as *S,R* from the Friedel pairs. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre publication number CCDC 980770. Copies of the data can be obtained free of charge from the Cambridge Crystallographic Data Centre from www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi.
11. UV-Circular Dichroism measurements were carried out using a Jasco J-815 CD-spectrometer. Samples were measured in methanolic solution (approx. $2 \cdot 10^{-3}$M) using a 1cm length prismatic cuvette.

Supplementary Material: copies of the ^{1}H and ^{13}C NMR spectra for diamines and carbamates, and UV circular dichroism spectra of selected monocarbamates are available in the Electronic Supporting Information.