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First Desymmetrization of 1,3-Propanediamine Derivatives in Organic Solvent. Development of a New Route for the Preparation of Optically Active Amines§

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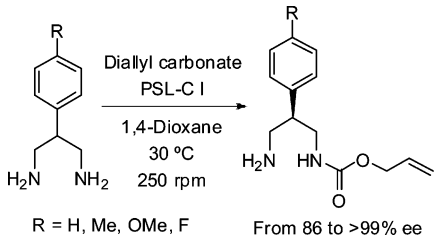
ABSTRACT



The chemical synthesis and enzymatic desymmetrization of a panel of prochiral diamines have been successfully described for the first time using lipases in organic solvents. A family of 2-aryl-1,3-propanediamines has been obtained with high enantiopurity and good yields in the PSL-catalyzed reaction using diallyl carbonate in 1,4-dioxane.

Design of enantioselective routes for the preparation of optically pure compounds is a highly important synthetic target, which provides solutions for many necessities in the academic and industrial sector. Many chemical methods have been developed during the last century for the preparation of these compounds, although the development of biocatalytic methods in organic media has emerged in the last decades as a valuable tool for the preparation of enantiomerically pure products.[1]

Nonracemic chiral amines are a class of organic compounds not easily prepared but which have important applications as building blocks for the synthesis of agrochemicals and pharmaceuticals and can also be used effectively as ligands for asymmetric catalysis and as resolving agents for crystallization.[2]

Among the hydrolases group, lipases are one of the most important biocatalysts to have found widespread application in the preparation of optically active compounds.[3] Kinetic

§ In memoriam of Professor Lorenzo Pueyo Casaus (1946−2007).
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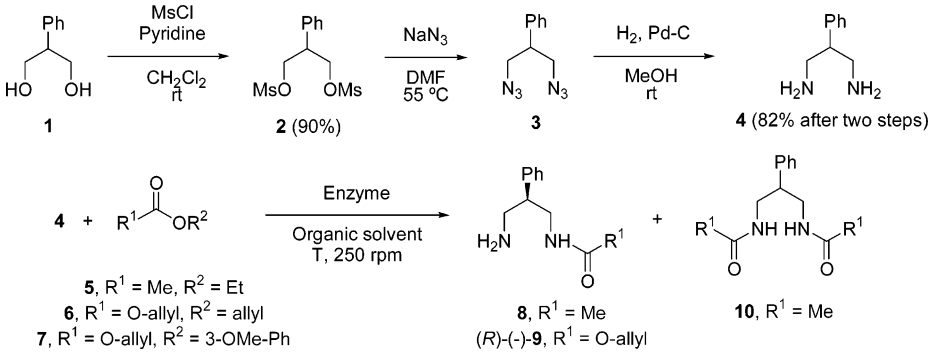
Scheme 1. Chemical Synthesis and Enzymatic Desymmetrization of Diamine **4**



resolutions are the most common stereoselective biotransformations, but they carry the limitation that only 50% yield can be attained. Because of this, many enzyme-catalyzed methodologies have been developed in recent years to avoid this limitation, such as dynamic kinetic resolutions, deracemization processes, or desymmetrizations of meso and prochiral compounds.[4] Enantioselective desymmetrization of symmetric compounds implies the elimination of one or more elements of symmetry from selected substrates that occur, thus inducing chirality. Carboxylic acid derivatives, alcohols, and ketones are the most common starting materials described for these processes.[5] However, little attention has been given to desymmetrisation either chemically or enzymatically using prochiral or *meso*-diamines as starting materials.[6]

Here we describe for the first time a chemoenzymatic approach to the synthesis and later desymmetrization of 1,3-propanediamine derivatives testing different lipases in organic solvents. We have focused our efforts in the development of a general, simple strategy for the synthesis of prochiral diamines and, in particular, for one that would allow their isolation without using difficult and tedious purification protocols before carrying out the enzymatic process. This we have done to ensure the reproducibility of the data. In this manner, we have considered the diamine **4** as a model substrate, selecting the diol **1** as an ideal commercially available precursor of the nitrogenated compound (Scheme 1).

Product **2** was obtained by reacting the diol with mesyl chloride. Then it was converted in the corresponding diazide **3**, which was chemically reduced to obtain the diamine **4** in good overall yield. The choice of a hydrogenation step for the production of the diamine is critical due to the easy isolation in high levels of purity of the final product after a simple filtration on Celite. This avoids extraction or flash chromatography procedures that could lead to the loss of most of the desired diamine and allow the quick handling of **4**, which is unstable after short storage in dryness or in normal atmospheric conditions.

Next, different enzymatic approaches were studied by reacting the prochiral diamine **4** with either nonactivated esters such as ethyl acetate (EtOAc, **5**) or carbonates such as diallyl carbonate (**6**) or 3-methoxyphenyl allyl carbonate (**7**). Enantiomeric excesses were measured by HPLC analysis after convenient protection of the remaining free amino group (see the Supporting Information). 1,4-Dioxane was selected as the ideal medium because the starting material **4** presented a better solubility in comparison with other organic solvents such as THF or CH_2Cl_2. An enzyme activity screening was done in the reaction of 0.20 mmol of **4** with 1 equiv of EtOAc. No reaction was observed with *Candida antarctica* lipase type A (CAL-A), *Candida rugosa* lipase (CRL), or lipase from porcine pancreas (PPL), while *C. antarctica* lipase type B (CAL-B) catalyzed the process toward the formation of a near equimolecular mixture of monoamide **8** and diacetylated compound **10**. The best regioselectivity was achieved using *Pseudomonas cepacia* lipase immobilized on a ceramic support (PSL-C) as biocatalyst, the formation of only one reaction product, the monoacetylated compound **8**, being observed. Unfortunately, this was recovered in racemic form possibly due to a poor enantiopreference shown by the lipase or by a possible migration of the acetyl group from one amino group to the other during or after the enzymatic process.

At that point, we decided to study the enzymatic desymmetrization using carbonates that would direct the synthesis toward the recovery of carbamates, which are more stable compounds than the corresponding amides and will probably prevent the migration of the group if that really is what has occurred. CAL-B and PSL-C were the biocatalysts considered for this study, as both had induced some reactivity in the previous investigation using EtOAc as acyl donor (Table 1).

The CAL-B showed good selectivity in the alkoxycarbonylation of **4**, leading to the formation of optically active **9** in 71% yield when diallyl carbonate was employed in the process (entry 1). However, the product was recovered in racemic form with a more reactive carbonate such as 3-methoxyphenyl allyl carbonate (entry 2). Better results were obtained using PSL-C, which showed moderate selec-

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Table 1. Enzymatic Desymmetrization of **4** Using 1 equiv of Allyl Carbonates **6** or **7** in 1,4-Dioxane at 30 °C and 250 rpm

entry	enzyme	carbonate	time (h)	yield[a] (%)	ee[b] (%)
1	CAL-B	**6**	96	75	71
2	CAL-B	**7**	46	77	0
3	PSL-C	**6**	96	63	90
4	PSL-C	**7**	96	73	37

[a] Isolated yield after *flash* chromatography. [b] Determined by HPLC after adequate derivatization (see the Supporting information).

tivity with carbonate **7** but very high selectivity with diallyl carbonate (entries 3 and 4). In all cases, the same stereopreference was observed and the corresponding dicarbamate compound was not detected, the longer reaction failing to significantly increase the conversion of the process. No reaction was observed with other reagents such as dimethyl carbonate or dibenzyl carbonate after 10 days of reaction at 30 °C. Initially, the absolute configuration of the resulting carbamate was assigned *R* in comparison with the results obtained in the enzymatic desymmetrisation of diol **1** using *P. cepacia* lipase.[7]

Once this enzymatic desymmetrization approach had been efficiently achieved, we decided to optimize the reaction conditions in order to find adequate parameters to isolate the optically active monocarbamate **9** in a high level of enantiopurity. To this end, the PSL-catalyzed reaction was conducted using different organic solvents (1,4-dioxane, THF, MeCN, ^{t}BuOMe, Et_2O, and toluene), the best results being obtained in 1,4-dioxane, due to the high solubility of the starting material and the stability showed by the diamine in this solvent. The influence shown through the use of different quantities of carbonate, temperatures, or the type or quantity of PSL-C slightly affects the results obtained in the enzymatic processes.

The desymmetrization of diamine **4** was scaled up to approximately 1 mmol of substrate using the optimum reaction conditions (PSL-C I as biocatalyst in double amount respect to the starting material and 1 equiv of diallyl carbonate in 1,4-dioxane at 30 °C) and avoiding as much as possible the manipulation of the diamine in moist conditions. The results obtained were better than those of previous studies on a smaller scale, with a total selectivity in the enzymatic process affording (*R*)-**9** in enantiopure form and 73% isolated yield after 70 h at 30 °C. This fact can be explained by the easy handling of the starting material; after the hydrogenation step and purification by filtration, the diamine can be placed directly in the vessel used for the enzymatic process, so there is no time for the oxidation of this unstable substrate under air conditions. It is worthwhile noting at this point that the enzymatic desymmetrization of prochiral diamines has been successfully achieved for the first time using organic solvents, in contrast with the hundreds of examples of the desymmetrization of diols, ketones, diesters, or other related compounds.[8]

With these results, we decided to extend our methodology in order to develop a general strategy for the desymmetrization of other prochiral diamines. 1,3-Diaminopropane derivatives are important enzyme inhibitors. Moreover, this core can be found in a wide range of biologically active compounds,[9] so the possibility of using a chemoenzymatic methodology would make the easy preparation of interesting orthogonally protected derivatives possible. Certain compounds differing in the substitution present in the aromatic ring were prepared in this way in order to go on and study in detail their enzymatic desymmetrisation.

Diamines **27**−**29** were considered at this point, and their chemical synthesis was achieved following a strategy similar to that used in the case of **4**, using diols **18**−**20** as key precursors for the overall preparation (Scheme 2). The diols were obtained following a described procedure from chloride acids **11** and **12**, respectively,[10] to later extend our methodology in the preparation of diamines **27**−**29**, which were isolated after a clean hydrogenation step and purified through a simple filtration. Enzymatic desymmetrization was immediately attempted in the same efficient reaction conditions employed for **4**, obtaining the corresponding monocarbamates (*R*)-**30**−**32** with good isolated yields (68−72%) and high enantiomeric excesses (86−96%) after 72 h at 30 °C, demonstrating the validity of this new approach for the production of enantiomerically enriched amines.

Different attempts were made to obtain suitable crystals for X-ray diffraction analysis from hydrochloride or hydrobromide salts, but all of them were unsuccessful. Fortunately, at the same time that ^{1}H NMR analysis was done, adequate crystals were obtained of the Mosher's amide prepared by reaction of optically active (−)-**32** with (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride shown in Figure 1.[11]

As can be seen, both stereogenic centers from the acid residue and the 2-position of the diamine fragment present (*R*)-configuration, which agrees with the hypothesis previously put forward, which considered the same preference for the lipases in the enzymatic desymmetrization of

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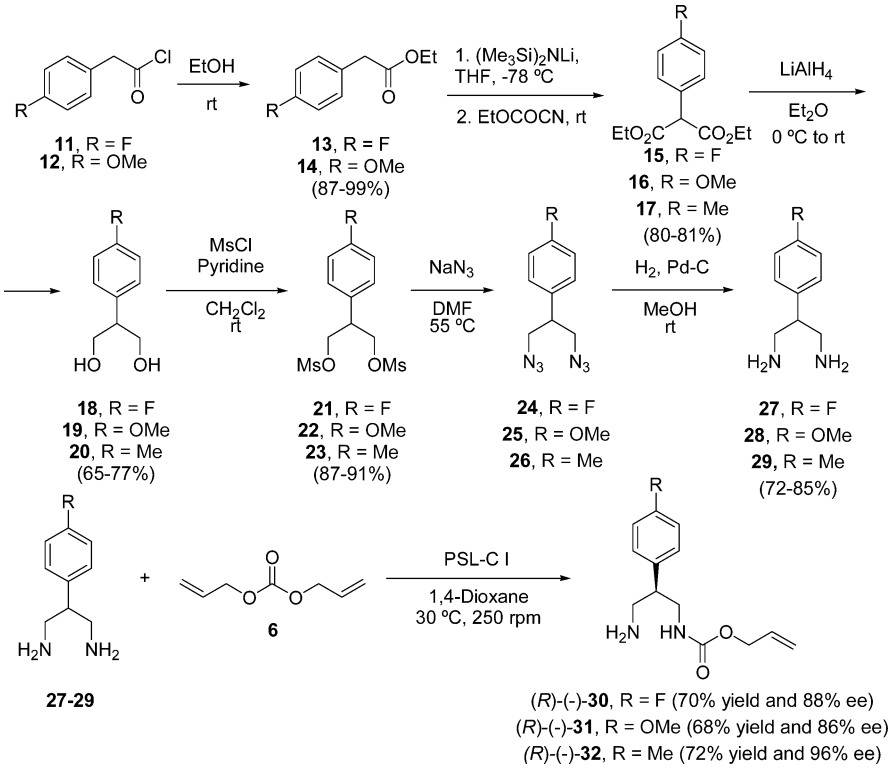
(11) Colorless crystal, crystal dimensions 0.22 × 0.06 × 0.02 mm^3; $C_{24}H_{27}F_3N_2O_4$ (M_r = 464.48); monoclinic, space group *P*21, a = 13.1146(15) Å, b = 9.4909(6) Å, c = 19.586(3) Å, β = 103.373(15)°, V = 2371.7(5) Å^3, Z = 2, D_x = 1.301 Mg m^{-3}, μ = 0.882 mm^{-1}. λ = 1.54180 Å (Cu Kα). Data collection at 100(2) K, $2\theta_{max}$ 104.62°, 7935 measured reflections and 4192 independent reflections (R_{int} 0.070). Final value of R1 ($F^2 > 2\sigma(F^2)$) = 0.0521, wR2 ($F^2 > 2\sigma(F^2)$) = 0.0877. Residual electron density 0.216/−0.220 e Å^{-3}. Data collection was made using the program CrysAlis CCD. Crystal structure was solved by direct methods using the program Sir2004. Anisotropic least-squares refinement was carried out with SHELXL-97. Absolute configuration was determined as *R*,*R* from the Friedel Pairs and the reference of one known center. Structure details were deposited at the CSD database (CCDC-651954 Cambridge).

Scheme 2. Chemical Synthesis and Enzymatic Desymmetrization of Diamines **27**−**29**



equivalent diols and diamines. The configurations of the carbamates (−)-**9**, (−)-**30**, and (−)-**31** were also assigned *R* because of their similar structure to (−)-**32**. At the same time, NMR analyses were performed, the results agreeing with the previous hypothesis (see the Supporting Information).

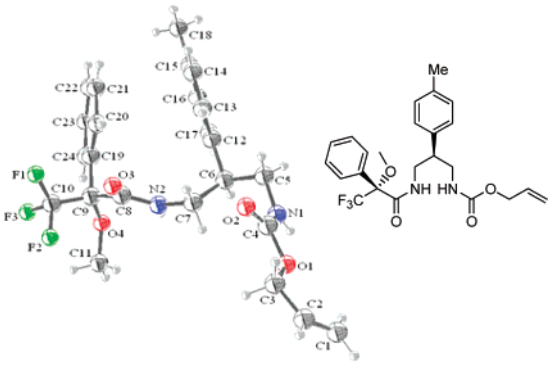


Figure 1. X-ray structure obtained for the (*R*,*R*)-amidocarbamate obtained from optically active **32** by reaction with (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride.

In conclusion, a general chemoenzymatic strategy has been developed for the production of interesting optically active carbamates in good overall yields and high levels of enantiopurity, and an enzymatic desymmetrization of prochiral diamines in organic solvents is described for the first time. Efforts to explore the behavior of different diamines with a variety of structural cores are currently ongoing.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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