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Candida antarctica B lipase catalysed resolution of (±)-1-(heteroaryl)ethylamines

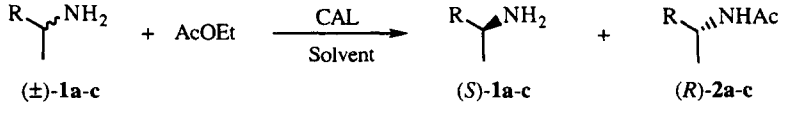
Luis E. Iglesias, Víctor M. Sánchez, Francisca Rebolledo and Vicente Gotor *
Laboratorio de Química Bioorgánica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

Abstract: *Candida antarctica* B lipase is an efficient catalyst for the enantioselective acetylation of (±)-1-(heteroaryl)ethylamines (±)-**1a–c**. © 1997 Elsevier Science Ltd

Optically active 1-(heteroaryl)ethylamines have proven utility as chiral ligands in metal complexes for stereoselective catalysis,[1] and they have been used as starting materials for the syntheses of important compounds such as alkaloids and aminoacids.[2] Although the preparation of some of these amines has been carried out by resolution of the racemate with an optically active acid,[3] a more general strategy involves the asymmetric alkylation of the corresponding imines bearing a suitable chiral auxiliary,[4] several steps of protection and deprotection being necessary.

Over the last few years, our group has been interested in the study of the enantioselective aminolysis reaction, and this biotransformation has provided us with a simple and efficient procedure for the preparation of optically active amines, esters and amides.[5] The efficiency and mildness of these biocatalytic reactions prompted us to try the enzymatic resolution of some chiral 1-(heteroaryl)ethyl amines (±)-**1a–c** through aminolysis processes. As the nature of some heterocyclic compounds may require mild reaction conditions to prevent ring degradation,[6] a direct and mild procedure for the resolution of such 1-(heteroaryl)ethylamines would be of great value.

To carry out these reactions, *Candida antarctica* B lipase (CAL-B) was chosen as the biocatalyst due to its well-documented activity in aminolysis processes.[5] First, the CAL-catalysed aminolyses of (±)-**1a–c**[7] were performed at 30°C using ethyl acetate as acyl donor and solvent (Scheme 1). To isolate the remaining amines (*S*)-**1a–c** and the amides (*R*)-**2a–c**, two procedures were followed. The reaction mixtures of **1a** and **1b** were treated with 3 N HCl, the amines isolated as their ammonium salts and the amides purified by flash-chromatography, and the reaction mixture of **1c** was directly separated by flash-chromatography isolating **1c** as the free base. Results obtained in these processes (see Table 1, entries 1, 3 and 5) show that CAL catalyses the acetylation of **1b** with moderate enantioselectivity (*E*=32).[8] However, it is an effective catalyst in the acetylation of **1a** and **1c** (*E*=>100 and 66, respectively), for which the corresponding (*R*)-amides (**2a,c**) were obtained with very high enantiomeric excesses (ee) at also very high conversion. When performed in other solvents such as 1,4-dioxane, the acetylations of (±)-**1a–c** were in all cases slower than in ethyl acetate (Table 1, entries 2, 4 and 6); the enzyme showed a poorer enantioselectivity for **1a**, but a significantly improved enantioselectivity for **1b**, affording amide (*R*)-**2b** with very high ee and yield.



(±)-**1a-c** (*S*)-**1a-c** (*R*)-**2a-c**

a, R= 2-furyl; **b**, R= 2-thienyl; **c**, R= 2-pyridyl;

Scheme 1.

* Corresponding author.

Table 1. Acetylation of (±)-**1** catalysed by CA lipase[a]

Entry	Amine	Solvent	t, h	amine (*S*)-**1** ee[b], %	amide (*R*)-**2** ee[b], %	conv,[c] %	E^c
1	(±)-**1a**	AcOEt	6	66	99	40	>100
2	(±)-**1a**	1,4-dioxane[d]	40	64	89	42	31
3	(±)-**1b**	AcOEt	14	52	90	37	32
4	(±)-**1b**	1,4-dioxane[d]	40	56	99	36	>100
5	(±)-**1c**	AcOEt	14	90	91	50	66
6	(±)-**1c**	1,4-dioxane[d]	40	84	93	47	72

[a] Typical scale: (±)-**1a-c** (5 mmol), CAL-SP 435 (150 mg), solvent (15 mL). [b] For determination, see text.
[c] See ref. 8. [d] AcOEt (1.5 mL)

The enantiomeric excesses were determined as follows. For the remaining amines (*S*)-**1a,b**, they were measured by HPLC analysis of their respective Cbz-derivatives[9] using a Chiralcel-OD column. This chromatographic technique also allowed us to determine the ee of the amide (*R*)-**2b**,[9] but it failed for the other amides. Compound (*R*)-**2a** was then hydrolyzed with 1 N KOH (reflux, 2 h) to the free amine (*R*)-**1a**, whose ee was established by HPLC analysis of its Cbz-derivative. Hydrolysis of amide (*R*)-**2c** (6 N HCl, reflux, 3 h) gave the amine (*R*)-**1c**, and its ee was determined by derivatization with (*S*)-MTPA-Cl[10] to the corresponding MTPA-amide derivative, which was subsequently analysed by ^{19}F NMR.[11] The same procedure was employed for the remaining amine (*S*)-**1c**.

The configuration of the unreacted amine (*S*)-**1a** was assigned by comparison of the specific rotation of its benzamide derivative ($[\alpha]_D^{25}$ +43.2, c=0.41, EtOH, 64% ee) with the reported data for (*S*)-*N*-[1-(2-furyl)ethyl]benzamide.[12] For (*S*)-**1c**, by comparison of the sign of the specific rotation ($[\alpha]_D^{25}$ −38.8, c=0.40, EtOH, 84% ee) with the reported data for (*S*)-(−)-**1c**.[3] These assignments are in agreement with previous results reported by us, in which CAL always preferentially transformed the (*R*)-enantiomer of all the tested racemic amines. To our knowledge, no data have been described for the specific rotation of **1b** nor of any derivative. For this compound, and taking into account the above-mentioned behaviour of the CAL, it seems reasonable to assume that the CAL shows the same enantiopreference as for **1a** and **1c**. Moreover, the *S*-configuration for the unreacted **1b** is also corroborated by comparison of the HPLC chromatograms obtained for the Cbz-derivatives of **1a** and **1b** (isolated in the enzymatic processes) with those of the derived from (±)-**1a** and (±)-**1b** (see Ref.[9]). In both cases, the peak at a higher retention time is that of smaller area in the chromatograms of optically active samples.

In summary, in this work we have developed a very simple, mild and efficient method for the resolution of several 1-(heteroaryl)ethyl amines (±)-**1a–c**. The high enantioselectivities achieved in these lipase-catalysed acetylations and the mild reaction conditions make this procedure a practical alternative for the resolution of these compounds. The extension of these biotransformations to other (±)-1-(heteroaryl)ethylamines is at present under investigation.

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