Chimia 48 (1994) 570

ISSN 0009–4293

Highly Efficient Lipase-Catalyzed Kinetic Resolution of Chiral Amines

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Abstract. The lipase *Candida antarctica* catalyzes the enantioselective acetylation of chiral primary amines, kinetic resolution leading to an enantiomeric excess (ee) of 90–98%.

1. Introduction

Chiral amines constitute an important class of organic compounds which have been synthesized in enantiomerically enriched or pure form by a variety of methods [1], including kinetic resolution by enzyme-catalyzed acylation [2]. The latter strategy has been shown to be effective using the protease subtilisin Carlsberg as the enzyme (60–99% ee), whereas lipases from such sources as *Candida cylindracea, Pseudomonas sp., Mucor sp., porcine pancreas,* and *Chromobacterium viscosum* were reported to be inefficient (< 20% ee) [2]. On the other hand, porcine pancreatic lipase has been used successfully in the kinetic resolution of a few select amino alcohols, specifically of racemic 1-aminopropan-2-ol and 2-aminobutan-1-ol (≥95% ee) [3]. Furthermore, the lipase *Candida antarctica* catalyzes the enantioselective aminolysis of β-ketoesters and chiral esters (54–98% ee) [4]. Here, we report that *Candida antarctica* is a highly effective catalyst in the enantioselective acetylation of chiral amines using acetic acid ethyl ester (AcOEt) as the acylating agent, kinetic resolution proceeding with 90–98% ee.

2. Results

Upon reacting a racemic mixture of an amine **1** in Et_2O with AcOEt in the presence of immobilized *Candida antarctica* (NOVOZYM 435)® at room temperature, the (*R*)-configurated form is enantioselectively acylated with formation of the amide **2** (*Table*).

Scheme

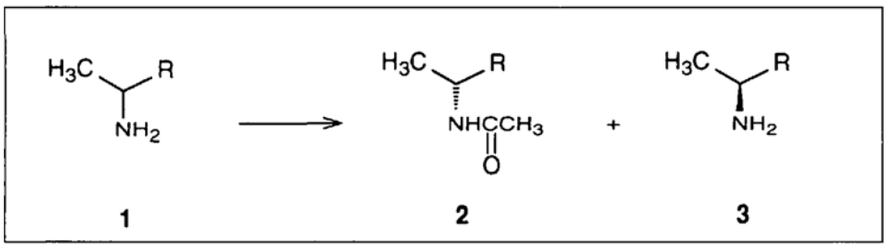

Table. *Kinetic Resolution of Racemic Amines* **1**

1 R	2 [% ee]	Conversion[a]) [%]
phenyl	97.6	25
phenyl	96.0	43
1-naphthyl	90.0	20
propyl	98.0	34
propyl	98.0	44

[a]) Theoretical maximum: 50%.

3. Discussion

The present study clearly shows that lipase-catalyzed kinetic resolution of chiral amines using AcOEt as the acylating agent can indeed be highly effective, provided the proper lipase is chosen. We do not suggest that *Candida antarctica* is the only lipase capable of this synthetically important transformation. Indeed, we are continuing our efforts in this field, especially in view of the fact that lipases belong to the most robust class of enzymes used in organic chemistry [5].

4. Experimental

The mixture of an amine **1** (2 mmol), AcOEt (8 mmol) and the lipase *Candida antarctica* (NOVOZYM 435)® (100 mg as immobilizate) in 5 ml of Et_2O is shaken until the conversion shown in the *Table* is reached (7–60 h). Conversion and % ee are determined directly by GC. In the case of **2** (R = phenyl), the product was isolated by passing gaseous HCl through the soln., filtering from the precipitated amine hydrochloride and evaporating the solvent: 25% of **2** (R = phenyl), 97.6% ee.

Received: November 22, 1994

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