SHORT PAPER

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Lipase catalysed preparation of optically active α-phenylethanol and the related substrates under solvent free condition†

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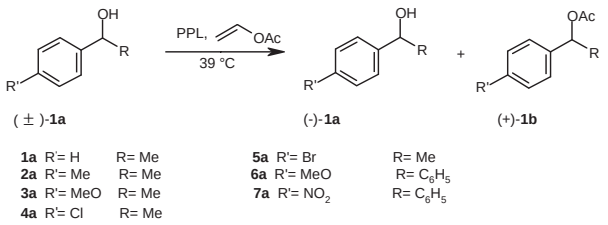
Porcine pancreatic lipase (PPL) has been used as a chiral catalyst for the kinetic resolution of α-phenylethanol and the related derivatives (p-R′$C_6H_4CH(OH)CH_3$, R′= CH_3, MeO, Cl, Br) under solvent free conditions, with excellent enantioselectivities (ee·s 81–98.5%).

Keywords: Acylation, solvent free, lipase catalysed, α-phenylethanol, transesterification

A large number of reports in the use of biotransformations for synthetic purposes have been published in the last decade.[1] Many of these studies have been relied on the ability of enzymes for asymmetric synthesis with the formation of enantiomerically enriched products.[2] In this context, hydrolases especially lipases have been widely employed for the optical resolution of chiral alcohols, esters and lactones either by hydrolysis or transesterification reactons.[3]

Reduction of toxic waste and by-products from chemical processes is also a prime objective in development of new, more environmentally friendly synthetic methods. Many organic solvents are ecologically harmful and their use renders an otherwise green technology non-biocompatible and should be minimised as far as possible or even avoided.[4] In this context the use of enzymes in organic synthesis under solvent free conditions has gained an especial attention and actively pursued.[5] Following our studies on the enzymatic kinetic resolution of racemates[6] with the aim of preparation of homochiral compounds of synthetic value, we have exploited the catalytic potential of porcine pancreatic lipase (PPL) in enantioselective acylation of α-phenylethanol and the related derivatives (**1a–7a**) under solvent free conditions. α-Phenylethanols (R′$C_6H_4CH(OH)Me$; R′= H, halo, alkyl, alkoxy) are useful intermediates for pharmaceuticals, agrochemicals and liquid crystal compounds.[7] The literature reports on the enzymatic resolution of these substrates **(1a–5a)** describe either longer reaction times or lower enantiomeric excesses.[8] In the case of substrate **3a** lipase PPL in organic media (CH_2Cl_2) using vinyl acetate proceeds very slowly and with lower streoselectivities factor.[8d] With this substrate to reach higher ee·s in organic media with lipase PFL a double kinetic resolution was required.[8d] In the studies undertaken in this research the racemic starting alcohols (**1a–7a**) were prepared by literature reports and the acylation was carried out using 0.07 g PPL per mmol of the substrate. Vinyl acetate was used as acyl donor and the reaction was conducted under solvent free conditions.



Scheme 1

The progress of the reaction was monitored by TLC and GC analysis and terminated when the half of the alcohol was consumed. Under these reaction conditions PPL exhibited very high enantioselectivity (81–98.5%) for both the remaining alcohol and the related acetate. After work up, the alcohol and acetate products were separated by column chromatography and their enantiomeric excesses were measured by comparison of the $[\alpha]_D$ of the products with those reported in the literature. Since there was no literature report on the specific rotation of (+)-**4b**, the enantiomeric excess of this product was measured after chemical hydrolysis (K_2CO_3/MeOH) to the related (+)-alcohol. The results are summarised in Table 1. The nature of substituent on benzene ring affects both the reaction time and ee·s. The best results for the remaining alcohol and acylated product on the basis of enantiomeric excesses were obtained with the MeO- substituent (**3a**). We also studied the enzymatic resolution of alcohols **6a** and **7a**. It was found that they are quite resistant to the enzymatic transesterification under these conditions and even prolonged treatment (90 h) under these reaction conditions did not produce the expected acylated products. It seems that there is only limited space in the enzyme cavity and changing the substituent (R) from Me- to C_6H_5- do not fulfil the steric requirement of this enzyme for enantioselective transesterification.

Table 1 Lipase catalysed resolution of α-phenylethanol and the related substrates

No.	Substrate	Reaction Time(h)	Conversion[a] (%)	Alcohol ee (%)	Alcohol Yield(%)	Acetate ee (%)	Acetate Yield (%)	E[12]
1	**1a**	18	52	95.8	44.2	86.5	31.4	48
2	**2a**	57	50	81.3	45.2	81	33.5	24
3	**3a**	32	49	95.5	39.7	98.5	25.5	488
4	**4a**	40	51	93.7	47.7	89.1	32.5	58
5	**5a**	75	48	86.4	50	94	33	91

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

(a) Conversion of the substrate, $c = \frac{ee_s}{ee_s + ee_p}$

We conclude that optically active α-phenylethanols and their acetylated derivatives, described in this paper can be prepared with high ee·s and acceptable yields by using lipase PPL, under solvent free conditions.

Experimental

General: PPL was purchased from Fluka. (Art.No 62300) as a dry powder and dried again under vacuum immediately prior to use. Optical rotations were measured by Atago (Polax) polarimeter. Chemicals were purchased from Merck and Fluka. Melting points were measured with Electro Thermal and are uncorrected. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC, FT-NMR (80 MHz) in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS). Column chromatography was carried out on Merck Kieselgel 60 H. GC was recorded using Buck Scientific 910 (capillary column, MXT-5, 15 m). All solvents used were dried and distilled according to standard procedures.

General procedure for PPL-catalysed acylation of α-phenylethanol and the related substrates: A mixture of racemic alcohols **1a–5a** (5.0 mmol), vinyl acetate (5.0 mmol) and lipase PPL (0.35 g) was stirred at 39 °C and the progress of the reaction was monitored by TLC ((EtOAc/ petroleum ether: 1/6) and GC. At ~50% conversion (see Table 1) the enzyme was filtered off, washed with dichloromethane (3×7 ml) and the volatile material was removed under vacuum. The residue was chromatographed on silica gel (EtOAc/ petroleum ether: 1/6) to provide (–)-**1a–5a** and (+)-**1b–5b** in 25.5–50% yield (Table 1). The structures of all the products were confirmed by spectroscopic analysis (IR, ^{1}H NMR) and the enantiomeric excesses of the products were established by comparison of their $[\alpha]_D$ with those reported in the literature.

Entry 1: After reaction for 18 h, (–)-**1a**, $[\alpha]_D^{20}$-54.15° (*c*=1.2, $CHCl_3$), ee=95.8% {$[\alpha]_D^{20}$–13°, ee=23%}[9] and (+)-**1b**, $[\alpha]_D^{24}$+118.8° (*c*=1.6, $CHCl_3$), ee=86.5% {$[\alpha]_D^{24}$+103°, ee=75%}[8b] were isolated using column chromatography.

Entry 2: Reaction for 57 h, followed by isolation of the products on column chromatography, gave (–)-**2a**, $[\alpha]_D^{20}$-41.7° (*c*=1.2, $CHCl_3$), ee=81.3% {$[\alpha]_D^{20}$ –39°, ee=76%}[8c] and (+)-**2b**, $[\alpha]_D^{20}$ +100° (*c*=1.1, $CHCl_3$), ee=81% {$[\alpha]_D^{20}$+116°, ee=94%}[10].

Entry 3: Reaction for 32 h followed by chromatography of the products, gave (–)-**3a**, $[\alpha]_D^{20}$-50° (*c*=0.4, $CHCl_3$), ee=95.5% {$[\alpha]_D^{20}$-45°, ee=86%}[8c] and (+)-**3b**, $[\alpha]_D^{20}$ +119.5° (*c*=0.75, $CHCl_3$), ee=98.5% {$[\alpha]_D^{20}$+89.8°, ee=74%}[8d].

Entry 4: After reaction for 40 h, (–)-**4a**, $[\alpha]_D^{21}$-47.5^0 (*c*=1.5, Et_2O), ee=93.8% {$[\alpha]_D^{21}$-46.1°, ee=91%}[11] and (+)-**4b**, $[\alpha]_D^{25}$+133.3° (*c*=1.2, $CHCl_3$), ee=89.1% {after hydrolysis to the related (+)-alcohol $[\alpha]_D^{21}$+45.1° (*c*=1.1, Et_2O), ee=89.1%}.

Entry 5: Reaction for 75 h followed by chromatography of the products, provided (–)-**5a**, $[\alpha]_D^{27}$-27.1^0 (*c*=2.4, MeOH), ee=86.4% {$[\alpha]_D^{27}$-16.0°, ee=51%}[8b] and (+)-**5b**, $[\alpha]_D^{26}$ +86.1° (*c*=1.1, $CHCl_3$), ee=94.0% {$[\alpha]_D^{26}$+88.9°, ee=97%}.[8b]

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