Highly Enantioselective Transformations of Ferrocene-containing Substrates by Bacterial Lipases

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The highly enantioselective hydrolysis and transesterification of ferrocene-containing substrates catalysed by the lipases from *Pseudomonas* sp. are described.

Although the potential of enzymes for use as catalysts in synthetic organic chemistry is well documented,[1–10] their application in organometallic chemistry is at an early stage.[11–15] In connection with our studies of the specificity of lipases from *Pseudomonas* sp. (PSL), we have explored the transformations of ferrocene derivatives by bacterial lipases. We herein describe that PSL transforms ferrocene-containing substrates with absolute specificity and provides enantiomerically enriched

products. The objective of this work was to see if substrates having both a small and a large hydrophobic substituent at the stereogenic centre are transformed by this enzyme with high enantioselectivity.

Recently two groups reported that PSL catalysed the transesterification of 1-ferrocenylethanol with fair to good enantioselectivity.[16,17] The preliminary specificity data obtained from our studies of PSL-catalysed hydrolysis indicated that enantioselectivity is almost absolute when the substrates, $R^1CH(OCOCH_3)R^2$, have at the stereogenic centre one small substituent (*e.g.* Me or Et) and one relatively large substituent carrying a hydrophobic ring or a branch (*e.g.* $PhCH_2$ or Bu^i). Thus, we envisaged that ferrocene derivatives **3** and **4** could be transformed by PSL with high enantioselectivity.

The ferrocenyl alcohol **3** (**a**, R=Me; **b**, R=Et) was prepared from ferrocene **1** and epoxide **2** according to the literature procedure[18] and then acetylated with acetic anhydride–pyridine at 23 °C to **4**. The alcohols **3a** and **3b** were subject to lipase-catalysed transesterification in organic solvent [eqn. (1)]. The acetates **4a** and **4b** were subject to lipase-catalysed hydrolysis in aqueous solution [eqn. (2)]. Three bacterial lipases (lipoprotein lipase, LPL; lipase AK, LAK; lipase PS, LPS) from *Pseudomonas* sp. were employed as the catalysts for these reactions.

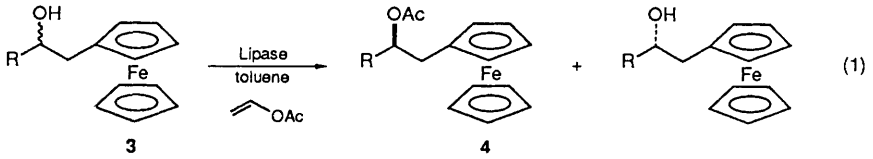
In a typical transesterification experiment, enzymes were added to an organic solution containing alcohol **2** (1 equiv.), vinyl acetate (10 equiv.) and toluene and the resulting mixture was stirred at room temperature. The reactions catalysed by LAK and LPS proceeded to near 50% conversion within a few hours and then stopped, whilst those catalysed by LPL made no detectable progress even after a few days. The acetylated products and the unchanged substrates from LAK and LPS catalysed reactions were separated by chromatography. The results are listed in Table 1. All the enzymatically acetylated products had a *R* configuration and high optical purities (>98% ee). All the recovered substrates had predominantly an *S* configuration and optical purities ranging from 66 to >98% ee. The lower optical purities of the recovered substrates are thought to result from contamination by small amounts of unchanged reactive enantiomers. The results thus indicate that lipase AK and PS catalyse the acetylation of **3** with absolute *R*-stereospecificity.

In a typical hydrolysis experiment, enzymes were added to a phosphate buffer (0.05 mol dm^{-3}; pH 7.0) containing acetate **3** and DMSO and the resulting mixture was stirred at room temperature. We observed that all three lipases catalysed effectively the hydrolyses and that all the reactions slowed down significantly, as they proceeded to near 50% conversion; they then levelled off. The results are listed in Table 2. All the enzymatically hydrolysed products have an *R* configuration and high optical purities (>98% ee). All the recovered substrates had predominantly an *S* configuration and optical purities ranging from 87 to >98% ee. The results thus indicate that all three lipases hydrolyse **4** with absolute *R*-stereospecificity.

The results given here demonstrate two important things. First, PSL-catalysed hydrolysis and transesterification provide a practical route to the optically pure ferrocene derivatives. Second, PSL discriminates perfectly between opposite enantiomers of the substrate having one small and one large substituent (carrying a hydrophobic ring at the β-position) at the chiral centre. The second strongly suggests that the proper positioning of a hydrophobic ring in the large substituent of the substrate is crucial for high enantioselection in lipase-catalysed hydrolysis and transesterification.

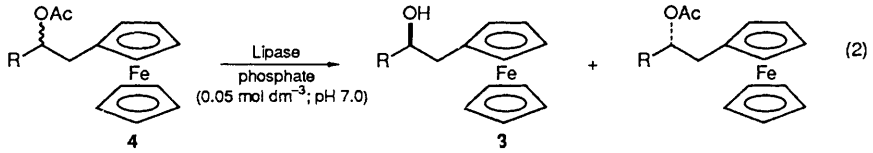
Experimental

Lipase-catalysed Transesterification of Ferrocen-1-ylpropan-2-ol **3a**.—Enzymes (lipase PS from Amano; 0.2 g) were added to a solution containing the alcohol (1 mmol), vinyl acetate (10 mmol) and toluene (10 cm^3). The resulting mixture was stirred at room temperature, with the reaction's progress being followed by TLC. The reaction proceeded to near 50% conversion in 3 h, although no detectable change could be observed. The reaction solution was stirred overnight after which the enzymes were filtered off and the filtrate was concentrated. The residue was then subjected to silica gel chromatography (n-hexane–ethyl acetate, 4:1) to give (*R*)-**4a** (0.114 g, 40%) and (*S*)-**3a** (0.110 g, 45%).



3 **4**

a, R = Me; **b**, R = Et



4 **3**

a, R = Me; **b**, R = Et

Table 1 Lipase-catalysed enantioselective transesterifications of **3**

		Product				Recovered substrate		
Substrate	Enzyme	% yield[a]	% ee[b]	$[\alpha]_D^{23}$[c,d]	AC[e]	% yield[a]	% ee[f]	AC[e]
3a	LAK	40	>98	+58.6	*R*	43	87	*S*
3a	LPS	40	>98	+57.5	*R*	45	98	*S*
3b	LAK	34	>98	+62.0	*R*	43	66	*S*
3b	LPS	41	>98	+61.7	*R*	47	>98	*S*

[a] Isolated; the theoretical maximum yield is 50%. [b] Determined by ^{1}H NMR spectroscopy in the presence of $Eu(hfc)_3$. [c] $[\alpha]_D^{23}$ Values in 10^{-1} deg cm^2 g^{-1}. [d] (*c* 4, CH_2Cl_2); −54.8 for (*S*)-**4a** prepared chemically from **1** and (*S*)-**2a**. [e] Absolute configuration. [f] Determinined in the chemically acetylated form by ^{1}H NMR spectroscopy in the presence of $Eu(hfc)_3$.

Table 2 Lipase-catalysed enantioselective hydrolysis of **4**

		Product				Recovered substrate		
Substrate	Enzyme	% yield[a]	% ee[b]	$[\alpha]_D^{23}$[c,d]	AC[e]	% yield[a]	% ee[f]	AC[e]
4a	LPL	46	>98	−16.7	*R*	50	90	*S*
4a	LAK	45	>98	−16.3	*R*	50	87	*S*
4a	LPS	45	>98	−16.3	*R*	46	>98	*S*
4b	LPL	40	>98	−22.1	*R*	43	88	*S*
4b	LAK	49	>98	−20.5	*R*	46	97	*S*
4b	LPS	47	>98	−21.8	*R*	47	98	*S*

[a] Isolated; the theoretical maximum yield is 50%. [b] Determined in the chemically acetylated form by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$. [c] $[\alpha]_D^{23}$ Values in 10^{-1} deg cm^2 g^{-1}. [d] (*c* 4, CH_2Cl_2); +15.5 for (*S*)-**3a** prepared chemically from **1** and (*S*)-**2a**. [e] Absolute configuration. [f] Determinined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$.

Lipase-catalysed Hydrolysis of 2-*Acetoxyferrocen*-1-*ylpropane* **4a**.—Enzymes (lipoprotein lipase from Amano; 50 mg) were added to an aqueous solution (pH 7.0; 30 cm^3) containing acetate (3.7 mmol), phosphate (0.05 mol dm^{-3}), and DMSO (10% v/v) and the resulting mixture was stirred at room temperature. The pH of the solution was maintained between 6.9 and 7.1 by the controlled addition of NaOH (0.1 mol dm^{-3}), the reaction's progress being followed from the amount of NaOH solution added. The reaction was stopped at 50% conversion when 18.7 cm^3 of NaOH (0.1 mol dm^{-3}) had been added (4.6 days). The reaction mixture was extracted with ether and the extracts were dried ($MgSO_4$), concentrated and the residue subjected to silica gel chromatography (n-hexane–ethyl acetate, 4:1) to give (*R*)-**3a** (0.419 g, 46%) and (*S*)-**4a** (0.530 g, 50%).

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