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DMSO-triggered enhancement of enantioselectivity in Novozyme[435]-catalyzed transesterification of chiral 1-phenylethanols

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Abstract—Dimethyl sulfoxide as cosolvent enhances the enantioselectivity of resolved products up to 100% in the Novozyme[435]-catalyzed transesterification of chiral 1-phenylethanols but not 1-phenyl-2-haloethanols in THF. The reaction does not proceed in lipophilic and water-miscible polar solvents.

Enantiomerically pure secondary alcohols are important synthetic intermediates and are also useful chiral auxiliaries for both synthetic and analytical applications.[1] However, some of the reported methods for preparing such compounds in pure form have limited practical applicability due to drawbacks including tedious work-up, expensive chiral auxiliaries, large reaction volumes, etc. Studies[2] on enzymatic reactions in low polarity organic solvents have widened their use in the resolution[3] of racemic mixtures for the preparation of enantiomerically pure secondary alcohols. This in turn helps to overcome some of the practical problems such as hydrolysis in water, recovery of the enzyme for recycling, pH adjustment during the reaction process, etc. Lipases have been established as valuable catalysts for such purposes.

Even though lipases have found various uses, their full potential has far from fully been explored. Sometimes a suitable lipase in a suitable medium does not exhibit satisfactory results, and only on fine tuning of the reaction conditions, can a shift of the thermodynamic equilibrium in favor of the forward direction be achieved. Application of reduced pressure plays a positive role in the equilibrium conversion in lipase catalyzed reactions. In the resolution[4] of racemic 2-octanol and several other secondary alcohols in the presence of a non-volatile acyl donor such as ethyl octanoate, the enantioselectivity was raised to 93–97% with enantiomeric ratios (*E*) of more than 100. The limitation of the reaction is that it strictly requires a non-volatile acyl donor to afford a volatile leaving group. It is known[5,6] that the enzyme *Candida antarctica lipase-B* (CAL-B) shows extremophile properties, but only a few systematic investigations[7] have been undertaken on the influence of additives on such lipase-catalyzed reactions. Accordingly we have studied the resolution of some secondary alcohols with CAL-B lipase under immobilized conditions (Novozyme[435]) in the presence of an additive.

A series of racemic alcohols (**2a**–**g**) prepared by sodium borohydride reduction of prochiral carbonyl compounds (**1a**–**g**) were subjected to Novozyme[435] using vinyl acetate as the acetylating agent and acetonitrile as solvent, however, in this solvent CAL-B was washed away from its support. When carried out in dry THF, the enantioselectivity of the products (**3a**–**e**) and (**4a**–**e**) was found to be moderate, low in the case of (**3f**) and (**4f**) and almost nil in the case of (**3g**) and (**4g**) (Table 1, data in parentheses). The rigid conformation[8,9] of CAL-B in an organic solvent may prevent its active site from accepting a non-natural substrate with a structure significantly different from that of the natural one. Although addition of a trace amount of water to enzymatic reactions in organic solvents has a lubricating effect with a consequent rise in conformational flexibility, the onset of hydrolytic pathways competing with the derived process[10] is a major drawback. It has been reported[11] that addition of a trace amount of a mild

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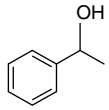
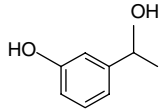
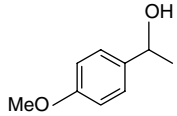
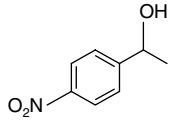
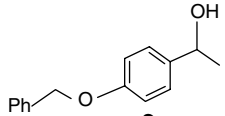
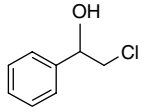
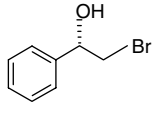
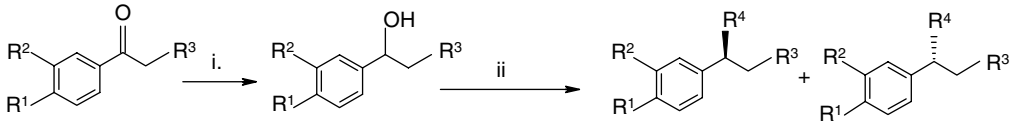
Table 1. Novozyme[435] mediated resolution of secondary alcohols in the presence and absence (parentheses) of DMSO

Substrates **2**	Time (h)	Temp (°C)	Yield (%)[a,b]		Conf.[c]	Ee[d]	Yield (%)[a,b]		Conf.[c]	Ee[d]	E[e]
 **a**	7	25	**3a**	51 (40)	*S*	100 (41)	**4a**	55 (42)	*R*	100 (43)	>200 (3.7)
 **b**	7	30	**3b**	29 (21)	*S*	51 (40)	**4b**	27 (19)	*R*	100 (39)	>200 (3.3)
			$3b_1$	17 (8)	*S*	73 (39)	**$4b_1$**	13 (8)	*R*	99 (60)	>200 (5.9)
 **c**	8	28 (25)	**3c**	45 (35)	*S*	99 (42)	**4c**	49 (38)	*R*	98 (45)	>200 (3.9)
 **d**	7	25	**3d**	50 (39)	*S*	>99 (39)	**4d**	47 (40)	*R*	>99 (42)	>200 (3.5)
 **e**	7	25	**3e**	57 (44)	*S*	100 (21)	**4e**	54 (24)	*R*	100 (37)	>200 (2.6)
 **f**	7	30 (25)	**3f**	28 (25)	*R*	90 (19)	**4f**	29 (20)	*S*	91 (18)	65 (1.7)
 **g**	75 (24)	70	**3g**	3 (Nil)	*R*	4 (Nil)	**4g**	3 (Nil)	*S*	4 (Nil)	1.1 (Nil)

[a] Characterized from their corresponding IR, NMR, LC–MS, and HPTLC data and by comparison with reported values.[14–18]
[b] Isolated yields after column chromatography.
[c] The absolute configuration was assigned by the sign of rotation and comparison with the literature values.
[d] Determined by chiral HPLC.
[e] Determined as reported.[19]

base enhances the enantioselectivity in *Pseudomonus lipase* catalyzed resolution of racemic 2-aryloxy propionate. Considering the above points we carried out the transesterification reactions of (**2a**–**g**) in the presence of a catalytic amount of the denaturing organic cosolvent DMSO (Scheme 1).

In the course of our study[12] it was indeed observed that although enzymes are denatured in solvents such as DMSO, addition of a catalytic amount (about 5% of the reaction volume) in the transesterification reaction strikingly enhanced the chemical yield and enantioselectivity of (**3a**–**f**) and (**4a**–**f**) (Table 1). However, in the case of (**3g**) and (**4g**) the enantioselectivity was enhanced only very poorly (4–60%) (Table 1). Increasing the amount of DMSO had a detrimental effect. The observed increase of the enantioselectivity may thus be attributed to DMSO-induced flexibility of the restricted conformation of the lipase. On the other hand, the poor selectivity in resolving (**3g**) and (**4g**) conforms to Kazlauskas'[13] rule. In the transesterification reaction of 1-(3-hydroxyphenyl ethanol (**2b**), four acetylated products viz (**3b**), (**$3b_1$**), (**4b**), and (**$4b_1$**) were produced due to the additional presence of a phenolic hydroxyl group. The ratio



1a-g **2a-g** **3a-g, b$_1$** **4a-g, b$_1$**

Scheme 1. Reagents and conditions: R^1 = H, OMe, NO_2, OCH_2Ph; R^2 = H, OH, OAc (for **3b$_1$** and **4b$_1$**); R^3 = H, Cl, Br; R^4 = OH, OAc; i = $NaBH_4$/MeOH/0–5 °C; ii = Novozyme[435]/THF/25–70 °C.

of (**3b**) to (**4b**) was 1.07:1 and that of (**3b$_1$**) to (**4b$_1$**) was 1.3:1.

From the foregoing studies we conclude that very high enantioselectivity in transesterification reactions of secondary alcohols with CAL-B (Novozyme[435]) in the presence of 5% DMSO by volume can be achieved when the sizes of the substituents at the chiral center are significantly different.

References and notes

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12. General procedure: To a solution of the racemic alcohol (1.86 mmol) in dry THF (5 mL) were added Novozyme[435] (0.318 g), vinyl acetate (32 mmol), and DMSO (5% of the total reaction volume). The mixture was stirred for about 7–75 h at 25–70 °C depending upon the substrate. After completion (TLC), the reaction mixture was filtered, the solvent evaporated under reduced pressure, and the residue quenched with water (20 mL). The products were extracted with ethyl acetate, the extract was dried and the solvent was distilled under reduced pressure. The two products formed were separated by silica gel column chromatography eluting with pet.ether–ethyl acetate mixture and were identified from their spectroscopic data which matched with the reported[14–18] values. The enantiomeric excesses of the products were determined by HPLC analysis in a Chiralcel OD column (250 × 46 mm i.d.), particle size 10 μm using 15% isopropanol in hexane as the mobile phase, flow rate 1 mL/min.
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