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Chemoenzymatic synthesis of enantiomerically pure 1,2-diols employing immobilized lipase in the ionic liquid [bmim]PF_6

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Abstract—Significantly enhanced enantioselectivity in the enzymatic kinetic resolution of 1,2-diols employing immobilized lipase from *Pseudomonas cepacia* (PS-C, 'Amano') results from the use of the ionic liquid [bmim]PF_6 as reaction medium.

1,2-Diols are important precursors and intermediates for a variety of synthetic applications[1] and this functionality is found in a number of pharmaceuticals or their intermediates[2] (Fig. 1). Therefore, the development of methodologies for the preparation of enantiomerically pure 1,2-diols is of considerable interest. Chemical methods for the preparation of optically active 1,2-diols include chiral-pool synthesis,[2a] asymmetric hydroxylation,[3] ring opening of epoxides[4] and reduction of optically active 2-hydroxy-carboxylic acid derivatives.[5] Optically active 1,2-diols have also been obtained by enzyme-mediated synthesis employing lipase-catalyzed transesterification or hydrolysis of monoprotected diols or their corresponding acylated compounds[6] respectively, or by lipase-catalyzed alcoholysis of the diacylated diols.[2b] The lipase-catalyzed transesterification of 1,2-diols is highly regioselective[7] but shows only low enantioselectivity in the monoacylation step.[8] Most of the kinetic resolution transesterification processes employing different lipases, exhibit moderate or low enantioselectivity.[8,9] Therefore, in an endeavour to improve the enantioselectivity, immobilized lipase PS-C has been investigated for the transesterification of 1,2-diols in ionic liquid medium. Ionic liquids are regarded as eco-friendly alternatives to volatile organic solvents in chemical and biocatalytic processes, due to their negligible vapor pressure and nonflammable nature.[10] Moreover, their hydrophobicities/hydrophilicities and solvent miscibility can be tuned by selecting the appropriate cation and anion. Their applications often result in marked improvements in catalytic performance.[11] Further, their use can enhance the activity, selectivity, and stability of biocatalysts.[12] Some reports in the literature have appeared recently on the use of ionic liquids in biocatalysis, especially using lipases.[13,14] These investigations suggested that the enhancement in enantioselectivity can be attributed to the possible interaction of ionic liquids with the charge residual found in or near the active center of the enzyme.

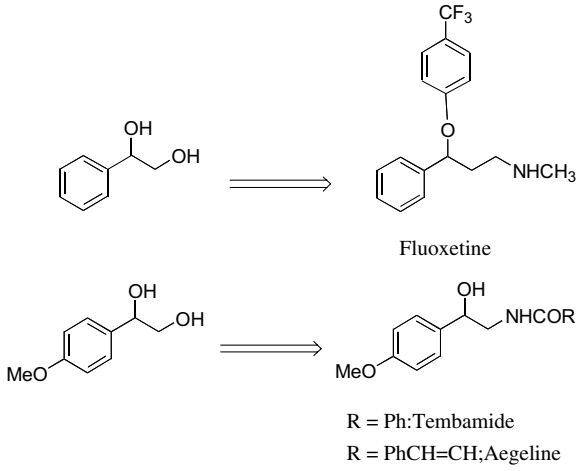

Figure 1.

The precursors, α-acetoxy ketones **2a–d** have usually been synthesized by substitution of a halogen with an acetoxy group under reflux.[15] In this investigation these transformations were performed in an ionic liquid [bmim]Br medium using KOAc, to provide the required

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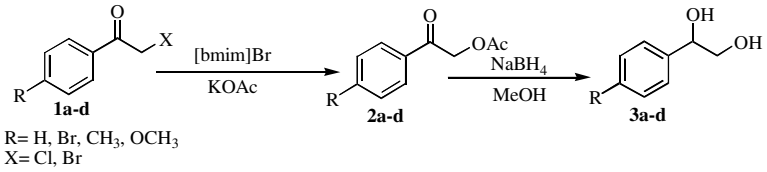


Scheme 1.

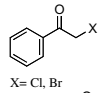
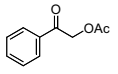
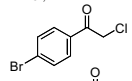
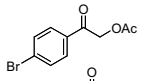
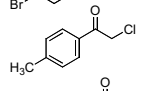
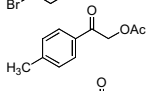
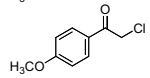
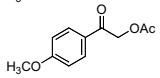
α-acetoxy ketones **2a**–**d** for the preparation of 1,2-diols **3a**–**d** through $NaBH_4$ reduction in methanol. It was observed that this process in an ionic liquid medium is not only efficient but takes place at room temperature in quantitative yields (Scheme 1, Table 1).[16]

In continuation of our interest in biocatalytic transformations employing lipases,[17] we report here the use of immobilized lipase from *P. cepacia* (PS-C, 'Amano') for the kinetic resolution of 1,2-diols. This transesterification process employing immobilized lipase (PS-C) has been investigated in the ionic liquid medium, using 1-phenylethane-1,2-diol **3a** as an example.

The results are shown in Table 2. By employing immobilized lipase (PS-C) for the resolution of the 1,2-diol, the enantioselectivity of diacetate **5a** as well as monoacetate **4a** were enhanced. In the case of the ionic liquid [bmim]PF_6 (prepared and purified by the literature procedure,[14f] water% = 0.6 by KF titration) the enhancement of this enantioselectivity is remarkable for both the acetates.

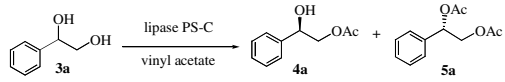
This enzymatic kinetic resolution process in the ionic liquid medium was studied for different substituted 1,2-diols as shown in Table 3. The transesterification of 1,2-diols **3a**–**d**[9,18] was carried out using lipase PS-C

Table 1. Acetoxylation of α-halo ketones with KOAc in the ionic liquid [bmim]Br

Entry	Substrate **1**	Product **2**[a]	Time (min)	Yield (%)
a	 X= Cl, Br		30	97
b			30	95
c			40	93
d			40	96

[a] All products were characterized by ^1H NMR, IR, and mass spectroscopy.

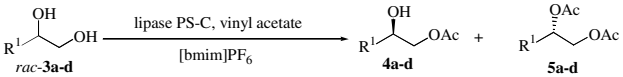
Table 2. Lipase PS-C catalyzed resolution of rac-1-phenylethane-1,2 diol[a]



Solvent	Conv.[b] (%)	**4a** ee_s[c] (%)	**5a** ee_p[c] (%)	E[d]
n-Hexane/THF (4/l)	48	92	>99	>150 (659)
Diisopropyl ether	49	94	>99	>150 (712)
Toluene	43	74	>99	>150 (400)
[bmim]PF_6	50	>99	>99	>150 (1050)

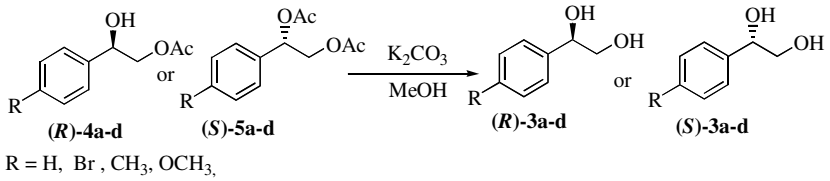
[a] Conditions: lipase PS-C 'Amano' (0.5 equiv w/w), vinyl acetate (6 equiv), solvent (2 mL), ionic liquid [bmim]PF_6 (0.5 mL) substrate (50 mg), l0 h.
[b] The values of conversion c, were calculated from the enantiomeric excesses of the starting material (ee_s) and product (ee_p).[21]
[c] Determined by HPLC after hydrolysis using a chiral column. Analytical conditions; chiral OD, hexane/2-propanol = 90:10, flow rate = 0.5 mL/min, UV = 254 nm.
[d] Determined from conversion c and ee_p.[21]

Table 3. Lipase PS-C catalyzed resolution of rac-phenyl-l,2-ethanediols in the ionic liquid [bmim]PF_6[a]



Substrate **3**	R^1	Time (h)	Conv.[b] (%)	**4**			**5**			E[f]
				Yield[c] (%)	ee_s[d] (%)	Conf.	Yield[c] (%)	ee_p[e] (%)	Conf.	
a	C_6H_5	10	50	43	>99	*R*	46	>99	*S*	>150 (1057)
b	*p*-Br–C_6H_4	10	50	45	>99	*R*	41	>99	*S*	>150 (1057)
c	*p*-Me–C_6H_4	10	50	42	>99	*R*	45	>99	*S*	>150 (1057)
d	*p*-MeO–C_6H_4	14	36	60	>99	*R*	34	>99	*S*	>150 (350)

[a] Conditions: lipase PS-C 'Amano' (0.5 equiv w/w), vinyl acetate (6 equiv), substrate (50 mg), [bmim]PF_6 (0.5 mL) with stirring at room temperature.
[b] The values of conversion c, were calculated from the enantiomeric excesses of the starting material (ee_s) and product (ee_p).[21]
[c] Isolated yields after column chromatography.
[d] Determined by HPLC after hydrolysis using a chiral column. Analytical conditions; chiral OD, hexane/2-propanol = 90/10, flow rate = 0.5 mL/min, UV = 254 nm.
[e] Determined by HPLC using a chiral column. Analytical conditions; chiral OD, hexane/2-propanol = 90/10 (**5a**), flow rate = 0.5 ml/min, UV=254 nm, chiral AD-H, hexene/2-propanol = 90/10 (**5b**–**d**), flow rate 0.5 mLVmin, UV = 254 nm.
[f] Determined from conversion c and ee_p.[21]



Scheme 2.

(0.5 equiv w/w) and vinyl acetate (6 equiv) as acyl donor in the ionic liquid (Table 3).[19] The literature reports that employing nonimmobilized lipase PS usually takes approximately 30–140 h in a variety of organic solvents.[8,9] This enzymatic kinetic resolution takes place in 10–14 h for nearly 50% conversion (reaction progress was monitored by HPLC using a silica column) by the use of immobilized lipase (PS-C). It is interesting to observe that this lipase in the immobilized form not only gives higher enantioselectivity but the reaction time was significantly shortened. In the lipase-mediated transesterification in ionic liquid medium, the acetylation process initially takes place regioselectively on the primary hydroxyl group of the 1,2-diols to afford their monoacetates in 1–2 h. Later, the formation of diacetate products takes place in an enantioselective manner. Various substituted 1,2-diols were converted enantioselectively into (*S*)-diacetates **5a**–**d** with high enantioselectivity (>99%) as described in Table 3. *p*-Methoxy-substituted phenylethane-1,2-diol **3d** afforded diacetate (*S*)-**5d** in >99% ee. In the case of phenylethane-1,2-diol **3a** and for *p*-bromo and *p*-methyl substituted phenylethane-1,2-diols **3b, 3c** both the monoacetates and diacetates were obtained in >99% ee. Further, deacetylation of both the acetates provided enantiomerically enriched diols **3a**–**d**, quantitatively, using K_2CO_3 in MeOH.[20] The absolute configuration for the resolved diols (*S*) and (*R*) was assigned by comparison of the sign of rotation with that obtained from the earlier methods (Scheme 2).

In summary, this investigation has demonstrated that lipase-catalyzed transesterification can be employed in the ionic liquid [bmim]PF_6 with enhancement in enantioselectivity for the enzymatic kinetic resolution of 1,2-diols. This process of resolution of 1,2-diols has been carried out for the first time employing a lipase in the ionicliquid [bmim]PF_6. Moreover, the easy recovery of the ionic liquid is environmentally interesting as it can be reused and recycled.

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16. In a typical procedure, to α-chloroacetophenone (1 mmol) in the ionic liquid [bmim]Br (1.5 mL) was added KOAc (1.2 mmol) at room temperature. The reaction mixture was stirred for 30 min then ether (3 × 5 mL) was added to the reaction mixture with vigorous stirring for 5 min. The reaction mixture was allowed to stand for a further 5 min and the clear supernatant liquid was decanted. The ether layers were concentrated in vacuo to obtain the α-acetoxy acetophenone which was sufficiently pure for the next step. The remaining ionic liquid was dissolved in CH_2Cl_2 (2 mL), filtered to remove solid materials and CH_2Cl_2 was removed in vacuo to afford the ionic liquid, which could be recycled in subsequent runs.
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19. General procedure for the resolution of 1,2-diols **3a**–**d**. To a stirred solution of the appropriate 1,2-diol (50 mg) in the ionic liquid [bmim]PF_6 (0.5 mL) was added vinyl acetate (6 equiv) and lipase PS-C (0.5 equiv w/w) at room temperature. The mixture was stirred at room temperature for the appropriate time (see Table 3). After about 50% conversion of the reaction as indicated by HPLC/TLC, ether (3 × 3 mL) was added to the reaction mixture with stirring for 5 min. The mixture was allowed to stand for a further 5 min and the clear supernatant liquid was decanted. The ether layers were concentrated in vacuum to give an oily residue, which was purified by silica gel column chromatography (eluent: ethyl acetate–*n*-hexane) to afford the monoacetate and diacetate products. The products were analyzed by HPLC using a chiral column (details of the chiral columns are given in the footnotes of Table 3) to determine their optical purity and measure the enantiomeric excess (ee).
Spectroscopic data: (*R*)-2-Hydroxy-2-phenylethyl acetate **4a**.[11] Yield: 43%; $[\alpha]_D^{25}$ −26.8 (*c* 1.1, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 3450, 1740; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 4.10 (dd, 1H, *J* = 11.89, 8.68 Hz), 4.20 (dd, 1H, *J* = 11.89, 3.39 Hz), 4.90 (dd, 1H, *J* = 8.25, 3.39 Hz), 7.2–7.4 (m, 5H); EIMS *m/z* = 120 ($M^+ - 60$). Elemental anal. calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.35; H, 6.62%.
(*S*)-2-Methylcarbonyloxy-1-phenylethyl acetate **5a**[11] Yield: 46%; $[\alpha]_D^{25}$ +54.2 (*c* 1, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 1740; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.15 (s, 3H), 4.20 (dd, 1H, *J* = 11.89, 8.17 Hz), 4.30 (dd, 1H, *J* = 11.89, 3.71 Hz), 6.0 (dd, 1H, *J* = 8.17, 3.71 Hz), 7.25–7.40 (m, 5H); EIMS *m/z* 162 ($M^+ - 60$). Elemental anal. calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.50; H, 6.29%.
(*R*)-2-Hydroxy-2-(4-bromophenyl)ethyl acetate **4b**. Yield: 45%; $[\alpha]_D^{25}$ −27.3 (*c* 1, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 3440, 1735; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 4.10 (dd, 1H, *J* = 11.89, 8.30 Hz), 4.20 (1H, dd, *J* = 11.89, 3.39 Hz), 4.85 (m, 1H), 7.20 (d, 2H, *J* = 8.68 Hz), 7.45 (d, 2H, *J* = 8.68 Hz); EIMS *m/z* = 200 ($M^+ - 59$). Elemental anal. calcd for $C_{10}H_{11}BrO_3$: C, 46.36; H, 4.28. Found: C, 46.25; H, 4.23%.
(*S*)-2-Methylcarbonyloxy-1-(4-bromophenyl)ethyl acetate **5b**. Yield: 41%; $[\alpha]_D^{25}$ +55 (*c* 1.7, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 1740; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.00 (s, 3H), 2.10 (s, 3 h), 4.2 (dd, 1H, *J* = 11.89, 8.17 Hz), 4.30 (dd, 1H, *J* = 11.89, 3.71 Hz), 5.90 (dd, 1H, *J* = 8.17, 3.71 Hz), 7.20 (d, 2H, *J* = 8.17 Hz), 7.50 (d, 2H, *J* = 8.17 Hz); EIMS *m/z* = 242 ($M^+ - 59$). Elemental anal. calcd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35. Found: C, 47.70; H, 4.30%.
(*R*)-2-Hydroxy-2-(4-methylphenyl)ethylacetate **4c**. Yield: 42%; $[\alpha]_D^{25}$ −34.1 (*c* 1.5, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 3450, 1730; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 2.30 (s, 3H), 4.10 (dd, 1H, *J* = 11.89, 8.17 Hz), 4.20 (dd, 1H, *J* = 11.89, 3.71 Hz), 4.9 (dd, 1H, *J* = 8.25, 3.71 Hz), 7.10 (d, 1H, *J* = 8.17 Hz), 7.20 (d, 1H, *J* = 8.17 Hz); EIMS *m/z* = 194 (M^+). Elemental anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.93; H, 7.18%.
(*S*)-2-Methylcarbonyloxy-1-(4-methylphenyl)ethyl acetate **5c**. Yield: 45%; $[\alpha]_D^{25}$ +70.2 (*c* 1.5, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 1730; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.0 (s, 3H), 2.15 (s, 3H), 2.40 (s, 3H), 4.15 (dd, 1H, *J* = 11.89, 8.17 Hz), 4.30 (dd, 1H, *J* = 11.89, 3.71 Hz), 5.90 (dd, 1H, *J* = 8.17, 3.71 Hz), 7.10 (d, 2H, *J* = 8.17 Hz), 7.20 (d, 2H, *J* = 8.17 Hz); EIMS *m/z* = 236 (M^+). Elemental anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.93; H, 6.66%.
(*R*)-2-Hydroxy-2-(4-methoxyphenyl)ethylacetate **4d**. Yield: 60% $[\alpha]_D^{25}$ −27 (*c* 1.2, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 3400, 1730; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.10 (s, 3H), 3.80 (s, 3H), 4.10 (dd, 1H, *J* = 11.15, 8.17 Hz), 4.20 (dd, 1H, *J* = 11.15, 3.71 Hz), 4.80 (dd, 1H, *J* = 8.17, 3.17 Hz), 6.85 (d, 2H, *J* = 8.92 Hz) 7.30 (d, 2H, *J* = 8.92 Hz); EIMS *m/z* = 210 (M^+). Elemental anal. calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.81; H, 6.68%.
(*S*)-2-Methylcarbonyloxy-1-(4-methoxyphenyl)ethyl acetate **5d**. Yield: 34%; $[\alpha]_D^{25}$ +81.4 (*c* 1, $CHCl_3$, >99% ee); IR (neat, cm^{-1}): 1730; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.10 (s, 3H), 3.80 (s, 3H), 4.20–4.30 (m, 2H), 5.95 (dd, 1H, *J* = 11.89, 3.71 Hz), 6.85 (d, 2H, *J* = 8.92 Hz), 7.30 (d, 2H, *J* = 8.92 Hz); EIMS *m/z* = 252 (M^+). Elemental anal. calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.85; H, 6.32%.
20. General procedure for the hydrolysis of **4a**–**d**. In a typical experiment K_2CO_3 (1.5 mmol) was added to a solution of **4a**–**d** (1 mmol) in methanol (10 mL). The mixture was stirred for 3–4 h, and then acidified with 1 N HCl. The mixture was evaporated and then extracted with diethyl

ether (3×10 mL). The combined ether phases were dried over Na_2SO_4 and evaporated to give the 1,2-diols.

(*R*)-1-Phenyl-1,2-ethane diol **3a.**[11] Yield: 94%; mp 60–63 °C; $[\alpha]_D^{25}$ −69.0 (*c* 1, $CHCl_3$; >99% ee); IR (KBr, cm^{-1}) 3330 (br); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.25 (bs, 1H), 2.70 (bs, 1H), 3.60 (dd, 1H, *J* = 11.15, 8.92 Hz), 3.70 (dd, 1H, *J* = 11.15, 2.29 Hz), 4.8 (dd, 1H, *J* = 2.23, 8.92 Hz), 7.30 (m, 5H); EIMS *m*/*z* = 138 (M^+). Elemental anal. calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.29. Found: C, 69.45; H, 7.21%.

(*R*)-1-(4-Bromophenyl)-1,2-ethanediol **3b.**[11] Yield: 95% mp 102–103 °C; $[\alpha]_D^{25}$ −50 (*c* 1, $CHCl_3$, >99% ee); IR (KBr, cm^{-1}) 3330 (br); ^1H NMR (200 MHz, $CDCl_3$): δ = 3.50 (dd, 1H, *J* = 11.15, 8.92 Hz), 3.70 (dd, 1H, *J* = 11.15, 2.23 Hz), 4.75 (dd, 1H, *J* = 8.92, 2.23 Hz), 7.20 (d, 2H, *J* = 8.17 Hz), 7.50 (d, 2H, *J* = 8.17 Hz); EIMS m/z = 217 (M^+). Elemental anal. calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.14; H, 4.09%.

(*R*)-1-(4-Methylphenyl)-1,2-ethanediol **3c.**[11] Yield: 94%; mp 70–72 °C $[\alpha]_D^{25}$ −68.2 (*c* 1, $CHCl_3$, >99% ee); IR (KBr, cm^{-1}); 3330 (br); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 3.50–3.65 (m, 2H), 4.70 (m, 1H), 7.15 (d, 2H, *J* = 8.17 Hz), 7.25 (d, 2H, *J* = 8.17 Hz); EIMS *m*/*z* = 152 (M^+). Elemental anal. calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.95; H, 7.84 %.

(*R*)-1-(4-Methoxyphenyl)-1,2-ethanediol **3d.**[11] Yield: 95%; mp 76–78 °C $[\alpha]_D^{25}$ −35 (*c* 1, $CHCl_3$, 56% ee); IR (KBr, cm^{-1}) 3330 (br); ^1H NMR (200 MHz, $CDCl_3$): δ = 2.30 (bs, 1H), 2.70 (bs, 1H), 3.60–3.70 (m, 2H), 3.80 (s, 3H), 4.75 (m, 1H), 6.90 (d, 2H, *J* = 8.17 Hz), 7.30 (d, 2H, *J* = 8.17 Hz); EIMS *m*/*z* = 168 (M^+). Elemental anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.22; H, 7.13%.

21. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Shi, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.