Hydrolase-catalyzed Kinetic Resolution of 5-[4-(1-Hydroxyethyl)phenyl]-10,15,20-tris(pentafluorophenyl)porphyrin in Ionic Liquids

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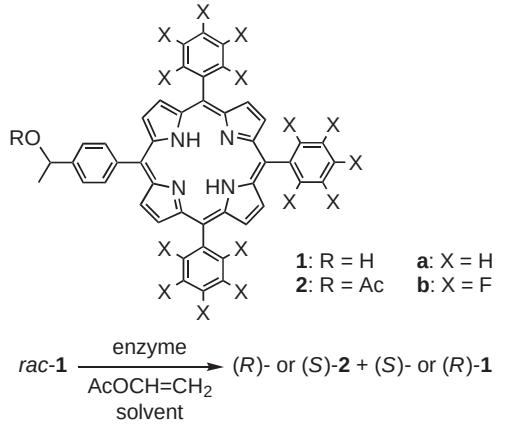
(Received November 13, 2007; CL-071258; E-mail: ema@cc.okayama-u.ac.jp)

Bulky alcohol, 5-[4-(1-hydroxyethyl)phenyl]-10,15,20-tris-(pentafluorophenyl)porphyrin (**1b**), was synthesized, and enantiomerically pure alcohol **1b** and ester **2b** were obtained by a single kinetic resolution catalyzed by *Candida antarctica* lipase in *i*-Pr_2O and in [bdmim][PF_6].

Lipases are useful biocatalysts for the preparation of optically active compounds.[1] The unique characteristics, such as (i) high catalytic activity in both aqueous and nonaqueous media, (ii) high enantioselectivity, and (iii) broad substrate specificity, are the key to the successful results reported so far. Previously, we have reported the lipase-catalyzed kinetic resolution of 5-[4-(1-hydroxyethyl)phenyl]-10,15,20-triphenylporphyrin (**1a**) (Scheme 1).[2] Enantiomerically pure alcohol **1a** and ester **2a** were obtained by a single kinetic resolution although the reaction was sluggish. No other separation methods could rival this method. Each of the enantiomers was then converted to a chiral molecular tweezer capable of functioning as a chiral shift reagent.[2b]

Metalloporphyrins have (i) a strong coordination power, (ii) a large ring-current effect, and (iii) a rigid structure as a scaffold useful for the construction of a molecular architecture. We envisioned that the introduction of electron-withdrawing groups, such as the pentafluorophenyl group, to the meso-positions of the porphyrin would increase further the binding ability of the molecular tweezer by enhancing the coordination capacity of the central metal. Taft's substituent constant, the σ^* value, of the pentafluorophenyl group is 1.50, which is greater than that of the 3,5-dinitrophenyl group (1.37).[3] Here we report the hydrolase-catalyzed kinetic resolution of **1b** in an organic solvent and ionic liquids.

Porphyrin **1b** was synthesized by the condensation of 2,3,4,5,6-pentafluorobenzaldehyde, 4-(1-hydroxyethyl)benzaldehyde, and pyrrole in the same way as reported for **1a**.[2a] The kinetic resolution of **1b** was performed with commercially available lipases and subtilisin (Scheme 1). The enantiomeric purities (% ee) of **1b** and **2b** were determined by means of chiral HPLC, and the *E* value and conversion were calculated according to the literature.[4] The absolute configurations of **1b** and **2b** were assigned by analogy to those of **1a** and **2a**, respectively. The results are listed in Table 1.



Scheme 1. Enzyme-catalyzed kinetic resolution of **1**.

Previously, we have optimized the reaction conditions for **1a**, where racemic alcohol **1a** was completely resolved into enantiomerically pure (*R*)-**2a** and (*S*)-**1a** in *i*-Pr_2O at 60 °C using lipase PS-C II (*Burkholderia cepacia* lipase immobilized to a porous ceramic support).[2b] Therefore, we initially employed the same enzyme for the kinetic resolution of the fluorinated counterpart **1b**. Although we conducted the lipase-catalyzed reactions in *i*-Pr_2O at various temperatures (30–80 °C) to obtain high *E* values, the conversions did not reach 50%, being the highest at 60 °C (39%, Entry 1). Obviously, the reactivity of **1b** is much lower than that of **1a**. We consider that the pentafluorophenyl group is bulkier than the phenyl group,[5] and that this increase in bulkiness makes the lipase-catalyzed acylation of **1b** more sluggish. Because the solubility of **1b** in *i*-Pr_2O was found to be very high, we performed the reaction at a higher concentration, which resulted in a faster reaction even at 40 °C (Entry 2).

Docking simulations using a crystal structure of *Burkholderia cepacia* lipase (PDB code 1OIL) suggested that the pentafluorophenyl groups in (*R*)-**1b** cause a severe steric repulsion with the enzyme in the transition state (not shown). We therefore decided to test other enzymes with a less crowded active site, such as *Candida antarctica* lipase and subtilisin Carlsberg. Chirazyme L-2 (*Candida antarctica* lipase) was found to resolve **1b** completely even at 40 °C (Entry 3), while ChiroCLEC-BL (cross-linked enzyme crystals of subtilisin Carlsberg) showed a lower conversion with a reduced *E* value (Entry 4). The opposite enantiopreferences of lipases (R-preference) and subtilisin (S-preference) were observed as reported previously for **1a**.[2a]

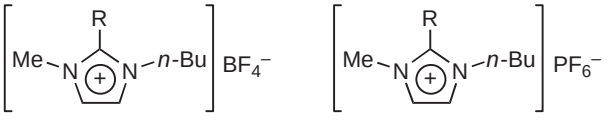
Ionic liquids have recently attracted much attention as "green" solvents.[6–11] They usually show (i) non-volatility, (ii) non-flammability, and (iii) good solubility. Among a variety of ionic liquids commercially available, we selected a 1-butyl-2,3-dimethylimidazolium salt, [bdmim][BF_4], because Itoh and co-workers have reported that lipase activity is higher in [bdmim][BF_4] than in [bmim][BF_4], the latter of which has an acidic proton at the 2-position (Figure 1).[10b]

Because the solubility of **1b** in [bdmim][BF_4] was found to be high, we conducted the enzyme-catalyzed acylation of **1b** in [bdmim][BF_4] under otherwise the same conditions, and found that the acylation proceeded successfully. Among the three enzymes examined, Chirazyme L-2 gave the highest conversion

Table 1. Hydrolase-catalyzed kinetic resolution of chiral porphyrin **1b**[a]

Entry	Enzyme	Solvent	T /°C	Time /h	C[b] /%	Yield/%[c] (% ee)[d] R/S				E value[e]
						2b		**1b**		
1	Lipase PS-C II[f]	*i*-Pr_2O[a]	60	15	39	35 (>99)	R	45 (63)	S	>382
2	Lipase PS-C II	*i*-Pr_2O	40	5	45	45 (>99)	R	55 (82)	S	>511
3	Chirazyme L-2[g]	*i*-Pr_2O	40	5	50	49 (>99)	R	50 (>99)	S	>1057
4	ChiroCLEC-BL[h]	*i*-Pr_2O	40	9	31	34 (96)	S	64 (44)	R	76
5	Lipase PS-C II	[bdmim][BF_4]	40	21	23	23 (>99)	R	76 (29)	S	>264
6	Chirazyme L-2	[bdmim][BF_4]	40	21	29	26 (>99)	R	56 (41)	S	>298
7	ChiroCLEC-BL	[bdmim][BF_4]	40	21	7	7 (99)	S	86 (7)	R	213
8	Lipase PS-C II	[bdmim][PF_6]	40	21	38	35 (>99)	R	53 (61)	S	>372
9	Chirazyme L-2	[bdmim][PF_6]	40	21	36	30 (>99)	R	58 (55)	S	>346
10	ChiroCLEC-BL	[bdmim][PF_6]	40	21	12	12 (99)	S	77 (13)	R	226
11	Chirazyme L-2	[bdmim][PF_6]	50	21	49	42 (>99)	R	43 (94)	S	>712
12	Chirazyme L-2[a]	[bdmim][PF_6]	50	18	50	43 (>99)	R	39 (>99)	S	>1057

[a]Conditions: **1b** (39 mg, 42 μmol), AcOCH=CH_2 (1.3 mmol), enzyme (90 mg except for Entry 12 (135 mg), solvent (1 mL except for Entry 1 (30 mL)). [b]Conversion calculated from ee(**1b**)/(ee(**1b**) + ee(**2b**)) according to Ref. 4. [c]Isolated yield. [d]Determined by HPLC (Chiralpak AD-H). [e]Calculated from $E = \ln[1 - c(1 + \mathrm{ee}(\mathbf{2b}))]/\ln[1 - c(1 - \mathrm{ee}(\mathbf{2b}))]$ according to Ref. 4. [f]*Burkholderia cepacia* lipase (Amano Enzyme). [g]*Candida antarctica* lipase B (Boehringer Mannheim). [h]Subtilisin Carlsberg (Altus Biologics).



[bdmim][BF_4]: R = Me
[bmim][BF_4]: R = H
[bdmim][PF_6]: R = Me
[bmim][PF_6]: R = H

Figure 1. Chemical structures of ionic liquids.

(29%, Entry 6). Another ionic liquid, [bdmim][PF_6], was also examined to investigate the effect of the counter anion. In all cases, the reactions were faster in [bdmim][PF_6] than in [bdmim][BF_4] (Entries 5–10). We also found that the acylation was faster in [bdmim][PF_6] than in [bmim][PF_6] (not shown). Table 1 also shows clearly that, unfortunately, the lipase-catalyzed reactions were slower in ionic liquids than in *i*-Pr_2O. To overcome this drawback of the ionic liquids, we attempted to accelerate the enzymatic reaction by increasing the reaction temperature. Because Chirazyme L-2 gave a higher conversion at 50 °C (Entry 11) than lipase PS-C II (42%, not shown), the former enzyme was found to be better. The reaction at a higher temperature, 60 °C, resulted in a decrease in the enantiomeric purity of **2b** (98% ee at 49% conversion). We therefore conducted the reaction at 50 °C using an increased amount of enzyme (135 mg, Entry 12). To our delight, complete kinetic resolution was achieved, giving enantiomerically pure **1b** and **2b** simultaneously.

In summary, a very large secondary alcohol **1b** was synthesized and resolved completely into the enantiomers by the *Candida antarctica* lipase-catalyzed acylation in *i*-Pr_2O and in [bdmim][PF_6]. Although ionic liquids are environmentally benign solvents, there is much room for improvement. Nevertheless, the fact that the enzymes showed catalytic activity and very high enantioselectivity for such a bulky substrate in ionic liquids is important, and the present results provide us with fundamental information to design new ionic liquids more suitable for enzymatic reactions.

This work was supported in part by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (JSPS). We are grateful to the SC-NMR Laboratory of Okayama University for the measurement of NMR spectra.

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Published on the web (Advance View) December 15, 2007; doi:10.1246/cl.2008.90