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Lipase-Catalyzed Kinetic Resolution of 2-Acyloxy-2-(pentafluorophenyl)acetonitrile

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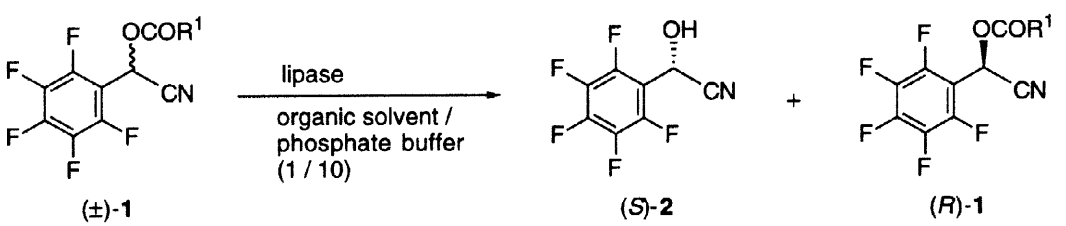
Abstract

The lipase-catalyzed kinetic resolution of (±)-2-acyloxy-2-(pentafluorophenyl)acetonitrile (±)-**1** gave optically active cyanohydrin (*S*)-**2** and its antipodal ester (*R*)-**1** (*E* = 211), the former of which was transformed (TBSOTf, DMAP) into its TBS-ether (*S*)-**3**, a new fluorinated chiral building block, and into naproxen ester **4** for X-ray analysis to determine the absolute configuration.

Keywords: cyanohydrins; enzymes and enzyme reactions; resolution; X-ray crystal structures

Optically active cyanohydrins [R–C*H(OH)CN] have been frequently utilized as useful chiral synthons for organic synthesis, since the two functional groups (CN, OH) can be transformed into a variety of functional groups [1–5]. The synthetic versatility has been applied, for example, to the syntheses of pyrethroid insecticides [6] and ferroelectric liquid crystals [7]. In general, cyanohydrins are optically stable enough to be prepared not only by resolutions with lipases [2], but also by asymmetric syntheses with other biocatalysts [2, 8, 9] or artificial catalysts [8, 10, 11]. Here we report new entries of optically active fluorinated cyanohydrins (R = C_6F_5), (*S*)-2-hydroxy-2-(pentafluorophenyl)acetonitrile **2** and its antipodal ester (*R*)-**1**, which were prepared by the lipase-catalyzed enantioselective hydrolysis of racemate (±)-**1** (Scheme 1). We have been interested in such polyfluorinated arene-containing molecules because of the attractive features such as the electron-withdrawing property [12, 13] and the stacking ability with electron-rich arenes [14–16]. In the course of this study, cyanohydrin **2** was found to be relatively optically and structurally unstable as

Scheme 1



(±)-**1** (*S*)-**2** (*R*)-**1**

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compared with the non-fluorinated one and, thus, required to take care both in the kinetic resolution and in subsequent chemical transformations.

The conditions for the hydrolytic resolution of racemic acetate (±)-**1a**[1] were optimized by screening lipases and organic solvents as additives. Among lipases examined (Table 1, entries 1–5), lipase PS in acetone–phosphate buffer (1 : 10) showed moderate selectivity (E = 15) but with slow reaction rate. In contrast, lipase A6 remarkably accelerated the reaction rate (1.7 h for conv. = 0.46), while the enantioselectivity was decreased (E = 7.5). Entries 5–8 showed the results of the use of lipase LIP with different ketonic solvents. Addition of a ketonic solvent to the media was found to be requisite to promote the reaction, probably facilitating to suspend crystalline (±)-**1a**. The best selectivity was obtained when the reaction of propionate (±)-**1b** was carried out by using lipase LIP and 3-pentanone (entry 9, E = 211). The suitability of lipase LIP for the fluorinated compound had been also observed in the case of 3-hydroxy-3-(pentafluorophenyl)propionitrile [17].

In the above experiments, the enantioselectivity for the hydrolytic resolution was found to be highly dependent on the pH of the buffer. The optimum buffer was determined by examination of the reaction with lipase LIP (entry 8 in Table 1) under various pH conditions. Figure 1 indicates that the ee of (*S*)-**2** was decreased dramatically by changing the pH from 5.0 to 8.0, while that of (*R*)-**1a** was retained within small differences. Under

Table 1
Screening of Lipases and Effect of Organic Solvents as additives.

entry	substrate	lipase	organic solvents	time (h)	conv.[a]	(*S*)-**2** % yield (% ee)[b]		(*R*)-**1** % yield (% ee)[c]		E[d]
1	**1a** (R^1 = Me)	lipase PS[e]	acetone	23	0.43	36	(70)	48	(84)	15
2		lipase AK[f]	acetone	27	0.35	29	(55)	62	(43)	5.1
3		lipase AY[g]	acetone	24	0.50	39	(48)[j]	42	(59)[j]	5.0
4		lipase A6[h]	acetone	1.7	0.48	44	(60)	46	(62)	7.5
5		lipase LIP[i]	acetone	4.3	0.37	27	(73)	45	(52)	11
6		lipase LIP	—	17	0.37	26	(59)	53	(68)	7.8
7		lipase LIP	2-butanone	5.5	0.47	38	(91)	42	(76)	49
8		lipase LIP	3-pentanone	8.0	0.50	39	(94)	39	(85)	92
9	**1b** (R^1 = Et)	lipase LIP	3-pentanone	10.5	0.46	38	(97)	46	(92)	211
10	**1c** (R^1 = Pr)	lipase LIP	3-pentanone	34	0.45	32	(89)	43	(96)	67

Conditions: lipase (entries 1–4, 100 mg; entries 5–10, 200 mg), (±)-**1** (100 mg), phosphate buffer (pH 5.6, 2.5 mL), organic solvent (0.25 mL). [a]Determined by GC analysis (column; 5% PEG-20M). [b]Determined by ^{1}H NMR spectra (200 MHz) of the corresponding MTPA ester. [c]Determined by ^{1}H NMR spectra (200 MHz) in the presence of Eu(hfc)$_3$ for **1a** (entries 1–8) and by HPLC analysis (column; CHIRALCEL OB-H, eluent; hexane / *i*-PrOH = 200 / 1) for **1b** and **1c** (entries 9, 10), respectively. [d]E = ln { 1 - c [1 + **2**(ee)]} / ln { 1 - c [1 - **2**(ee)]}, c = **1**(ee) / [**1**(ee) + **2**(ee)] (Ref. [18]). [e]*Pseudomonas cepacia*. [f]*Pseudomonas fluorescens*. [g]*Candida rugosa*. [h]*Aspergillus niger*. [i]*Pseudomonas aeruginosa* lipase immobilized on hyflo Super-Cel. [j]Obtained with antipodal enantioselectivity; (*R*)-**2** and (*S*)-**1**.

1. Racemic acetate (±)-**1a** was prepared as follows: Pentafluorobenzaldehyde (1 equiv), sodium cyanide (2 equiv), acetyl chloride (2 equiv), $ZnBr_2$ (cat.), in CH_3CN, rt (92% yield): mp 47–48 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (3H, s, CH_3), 6.66 (1H, s, CH); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 2.4–2.8 (2F, m, *m*-ArF), 13.88 (1F, t, J = 21.6 Hz, *p*-ArF), 22.5–22.9 (2F, m, *o*-ArF). Compounds of (±)-**1b** and **1c** were prepared in a similar way to that of **1a**.

the conditions at pH 6.5 – 8.0, a trace of liberated aldehyde was detected by ^{1}H NMR analysis. Both (*S*)-**2** and (*R*)-**1a** were obtained with acceptable ee(s) by the reaction at pH 5.6. These results suggest that racemization of compound **2** occurred gradually *via* cyanohydrin–aldehyde equilibrium, and can be suppressed considerably at pH 5.6.

Optical purity of (*S*)-**2** was raised up to >99% ee by recrystallization from petroleum ether ($[\alpha]^{26}_D$ = –30.5 (*c* = 1.10, $CHCl_3$), mp 67–69 °C) and then it was immediately converted to its optically stable TBS-ether (*S*)-**3**[2] in 83% yield without loss of the optical purity (Scheme 2).

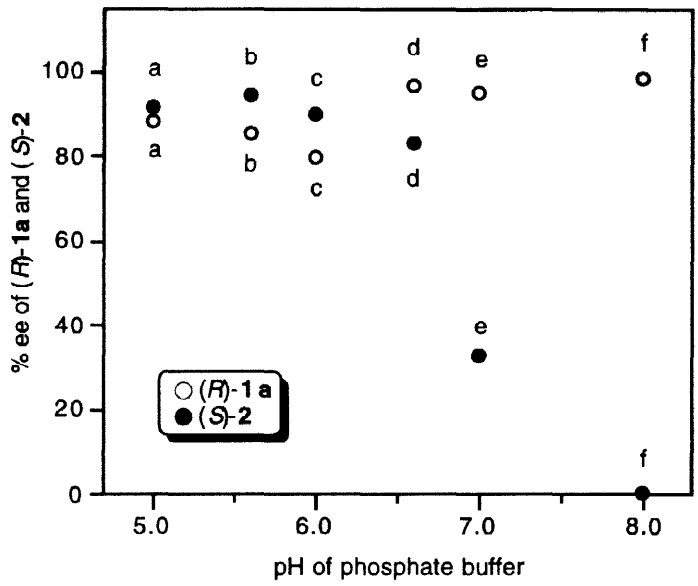
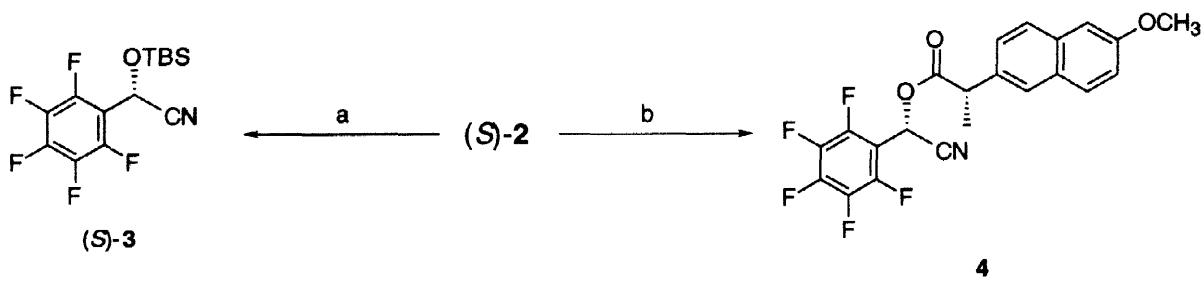


Figure 1 The correlation between the enantiomeric excess ((*R*)-**1a** and (*S*)-**2**) and pH of phosphate buffer (pH 5.0 – 8.0)–3-pentanone in the lipase LIP-catalyzed resolution. pH, reaction time and conversion; **a** (pH 5.0, 9.0 h, conv. = 0.45), **b** (5.6, 8.0, 0.50), **c** (6.0, 8.0, 0.48), **d** (6.6, 7.0, 0.45), **e** (7.0, 7.5, 0.53), **f** (8.0, 7.5, 0.45).

The absolute configuration of (*S*)-**2** was determined by X-ray analysis of its naproxen ester **4** (56% yield) as shown in Scheme 2 and Figure 2[3]. The (*S*)-preference observed in the lipase-catalyzed resolution is in agreement with the empirical rule proposed by Kazlauskas *et al.*[19].

Scheme 2



Reagents and conditions; a) TBSOTf (2 equiv), DMAP (3 equiv), in CH_2Cl_2, 0 °C, 1.5 h. b) (*S*)-(+)-2-(6-methoxy-2-naphthyl)propionyl chloride (2 equiv), pyridine (10 equiv), in benzene, 0 °C–rt, 20 h.

2. (*S*)-**3**: Optical purity was determined by HPLC analysis (column; CHIRALCEL OD-H, eluent; hexane / *i*-PrOH = 200 / 1): $[\alpha]^{24}_D$ = –28.5 (*c* = 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (3H, s, CH_3), 0.26 (3H, s, CH_3), 0.90 (9H, s, $(CH_3)_3$), 5.77 (1H, s, CH); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 1.7–2.1 (2F, m, *m*-ArF), 11.59(1F, t, *J* = 20.3 Hz, *p*-ArF), 19.9–20.2 (2F, m, *o*-ArF).

3. X-ray crystal data for **4**: $C_{22}H_{14}F_5NO_3$, *M* = 435.35, monoclinic, space group $P2_1$, *a* = 9.602(6), *b* = 15.545(8), *c* = 9.449(1) Å, β = 135.030(6) °, *V* = 996.89(0) Å^3, *Z* = 2, D_{calc} = 1.45(0) g / cm^3, *R* = 0.080 for 1273 observed reflections (I > 3.00 σ (I)) and 280 variable parameters. All measurements were made on a Rigaku RAXIS-IV imaging plate area detector with Mo-Kα radiation.

Quite interesting in the structure **4** is that the naphthalene ring is stacked in parallel with the pentafluorophenyl group at a distance of approximately 3.5 Å (Figure 2). We wish to apply such a fluorobenzene-directed structural and/or conformational regulation to a new supramolecular system [20–22]. At present, a few examples have been reported for such arene–polyfluorinated arene interaction and the detailed structural features of **4** will be reported elsewhere.

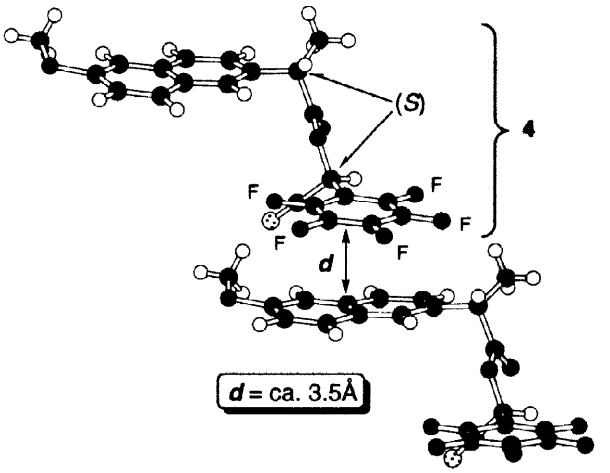


Figure 2 X-ray crystal structure of naproxen ester **4**.

Acknowledgments

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