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Lipase-catalyzed optical resolution of trifluoro(aryl) ethanols

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Abstract

Optical resolutions of racemic 2,2,2-trifluoro-1-(aryl)ethanols — (1-naphthyl), (2-naphthyl), (4-methylnaphthyl), (phenyl), (1-pyrenyl) — were achieved by lipase-catalyzed enantioselective acetylations with vinyl acetate as an acetyl donor in octane, and (*S*)-acetates and (*R*)-alcohols were obtained. Among the lipases tested, lipase from *Pseudomonas aeruginosa* (lipase LIP, Toyobo) showed good enantioselectivity for above ethanols. However, no acetylation occurred with sterically hindered alcohols — (9-phenanthryl), (9-anthryl), (2-methylnaphthyl), (2, 4, 6-trimethylphenyl) — by various lipases. The resolutions of the three alcohols were carried out by the enantioselective alcoholysis or hydrolysis of their chloroacetates by lipase LIP.

Keywords: Lipase; Enantioselective reactions; Trifluoro(aryl)ethanols; Optical resolution

1. Introduction

Recently, fluorinated analogs of biologically active molecules have been important tools for studying the function of these molecules, receptors, and active site of enzymes [1–3]. Replacement of hydrogen with fluorine or fluorination in the molecules results in a slight change in the size or shape, but greatly affects the electronic nature of the molecule due to the strong electronegativity of fluorine. In particular, optically active trifluoromethyl carbinols are important intermediates in the synthesis of polyfunctional bioactive molecules [4] and have been used as synthons in the construction of ferroelectric crystals [5]. Furthermore, optically active 2,2,2-trifluoro-1-(aryl)ethanols are commonly used as solvents in nuclear magnetic resonance (NMR) spectroscopy for the determination of the enantiomeric purity and absolute configuration of a variety of chiral substances [6]. In recent years, there has been an increasing interest in the use of hydrolytic enzymes to produce optically active compounds. In particular, lipase has been widely used for the kinetic resolution of racemic alcohols and carboxylic esters [7–10]. Their commercial availability and relative stability make them an attractive class of catalysts effecting industrial-scale kinetic resolution. However, there are only a few reports of lipase-catalyzed optical resolution of (±)-trifluoromethylated alcohols and acid [11–13]. In this paper, we wish to describe the recent advances in the study of the relationship of the reactivity and enantioselectivity of lipases and the structures of trifluoromethylated alcohols.

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2. Results and discussion

2.1. Lipase-catalyzed enantioselective acetylation of 2,2,2-trifluoro-1-(naphthyl)ethanols

We have successfully developed a practical method for synthesizing the 2,2,2-trifluoro-1-(naphthyl)ethanols from corresponding naphthyl magnesium bromide and trifluoroacetaldehyde generated from trifluoroacetaldehyde ethyl hemiacetal (Fig. 1). These alcohols were previously obtained by the reduction of the ketones, prepared from the corresponding naphthyllitium and ethyl trifluoroacetate. The yields are not so different; however, the conditions of the present reaction are milder than those for preparing trifluoroacetylnaphthalenes, and the reduction step is avoided.

We first performed the lipase-catalyzed acetylation toward 2,2,2-trifluoro-1-(1-naphthyl)ethanol, (±)-**1**, with vinyl acetate as an acetyl donor in octane (Table 1, Fig. 2). The enantioselectivity of each reaction was evaluated by the E value [14]. Of the lipases examined, lipases PS and AK showed low enantioselectivity (E value < 10). Lipases LIP, PLC, and ALC showed high enantioselectivity, and these lipases preferentially acetylated the (*S*)-enantiomer. In particular, lipase LIP manifested the highest enantioselectivity ($E > 100$) (Table 2).

In order to determine optimum conditions, we examined the lipase-catalyzed acetylation of (±)-**1** with various acetyl donors (isopropenyl acetate, acetic anhydride, 2,2,2-trifluoroethyl acetate, and ethyl acetate) in the presence of organic solvents (octane, heptane, hexane, cyclohexane, benzene, diisopropyl ether, and tetrahydrofuran), which have been reported to affect the rate and the selectivity of the reaction [15–18]. Isopropenyl acetate was similar to vinyl acetate in terms of reactivity and enantioselectivity. Acetic anhydride showed a very high reactivity with a conversion of 40% in 8 h, but it remarkably decreased enantioselectivity ($E \leq 1$). On the other hand, although 2,2,2-trifluoroethyl acetate gave high enantioselectivity ($E > 100$), the reaction resulted in a conversion of only 23% even after 330 h. No reaction was observed when ethyl acetate was used. The highest rate of acetylation was obtained in octane; however, there was little effect on the E value with organic solvents. We thus confirmed the potential of vinyl acetate as acetyl donor for the lipase LIP-catalyzed acetylation of (±)-**1** in octane. Hence, these enzymatic conditions were applied to an enantioselective acetylation of related compounds.

By using the optimal conditions described above, we performed lipase-catalyzed acetylation with two types of methyl-substituted TFNEs: one [2,2,2-trifluoro-1-(4-methylnaphthyl)ethanol, (±)-**2**] having a

Table 1
List of enzymes used in this research

Lipase AK	(*Pseudomonas fluorescens*; Amano Pharmaceutical)
Lipase PS	(*P. cepacia*; Amano Pharmaceutical)
Lipase LIP	(*P. aeruginosa*; Toyobo)
Lipase PLC	(*Alcaligenes* sp.; Meito sangyo)
Lipase ALC	(*Achromobactor* sp.; Meito sangyo)
Lipase SP 435	(*Candida antarctica*; Novo Nordisk BioIndustry)

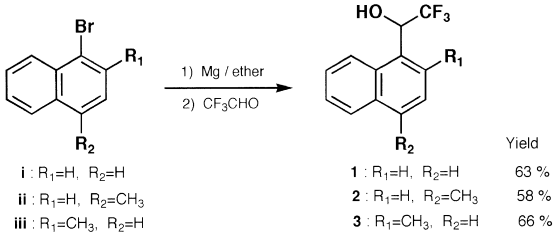


Fig. 1. Synthetic route for 2,2,2-trifluoro-1-(naphthyl)ethanols.

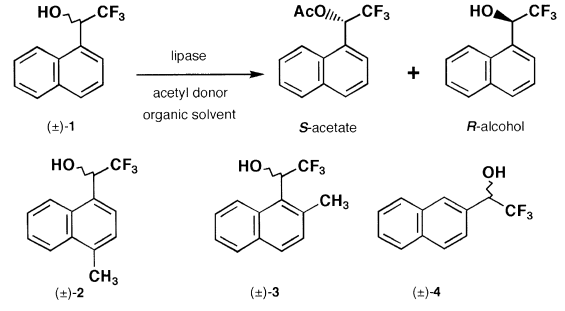


Fig. 2. Lipase-catalyzed optical resolution of 2,2,2-trifluoro-1-(naphthyl)ethanols.

Table 2
Lipase-catalyzed enantioselective acetylation of alcohols[a]

	Lipase	Time (h)	Conversion[b] (%)	*ee*[c] (%)/yield (%)		E[d]
				Acetate	Alcohol	
(±)-**1**	AK	45	35[e]	3/35 (*S*)	6/62 (*R*)	1
	PS	45	27	41/25 (*S*)	15/72 (*R*)	2.8
	LIP	24	51	94/49 (*S*)	> 99/49 (*R*)	> 100
	PLC	45	41	93/38 (*S*)	65/61 (*R*)	54
	ALC	90	14	96/11 (*S*)	15/88 (*R*)	57
(±)-**2**	AK	130	29[e]	2/29 (*S*)	1/68 (*R*)	1
	PS	65	15	80/35 (*S*)	14/62 (*R*)	10
	LIP	65	49	98/47 (*S*)	94/51 (*R*)	> 100
	PLC	65	53	89/54 (*S*)	> 99/42 (*R*)	> 100
	ALC	380	16	96/13 (*S*)	18/50 (*R*)	58
(±)-**3**	AK	330	–[f]	90/20 (*S*)	25/73 (*R*)	24
	PS	330	23			
	LIP	330	–[f]			
	PLC	330	15	91/17 (*S*)	16/82 (*R*)	25
	ALC	330	–[f]			
(±)-**4**	AK	17	44	88/39 (*S*)	69/55 (*R*)	32
	PS	17	54	83/48 (*S*)	99/45 (*R*)	55
	LIP	0.15	52	86/48 (*S*)	92/50 (*R*)	46
	PLC	0.3	37	65/30 (*S*)	38/67 (*R*)	6.7
	ALC	26	61	44/57 (*S*)	68/41 (*R*)	5.0

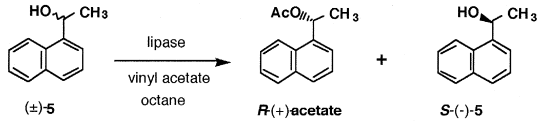
[a] Reaction conditions: (±)-alcohol (1.5 mg), lipase (100 mg), vinyl acetate (0.3 ml), 4A molecular sieves (30 mg), and octane (3 ml), 30°C.
[b] Calculated on the basis of *ee* (alcohol) and *ee* (acetate) [Conversion = *ee* (alcohol)/{*ee* (alcohol) + *ee* (acetate)} × 100].
[c] The *ee* value was determined by HPLC analysis equipped with chiral stationary phase.
[d] E value = In[1 − c{1 + *ee* (acetate)}]/In[1 − c{1 − *ee* (acetate)}].
[e] Determined by HPLC.
[f] Conversion: < 5%.

methyl group at a position remote from the chiral center and the other [2,2,2-trifluoro-1-(2-methylnaphthyl)ethanol, (±)-**3**] having a methyl group proximal to the chiral center. For (±)-**2**, lipases LIP and PLC showed the same high enantioselectivity as with (±)-**1**. The reactivity of all lipases decreased. All lipases showed especially poor reactivity for (±)-**3**. Thus, the methyl substituent seems to reduce the binding affinity of the lipases to the substrate, particularly if close to chiral center.

We also explored the lipase-catalyzed acetylation of 2,2,2-trifluoro-1-(2-naphthyl)ethanol, (±)-**4**. Lipases AK, PS, and LIP showed moderate enantioselectivity (E = 30–60), and the enantioselectivity of AK and PS for (±)-**4** increased as compared to (±)-**1**. Although lipases AK and PS are effective for resolution of (±)-**4**, these lipases apparently are not suitable for resolution of (±)-**1**. However, enantioselectivity of LIP, PLC, and ALC decreased for (±)-**4** as compared to (±)-**1** (Table 2). To rationalize these results, we suggest that the active sites of LIP, PLC, and ALC are similar to one another but different from the active sites of AK and PS.

To investigate further the effect of the trifluoromethyl group, we studied the lipase-catalyzed reactions with the non-fluorinated analog, 1-(1-naphthyl)ethanol, (±)-**5** [19] (Table 3). Interestingly, all lipases, except for AK, resolved (±)-**5** with high enantioselectivity (E > 100) and the rate of acetylation increased remarkably compared to the fluorinated compound (**1**). A similar tendency also was observed in our previous work when ethyl 4,4,4-trifluoro-3-(indole-3-)butyrate was subjected to lipase-catalyzed enantioselective hydrolysis [20]. In this

Table 3
Lipase-catalyzed enantioselective acetylation of (±)-**5**[a]



Lipase	Time (h)	Conversion (%)	*ee* (%)/recovery (%)		*E*
			Acetate	Alcohol	
AK	6	52	85/49 (*R*)	92/50 (*S*)	40
PS	8	51	93/53 (*R*)	99/45 (*S*)	> 100
LIP	0.15	49	99/46 (*R*)	95/50 (*S*)	> 100
PLC	1	43	99/41 (*R*)	75/56 (*S*)	> 100
ALC	45	40	98/40 (*R*)	64/57 (*S*)	> 100

[a]Reaction conditions: (±)-alcohol (1.5 mg), lipase (100 mg), vinyl acetate (0.3 ml), 4A molecular sieves (30 mg), and octane (3 ml), 30°C.

case as well, the bulky and low-affinity trifluoromethyl group reduced not only the reactivity but also the enantioselectivity of lipases.

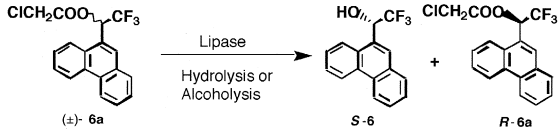
2.2. Optical resolution of highly sterically hindered trifluoromethylated alcohols

At first, we attempted the optical resolution of sterically hindered secondary alcohol, 2,2,2-trifluoro-1-(9-phenanthryl)ethanol, (±)-**6**, by lipase-catalyzed enantioselective acetylation. However, the acetylation progressed slowly, and the best result we obtained was 8% conversion and an *E* value of 15, which was achieved after (±)-**6** was stirred for 330 h at 30°C with a large excess of lipase LIP and vinyl acetate in octane.

In order to increase the rate of lipase-catalyzed hydrolysis and alcoholysis, the activated chloroacetyl ester, (±)-2,2,2-trifluoro-1-(9-phenanthryl)ethyl chloroacetate, (±)-**6a**, was used [21,22]. The results are summarized in Table 4. As expected, it was possible to increase the rate of lipase-catalyzed reactions. In the case of hydrolysis, lipases AK and LIP showed good reactivity, and lipase LIP manifested good enantioselectivity ($E = 26$). Lipase SP 435 exhibited moderate enantioselectivity ($E = 18$), but showed a low reaction rate. Lipase AK showed a reverse selectivity, since (*R*)-**5** was preferably converted enantiomer.

In the case of alcoholysis, lipase LIP produced the best result in which (±)-**6a** was resolved with excellent enantioselectivity ($E > 100$), while lipases AK and SP 435 were less effective ($E < 10$). The optical purities of the alcohol and the acetate were enhanced by carrying out the alcoholysis in an organic solvent, and almost complete resolution was attained when the reaction was allowed to proceed for 10 h.

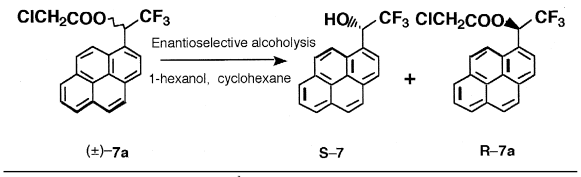
Table 4
Lipase-catalyzed enantioselective hydrolysis and alcoholysis of (±)-**6a**



Reaction[a]	Lipase	Time (h)	Conversion (%)	*ee* (%)/yield (%)		*E*
				Alcohol	Acetate	
Hydrolysis	AK	2	16	32/19 (*R*)	6/75 (*S*)	2.1
	SP 435	20	31	80/35 (*S*)	36/62 (*R*)	13
	LIP	2	26	90/30 (*S*)	31/67 (*R*)	26
Alcoholysis	AK	160	18	74/20 (*R*)	16/76 (*S*)	7.8
	SP 435	4	65	35/63 (*S*)	64/35 (*R*)	3.8
	LIP	10	48	95/49 (*S*)	88/49 (*R*)	> 100

[a]Hydrolysis: To a solution of (±)-**6a** (1.5 mg) in 0.1 M phosphate buffer (pH 7.0) containing 10% acetone was added lipase (100 mg). Alcoholysis: To a mixture of (±)-**6a** (1.5 mg), 1-propanol (25 μl) and 4A molecular sieves (30 mg) in hexane (3.0 ml) was added lipase (100 mg).

Table 5
Lipase-catalyzed enantioselective alcoholysis of (±)-**7a**[a]



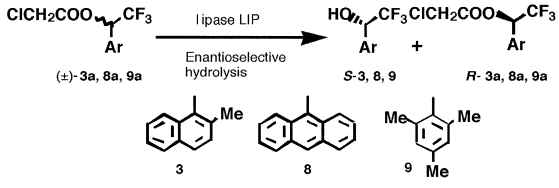
Lipase	Time (h)	Conversion[b] (%)	*ee* (%)/yield (%)		*E*
			Alcohol	Chloroacetate	
AK	40	23	86/23 (*S*)	26/77 (*R*)	17
PS	16	40	93/40 (*S*)	61/60 (*R*)	52
LIP	3	49	98/48 (*S*)	94/51 (*R*)	> 100
PLC	7	42	94/42 (*S*)	68/58 (*R*)	66
ALC	90	32	88/29 (*S*)	42/70 (*R*)	24

[a]To a mixture of (±)-**7a** (1.5 mg), 1-hexanol (25 μl), 4A molecular sieves (30 mg) and cyclohexane (3.0 ml) was added lipase (100 mg).

The above results prompted us to explore the optical resolution of 2,2,2-trifluoro-1-(1-pyrenyl)-ethanol, (±)-**7**. Alcohol (±)-**7** is a very effective probe for clarifying the relationship between the enantioselectivity of lipases and the structure of aryl groups because it contains both 1-naphthyl and 2-naphthyl structures in the molecule. At first, we acetylated (±)-**7** with vinyl acetate by using lipases. Among the lipases tested, the enantioselectivity of lipases PS, LIP, and PLC was high ($E > 100$), while lipases AK ($E = 25$) and ALC ($E = 73$) had moderate enantioselectivity. Lipases LIP, PLC, and ALC showed similar enantioselectivity toward (±)-**7**, as was found for (±)-**2**. However, the enantioselectivity shown by lipases AK and PS toward (±)-**7** was markedly higher than that shown for (±)-**2**.

Although the optical resolution of (±)-**7** was achieved by the lipase-catalyzed acetylation of one antipode, all five lipases had low reactivity for (±)-**7**. For this reason, this procedure is not readily applicable for the preparative-scale optical resolution of (±)-**7**. We therefore explored the alcoholysis of its chloroacetate, (±)-**7a**, with the results being summarized in Table 5. In this case as well, the reaction rate for alcoholysis of the chloroacetate was several times greater than that for acetylation of the alcohol. The enantioselectivity of lipase LIP was also retained, although the other three lipases had lower enantioselectivity. Thus, an improvement in the reac-

Table 6
Effect of reaction conditions on hydrolysis of (±)-**3a, 8a, 9a** by lipase LIP[a]



Substrate	Condition (solvent/pH/°C)	Time (h)	Conversion (%)	*ee* (%)/recovery (%)		*E*
				Alcohol	Ester	
(±)-**3a**	Hexane/7/30	17	14	72/15 (*S*)	12/80 (*R*)	7
(±)-**3a**	*tert*-BME[b]/7/30	17	39	90/38 (*S*)	58/51 (*R*)	36
(±)-**3a**	Chloroform/7/30	17	2	63/3 (*S*)	1/89 (*R*)	4
(±)-**3a**	*tert*-BuOH[b]/7/30	17	43	65/42 (*S*)	48/50 (*R*)	8
(±)-**3a**	*tert*-BME/6/30	17	37	94/39 (*S*)	56/56 (*R*)	61
(±)-**3a**	*tert*-BME/8/30	17	52	78/50 (*S*)	72/46 (*R*)	14
(±)-**3a**	*tert*-BME/6/20	45	32	99/32 (*S*)	46/64 (*R*)	> 100
(±)-**8a**	*tert*-BME/6/20	90	40	98/32 (*S*)	66/54 (*R*)	> 100
(±)-**9a**	*tert*-BME/6/20	150	38	99/40 (*S*)	61/56 (*R*)	> 100

[a]All reactions were carried out in a mixture of 0.1 M phosphate buffer containing 10% organic co-solvent (3 ml) and lipase LIP (100 mg).
[b]*tert*-BME, *tert*-butyl methyl ether; *tert*-BuOH, *tert*-butyl alcohol.

tion rate was achieved by using lipase LIP, and the enantioselectivity of the alcoholysis ($E \geqslant 100$) was retained.

We next explored the lipase-catalyzed enantioselective reactions of other alcohols: (±)-**3**, 2,2,2-trifluoro-1-(9-anthryl)ethanol, (±)-**8**, and 2,2,2-trifluoro-1-(2,4,6-trimethylphenyl)ethanol, (±)-**9**. Preliminary experiments involving the alcoholysis (with 1-hexanol in hexane) of (±)-**3** chloroacetate: (±)-**3a** showed that five lipases (lipases AK, PS, LIP, PLC, and SP 435) were effective in catalysis. In accordance with our expectations, the alcoholysis proceeded smoothly with all lipases studied. In the alcoholysis of (±)-**3a**, lipase PS showed good enantioselectivity ($E = 33$). All other lipases showed low or no enantioselectivity. Furthermore, lipase PS exhibited a similar selectivities for (±)-**8** chloroacetate: (±)-**8a** ($E = 28$) and (±)-**9** chloroacetate: (±)-**9a** ($E = 35$) compared to one for (±)-**3a** ($E = 33$). As already described, lipase LIP showed high enantioselectivity for (±)-**1a**, (±)-**6a**, and (±)-**7a**, but showed no enantioselectivity for (±)-**3a**, (±)-**8a**, and (±)-**9a**. These results suggest that the enantioselectivity of lipase LIP depends greatly upon the structure of aryl group. We reported [23] that lipase LIP exhibited high enantioselectivity for all non-fluorinated alcohols: 1-(aryl)ethanols (aryl: 1-naphthyl, 2-naphthyl, 1-pyrenyl, 9-phenanthryl, 9-anthryl, 1-phenanthryl, and 2-phenanthryl). This results indicates that (±)-2,2,2-trifluoro-1-(aryl)ethanols are very effective probes for clarifying the relationship between the enantioselectivity of lipases and the structure of aryl groups.

To achieve the optical resolution of (±)-**3**, (±)-**8**, and (±)-**9** by lipase, we examined the lipase-catalyzed hydrolysis in various conditions (Table 6). As results, an addition of 10% *tert*-butyl methyl ether to a phosphate buffer (pH 7.0) improved the selectivity of lipase LIP toward (±)-**3a** ($E = 45$). Furthermore, changing the pH of phosphate buffer to 6.0 had a significant effect on the selectivity of the reaction ($E = 65$). Consequently, temperature effects, the final reaction parameter explored, were studied in a pH 6.0 phosphate buffer containing 10% *tert*-butyl methyl ether. We determined that lowering the temperature to 20°C resulted in improved selectivity and rate of reaction, giving an excellent E value of > 100.

Under the best conditions described above, lipase LIP could resolve for other two chloroacetate (±)-**8a** and (±)-**9a** with the same selectivity ($E > 100$).

3. Conclusion

In this article, we have described our results on the preparation of optically active trifluoromethylated compounds as well as the consideration of the relationship of the lipase enantioselectivity and the structures of substrates. It is our hope that this information will be helpful in performing the optical resolution by lipases for "special substrates" that are difficult to be reacted by enzymes.

4. Experimental

4.1. General

IR spectra were recorded as neat for oils or as KBr disc for solids using a JASCO IR-810 spectrometer. ^{1}H NMR spectra were recorded with tetramethylsilane (TMS) as an internal standard at 90 MHz on a Hitachi R-90H FT spectrometer. ^{19}F NMR spectra were recorded with hexafluorobenzene (C_6F_6) as an internal standard at 84.7 MHz on the same spectrometer. Mass spectra (70 eV) were recorded on a Hitachi M-80 instrument. Optical rotation values were recorded on a JASCO DIP polarimeter. All melting points are uncorrected. All other chemicals were reagent-grade, and were used without further purification.

4.2. Synthesis of racemic 2,2,2-trifluoro-1-(aryl)ethanols

Alcohols (±)-**1** (isolated yield; 63%), (±)-**2** (58%), (±)-**3** (66%), (±)-**4** (65%), (±)-**6** (28%), and (±)-**9** (28%) are prepared from corresponding arylmagnesium bromide and trifluoroacetaldehyde generated from trifluoroacetaldehyde ethyl hemiacetal. The synthetic procedure of (±)-**9** is as follows: to a suspension of 2,4,6-trimethylphenyl magnesium bromide, which was prepared from 1-bromo-2,4,6-trimethylbenzene (10.8 g, 50 mmol) and magnesium

chips (1.2 g, 50 mmol) in diethyl ether (50 ml) was introduced trifluoroacetaldehyde, which was separately generated from trifluoroacetaldehyde ethyl hemiacetal (18.0 g, 0.13 mol; Central Glass, Tokyo, Japan). After being stirred for 3 h at room temperature, the mixture was quenched with 4 N hydrochloric acid (100 ml) and then extracted three times with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was removed. Column chromatography on silica gel, eluting with dichloromethane, afforded (±)-**9** (3.8 g, 27.6% yield): colorless columns, mp 58–60°C from hexane; MS *m/z* (ion, relative intensity %): 218 (M^+, 36), 149 (M^+-CF_3, 100), 121 (M^+-CF_3-CO, 29); IR (KBr) ν_{max} cm^{-1}: 3300, 1280, 1170, 1080, 850, 800, 700; ^{1}H NMR δ ($CDCl_3$): 2.25 (3H, s, 4-CH_3), 2.42 (6H, s, 2-, 6-CH_3), 2.47 (1H, d, $J = 4.8$ Hz, OH), 5.51 (1H, dq, $J = 4.8$ and 8.1 Hz, CH), 6.87 (2H, s, *Ar*-H); ^{19}F NMR δ ($CDCl_3$): 86.4 (d, $J = 8.1$ Hz, CF_3).

Alcohols (±)-**7** (isolated yield 32%) and (±)-**8** (25%) were synthesized by the direct condensation of trifluoroacetyl triflate with the corresponding aromatic ring with sequential reduction with sodium borohydride. The synthetic procedure of (±)-**8** is as follows: to a solution of anthracene (3.3 g, 18.3 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (4.2 g, 20.3 mmol) in benzene (40 ml) was carefully added trifluoroacetyl triflate (5.0 g, 20.3 mmol). The solution was sealed in a glass tube and heated at 80°C for 90 h. The reaction was cooled and quenched by addition of 2 N hydrochloric acid and extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to give crude 1-(trifluoroacetyl)-anthracene (2.75 g). This ketone was immediately subjected to reduction with sodium borohydride ($NaBH_4$) without purification. To a methanol solution (50 ml) of the crude ketone was added $NaBH_4$ (20 mmol) in several portions at 0°C. After 5 h stirring at room temperature, the reaction mixture was quenched with aqueous 5% ammonium chloride. Oily material was extracted with ethyl acetate, and washed with brine and distilled water. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness, and the residue was purified by column chromatography on silica gel, eluting with dichloromethane–hexane (1:1), affording (±)-**8** (1.26 g, 25.0%): yellow plates, mp 140–142°C from dichloromethane–hexane (1:1); MS *m/z* (ion, relative intensity %): 276 (M^+, 75), 207 (M^+-CF_3, 84), 179 (M^+-CF_3-CO, 89), 178 (M^+-CF_3-CHO, 100); IR (KBr) ν_{max} cm^{-1}: 3560, 1460, 1350, 1270, 1170, 1100, 900, 740; ^{1}H NMR δ ($CDCl_3$): 2.91 (1H, d, $J = 4.2$ Hz, OH), 6.65 (1H, dq, $J = 4.2$ and 8.0 Hz, CH), 7.35–7.70 (4H, m, *Ar*-H), 7.90–8.10 (2H, m, *Ar*-H), 8.00–9.30 (2H, m, broad, peri H), 8.53 (1H, s, 10-H); ^{19}F NMR δ ($CDCl_3$): 87.9 (d, $J = 8.0$ Hz, CF_3).

All choroacetates (±)-**1a**–**9a** were prepared with choroacetic anhydride by usual manner in good yields (75–89% isolated yields).

4.3. Lipase-catalyzed enantioselective acetylation, alcoholysis and hydrolysis

4.3.1. Acetylation

To a solution of (±)-alcohol (1.5 mg) in octane (3 ml) were added vinyl acetate (25 μl), 4A molecular sieves (30 mg), and the lipase (100 mg). After stirring at 30°C for an adequate time, the solid materials were removed by filtration and the filtrate was evaporated to dryness. The residual material was subjected to high-performance liquid chromatography (HPLC) analysis to determine the optical purity.

4.3.2. Alcoholysis

To a solution of (±)-chloroacetate (1.5 mg) in octane (3 ml) were added 1-hexanol (25 μl), 4A molecular sieves (30 mg), and the lipase (100 mg). After stirring at 30°C for an adequate time, the solid materials were worked up as described above.

4.3.3. Hydrolysis

To a solution of (±)-chloroacetate (1.5 mg) in a phosphate buffer containing 10% organic solvent (3 ml) was added the lipase (100 mg). After stirring at 30°C for an adequate time, the suspension was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residual material was subjected to HPLC analysis.

4.4. Determination of optical purity

The optical purity of the products was determined using an HPLC equipped with a chiral stationary phase (Chiralcel OD, Chiralcel OJ, and Chiralpak AD 4.6 × 250 mm^2; Daicel Chemical Industry, Osaka). The mobile phase was a volume per volume mixture of hexane and 2-propanol, at a flow rate of 1.0 ml/min. UV detection at 254 nm was used for quantification at ambient temperature.

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