Kinetic Resolution of Enantiomers in Enantiomerically Enriched 2-Alkanol by *Pseudomonas cepacia* Lipase Catalyzed Transesterification with Vinyl Acetate in Organic Solvent

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Abstract: Kinetic resolution of (*R*)- and (*S*)-2-alkanols by *Pseudomonas cepacia* lipase catalyzed transesterification has been studied using vinyl acetate as an acetylating reagent, six 2-alkanols and three organic solvents. The optical resolution of (*S*)-2-alkanol with enantiomeric excess (*ee*) >95% was attained by controlling the extent of conversion, but (*R*)-2-alkanol with *ee*>95% could not be resolved from the racemate due to the moderate enantioselectivity. New equations as functions of the optical resolution data were introduced for predicting the *ee* values of enantiomers resolved by the transesterification with enantiomerically enriched 2-alkanol and they were experimentally verified: the predicted and experimentally obtained *ee* values showed an excellent agreement in all systems studied. Based on these observations, optically pure (*R*)- and (*S*)-2-alkanols (*ee* ≥ 99%) were resolved from the racemates in a preparative scale by repeating the transesterification.

Key words: *Pseudomonas cepacia* lipase (PCL), transesterification with vinyl acetate, kinetic resolution, enantiomerically enriched substrate, optically pure 2-alkanol

1 Introduction

According to the optical resolution theory (1-3), the enantioselectivity (*E*: the enantiomeric ratio) is expressed as Eq. (1) when the enzymatic reaction is reversible:

$$E = \frac{\ln[1 - (1 + K)c(1 + ee_p)]}{\ln[1 - (1 + K)c(1 - ee_p)]}$$

$$= \frac{\ln[1 - (1 + K)(c + ee_s\{1 - c\})]}{\ln[1 - (1 + K)(c + ee_s\{1 + c\})]} \quad (1)$$

where *K* is the equilibrium constant, *c* is the extent of conversion, and *ee_p* and *ee_s* are optical purities in enantiomeric excess of the product and the unreacted substrate, respectively. When the reaction is irreversible or the reverse reaction is negligible (*K*=0), Eq. (1) is reduced to Eq. (2).

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$$E = \frac{\ln[1-c(1+ee_p)]}{\ln[1-c(1-ee_p)]} = \frac{\ln[(1-c)(1-ee_s)]}{\ln[(1-c)(1+ee_s)]} \quad (2)$$

Kinetic resolution of chiral compounds with $ee > 95\%$ is considered to be important in a practical sense. For satisfying it, E should be above 150 for the optical resolution at $c=0.5$ even though the reaction is irreversible [Eq. (2)]. If the reaction is reversible, for example in the case of $K=0.02$ [Eq. (1)], above 210 of E is required at $c=0.5$. Such cases are not necessarily obtained for the common enzymatic reaction because available enzymes are limited and the enantioselectivity is also restricted. Thus, kinetic resolution from enantiomerically enriched substrates becomes important for the preparation of highly enantiomerically enriched compounds.

The problem is how to confirm the conversion ($c\%$) that the reaction should be stopped and predict the optical purities (ee) of enantiomers resolved from the enantiomerically enriched substrate. When enzymatic reactions are irreversible and their optical resolution data obey Eq. (2), the optical purity of fast-reacting enantiomer is predicted by

$$\left[1 - c \left(\frac{1+ee_p'}{1+ee_0} \right)\right] = \left[1 - c \left(\frac{1-ee_p'}{1-ee_0} \right)\right]^E \quad (3)$$

where ee_0 and ee_p' are optical purities of the starting substrate and the product, and c' is the extent of conversion based on the starting substrate (4). Similarly we obtained

$$\left[\frac{(1-c)(1-ee_s')}{1+ee_0} \right] = \left[\frac{(1-c)(1+ee_s')}{1-ee_0} \right]^E \quad (4)$$

for optical purity (ee_s') of the unreacted substrate. Equations (3)–(4) are, however, restricted to the reaction of $E=0$ and $K=0$.

In the previous paper (5), we reported that lipase (triacylglycerol hydrolase, EC 3.1.1.3) catalyzed transesterification between tributylglycerol (TB) and secondary alcohol was reversible in organic solvent and that the optical resolution data satisfied Eq. (1). Recently, it was reported that E determined by Eq. (2) showed the maximum against c , i.e., the resolution data did not obey Eq. (1) nor Eq. (2) in *Pseudomonas cepacia* lipase (PCL) catalyzed transesterification between vinyl acetate (VA) and 2-alkanol (1) (Scheme 1) (6).

Thus, we selected the reaction in Scheme 1, introduced new equations for predicting the optical purities of enantiomers resolved from enantiomerically enriched substrate and investigated the titled resolution to obtain optically pure (1) ($ee \geq 99\%$). In this paper, individual 2-alkanol was abbreviated to X2-OH, where X is carbon number of the alcohol and 2- shows the position of hydroxy group, and its acetate was also abbreviated to X2-OAc.

2 Experimental

2.1 Materials

Chemical reagents [vinyl acetate (VA), triacetylglyc-

Enz : *Pseudomonas cepacia* Lipase (PCL)

2-Alkanol (Abbreviation)

R = C ₅ H ₁₁ (72-OH)	C ₆ H ₁₃ (82-OH)	C ₇ H ₁₅ (92-OH)
C ₈ H ₁₇ (102-OH)	C ₉ H ₁₉ (112-OH)	C ₁₀ H ₂₁ (122-OH)

Scheme 1

erol (TA), 2-alkanol (**1**) and (*R*)-1-(1-naphthyl)ethyl isocyanate], solvents, silica gel and PCL (43 U/mg) were used as received or after purification (6).

2.2 Kinetic Resolution from Enantiomerically Enriched Alcohol

2.2.1 Reaction with VA

To a stirred solution (33 mL) containing VA (1.53 M) (1 M=1 mol dm⁻³) and enantiomerically enriched 2-alkanol [(*R*)-enriched-(**1**) (*ee*₀=0.40-0.86) or (*S*)-enriched-(**1**) (*ee*₀=0.40-0.71)] (0.39-0.63 M) at 30°C was added PCL powder (50-100 mg/mL) and the stirring was continued. The time course was followed by GC and the reaction was terminated by filtration at the desired conversion. The reaction mixture was treated by a similar method as described in the previous paper (6). Similarly the resolution from (*RS*)-(**1**) was carried out.

2.2.2 Reaction with TA

PCL (3.30 g, 100 mg/mL) was added to a stirred mixture (33 mL) of TA (0.81 M) and enantiomerically enriched 2-octanol [(*R*)-enriched 82-OH (*ee*₀=0.40-0.80) or (*S*)-enriched 82-OH (*ee*₀=0.40-0.80)] (0.56 M) dissolved in 1,2-dichloroethane at 30°C. The reaction mixture was filtered at the desired conversion (determined by GC). The reaction mixture was treated by a similar method as described in the previous paper (6). Similarly the resolution from (*RS*)-82-OH was performed.

2.3 Resolution of Optically Pure 2-Alkanol in a Preparative Scale

2.3.1 Optically pure (*R*)-(1)

1st Reaction—To a stirred mixture of (*RS*)-82-OH (0.62 mol), VA (1.08 mol) and 1,2-dichloroethane (500 mL) at 30°C was added PCL (70 g) and the stirring was continued. After 6.5 h (56% of conversion), the reaction mixture was filtered and the enzyme was washed with three 150 mL portions of 1,2-dichloroethane. The filtrates were combined and evaporated. The residue was dissolved with 500 mL of hexane, left for 1-3 h, filtered and evaporated. This procedure was repeated twice for removing the crystalline impurities. The refined residue was divided into 7.1-7.2 g portions. Each portion was dissolved with 30 mL of benzene, loaded on a silica gel column (Silica gel 100g, $\phi 30 \times 600$ mm), and treated by a similar method described above (2.2.1). As a result, we obtained (*R*)-82-OH (*ee*=75%) and (*S*)-82-OH (*ee*=94%) in yields of 69 and 85%, respectively. These compounds were used as the starting substrates in the following 2nd and 3rd reactions.

2nd Reaction—A mixture of (*R*)-82-OH (*ee*=75%, 0.44 mol), VA (0.78 mol), 1,2-dichloroethane (360 mL) and PCL (50 g) was stirred at 30°C for 3.5 h (73% of conversion). The reaction mixture was treated by a similar method as described above (the 1st reaction and 2.2.1), giving (*R*)-82-OH (*ee*=95%) in a yield of 70%.

3rd Reaction—A mixture of (*R*)-82-OH (*ee*=95%, 0.30 mol), VA (0.43 mol), 1,2-dichloroethane (250 mL) and PCL (35 g) was stirred at 30°C for 3 h (88% of con-

Table 1 A Preparative Scale Resolution of Optically Pure (*R*)-(1) from (*RS*)-(1) by PCL Catalyzed Transesterification with VA in 1,2-dichloroethane at 30°C.

(<i>R</i>)-(1)	1st Reaction ^{a)}			2nd Reaction			3rd Reaction		
	<i>c</i> /%	<i>Y</i> /%	<i>ee</i> _p /%	<i>c</i> /%	<i>Y</i> /%	<i>ee</i> _p /%	<i>c</i> /%	<i>Y</i> /%	<i>ee</i> _p /%
72-OH	53	52	76	77	51	96	86	52	99
82-OH	56	69	76	73	70	95	88	63	99
92-OH	52	88	68	79	78	97	88	78	99
102-OH	53	97	75	79	69	96	87	78	99
112-OH	—	—	81 ^{b)}	76	83	98	89	71	>99
122-OH	53	99	84	79	75	98	88	72	>99

a) VA=1.08 mol, 72-OH=0.69 mol, 82-OH=0.62mol, 92-OH=0.56 mol, 102-OH=0.51 mol, 112-OH=0.43 mol and PCL=70.0g. Similar reaction conditions were used in the 2nd and 3rd reactions. *Y*: Yield of isolated alcohol.

b) The stocked sample of our laboratory.

version). The reaction mixture was treated by a similar method as described above. Finally we obtained optically pure (*R*)-82-OH with 99% of *ee* in a yield of 63%.

Similarly optically pure (*R*)-(1) was resolved from (*RS*)-(1) in a preparative scale. The results were summarized in **Table 1**.

2·3·2 Optically pure (*S*)-(1)

1st Reaction is identical to the 1st reaction for (*R*)-82-OH (2·3·1).

2nd Reaction—A mixture of (*S*)-82-OH (*ee*=94%, 0.38 mol), VA (0.68 mol), 1,2-dichloroethane (315 mL) and PCL (22 g) was stirred at 30°C for 19 h (28% of conversion). The reaction mixture was treated by a similar method as described above (2·2·1 and 2·3·1). As a result, we obtained optically pure (*S*)-82-OH with *ee*>99% from the unreacted substrate in a yield of 78%.

Table 2 A Preparative Scale Resolution of Optically Pure (*S*)-(1) from (*RS*)-(1) by PCL Catalyzed Transesterification with VA in 1,2-dichloroethane at 30°C^a.

(<i>S</i>)-(1)	1st Reaction ^a			2nd Reaction ^b		
	<i>c</i> /%	<i>Y</i> /%	<i>ee_S</i> /%	<i>c</i> /%	<i>Y</i> /%	<i>ee_S</i> /%
72-OH	53	62	94	19	63	>99
82-OH	56	85	95	28	78	>99
92-OH	52	90	85	28	77	>99
102-OH	53	95	89	29	86	>99
112-OH	—	—	87 ^b	20	78	>99
122-OH	53	95	92	12	85	>99

a) The reaction conditions were described in **Table 1**.

Y: Yield of isolated alcohol.

b) PCL= 50 mg/mL.

c) Stocked sample of our laboratory.

Similarly optically pure (*S*)-(1) was resolved from (*RS*)-(1) in a preparative scale. The results were summarized in **Table 2**.

2·4 Analytical Methods

GC and HPLC analyses were carried out by the same methods as described in the previous paper (6). Optical rotations of optically pure (*R*)- and (*S*)-(1) were measured by a JASCO DIP-370 Polarimeter using sodium D line (589 nm) and mercury lines (405–577 nm) at 20°C. The results were summarized in **Table 3**.

3 Results and Discussion

3·1 Optical Resolution Data

First of all we examined the optical resolution data for PCL catalyzed transesterification between VA and (*RS*)-82-OH in 1,2-dichloroethane and compared them with those for TA (**Scheme 2**) to find out the difference between VA and TA as acetylating reagents. The results were shown in **Fig. 1**. The *ee_P* value decreased with *c* in both reactions as expected. The decrease in *ee_P* for the reaction with VA (**Fig. 1A**) was, however, more sluggish than that for TA (**Fig. 1B**). This suggests that the reverse reaction in the former is less significant relative to that in the latter.

A characteristic observation is *ee_P*=*ee_S* at *c*=0.5 in both reactions (**Fig. 1**). Based on the definitions of *ee_P*, *ee_S* and *c*,

$$c = \frac{ee_S}{ee_P + ee_S} \quad (5)$$

was obtained. When *c*=0.5 in Eq. (5), *ee_P*=*ee_S*. A similar correlation was observed in all systems studied.

Table 3 Specific Rotation Values ($[\alpha]^\circ$) of Optically Pure (*R*)-(1) and (*S*)-(1)^a.

λ /nm ^d	(<i>R</i>)-(1) ^b					(<i>S</i>)-(1) ^c				
	589	577	546	435	405	589	577	546	435	405
72-OH	-10	-10	-11	-18	-21	9	9	11	18	22
82-OH	-9	-9	-10	-16	-19	8	8	9	16	19
92-OH	-8	-8	-9	-15	-17	7	8	9	15	17
102-OH	-7	-8	-9	-14	-16	7	7	8	13	16
112-OH	-7	-7	-8	-13	-15	6	6	7	12	14
122-OH	-6	-7	-8	-12	-14	5	6	6	11	13

a) *C*=5 (g/100 mL) in chloroform at 20°C.

b) The optical purity was listed in **Table 1**.

c) The optical purity was listed in **Table 2**.

d) 589 nm: Sodium lamp (D line). 577–405 nm: Mercury lamp.

Scheme 2

The notable difference between VA and TA was the dependence of ee_S on c (**Fig. 1**). In the case of TA, ee_S decreased in the range of $c > 0.65$ (**Fig. 1B**), which demonstrates that the reaction with TA is reversible. A similar reversibility has been reported in lipase catalyzed transesterification between TB and (1) in several organic solvents (7). The resolution data in **Fig. 1B** satisfied Eq. (1) with $E=18$ and $K=0.01$. In contrast, ee_S increased with c in the reaction with VA (**Fig. 1A**). These again suggest that the reverse reaction for VA is less significant than TA. In PCL catalyzed transesterification, the reverse reaction is initiated by the competi-

tive reaction of the free active serine residue in PCL between the acylating reagent and the product to give the acyl-enzyme intermediate [Enz-Ac]. In the case of VA, the intermediate reacts with unreacted (*R*)- and (*S*)-82-OH, in contrast, the intermediate reacts with the primary alcohol (DA) and unreacted 82-OH in the transesterification with TA. It is generally recognized that primary alcohol reacts more rapidly than secondary alcohol in lipase catalyzed reactions. Thus, the reverse reaction for TA becomes more significant than that for VA (**Fig. 1**).

From the above facts, we concluded that VA had an advantage for the optical resolution of (*S*) isomer (the unreacted substrate) with higher ee_S relative to TA via PCL catalyzed transesterification. In addition, we should be borne in mind advantages of acceleration in the reaction rate (8) and easy removal of the unreacted acetylating reagent from the reaction mixture in the transesterification with VA.

3·2 Optical Resolution [Resolution from Racemate]

Figure 1 suggests that (*S*)-(1) with $ee > 95\%$ can be resolved from (*RS*)-(1) by controlling c of PCL cat-

Fig. 1 Plots of ee vs. c for PCL Catalyzed Transesterification with (*RS*)-82-OH in 1,2-dichloroethane at 30°C.

○ : ee_P vs. c , □ : ee_S vs. c

A : [VA]=0.98-1.63 M, [82-OH]=0.56-0.93 M and PCL=50 mg/mL.

B : [TA]=0.76-1.33 M, [82-OH]=0.56-0.77 M and PCL=100 mg/mL.

The resolution data in **Fig. 1B** fit Eq. (1) with $E=18$ and $K=0.01$.

Table 4 Resolution of (*R*)- and (*S*)-(**1**) from (*RS*)-(**1**) by PCL Catalyzed Transesterification with VA in Organic Solvent at 30 °C^a).

(R)-(1)	Hexane ^a)			1,2-Dichloroethane ^a)			Acetonitrile ^b)		
	<i>c</i> /%	<i>ee_p</i> /%	<i>E</i> /- ^b)	<i>c</i> /%	<i>ee_p</i> /%	<i>E</i> /- ^b)	<i>c</i> /%	<i>ee_p</i> /%	<i>E</i> /- ^b)
72-OH	28	87	20	34	88	24	30	88	23
82-OH	27	78	11	33	81	14	28	82	13
92-OH	34	86	21	32	92	37	31	86	20
102-OH	31	80	13	34	84	17	32	84	17
112-OH	30	87	21	34	92	39	32	89	27
122-OH	33	90	27	33	94	53	34	91	33
(R)-(1)	<i>c</i> /%	<i>ee_S</i> /%	<i>E</i> /- ^b)	<i>c</i> /%	<i>ee_S</i> /%	<i>E</i> /- ^b)	<i>c</i> /%	<i>ee_S</i> /%	<i>E</i> /- ^b)
72-OH	73	>99	10	68	>99	14	67	>99	15
82-OH	72	98	9	65	99	14	69	99	11
92-OH	73	98	9	63	99	19	65	99	16
102-OH	73	>99	10	66	>99	16	69	>99	14
112-OH	67	>99	15	61	>99	24	67	>99	16
122-OH	72	99	10	64	>99	18	71	>99	11

a) [VA]=1.63 M, [72-OH]=0.63 M, [82-OH]=0.56 M, [92-OH]=0.51 M, [102-OH]=0.46 M, [112-OH]=0.42 M, [122-OH]=0.39 M and PCL=30-50 mg/mL.

b) Determined by Eq. (2).

alyzed transesterification with VA. In the previous papers, we reported that the reversibility, *i.e.*, the reverse reaction, became critical in the optical resolution of (*S*) isomer at high *c* by PCL catalyzed transesterification with TB (7) and that *E* determined by Eq. (2) was sharply decreased with *c* in the range of *c*>0.55 in the transesterification with VA (6). In the consideration of these observations, we carried out the resolution of (*S*)-(**1**) with *ee*>95% from (*RS*)-(**1**) by PCL catalyzed transesterification with VA. The results were summarized in **Table 4**.

1,2-Dichloroethane and acetonitrile, which gave higher *E* than the other solvents in the resolution from (*RS*)-82-OH (6), were used as the reaction solvents and hexane was also used as a standard solvent. **Table 4** shows that (*S*)-(**1**) with *ee*>95% can be resolved from (*RS*)-(**1**) by controlling *c* of the reaction with VA although in the expense of chemical yield.

As shown in **Table 4**, (*R*)-(**1**) with *ee*>95% could not be resolved from (*RS*)-(**1**) in all cases because the enantioselectivity (*E*) was not enough high for the optical resolution (see also **Fig. 1A**).

3.3 Kinetic Resolution from Enantiomerically Enriched Substrate

3.3.1 Introduction of new equations

In the previous paper (6), we reported that *E* determined by Eq. (2) decreased with *c* in the range of *c*<0.5 because acetylation of the (*S*) isomer was suppressed during the reaction in PCL catalyzed transesterification between VA and (**1**): the pseudo first order plot with respect to enantiomer gave a linearity for (*R*)-(**1**) but curvature for (*S*)-(**1**). It was also reported that the optical resolution data fit Eq. (1) in lipase catalyzed transesterification between TB and secondary alcohol, *i.e.*, the reaction is reversible (5, 7). A similar result was obtained for the reaction with TA (**Fig. 1B**). Recently, we found out that the pseudo first order plot gave curvature for both enantiomers in PCL catalyzed transesterification between TA and (*RS*)-82-OH in 1, 2-dichloroethane.

In the consideration of above observations, we introduced new equations for predicting the optical purities of enantiomers resolved from enantiomerically enriched substrate. Our idea is the use of optical resolution data because *ee_p* and *ee_S* are the functions of *E*, *K* and *c*.

*Equations for the Resolution of (R)-(**1**)*—In the previous paper (6), we reported that the optical resolution data were expressed as

$$ee_p = \frac{c_R - c_S}{c_R + c_S} \quad (6)$$

$$ee_S = \frac{c_R - c_S}{2 - (c_R + c_S)} \quad (7)$$

and

$$c = \frac{c_R + c_S}{2} \quad (8)$$

where c_R and c_S are the extents of conversion of (*R*)- and (*S*)-(1) in (*RS*)-(1). In the enzymatic resolution, the reactions of enantiomers are simply expressed as

and

where A and B are the fast- and slow-reacting enantiomers in (*R*)-enriched substrate (initial optical purity: ee_0), and P and Q are the products from A and B, respectively. One can write down as follows:

$$ee_0 = \frac{[A]_0 - [B]_0}{[A]_0 + [B]_0} \quad (11)$$

$$ee_P' = \frac{[P] - [Q]}{[P] + [Q]} \quad (12)$$

$$ee_S' = \frac{[A] - [B]}{[A] + [B]} \quad (13)$$

and

$$c' = \frac{[P] + [Q]}{[A]_0 + [B]_0} \quad (14)$$

where $[A]_0$ and $[B]_0$ are the initial concentrations of A and B, ee_P' and ee_S' are optical purities of the product and the unreacted substrate and c' is the extent of conversion based on (*R*)-enriched substrate.

Let $[A]_0/[B]_0 = r_1$, one obtains

$$ee_0 = \frac{r_1 - 1}{r_1 + 1} \quad \text{or} \quad r_1 = \frac{1 + ee_0}{1 - ee_0} \quad (15)$$

Assuming that the extent of conversion is independent of the concentration, one obtains

$$c_R = \frac{[P]}{[A]_0} \quad (16)$$

and

$$c_S = \frac{[Q]}{[B]_0} \quad (17)$$

Thus

$$ee_P' = \frac{r_1 c_R - c_S}{r_1 c_R + c_S} = \frac{ee_0 + \frac{c_R - c_S}{c_R + c_S}}{1 + ee_0 \frac{c_R - c_S}{c_R + c_S}} = \frac{ee_0 + ee_P}{1 + ee_0 ee_P} \quad (18)$$

$$ee_S' = \frac{r_1(1 - c_R) - (1 - c_S)}{r_1(1 - c_R) + (1 - c_S)} = \frac{ee_0 - \frac{c_R - c_S}{2 - (c_R + c_S)}}{1 - ee_0 \frac{c_R - c_S}{2 - (c_R + c_S)}} = \frac{ee_0 - ee_S}{1 - ee_0 ee_S} \quad (19)$$

$$c' = \frac{r_1 c_R + c_S}{r_1 + 1} = \frac{c_R + c_S}{2} + \frac{ee_0(c_R - c_S)}{2} = \frac{ee_S(1 + ee_0 ee_P)}{ee_S + ee_P} \quad (20)$$

and

$$c' = \frac{ee_0 - ee_S'}{ee_P' - ee_S'} \quad (21)$$

where $ee_S' > 0$ and $ee_S' < 0$ mean that configurations of the unreacted substrate are (*R*) and (*S*), respectively.

Equations for the Resolution of (S)-(1)—Similarly we obtained optical purities of the product (ee_P'') and the unreacted substrate (ee_S''), and the extent of conversion (c'') in the resolution from (*S*)-enriched substrate (initial optical purity: ee_0 , $r_2 = [B]_0/[A]_0$):

$$ee_P'' = \frac{[Q] - [P]}{[Q] + [P]} = \frac{r_2 c_S - c_R}{r_2 c_S + c_R} = \frac{ee_0 - \frac{c_R - c_S}{c_R + c_S}}{1 - ee_0 \frac{c_R - c_S}{c_R + c_S}} = \frac{ee_0 - ee_P}{1 - ee_0 ee_P} \quad (22)$$

$$ee_S'' = \frac{[B] - [A]}{[B] + [A]} = \frac{r_2(1 - c_S) - (1 - c_R)}{r_2(1 - c_S) + (1 - c_R)} = \frac{ee_0 + \frac{c_R - c_S}{2 - (c_R + c_S)}}{1 + ee_0 \frac{c_R - c_S}{2 - (c_R + c_S)}} = \frac{ee_0 - ee_S}{1 + ee_0 ee_S} \quad (23)$$

$$c'' = \frac{[Q] + [P]}{[B]_0 + [A]_0} = \frac{r_1 c_S + c_R}{r_2 + 1} = \frac{c_R + c_S}{2} - \frac{ee_0(c_R - c_S)}{2} = \frac{ee_S(1 - ee_0 ee_P)}{ee_S - ee_P} \quad (24)$$

and

$$c'' = \frac{ee_S'' - ee_0}{ee_S'' - ee_P''} \quad (25)$$

where $ee_P'' > 0$ and $ee_P'' < 0$ mean that configurations of the product are (*S*) and (*R*), respectively.

3.3.2 Resolution from (*R*)-enriched-(1)

As mentioned above, the kinetic resolution data (ee_P' ,

Fig. 2 Plots of ee' vs. c' for PCL Catalyzed Transesterification with (*R*)-Enriched 82-OH in 1,2-dichloroethane 30°C.

ee_0 : (a) 0.802, (b) 0.554 and (c) 0.400.

A : [VA]=1.63 M, [82-OH]=0.56 M and PCL=50 mg/mL.

B : [TA]=0.81 M, [82-OH]=0.56 M and PCL=100 mg/mL.

○, △, □ : $ee'(\text{calc})$ vs. $c'(\text{calc})$.

●, ▲, ■ : $ee'(\text{meas})$ vs. $c'(\text{meas})$.

ee_s' and c') are able to be predicted by Eqs. (18)-(21) for the resolution from enantiomerically enriched substrate by enzymatic reaction. In order to verify these equations, we examined the resolution from (*R*)-enriched 82-OH ($ee_0=0.40$ -0.80) by PCL catalyzed transesterifications with VA and TA in 1,2-dichloroethane. The results were illustrated in **Fig. 2**, which obviously shows an excellent agreement between the calculated [$ee'(\text{calc})$ vs. $c'(\text{calc})$] and measured [$ee'(\text{meas})$ vs. $c'(\text{meas})$] plots in both reactions. **Figure 2** also shows that the conversion, at which one should terminate the reaction to obtain the product with a desired optical purity in a good chemical yield, can be estimated from the plots of $ee_p'(\text{calc})$ vs. $c'(\text{calc})$ determined by Eqs. (18) and (20).

Based on the above observations and Eqs. (18)-(21), the starting material with at least 70% of ee_0 , more favorably 80% of ee_0 , was required for the resolution of (*R*)-(1) with $ee \geq 95\%$. In order to prove it, we examined the resolution from (*R*)-enriched-(1) by the transesterification with VA. The results were summarized in **Table 5**. This also showed that the values of $ee_p'(\text{calc})$ determined by Eq. (18) were in an excellent accordance with those of $ee_p'(\text{meas})$.

The results in **Fig. 2** and **Table 5** demonstrate that Eqs. (18)-(21) are generally applicable to predict optical purities of enantiomers resolved from enantiomerically enriched substrate by enzymatic and catalytic reactions and that their equations are independent of reversibility/irreversibility of the reaction and of obedi-

Table 5 Kinetic Resolution of Highly Enantiomerically Enriched (*R*)-(1) from (*R*)-enriched-(1) by PCL Catalyzed Transesterification with VA in Organic Solvent at 30°C^a.

(R)-(1)	Hexane				1,2-Dichloroethane				Acetonitrile			
	$ee_0/\%$	$c'/\%$	$ee_p'/\%^{(b)}$		$ee_0/\%$	$c'/\%$	$ee_p'/\%^{(b)}$		$ee_0/\%$	$c'/\%$	$ee_p'/\%^{(b)}$	
			meas	calc ^c			meas	calc ^c			meas	calc ^c
72-OH	85	77	98	98	85	77	98	98	85	76	98	98
82-OH	76	72	95	95	80	76	98	98	76	70	96	97
92-OH	70	74	96	95	86	62	98	98	70	73	96	96
102-OH	75	74	96	95	75	69	98	98	75	73	98	98
112-OH	79	75	97	98	79	76	98	98	79	77	97	98
122-OH	80	76	98	98	80	75	99	99	80	76	98	99

a) [VA]=1.63 M, [72-OH]=0.63 M, [82-OH]=0.56 M, [92-OH]=0.51 M, [102-OH]=0.46 M, [112-OH]=0.42 M, [122-OH]=0.39 M and PCL=100 mg/mL.

b) Errors were $\pm 1\%$.

c) Determined by Eq. (18).

Fig. 3 Plots of ee'' vs. c'' for PCL Catalyzed Transesterification with (S)-Enriched 82-OH in 1,2-dichloroethane at 30°C.

ee_0 : (a) 0.694 and (b) 0.400.

A : [VA]=1.63 M, [82-OH]=0.56 M and PCL=50 mg/mL.

B : [TA]=0.81 M, [82-OH]=0.56 M and PCL=100 mg/mL.

○, □ : $ee''(\text{calc})$ vs. $c''(\text{calc})$.

●, ■ : $ee''(\text{meas})$ vs. $c''(\text{meas})$.

ence to the optical resolution theory [Eqs. (1)-(2)].

3.3.3 Resolution (S)-enriched-(1)

As shown in **Table 4**, (S)-(1) with $ee_s \geq 98\%$ could be resolved by controlling c of the reaction with VA. However, this method has a disadvantage of low chemical yield. In the case of TA, the optical purity of (S)-82-OH was below 96% due to the reverse reaction (**Fig. 1B**). A similar tendency has been reported in lipase catalyzed transesterification with TB (7). In such cases, a useful strategy is the use of enantiomerically enriched substrate. Then, we examined the resolution of (S)-(1) from (S)-enriched-(1) by the transesterifications.

As shown in **Fig. 3**, the plots of $ee''(\text{meas})$ vs. $c''(\text{meas})$ were in an excellent accordance with those of $ee''(\text{calc})$ vs. $c''(\text{calc})$ determined by Eqs. (22)-(25) and the disadvantages described above were relieved: opti-

cally pure (S)-(1) ($ee_s > 99\%$) was recovered at low conversion, *i.e.*, in a good chemical yield (**Fig. 3A**) and $ee_s > 99\%$ was attained for the reaction with TA (**Fig. 3B**, curve a).

3.4 Resolution of Optically Pure (R)- and (S)-(1) in a Preparative Scale

Finally we attempted the resolution of optically pure (R)- and (S)-(1) ($ee \geq 99\%$) from (RS)-(1) in a preparative scale by repeating the transesterification with VA in 1,2-dichloroethane. The results were summarized in **Tables 1** and **2**. The ee values of the resolved alcohols agreed with those determined by Eqs. (18)-(20) and (22)-(24). Optically pure (R)-(1) was resolved by repeating the transesterification three times and twice for optically pure (S)-(1). This procedure will be useful for kinetic resolution of highly enantiomerically enriched fast reacting enantiomer in the racemate by enzymatic reactions with a moderate enantioselectivity and for the resolution of optically pure slow reacting enantiomer by the reversible enzymatic reactions.

The specific rotations of optically pure (R)- and (S)-(1) were summarized in **Table 3**. The former is negative and positive for the latter. The absolute value of specific rotation decreased with carbon number of the alcohol and the wavelength.

4 Conclusion

New equations as functions of the optical resolution data were introduced for predicting optical purities of enantiomers resolved by PCL catalyzed transesterification with enantiomerically enriched 2-alkanols and they were verified experimentally. The results in this paper demonstrate that the proposed equations are applicable to enzymatic and catalytic reactions and that they are independent of reversibility /irreversibility of the reactions and of obedience to the optical resolution theory [Eqs. (1) and (2)]. The present procedure will be a powerful strategy for the preparation of optically pure enantiomers from enantiomerically enriched substrates, especially the resolutions of fast-reacting enantiomer by the enzymatic reactions with a moderate enantioselectivity and slow-reacting enantiomer by the reversible enzymatic reactions.

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