Pergamon

Tetrahedron Letters 39 (1998) 7881–7884

TETRAHEDRON LETTERS

Low-Temperature Method for Enhancement of Enantioselectivity in the Lipase-Catalyzed Kinetic Resolutions of Solketal and Some Chiral Alcohols

Takashi Sakai,* Tetsuo Kishimoto, Yukie Tanaka, Tadashi Ema, and Masanori Utaka*

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushima-naka, Okayama 700-8530, Japan

Received 22 June 1998; revised 6 August 1998; accepted 17 August 1998

Abstract:
Low-temperature method (–40 °C at best) for enhancement of the enantioselectivity in a lipase-catalyzed transesterification was proved to be widely applicable to primary and secondary alcohols and enabled theoretical prediction of the course of enhancement of the enantioselectivity physicochemically.

Keywords: *acylation, enantiospecificity, enzymes and enzyme reactions, resolution*

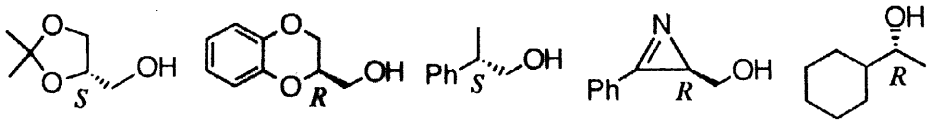
In recent advances on the lipase-catalyzed kinetic resolutions of chiral alcohols,[1–5] various methods for the artificial modulating method have been devised to improve the enantioselectivity.[4–7] However, the development of a generally applicable method for relatively unsuitable primary alcohols is still an urgent subject. As a readily available method for synthetic organic chemists, we recently proposed a low-temperature method (0 °C to –40 °C) in the lipase-catalyzed resolution of 3-phenyl-2*H*-azirine-2-methanol (**4**).[7] It was the first example of an enzymatic reaction carried out at such very low temperatures as far as we know. The method enabled us not only to improve the enantioselectivity (*E* value[8]) even for a primary alcohol, but also to theoretically predict the course of enhancement of the enantioselectivity on the basis of the following physicochemical equation (1):[9]

$$\ln E = \Delta\Delta S^{\ddagger}/R - \Delta\Delta H^{\ddagger}/(RT) \qquad \text{(Eq. 1)}$$

Equation 1 is derived from the transition-state theory, $\Delta\Delta G^{\ddagger} = -RT \ln E$, and thus should be applicable generally to the lipase-catalyzed resolutions, as far as the lipases work at the very low temperatures unusual for enzymes and the reactions proceed through an identical transition-state at all the temperatures examined. However, no such example is available except our case.[7] We here explored the applicability of the low-temperature method to secondary and primary racemic alcohols of **1**–**3** and **5**, and found that *E* values for all reactions, even with different kinds of lipases, are expectable by correlation to the reaction temperature (Eq. 1).

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01747-X

Figure 1. Faster-Reacting Enantiomers.

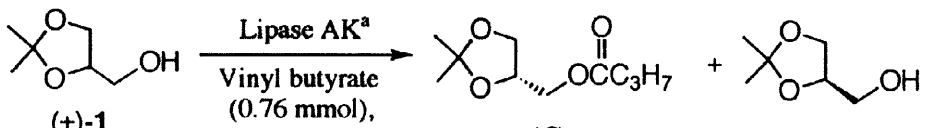


1 **2** **3** **4** **5**

As a typical example, the low-temperature method was applied to solketal, 2,2-dimethyl-1,3-dioxolane-4-methanol (±)-**1**, which is known as a useful C_3-synthon.[10-13] The lipase-catalyzed resolution of (±)-**1** has not been well established because of the low enantioselectivity of the primary alcohols. Kanerva *et al.*[10] have recently reported that the lipase AK (*Pseudomonas fluorescens*)-catalyzed resolution in the transesterification of (±)-**1** with 2,2,2-trifluoroethyl 3-methylbutyrate gave moderate E values (16 at 23 °C and 27 at 0 °C) and thus utilized a double kinetic resolution to improve the efficiency. In contrast, we succeeded in increasing the E value up to 55 by simply lowering the reaction temperature to –40 °C in *i*-Pr_2O as shown in Table 1.[14] The plot of ln E *vs* $1/T$ was found to obey Eq. 1 in the range of 30 °C to –40 °C (Figure 2). Surprisingly, the reaction itself proceeded even at –60 °C, although the E values were decreased irregularly. Reasons for the loss of the enantioselectivity below –40 °C are now under investigation, but we confirmed that the loss does not arise from irreversible structural damage to the lipase. The lipase PS once cooled to –60 °C for 3 h in *i*-Pr_2O exerted an efficiency similar to that of fresh lipase at temperatures higher than –40 °C. These results suggest that –40 °C is the lowest practically feasible temperture giving the highest E values with sufficient total turnover number (TTN) as previously observed for (±)-**4**.[7]

Similar reactions using other racemic alcohols such as 2-hydroxymethyl-1,4-benzodioxane (±)-(**2**),[15] 2-phenylpropanol (±)-(**3**) [16,17] and 1-cyclohexylethanol (±)-(**5**)[18] were also proved to obey Eq. 1 as shown in Figure 2.[19] The reaction conditions, except the temperatures, followed those reported in the literature.[10,15-18] Alcohol (±)-**3** gave very low selectivities ($E = 4$) even at –40 °C with lipase PS (*Pseudomonas cepacia*);

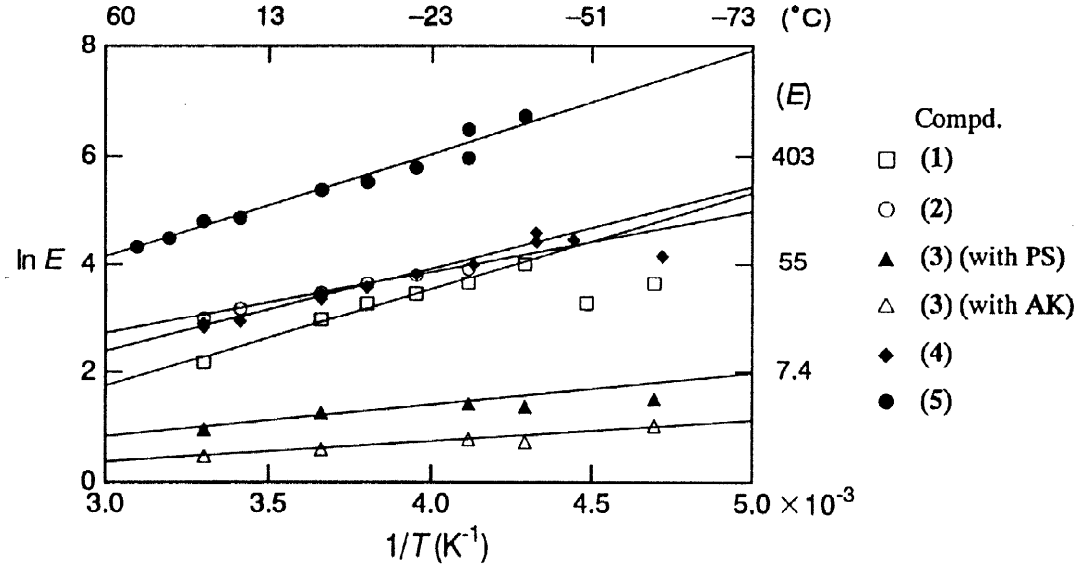
Table 1. Temperature Effect in the Lipase-Catalyzed Kinetic Resolution of Solketal.



Entry	Temp. (°C)	Lipase (mg)	Time (h)	Ester (% ee)	Alcohol (% ee)	Conv.[b]	E
1	30	20	3	63	69	0.52	9
2	0	20	6	88	25	0.22	20
3	–10	60	8	84	77	0.48	26
4	–20	60	11	92	32	0.26	31
5	–30	100	16	93	39	0.30	39
6	–40	200[c]	24	93	63	0.41	55
7	–50	200[c]	48	74	97	0.57	27
8	–60	200[c]	48	93	51	0.35	44

[a]MW = ca. 33,000. Lipase (ca.1% w/w) is adsorbed on Celite. [b]Calculated from *ee*(s). [c]TTN is ca. 3,000 at 50% conversion..

Figure 2. Plots of ln E vs $1/T$ for the Lipase-Catalyzed Resolutions.



however, the plot of ln E vs $1/T$ is correlated in its own way. Changing the lipase to AK for (±)-**3** further decreased the E values (E = 2 at –40 °C), which, however, still exhibited a linear-correlation to the temperature ($1/T$). Oxygen-containing heterocycles (±)-**1** and (±)-**2** were found to show a tendency similar to that of previous data for (±)-**4**.[7]

The thermodynamic parameters ($\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$) and racemic temperatures T_r^{o} are calculated from Fig. 2 and listed in Table 2, which indicates activation-enthalpy differences ($\Delta\Delta H^{\ddagger}$) govern the enantioselectivity. We understand that the $\Delta\Delta H^{\ddagger}$ orginates from the difference in the steric interactions opperating between the enantiomers in the transition-state.[20] The negative values of $\Delta\Delta H^{\ddagger}$ are compensated by negative activation-entropy differences ($\Delta\Delta S^{\ddagger}$) in all cases. The higher enantioselectivity for secondary alcohol **5** comes from the larger negative difference in $\Delta\Delta H^{\ddagger}$ and the low selectivity for **3** depends on the smaller values in $\Delta\Delta H^{\ddagger}$.

Table 2. Thermodinamic Parameters for the Lipase-Catalyzed Resolutions (i-Pr_2O, Vinyl Acetate).

Compd	Lipase	$\Delta\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	T_r (°C)
1	AK[a]	–3.53 ± 0.20	–7.18 ± 0.79	219
2	AK	–2.24 ± 0.12	–1.35 ± 0.40	1386
3	PS	–1.13 ± 0.05	–1.77 ± 0.96	365
3	AK	–0.74 ± 0.05	–1.51 ± 0.19	217
4	PS[b]	–3.01 ± 0.13	–4.31 ± 0.50	425
5	PS	–3.73 ± 0.25	–3.02 ± 0.92	962

[a]With vinyl butyrate, [b]In Et_2O.

In recent asymmetric synthesis with artificial catalysts, the temperature effect has been an attractive method for fine-tuning of the enantioselectivity.[21] We here demonstrated that lipases can be used as thermostable macromolecular catalysts even at such very low temperatures in an organic solvent to enhance the enantioselectivity (E values) similarly to artificial catalysts. Further applications of the low-temperature method to a wide range of alcohols are in progress.

Acknowledgments
This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan. We are grateful to Amano Pharmaceutical Co., Ltd., Sumitomo Chemical Co., Ltd. and Toyobo Co., Ltd. for kind supply of the lipases, and the SC-NMR laboratory of Okayama University for ^{19}F NMR (188 MHz) and ^{1}H NMR (500 and 200 MHz) analyses.

References

1. Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994.
2. Faber, K. *Biotransformations in Organic Chemistry*; Springer-Verlag: Berlin, 1995.
3. Koskinen, A. M. P.; Klibanov, A. M. *Enzymatic Reactions in Organic Media*; Eds.; Blackie Academic: Glasgow, 1996.
4. Itoh, T.; Takagi, Y.; Tsukube, H. *Trends in Organic Chemistry*, **1997**, 6, 1-22.
5. Kazlauskas, R. J.; Bornscheuer, U. T. *Biotransformations*, in *Biotechnology*, Vol. 8a, Rehm, H.-J.; Reed, G. Eds.; Wiley-VCH: Weinheim, 1998, Chapter 3, 37-192.
6. Ema, T.; Maeno, S.; Takaya, Y.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1996**, 61, 8610-8616.
7. Sakai,T.; Kawabata, I.; Kishimoto, T.; Ema, T.; Utaka, M. *J. Org. Chem.* **1997**, 62, 4906-4907 and the literatures cited therein.
8. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, 104, 7294-7299.
9. Phillips, R. S. *Trend Biotechnol.* **1996**, 14, 13-16.
10. Vanttinen, E.; Kanerva, L. T. *Tetrahedron: Asymmetry* **1997**, 6, 923-933.
11. Krief, A.; Provins, L.; Froidbise, A. *Tetrahedron Lett.* **1998**, 39, 1437-1440.
12. Bianchi, D.; Bosetti, A.; Golini, P.; Cesti, P.; Pina, C. *Tetrahedron: Asymmetry* **1997**, 8, 817-819.
13. Chenault, H. K.; Chafin, L. F.; Liehr, S. *J. Org. Chem.* **1998**, 63, 4039-4045.
14. General procedure for Table 1: To a cooled mixture of solketal, lipase, and diisopropyl ether (dried over benzophenone ketyl) was added freshly distilled vinyl butyrate through a syringe. Progress of the reaction was monitored by TLC analysis. After the reaction time indicated, the mixture was filtered as quickly as possible by suction through Celite pad to remove the lipase and the filtrate was concentrated under reduced pressure. The products without isolation were allowed to react with excess of propanoic anhydride (0.2 ml, 1.55 mmol) in pyridine (0.2 ml) overnight and then treated in the usual manner. Optical purities (% ee) of the obtained mixture of (*S*)-butyrate and (*R*)-propanoate were determined by GLC analysis with a chiral column (Tokyo Chemical Co. Ltd., CP-cyclodextrin-B-236-M-19, oven temp. 100 °C), compound (retention time): (*R*)- (26.3 min) and (*S*)-propanoates (27.7 min); (*R*)- (43.4 min) and (*S*)-butyrates (45.8 min). Reuse of these lipases (PS and AK) tends to reduce the selectivity. Reusable immobilized lipases are now under investigation.
15. Antus, S.; Gottsegen, A.; Kajtár, J.; Kovács, T.; Tóth, T.; Wagner, H. *Tetrahedron: Asymmetry* **1993**, 3, 339-344.
16. Weissfloch, A. N. E.; Kazlauskas, R. J. *J. Org. Chem.* **1995**, 60, 6959-6969.
17. Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, 53, 5531-5534.
18. Morgan, B.; Oehlschlager, A. C.; Stokes, T. M. *J. Org. Chem.* **1992**, 57, 3231-3236.
19. Ee(s) of **2**, its acetate and **3** were determined by HPLC analysis with Chiralcel OB-H (hexane—*i*-PrOH). Acetate of **3** was analyzed by HPLC after hydrolysis to alcohol **3**. Ee(s) of acetate of **5** were determined by the GLC analysis in a similar way to that for **1** and those of **5** were determined after conversion to its acetate.
20. Ema, T.; Kobayashi, J.; Maeno, S.; Sakai, T.; Utaka, M. *Bull. Chem. Soc. Jpn.* **1998**, 71, 443-453.
21. Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, 39, 3201-3204.