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Thiacrown Ether as Regulator of Lipase-Catalyzed Trans-Esterification in Organic Media: Practical Optical Resolution of Allyl Alcohols

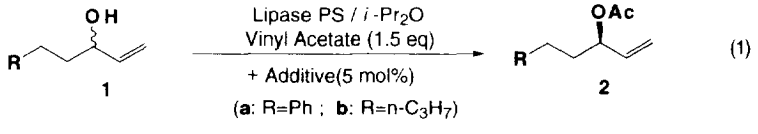
Yumiko Takagi,* Jun Teramoto, Hiroshi Kihara,
Toshiyuki Itoh,† and Hiroshi Tsukube ‡

Department of Natural Science, Hyogo University of Teacher Education, Yashiro, Hyogo 673-14, Japan. †Department of Chemistry, Faculty of Education, Okayama University, Okayama 700, Japan. ‡Department of Chemistry, Faculty of Science, Osaka City University, Osaka 558, Japan

Abstract: Thiacrown ether additive enhanced enantioselectivity in lipase-catalyzed trans-esterification of allyl alcohols. Small amounts of thiacrown ether offered highly enantioselective reaction when 5-phenylpentene-3-ol was subjected to the reaction of *Pseudomonas cepacia* lipase. Copyright © 1996 Elsevier Science Ltd

Lipase-catalyzed enantioselective acetylation of racemate in organic solvent is well recognized as a useful procedure for preparing chiral building blocks for organic synthesis.[1] Because a number of lipases and substrates applicable for practical enantiomer resolution is limited, development of a conventional method to improve enzyme performance is very important.[1] We recently found that crown ether additive enhanced both enantioselectivity and reaction rate in the hydrolysis of 2-cyano-1-methylethyl acetate catalyzed by *Pseudomonas cepacia* lipase (lipase PS).[2] We wish to report here that small amounts of thiacrown ether enhances enantioselectivity of lipase-catalyzed acetylation of allyl alcohols in organic solvent. This is the first examples of practical resolution of the allyl alcohols in which crown ether additive promotes enzymatic acetylation.

Typically, thiacrown **4** (4 mg) and lipase PS (24.4mg) were added to an *i*-Pr_2O solution (1.5 mL) of racemic allyl alcohol (±)-**1a** (48.7mg), and the resulting mixture was stirred at 35°C. The optical purity of product acetate **2a** and the remaining alcohol (+)-**1a** was determined by capillary GPC analysis (Chiraldex G-TA). Trans-esterification was carried out in the presence of 5 mol% of crown ether additives: 1,4,8,11-tetrathiacyclotetradecane (**4**), 1,4,7,10-tetrathiacyclododecane (**5**), 1,4,7,10-tetraazacyclododecane (**6**), and 1,4,7,10-tetraoxacyclododecane (**7**). Some of these have been demonstrated to be an effective enhancer in the enzymatic hydrolysis of 2-cyano-1-methylethyl acetate.[2]



(1)

Table. Enantioselective acetylation of allyl alcohol **1** catalyzed by lipase PS in the presence of additive

Entry	R	Additive	Solvent	Time(h)	%conv.	%ee of **2** (Yield)	%ee of **1** (Yield)	E[a]
1	Ph	none	Hexane	93	38	97 (38)	59 (60)	105
2	Ph	none	*i*-Pr_2O	65	48	98 (48)	92 (48)	305
3	Ph	**4**	Hexane	93	50	97 (50)	98 (50)	407
4	Ph	**4**	i-Pr_2O	65	49	>99 (49)	98 (51)	>1200
5	Ph	**5**	Hexane	15	19	97 (19)	23 (81)	76
6	Ph	**6**	Hexane	15	13	97 (13)	14 (87)	88
7	Ph	**7**	Hexane	15	30	97 (30)	42 (54)	94
8	n-C_3H_7	none	Hexane	72	47	50 (47)	45 (45)	5
9	n-C_3H_7	none	*i*-Pr_2O	72	12	7 (12)	52 (45)	3
10	n-C_3H_7	**4**	Hexane	72	42	37 (42)	52 (53)	5
11	n-C_3H_7	**4**	*i*-Pr_2O	72	36	45 (31)	82 (63)	16

a) E =ln[1-c(1+ee**2**)]/ln[1-c(1-ee**2**)], c=ee**3** /ee**2**+ee**3**.(see ref. 5)

Among the examined additives, thiacrown ether **4** remarkably increased enantioselectivity in acetylation of 5-phenylpentene-3-ol **1a**, while it moderately enhanced E value of the acetylation of 1-octene-3-ol **1b** (Entry 11). When the (±)-**1a** was employed as a substrate, the enantioselectivity was dependent on the solvent system : lipase PS itself offered E value of 105 in hexane and 305 in *i*-Pr_2O (Entries 1 and 2). Interestingly, more highly enhanced E values of 407 (in hexane) and >1200 (in *i*-Pr_2O) were recorded in the presence of 5 mol% of thiacrown ether **4** (Entries 3 and 4).[3] Macrocycles **5**-**7** affected reaction rates but rarely modified E values of the reactions. It was particularly noteworthy that the E value was recorded as >1200 even when the reaction was carried out in the presence of only 0.5 mol% of **4** towards the substrate. This corresponds to *twenty five times the thiacrown ether with molarity based on the enzyme*. Thus, this additive method is simple to use and effective in practical enzymatic resolution of racemic allyl alcohols. Reinhoudt et al.[4] recently reported that crown ethers could solubilize the lipase in organic solvents and accelerate the rate of trans-esterification. Although they had not examined thiacrown ether additives, we found that thiacrown ether could improve both reaction rate and enantioselectivity in lipase-catalyzed esterification with the enantioselectivity in particular reaching a higher level for practical use. Preliminary ^{13}C NMR studies suggested that thiacrown **4** bound allyl alcohol **1**.[5] This may facilitate the penetration of the allyl alcohol into the active site of the lipase, although further mechanistic investigation is required to confirm this.

References and notes

1) Wong, C. H.; Whitesides, G. M., Enzymes in Synthetic Organic Chemistry, Pergamon, Oxford, **1994**.
2) Itoh, T.; Takagi, Y.; Murakami, T.; Hiyama, Y.; Tsukube, H. *J. Org. Chem.*, **1996**, *61*, 2158.: Itoh, T.; Hiyama, Y.; Betchaku, A.; Tsukube, H. *Tetrahedron Lett.* **1993**, *34*, 2617.
3) Water concentration in the employed solvents were determined, but no significant change in water concentration was observed when additives were added.
4) Broos, J.; Sakodinskaya, I K.; Engbersen, J. F. J.; Verboom, W.; Reinhoudt, D. N; *J. Chem. Soc., Chem., Commum.*, **1995**, 255-256.
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6) An aqueous solution (9.4 mL) of the employed lipase (54 mg) was found to contain the following metal cations which were not good guests for thiacrown ether **4** : Na^+, $6.5x10^{-4}$ mol/L; K^+, $4.6x10^{-4}$ mol/L; Mg^{2+}, $6.0x10^{-4}$ mol/L; Ca^{2+}, $6.5x10^{-4}$ mol/L.
7) The authors are grateful to Amano Pharmaceutical Co., Ltd. for providing lipase and to the SC-NMR Laboratory of Okayama University for the NMR measurements.

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