Highly Enantioselective Lipase-catalyzed Kinetic Resolution of 2-Silyloxy-1-propanol

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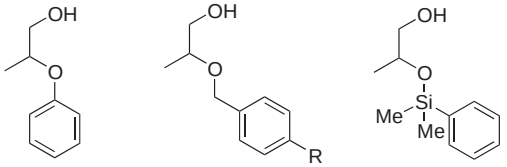
The lipase-catalyzed kinetic resolutions of 2-benzyloxy- and 2-silyloxy-1-propanols have been investigated. Efficient modification of the substrate structure with the dimethylphenylsilyl protecting group and the use of lipase PS-D immobilized on diatomaceous earth were found to enhance the enantioselectivity and reactivity up to $E = 240$ at 0 °C.

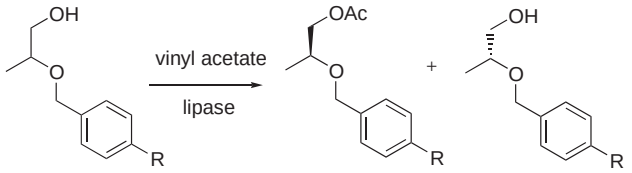
Lipase have been widely used for the synthesis of various optically active alcohols.[1] Although high enantioselectivities for many secondary alcohols have been obtained using a lipase such as lipase PS from *Pseidomonas cepacia* (PCL),[2] only low to moderate enantioselectivities for primary alcohols have been achieved owing to the conformational flexibility.[3] To enhance the enantioselectivity for primary alcohols, Sakai et al. reported a low-temperature method,[4] for example, the E value for the kinetic resolution of 2,2-dimethyl-1,3-dioxolane-4-methanol using lipase AK from *Pseudomonas fluorescens* increased from $E = 9$ to 55 by lowering the reaction temperature to −40 °C,[4c] at the expense of amount of lipase and reaction time. Recently, Kazlauskas et al. reported another approach in which the accurate choice of the acyl chain length and solvent increased the enantioselectivity of PCL from $E = 17$ to 70 for the hydrolysis of 2-phenoxy-1-propyl heptanoate, **1**-heptanoate.[5] As an alternative approach, we investigated the substrate-tuning method for the glycerol derivatives and *trans*-2,5-substituted pyrrolidine derivative by altering the protecting group and found that the bis(4-bromophenyl) ketal[6] and the *N*-3,5-dimethylbenzyl group[7] were found to enhance the enantioselectivity up to $E = 57$ and 108, respectively. Thus, we expected that the proper protecting groups in place of the phenyl group of primary alcohol **1** could improve the enantioselectivity. In this paper, we describe the lipase-catalyzed kinetic resolutions of 2-benzyloxy- and 2-silyloxy-1-propanols **2**–**4**, which are useful chiral building blocks for the synthesis of optically active bioactive compounds.



1 **2** R = H, **3** R = Br **4**

The substrates **2** and **3** were prepared from methyl lactate by benzylation with benzyl bromide and 4-bromobenzyl bromide in the presence of silver oxide followed by the reduction with $LiAlH_4$. The transesterifications catalyzed by lipase PS and AK were carried out in various solvents at 25 °C (Scheme 1). The enantiomeric excess (ee) values of alcohols **2** and **3** and the resulting acetates were determined by HPLC analyses using a chiral column. The absolute configurations of the remaining alcohols were determined to be *R* by comparison with the authentic (*S*)-alcohols derived from methyl (*S*)-(−)-lactate *via* the same procedure as described above. These results were consistent with the empirical rule for chiral primary alcohols with an oxygen atom at the stereocenter.[3] These results are summarized in Table 1.

The acylation of benzyl ether **2** with lipases PS and AK in hexane, toluene, or *i*-Pr_2O proceeded with a much lower enantioselectivity than that of the phenyl ether **1**. The acylation of 4-bromobenzyl ether **3** showed a slightly higher enantioselectivity ($E = 12$–19) under similar reaction conditions. Although the low temperature method slightly increased the enantioselectivity from $E = 19$ to 27 at 0 °C in the lipase AK-catalyzed transesterification in *i*-Pr_2O, the enantioselectivity of the benzyl ether **3** was still lower than that of the phenyl ether **1**.[9] These results sug-



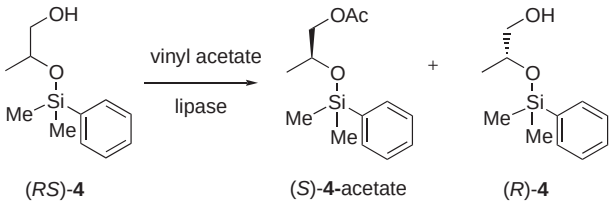
(*RS*)-**2** R = H
(*RS*)-**3** R = Br
(*S*)-**2**-acetate
(*S*)-**3**-acetate
(*R*)-**2**
(*R*)-**3**

Scheme 1.

Table 1. Acylations of **2** and **3** with vinyl acetate catalyzed by lipases PS and AK

Substrate	Lipase	Solvent	Time /h	ee_s /%[b]	ee_p /%[b]	Convn. /%[c]	E[c]
2	PS	hexane	1	79	54	59	7.7
2	PS	toluene	1	56	57	49	6.3
2	PS	*i*-Pr_2O	1	37	72	34	8.8
2	AK	hexane	1	46	67	41	8.0
2	AK	toluene	1	62	65	48	8.7
2	AK	*i*-Pr_2O	1	52	59	46	6.4
3	PS	hexane	3	21	86	19	16
3	PS	toluene	2	48	78	38	13
3	PS	*i*-Pr_2O	1.5	73	69	52	12
3	AK	hexane	2.5	51	83	38	18
3	AK	toluene	4	33	82	29	14
3	AK	*i*-Pr_2O	1.5	83	76	52	19
3	AK	*i*-Pr_2O[d]	2.5	86	82	51	27

[a]Reaction conditions: substrate (0.1 mmol), vinyl acetate (0.3 mmol), lipase (PS, 6 mg; AK, 4 mg), solvent (0.5 mL) at 25 °C. [b]Determined by HPLC analysis using chiralcel OD and OD–H column; ee_s, (*R*)-**2** and **3**; ee_p, (*S*)-**2**- and **3**-acetates. [c]Calculated using the equation in Ref. 8. [d]0 °C.



Scheme 2.

Table 2. Acylations of **4** with vinyl acetate catalyzed various lipase

Lipase	Solvent	Time/h	ee_s/%[b]	ee_p/%[b]	Convn./%[c]	E[c]
AK	hexane	1	74	90	45	43
AK	*i*-Pr_2O	12	—	——	0	—
AK	toluene	1.5	61	94	39	62
PS	hexane	1	80	93	46	63
PS	*i*-Pr_2O	12	—	—	0	—
PS	toluene	4	58	97	37	118
PS	toluene[d]	4	49	96	34	88
PS	toluene[e]	8	20	98	17	134
PS-C	toluene[e]	1	85	96	47	120
PS-D	toluene[e]	1	99	95	51	240

[a]Reaction conditions: substrate (0.1 mmol), vinyl acetate (0.3 mmol), lipase (PS, PS-C, PS-D, 10 mg; AK, 4 mg), solvent (0.5 mL) at 25 °C. [b]Determined by HPLC analysis using chiralcel OD column; ee_s, (*R*)-**4**; ee_p, (*S*)-**4**-acetate. [c]Calculated using the equation in Ref. 8. [d]Vinyl butanoate was used. [e]0 °C.

gest that the flexibility of the benzyl ethers **2** and **3** compared to the phenyl ether **1** might cause the lower enantioselectivity.

To overcome this disadvantage, we expected that dimethylphenylsilyl ether should be the proper protcting group because two additional dimethyl groups might decrease the flexibility. The silyl ether **4** was prepared from methyl lactate by silylation with dimethylphenylsilyl chloride and imidazol in DMF followed by the reduction with BH_3-THF. The transesterifications catalyzed by lipases PS and AK were carried out in various solvents at 25 °C (Scheme 2), and the absolute configurations of the remaining alcohols were also determined to be *R* by a method similar to that described above. These results are summarized in Table 2.

Higher enantioselectivities were observed for the silyl ether **4** using lipase PS and AK, although the acylation of **4** with lipase PS proceed slowly as compared with that of **2** and **3**. Among the solvent examined, toluene was found to afford the highest enantioselectivity ($E = 118$). Interestingly, no reaction using either lipase PS or AK occurred in *i*-Pr_2O after 12 h. The effect of acyl chain length on the enantioselectivity was not observed in this transesterification with vinyl butanoate in contrast to the hydrolysis.[5] Next, the temperature effect on the enantioselectivitiy was examined using lipase PS in toluene at 0 °C. Although the *E* values of lipase PS for the silyl ether **4** increased from 118 to 134, the reaction rate decreased considerably. To increase the reaction rate at 0 °C, lipase immobilized on porous ceramic[10] (lipase PS-C) and on diatomaceous earth (lipase PS-D) was examined and lipase PS-D was found to enhance not only the reaction rate but also the enantioselectivity to $E = 240$. This result is similar tendency to that of kinetic resolution of *trans*-4-phenyl-3-buten-2-ol with lipase PS-C and PS-D.[11] Thus, the combination of dimethylphenylsilyl protecting group and lipase PS-D could lead to the enhancement of both the enantioselectivity and reactivity.

In summary, we demonstrated that the efficient modification of the substrate structure with dimethylphenylsilyl group as a protecting group enhanced the enantioselectivity of the lipase-catalyzed kinetic resolution of racemic 1,2-propanediol. This substrate-tuning method by proper protecting group would provide an alternative approach to improve the lipase-catalyzed kinetic resolution of primary alcohols with an oxygen atom at the stereocenter.

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