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Lipase-Catalyzed Transesterification of 2-Phenyl-1-propanol with Vinyl Esters Having Aromatic Ring in Acyl Moiety

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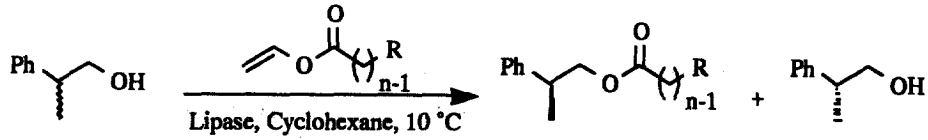
Abstract: The highly enantioselective transesterification of 2-phenyl-1-propanol, which has not been efficiently resolved by lipase-catalyzed reactions, was attained by using either vinyl 3-(*p*-tolyl)propanoate or vinyl 3-(2-naphthyl)propanoate as the acyl donor.

Keywords: Enantioselection; Enzymes and Enzyme reactions; Resolution

The kinetic resolution of racemic alcohols through lipase-catalyzed asymmetric transesterification in organic solvents is widely used by many organic chemists today.[1] The screening of lipase is the most important method for highly enantioselective reactions.[2] However, almost all racemic alcohols are unnatural compounds and, therefore, many low enantioselective transesterifications are known. To increase enantioselectivity, several methods using different reaction conditions have been examined: (1) changing the organic solvent;[3] (2) additives to the reaction mixture;[4,5] (3) lowering the reaction temperature;[6] and (4) microwave irradiation.[7] Another method is to change the structure of the acyl donor into longer chain length-possessing vinyl esters from the vinyl acetate.[2,8] We now report successful results using the new series of acyl donors having an aromatic ring in the acyl moiety.

There are several reports that low enantioselective transesterifications with vinyl acetate were improved using other acyl donors which have longer chain length in the acyl moiety, e.g. vinyl propanoate or vinyl butanoate.[7-9] However, we have found in the literature only a few references where poorly selective transesterifications with vinyl acetate ($E^{10} < 20$) were enhanced by changing the vinyl esters.[9a,d,11,12] Thus, changing the alkyl chain length of the acyl donor alone does not significantly affect the enantioselectivity of the transesterification. In the present study, we tried the vinyl esters which have a bulky substituent in acyl moiety in order to make low enantioselective transesterification highly enantioselective one. These esters have rarely been employed as acyl donors in the transesterification.[13-15] We selected 2-phenyl-1-propanol ((±)-**1**) as the model alcohol, since it has not been resolved efficiently through lipase-catalyzed reactions.[16] For the lipase catalyst, Amano PS from *Pseudomonas cepacia*, which is one of the most popular lipases, was selected (Scheme 1). Vinyl esters except vinyl acetate, butanoate and dodecanoate were synthesized according to the literature.[17]



(±)-**1** (*S*)-**2** (*R*)-**1**

Scheme 1. Lipase-catalyzed transesterification of 2-phenyl-1-propanol with various acyl donors.

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As a typical run, 10 mg of Amano PS was placed in a vial to which was added 2 ml of a cyclohexane solution containing 60 μmol of (±)-1 and 60 μmol of vinyl 3-phenylpropanoate (R = Ph, n = 3). The resulting suspension was then magnetically stirred at 10 °C[18] for 5 h. The reaction was quenched by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed on a silica gel column using hexane-ethyl acetate (5 : 1 (v / v)) as the eluent. An aliquot of the combined fractions containing the unreacted alcohol was analyzed on HPLC (Daicel, Chiralcel OB-H column, hexane : 2-propanol = 30 : 1 (v / v)) to determine the ee of the alcohol. The ee of the produced ester was determined after hydrolysis (1 mol dm^{-3} NaOH, MeOH) to the corresponding alcohol. The absolute configuration of the unreacted alcohol was established by comparing its retention time on HPLC with a purchased authentic sample. The enantiomer, which was preferentially esterified by the lipase, had the (*S*)-configuration in all the systems.

The results are summarized in Table 1. We calculated the relative reaction rates of each enantiomer from the results.[19] In the case of vinyl acetate (R = H, n = 2), the enantioselectivity toward (±)-1 was very low (*E* = 5). The longer chain aliphatic acid vinyl esters (R = H, n = 4 and 12) afforded little variation in the *E* values and reaction rates.

Table 1. Lipase-catalyzed transesterification of (±)-1 with various acyl donors in cyclohexane.

acyl donor R	n	time (h)	(*S*)-2 (% ee)	(*R*)-1 (% ee)	conversion[a] (%)	*E*[a]	relative reaction rate[b] (*S*)-1	(*R*)-1
H	2	2.5	59.6	19.5	25	5	100	25
H	4	3.5	51.6	24.4	32	4	84	27
H	12	2.0	41.5	21.3	34	3	152	63
Ph[c]	1	53.0	80.8	17.5	18	11	0.8	<0.1
Ph[c]	2	22.0	17.5	3.93	18	1.5	1	0.9
Ph	3	5.0	90.8	42.6	32	31	77	4
Ph[c]	4	1.5	70.8	44.2	38	9	55	9
c-C_6H_{11}[c]	3	24.0	73.7	18.2	20	8	2	0.3
PhO[c,d]	2	91.0	72.9	13.3	15	7	0.4	<0.1
Ph_2CH[e]	2	115.0	—	—	~0	—	—	—
p-Tolyl	3	4.0	95.8	23.6	20	58	61	1
1-Naphthyl	3	9.0	93.8	26.9	22	40	30	1
2-Naphthyl	3	4.5	95.2	36.8	28	58	75	2
H[f]	2	8.0	78.2	10.7	12	9	3	0.4
Ph[f]	3	38.5	93.1	38.5	29	41	2	<0.1
2-Naphthyl[f]	3	32.0	96.3	28.8	23	70	2	≪0.1

[a] Calculated from ees.[10] [b] Calculated from ees of (*S*)-2 and conversion.[19] [c] 50 mg of Amano PS was used. [d] Vinyl phenoxyacetate. [e] Vinyl 3, 3-diphenylpropanoate. [f] 50 mg of porcine pancreatic lipase (PPL) was used.

Thus, we used the ω-phenylalkanoic acid vinyl esters (R = Ph, n = 1-4). In the case of vinyl benzoate (R = Ph, n = 1),[8,9b,d,13b] the enantiomeric ratio was approximately two times larger than the one with vinyl acetate accompanied by a drastic decrease in the reaction rate. The highest enantiomeric ratio (*E* = 31) was found for vinyl 3-phenylpropanoate (R = Ph, n = 3) in this series. Therefore, we replaced the benzene ring of vinyl 3-phenylpropanoate with a cyclohexyl group (R = *c*-C_6H_{11}, n = 3). However, the *E* value and reaction

rate significantly dropped. This suggests that the existence of an aromatic ring on the β-position is effective. Furthermore, exchanging the one methylene group adjacent to the benzene ring of vinyl 3-phenylpropanoate for an oxygen atom (R = PhO, n = 2) also led to similar results. When vinyl 3,3-diphenylpropanoate (R = Ph_2CH, n = 2) was used, transesterification did not occur. Finally, we tried other vinyl esters having a more bulky aromatic ring, vinyl 3-(1-naphthyl)propanoate (R = 1-Naphthyl, n = 3), vinyl 3-(2-naphthyl)propanoate (R = 2-Naphthyl, n = 3) and vinyl 3-(*p*-tolyl)propanoate (R = *p*-Tolyl, n = 3). All esters enhanced the enantioselectivity of Amano PS toward (±)-**1**; especially, both vinyl 3-(2-naphthyl)propanoate and vinyl 3-(*p*-tolyl)propanoate showed the best selectivity (E = 58, respectively) of all the acyl donors listed in Table 1.

While the relative rates of (*S*)-**1** with any one of three following vinyl esters, vinyl 3-phenylpropanoate, vinyl 3-(*p*-tolyl)propanoate and vinyl 3-(2-naphthyl)propanoate are similar to that of (*S*)-**1** with vinyl acetate, the rates of (*R*)-**1** with any one of the three acyl donors are largely depressed relative to that with vinyl acetate. Therefore, the drastic enhancement of selectivity, which was concomitant with the change of the acyl donor from vinyl acetate to vinyl esters described above, is based on the lowering of the reaction rates of (*R*)-**1**.

It can be postulated that the acyl moiety of an acylated lipase enters its recognition site for an alcohol and this entrance causes the variation in the environment of the site. This effect leads to the variation in the stereoselectivity (direct effect).[8] Even if the acyl moiety of the acyl-lipase does not enter the recognition site, the acyl group may interact with other parts of the enzyme. This interaction may also cause a change in environment of the recognition site (indirect effect). Thus, it is assumed that although the bulky alkyl group, the dodecanoyl or cyclohexyl group, directly or indirectly affects the environment of the recognition pocket, each enantiomer of (±)-**1** recognizes the change in the environment to a similar extent. On the other hand, the aromatic ring of the lipase acylated with any one of three following vinyl esters, vinyl 3-phenylpropanoate, vinyl 3-(*p*-tolyl)propanoate and vinyl 3-(2-naphthyl)propanoate affects the recognition site up to the extent of providing a definite stereodifferential ability towards (±)-**1**. Any of the aromatic rings can induce the effective enzyme conformation which makes the rate of (*R*)-**1** slower; nevertheless, the conformation keeps the rate of (*S*)-**1** unchanged. This leads to the high enantioselectivity of the lipase-catalyzed transesterification of (±)-**1** with any of the vinyl esters having an aromatic ring.

The resolution of (±)-**1** was also tried with porcine pancreatic lipase (PPL) from Sigma. PPL displayed poor enantioselectivity (E = 9) with vinyl acetate and showed high selectivity with either vinyl 3-phenylpropanoate (E = 41) or vinyl 3-(2-naphthyl)propanoate (E = 70). The E value of 70 is the highest among those which have been reported for the lipase-catalyzed kinetic resolution of (±)-**1**.[16] As PPL is not so pure enzyme, we consider further discussion about the PPL-catalyzed reactions to be meaningless.

By using either vinyl 3-(2-naphthyl)propanoate or vinyl 3-(*p*-tolyl)propanoate we could attain the highly enantioselective transesterification of (±)-**1** which has not been efficiently resolved by lipase-catalyzed reactions. This is the first example that shows the utility of the vinyl esters having a bulky aromatic ring for the lipase-catalyzed transesterification. We are now investigating their validity for the resolution of a wide variety of alcohols and the development of more effective acyl donors.

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18. The resolution of (±)-**1** was also carried out at 30 °C. For example, *E* value with vinyl 3-phenylpropanoate ($E = 18$) was six times larger than that with vinyl acetate ($E = 3$). This ratio was almost the same value as that at 10 °C. However, some reactions proceeded very fast at 30 °C. Therefore, we decided to evaluate the resolution at 10 °C more exactly.
19. Although an initial rate should be determined using pure enantiomers, we used the rates calculated from the racemic 2-phenyl-1-propanol results. Therefore, the relative rates are "rough relative initial rates".