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1-Ethoxyvinyl Acetate as a Novel, Highly Reactive, and Reliable Acyl Donor for Enzymatic Resolution of Alcohols

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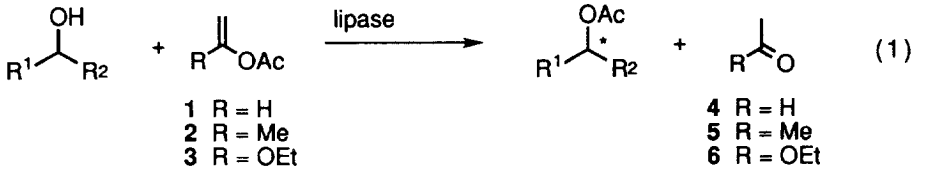
Abstract: 1-Ethoxyvinyl acetate **3** was found to be a high performance acyl donor for enzymatic resolution of alcohols featuring that (i) **3** shows high reactivity and high selectivity comparable to the most widely used vinyl acetate **1** and (ii) reaction of **3** generates low reactivity ethyl acetate **6** as a single side product, while that of **1** releases unfavorable acetaldehyde **4**. Copyright © 1996 Elsevier Science Ltd

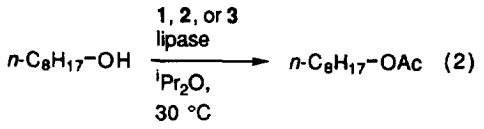
In this decade, lipase-catalyzed transesterification of alcohols with acylating reagents (acyl donors) has extensively been studied for resolution of alcohols.[1] Because the enzymatic process is originally reversible, efforts have been devoted to elucidate effective acyl donors which facilitate the reaction and make it kinetically irreversible. Among them, several activated esters such as trifluoroethyl esters,[2] chloroethyl esters,[2] cyanomethyl esters,[3] oxime esters,[4] and acid anhydrides[5] were reported; however, the reactions using them are pseudoirreversible and some drawbacks also remained, for example, insufficient reactivity, difficulty in isolating the side products, generation of toxic side products, and product inhibition caused by the side products.[1a,c] On the other hand, vinyl esters (e.g., **1**) and isopropenyl esters (e.g., **2**) are appreciated as the best kind of reagents nowadays, because they are highly reactive and generate volatile acetaldehyde **4** and acetone **5** as the side products, which make the reaction completely irreversible and afford the products in high chemical and optical yields in a short reaction time (eq. 1).[6,7] Especially, vinyl esters are the most often employed because they are more reactive than the isopropenyl esters. However, acetaldehyde **4** liberated from **1** inactivates some enzymes [e.g., *Candida cylindracea* lipase (CCL)] through the formation of a Schiff base with Lys residues and limits the reliable use of **1**.[1a,8] Although one way to resolve this problem was reported by covalent immobilization of the enzyme on a support,[8] use of a highly reactive, alternative acyl donor which does not produce enzyme inhibitors must expand the convenient use of a vast number of enzymes as naked forms. Here we present that 1-ethoxyvinyl acetate **3** is such a reagent suitable for this requirement. This reagent carries out the enzymatic resolution in high chemical and optical yields releasing volatile and low reactivity ethyl acetate **6** as the single side product.[9]



1 R = H
2 R = Me
3 R = OEt

4 R = H
5 R = Me
6 R = OEt

At first, the applicability and reactivity of **3** for the enzymatic reactions were examined by the lipase catalyzed reaction of 1-octanol and **3** compared with that of **1** and **2** (eq. 2).[10] As shown in Figs. 1 and 2, **3** showed nearly equal reactivity to that of **1** for the reaction using lipase Amano PS and Amano AK and was about 4 times more reactive than **2**. On the other hand, for the reaction using lipase Amano AY (*Candida rugosa*)[11], which was reported to be deactivated by **4**, **3** was about 4 times more reactive than **1** (Fig. 3). In these reactions of **3**, 100% conversion of the alcohol was attained. Thus, the excellent applicability of **3** to the enzymatic reactions was disclosed.



General Footnote for Figs. 1-3.
The reaction was carried out using 1-octanol (0.77 mmol), acyl donor (1.54 mmol for Figs. 1 and 2, 2.3 mmol for Fig. 3), lipase [PS (50 mg), AK (15 mg), or AY (500 mg)] in $^{i}Pr_2O$ (20 mL) (for Figs. 1 and 2) or $^{i}Pr_2O$-H_2O (1000:1, 20 mL) (for Fig. 3). The conversion was determined by GC (PEG-20M): **1** (●), **2** (▲), **3** (□).

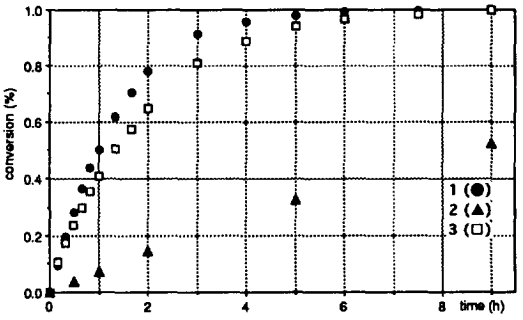


Fig. 1 Reaction using Amano PS.

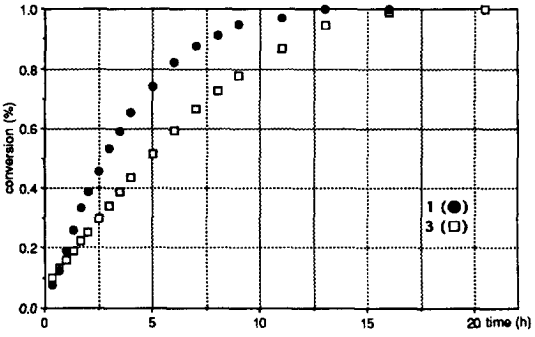


Fig. 2 Reaction using Amano AK.

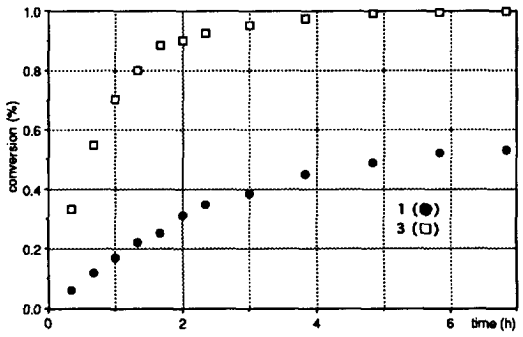
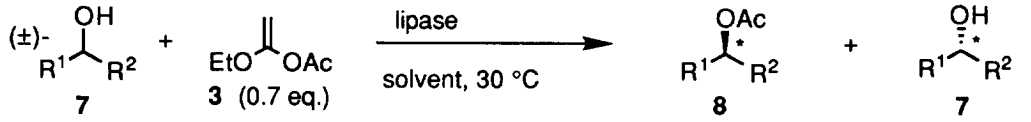


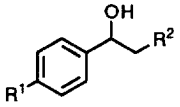
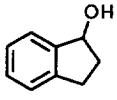
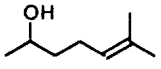
Fig. 3 Reaction using Amano AY.

The optical resolution of several types of racemic *sec*-alcohols **7** by lipase Amano PS and Amano AK using **3** is summarized in Table 1. In every run, the reaction proceeded within a reasonable time *using only a slight excess amount (0.7 equiv.) of 3*. After the conversion reached about 50%, the reaction mixture was filtered, concentrated *in vacuo*, and purified by SiO_2 column chromatography to give the acetate **8** and the unreacted alcohol **7** (a typical procedure; see; footnote a in Table 1).[12] The E values[13] of these reactions were good to excellent and are comparable to those of the reported reactions using **1**.

1-Ethoxyvinyl acetate **3** is readily prepared by the ruthenium-catalyzed addition of acetic acid to ethoxyacetylene and is storable and easily handled.[14] Considering that various 1-ethoxyvinyl esters are similarly available[14] and that this type of reagent features high reactivity and generation of a low reactivity side product, ethyl acetate, use of the 1-ethoxyvinyl esters instead of the vinyl esters is expected to extend the utility of enzymatic resolution of alcohols and also their related use for site-selective acylation of polyhydroxy compounds.[15] Further study using various kinds of 1-ethoxyvinyl esters for enzymatic resolution is in progress.

Table 1. Optical resolution of secondary alcohols **7** using lipases and 1-ethoxyvinyl acetate **3**.[a]



run	(±)-alcohol **7**		lipase (mg/mmol) / solvent	reaction time (h)	conversion (%)	acetate **8** config./ ee (%)[b,c]	recovered alcohol **7** config.[d]/ ee (%)[b]	E value (lit. value using **1**)
1		$R^1 = R^2 =$ H	Amano PS (40) $^iPr_2O$	11	51	R/ 96.2	S[e]/ >99	>390 (>684 [7a])
2		$R^1 = R^2 =$ H	Amano AK (40) $^iPr_2O$	6.5	46	R/ 94.5	S/ 82.1	91
3		R^1 = OMe, R^2 = H	Amano PS (40) $^iPr_2O$	56	58	R/ 72.1	S[f]/ >99	44 (20 [7a])
4		R^1 = Cl, R^2 = H	Amano PS (40) $^iPr_2O$	21	52	R/ 91.1	S[g]/ >99	>110
5		R^1 = H, R^2 = Me	Amano PS (80) $^iPr_2O$	25	48	R/ >99	S[h]/ 91.1	>630 (>280 [7a])
6		R^1 = H, R^2 = Cl	Amano PS (80) $^iPr_2O$	96	53	S/ 89.4	R[i]/ >99	>93 (98 [7c])
7			Amano PS (40) $^iPr_2O$	7	48	R/ >99	S[j]/ 91.2	>640 (>747 [7a])
8			Amano PS (40) BuOMe	20	50	R/ 82.1[k]	S[l]/ 82.8[m]	27 (27.7 [16])

a) **A typical procedure:** Lipase Amano PS (80 mg) was added to the solution of (±)-1-phenethyl alcohol **7** (244 mg, 2.0 mmol) and **3** (182 mg, 1.4 mmol) in $^iPr_2O$ (6 mL). The reaction mixture was stirred at 30 °C for 11 h and filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography (hexane-Et_2O) to give (*R*)-1-phenethyl acetate **8** (155 mg, 47%) and (*S*)-1-phenethyl alcohol **7** (117 mg, 48%). *b*) Determined by Daisel CHIRALCEL OD (hexane-^iPrOH). *c*) Determined after saponification of **8** into the corresponding **7**. *d*) Determined by comparison of the specific rotation of the recovered **7** with that of an authentic sample: *e*) $[\alpha]_D$ -58.8 (c 1.1, c-C_5H_{10}) [Lit.[17] $[\alpha]_D$ -49.7 (c 2.0, c-C_5H_{10}) for 91% e.e.]. *f*) $[\alpha]_D$ -52.5 (c 0.7, $CHCl_3$) [Lit.[18] $[\alpha]_D$ +47.2 (c 0.9-1.1, $CHCl_3$) for 89% e.e. of (*R*)-form]. *g*) $[\alpha]_D$ +49.6 (c 1.8, Et_2O) [Lit.[18] $[\alpha]_D$ +46.1 (c 0.9-1.1, Et_2O) for 91% e.e. of (*R*)-form]. *h*) $[\alpha]_D$ -43.9 (c 1.7, $CHCl_3$) [Lit.[17] $[\alpha]_D$ -47.6 (c 6.1, $CHCl_3$) for 98% e.e.]. *i*) $[\alpha]_D$ -58.9 (c 1.3, c-C_6H_{12}) [Lit.[19] $[\alpha]_D$ +53.3 (c 2, c-C_6H_{12}) for (*S*)-form]. *j*) $[\alpha]_D$ +30.8 (c 0.8, $CHCl_3$) [Lit.[20] $[\alpha]_D$ +24.4 (c 2.0, $CHCl_3$) for 71% e.e.]. *k*) Determined after conversion to the corresponding 2,4-dinitrobenzoate by saponification followed by

esterification. *l*) $[\alpha]_D$ +14.0 (c 0.7, EtOH) [Lit.[16] $[\alpha]_D$ +16.2 (c 1.0, EtOH). *m*) Determined after conversion to the corresponding 2,4-dinitrobenzoate.

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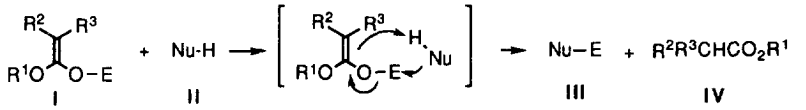
9. We have disclosed various types of very mild and convenient reactions utilizing the ketene acetal reagents **I**. Thus, the reactions proceed in inert solvents at room to moderate temperature to give the products **III** accompanied by formation of volatile esters **IV** as the only side products. Simple concentration of the reaction mixture *in vacuo* gives pure products **III** in high yields. Reviews; see, Kita, Y.; Shibata, N. *Yuki Gosei Kagaku Kyokai Shi*, **1994**, *52*, 746-753; *Idem, Synlett*, **1996**, 289-296.



E = COR, CO_2R, $CO(CH_2)_nCOOR'$, SiR_3, etc.

10. Higher reactivity of **1** and **2** compared to other well known acyl donors was presented by Oda and co-workers.[7c]
11. Formerly *Candida cylindracea.*
12. A blank experiment without the lipase (other conditions are the same as shown in the typical procedure) resulted in only 5% conversion after 7 d.
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