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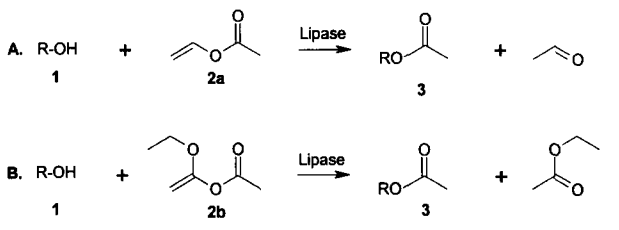
Enzyme Catalyzed Resolution of Alcohols using Ethoxyvinyl Acetate

Manfred Schudok and Gerhard Kretzschmar*

Corporate Research & Technology, Hoechst AG, D-65926 Frankfurt, Germany

Abstract: 1-Ethoxyvinyl acetate is an efficient irreversible acyl transfer reagent for lipase catalyzed esterification in organic solvents. The use of this reagent avoids reactive byproducts resulting in enzyme deactivation, in particular the formation of acetaldehyde using the widely employed vinyl acetate transesterification reagent. Copyright © 1996 Elsevier Science Ltd

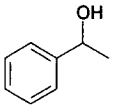
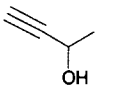
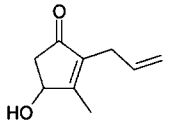
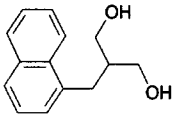
A convenient way to make an enzymatic transesterification essentially irreversible in organic solvents is to employ enol esters as the acylating agents[1]. The enols released from such esters tautomerize to carbonyl compounds, thus shifting the equilibrium completely to the acylation products. This discovery has been developed further for the resolution of racemic alcohols[2], and since then especially the transesterification using vinyl acetate (Scheme 1, path A) has been employed by numerous working groups as a standard laboratory method for the preparation of enantiomerically pure alcohols and acetates from chiral secondary or prochiral primary alcohols[3]. Reactive aldehydes such as acetaldehyde, however, can enter into reactions with many functional groups, particularly with the lysine side chains in enzymes, and similar reactions were used for the irreversible modification of proteins[4]. The possibly harmful effect of acetaldehyde on enzymes in most reactions performed on small laboratory scales[5] may not cause severe trouble, since a relatively large excess of biocatalyst can be employed. On the other hand, on larger scales or in acylations performed with immobilized enzymes or precious catalyst preparations, the acetaldehyde byproduct must be removed and separated from low-boiling organic solvents. In contrast to the transesterification with vinyl acetate, alkoxyvinyl acetates only release the correponding esters, for example, ethyl acetate is formed from 1-ethoxyvinyl acetate (**2b**) (Scheme 1, path B). Ethyl acetate has often been used as a solvent in lipase catalyzed acylations. To our knowledge, this surprisingly simple way to circumvent the formation of reactive acetaldehyde in enzyme-catalyzed resolutions of alcohols has not yet been reported in the scientific literature[10]. Recently reported approaches to avoid the formation of acetaldehyde used diketene[6] or mixed anhydrides[7], which *per se* are quite reactive with respect to other functional groups which may be present in the substrates **1**. Here we report that vinyl acetate (**2a**) can be conveniently replaced without disadvantage by the 1-ethoxyvinyl acetate (**2b**). The latter, as well as other alkoxy derivatives, can be prepared in good yields by known procedures from the appropriate alkoxyacetylene[8]. The results obtained with a representative set of alcohol substrates **1** are shown in Table 1. In summary, a versatile variant of the enzymatic transesterification of alcohols with vinyl acetate has been developed by means of 1-ethoxyvinyl acetate as acyl donor[10]. This method may be valuable for continuous processes employing immobilized or precious enzymes, and under the very mild reaction conditions employed



Scheme 1: *Acylation of alcohols with vinyl ester* ***2a*** *or alkoxyvinyl ester* ***2b****.*

here, it should be applicable especially to polyfunctional compounds without prior protection of other functionalities[9].

Table 1: Enantioselective transesterification of the alcohols 1 with 1-ethoxyvinyl acetate (**2b**).

Educt alcohol **1**	Scale[a]	Reaction time (h)	Conversion (%)	Isol. yield (%) (R)-Acetate	(S)-/Alcohol	Acetate $[\alpha]^{20}_D$ (°)	[ee][b] Acetate (%)
 **1a**	100 mg	3	50	40	39	+ 103.5	>95
 **1b**	100 mg	24	50	31	n.d.	n.d.	70
 **1c**	1.0 g	10	50	45	46	-29.1 (c=1, $CHCl_3$)	90
 **1d**	0.5 g	10	94	89	n.d.	+39.5 (c=1, $CHCl_3$)	94

a) The reactions were run in *n*-hexane as solvent at room temperature, except for **1d**, which was treated in dimethoxyethane/diisopropyl ether (1/1). The biocatalyst used was lipase PS (*Pseudomonas sp.* from Amano), but the lipase SP 625 from *Candida antarctica* could likewise be used with similiar results. Typically, 100 mg of **1a** were dissolved in 2 ml of a 10% strength solution of 1-ethoxyvinyl acetate (**2b**) in hexane (5 ml). After 3 h at room temperature, about 50% conversion was detected by TLC. Isolation of alcohol and acetate was performed by flash chromatography on Kieselgel 60 in ethyl acetate/hexane. b) The enantiomeric excess (ee) was calculated from ^{1}H NMR shift experiments with 10 mg of the respective acetate and 40 mg of the shift reagent Eu(hfc)$_3$.; n.d.: not determined.

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