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Synthesis of Optically Active Novel 1,1,2-Trifluoro-1-alken-3-ols Through Lipase-Catalyzed Reaction

Yumiko Takagi, *Masaya Kashiwagi, Hiroshi Kihara,
and Toshiyuki Itoh* †

Department of Natural Science, Hyogo University of Teacher Education, Yashiro, Hyogo 673-1494, Japan. †Department of Chemistry, Faculty of Education, Okayama University, Okayama 700-8530, Japan.

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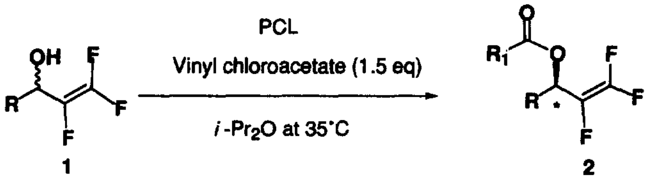
Abstract: The first synthesis of several types of optically active 1,1,2-trifluoro-1-alken-3-ols has been accomplished through the *Pseudomonas cepacia* lipase-catalyzed trans-esterification. The PCL catalyzed acylation using vinyl chloroacetate as the acyl donor provided the corresponding fluorinated-allyl alcohols that possess an aromatic functional group with sufficient enantioselectivity.

Partially-fluorinated organic molecules have been shown to be important in the fields of material science, agrochemical, and medical chemistry.[1] A large number of chiral fluorinated compounds have been synthesized and various types of chiral synthones have thus been developed for the synthesis of fluorinated bioactive molecules.[2] We have recently reported that multifluorinated γ-lactones were efficiently synthesized through the intramolecular radical cyclization of O-trimethylsilyl acetals that were derived from the corresponding allyl esters of α,α-difluoroacetate.[3] Various types of fluorinated chiral α,α-difluoro-γ-lactones can be easily synthesized if we could prepare suitably fluorinated-allyl alcohols in the optically active form using our reaction protocol. We describe here the first synthesis of optically active 1,1,2-trifluoro-1-alken-3-ols through the lipase-catalyzed trans-esterification in organic media (Eq. 1).



(1)

The lipase-catalyzed trans-esterification in an organic solvent system has been recognized as a very useful method for the synthesis of optically active compounds.[4] Typically, the reaction was carried out as follows: to a mixture of *Pseudomonas cepacia* lipase (PCL) (50 weight % of the substrate), 2,6-di-*t*-butyl-4-methylphenol (BHT) as the anti-oxidant was added a 2.5 mL *i*-propyl ether (*i*-Pr_2O) solution of racemic alcohol (±)-1 (0.5mmol)[5] and vinyl chloroacetate (1.5 eq) as the acyl donor. The resulting mixture was then stirred at 35°C. The optical purity of the acetate **2** produced and the remaining alcohol (+)-**1** was determined by capillary GC analysis using a chiral column (Chiraldex G-TA). Excellent enantioselectivity was observed when the

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Table 1. Results of PCL-catalyzed enantioselective trans-esterification of fluorinated allyl alcohols **1**

Entry	R	Time (h)	Conv.(%)	%ee of **2** (%Yield)[a]	%ee of **1** (%Yield)[a]	E[6]	Relative Rate %conv./h x 10^2
1	$PhCH_2CH_2$	36	29	97 (24)	40 (66)	100	82
2	Ph	22	30	95 (32)	46 (61)	65	150
3	c-Hexyl	139	4	85 (4)	2 (32)	13	1
4	PhCH=CH	416	0	0	0	-	-
5	n-C_5H_{11}	5	26	20 (24)	6 (67)	2	430
6	n-$C_{12}H_{25}$	72	20	9 (20)	4 (62)	1	45

a) Isolated yield.

substrate **1a** (R=$PhCH_2CH_2$) and **1b** (R=Ph) were subjected to the reaction (Table 1, Entries 1 and 2). *This is the first example of preparing optically active 1,1,2-trifluoro-1-alken-3-ols.*[7] Although moderate selectivity was obtained for **1c** (R= c-Hexyl) (Entry 3), no enantioselection was observed when linear aliphatic allyl alcohols, **1e** and **1g**, were employed as substrates (Entries 5 and 6). Twenty-eight types of commercial enzymes have been investigated for the acylation of **1e**, unfortunately, no enzyme was found to provide the acetate **2e** with sufficient enantioselectivity. Since **1d** (R=PhCH=CH) was so easily polymerized under the reaction conditions even in the presence of BHT, neither the acylated product nor the unreacted substrate were obtained (Entry 4). We reported that the enantioselectivity of the lipase-catalyzed reaction was greatly improved by the addition of a thiacrown ether.[8] However, little improvement in enantioselectivity was observed with the addition of 5 mol% of the thiacrown ether in these reactions; this is probably due to the influence of BHT, because the thiacrown modification of the lipase-catalyzed reaction was inhibited by the addition of BHT.[9]

The lipase-catalyzed reaction can be used in a large-scale preparation; the present method, therefore, affords a valuable means of preparing optically active fluorinated-allyl alcohols that possess an aromatic substituent in the molecules. A further study of the scope and limitations of this reaction will make it even more beneficial.

References and Notes

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9) Enatioselectivity was improved up to 100 by the addition of 5 mol% of the thiacrown ether when **1b** (R=Ph) was subjected to the reaction in the absence of BHT, though the recovered yield was significantly reduced by polymerization. On the contrary, no such effect was observed when the reaction was carried out in the presence of BHT.

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