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Chemoenzymatic Dynamic Kinetic Resolution of Allylic Alcohols: A Highly Enantioselective Route to Acyloin Acetates

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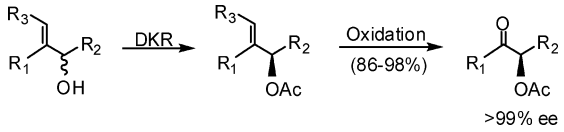
ABSTRACT



Dynamic kinetic resolution (DKR) of a series of sterically hindered allylic alcohols has been conducted with *Candida antarctica* lipase B (CALB) and ruthenium catalyst 1. The optically pure allylic acetates obtained were subjected to oxidative cleavage to give the corresponding acylated acyloins in high yields without loss of chiral information.

Chiral allylic alcohols and their derivatives in optically enriched forms are useful intermediates in the synthesis of natural and non-natural compounds.[1] Optically active alcohols can be synthesized via enantioselective hydrogenation,[2] asymmetric transfer hydrogenation,[3] or hydride reduction[4] of the corresponding prochiral ketones, via asymmetric aldol reaction,[5] or via resolution.[6] Lipase-catalyzed kinetic resolution (KR) has proven to be a useful method to obtain enantiomerically enriched secondary alcohols.[7] In these enzymatic KRs, which are popular in industry, one of two enantiomers of the substrate alcohol is acylated selectively with an acyl donor (e.g., vinyl or isopropenyl acetate) to give the acylated alcohol with a maximum theoretical yield of 50%.[8] This limitation can be overcome in dynamic kinetic resolution (DKR) in which the enantioselective acylation is combined with in situ racemization of the starting material.[9] Some DKR protocols of allylic alcohols have been published during recent years; however, byproduct formation was obtained due to the transition metal-mediated isomerization of allylic alcohols to saturated ketones during the racemiza-

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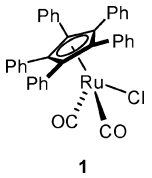
tion step.[10] Allylic alcohols have a C−C double bond that can be functionalized via different chemical transformations, such as epoxidation, cyclopropanation, hydrogenation, aziridination, or it can simply be cleaved under oxidative conditions, providing synthetically useful acyloins.[11]

Acyloins are α-hydroxy ketones, and they are convenient building blocks in the asymmetric synthesis of biological active compounds.[12] Recently, several methods have been developed for their enantioselective preparation. For example, lipase-catalyzed kinetic resolution[13] and chemoenzymatic dynamic kinetic resolution[14] have been reported as attractive routes. The use of α-hydroxy ketones as substrates in combined metal- and enzyme-catalyzed DKR is not feasible because of the formation of an intermediate diketone, which would lead to rearrangement of the starting material. Furthermore, enzymatic resolution of α-hydroxy ketones is associated with either long reaction times or moderate enantioselectivity (moderate E values). Herein, we report on a highly efficient approach toward α-hydroxy ketones via *chemoenzymatic dynamic kinetic resolution of allylic alcohols* (using catalyst **1**, Figure 1) and subsequent oxidation of the



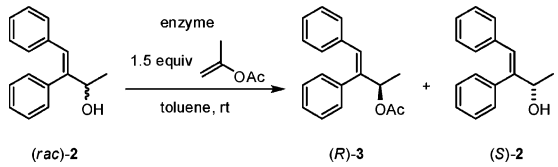
1

Figure 1. Racemization catalyst **1**.

enantiopure (*R*)-allylic acetates to give optically pure α-acetoxy ketones as protected acyloins.

First, we studied enzymatic kinetic resolution of (*rac*)-3,4-diphenyl-3-buten-2-ol, (*rac*)-**2**, as model substrate using different commercially available lipases such as *Candida antarctica* lipase B (CALB), *Pseudomonas cepacia* lipase I (PS-C "Amano" I) and *Pseudomonas cepacia* lipase II (PS-C "Amano" II), *Pseudomonas stutzeri* lipase, *Candida rugosa* lipase, *Candida cylindracea* lipase in toluene at room temperature. The results are summarized in Table 1. All of the tested enzymes catalyzed the desired transesterification reaction with excellent enantioselectivity. Three of the six enzymes employed, CALB, PS-C "Amano" I, and PS-C "Amano" II showed reasonably good activity, and the calculated E values were high (entries 1−3, Table 1). When the reaction was run with CALB and PS-C "Amano" II, 17 and 18% of enantiopure acetate (*R*)-**3** was obtained after 24 h, respectively. With PS-C "Amano" I, 30% of (*R*)-**2** was produced under the same reaction conditions. However, we chose to use CALB in the DKR since it is less expensive than the Amano enzymes.

Table 1. Enzymatic Kinetic Resolution of (*rac*)-3,4-Diphenyl-3-buten-2-ol (**2**)[a]



(*rac*)-**2** (*R*)-**3** (*S*)-**2**

entry	enzyme	time (h)	% convn.[b]	% ee of **3**[b]	% ee of **2**[b]	E
1	CALB	24	17	>99	20	>240
2	PS-C Amano I	24	30	>99	43	>240
3	PS-C Amano II	24	18	>99	23	>240
4[c]	*P. stutzeri* lipase	24	2	>99	3	-
5	*C. rugosa* lipase	24	1	>99	1	-
6	*C. cylindracea* lipase	24	<1	>99	<2	-

[a] Conditions: (*rac*)-**2** (0.2 mmol), isopropenyl acetate (0.3 mmol), CALB (6 mg)/PS-C Amano I (20 mg)/PS-C Amano II (20 mg)/*Pseudomonas stutzeri* lipase (5 mg)/*Candida rugosa* lipase (20 mg)/*Candida cylindracea* lipase (20 mg) in toluene (1 mL) at rt under argon. [b] Determined by HPLC equipped with a chiral column (Chiralcel OD-H, 0.46 cm Ø*25 cm). [c] THF (1 mL) was used as the solvent.

Next, the effect of the temperature on the CALB-catalyzed kinetic resolution of (*rac*)-**2** was studied. The reaction was carried out at rt, 50 °C, and 80 °C, and the reaction was monitored by analytical HPLC (Table 2). The enzymatic resolution was complete after 24 h at 80 °C (entry 3).

Table 2. CALB-Catalyzed Enzymatic KR of (*rac*)-3,4-Diphenyl-3-buten-2-ol (**2**) at Different Temperatures[a]

entry	temp	time (h)	% convn.[b]	% ee of **3**[b]	% ee of **2**[b]
1	rt	24	17	>99	20
2	50 °C	24	42	>99	74
3	80 °C	24	50	>99	>99

[a] Conditions: (*rac*)-**2** (0.2 mmol), isopropenyl acetate (0.3 mmol), CALB (6 mg) in toluene (1 mL) under argon. [b] It was determined by HPLC equipped with chiral column (Chiralcel OD−H, 0.46 cm Ø*25 cm).

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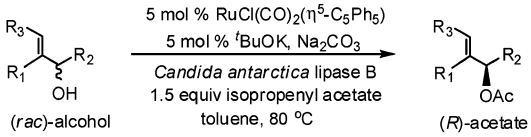
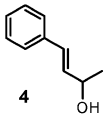
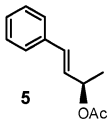
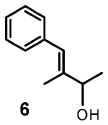
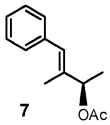
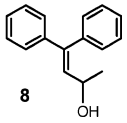
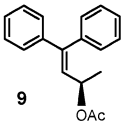
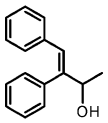
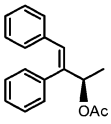
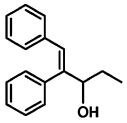
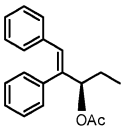
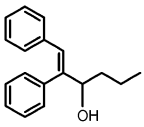
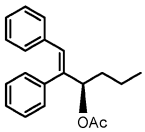
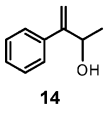
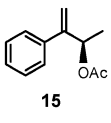
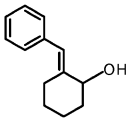
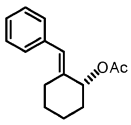
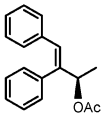
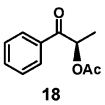
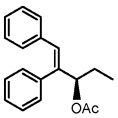
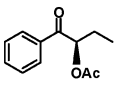
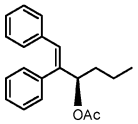
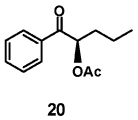
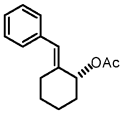
Table 3. Chemoenzymatic DKR of Various Allylic Alcohols[a]



entry	substrate	product	time (h)	% yield[b,c]	% *ee*[b]
1[d]	 **4**	 **5**	18	89	>99
2[d]	 **6**	 **7**	26	93	>99
3	 **8**	 **9**	24	>99 (>97)	>99
4[e]	 **2**	 **3**	20	>99 (96)	>99
5[f]	 **10**	 **11**	24	>99 (97)	>99
6[f]	 **12**	 **13**	24	>99 (>95)	>99
7[d,g]	 **14**	 **15**	17	71	97
8[f]	 **16**	 **17**	24	>99 (97)	>99

[a] Conditions: Ru-cat. **1** (5 mol %), ^{t}BuOK (5 mol %), substrate alcohol (1 mmol), isopropenyl acetate (1.5 equiv), CALB (6 mg), Na_2CO_3 (1 equiv) in toluene (2 mL) under argon. [b] Determined by HPLC equipped with chiral a column (Chiralcel OD-H, 0.46 cm Ø × 25 cm). [c] Isolated yield in parentheses. [d] The reaction was carried out at rt, and the analysis was done by GC equipped with a chiral capillary column (CP-Chirasil-DEX CB 25 m × 0.32 mm × 0.25 μm). [e] 5 mmol scale. [f] 2 mmol scale. [g] 23% of racemic 3-phenyl-2-butanone was formed.

Table 4. Ruthenium-Catalyzed Oxidative Cleavage[a]

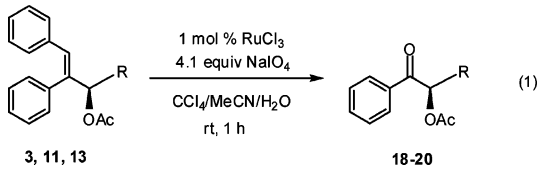
entry	substrate	product	% yield[b]	% *ee*[c]
1	 **3**	 **18**	98	>99
2	 **11**	 **19**	>98	>99
3	 **13**	 **20**	96	>99
4	 **17**	 **21**	86	99[d]

[a] Conditions: The corresponding acetate (1 mmol) dissolved in a mixture of acetonitrile (2 mL), and carbon tetrachloride (2 mL) was added to a solution of $RuCl_3 \cdot nH_2O$ (1 mol %) and $NaIO_4$ (4.1 mmol) dissolved in water (3 mL) at rt. [b] Isolated yield. [c] Unless otherwise noted the ee was determined by HPLC equipped with a chiral column (Chiralcel OD-H, 0.46 cm Ø × 25 cm). The absolute configuration of compounds **18** and **21** was confirmed by comparing their optical rotation with literature values (see Supporting Information). [d] The ee was determined by GC equipped with a chiral capillary column (CP-Chirasil-DEX CB 25 m × 0.32 mm × 0.25 μm).

We have previously found that Ru-catalyst **1** can racemize different functionalized alcohols successfully under mild reaction conditions.[10c] This ability of **1** has now been utilized in combination with CALB to provide an efficient chemoenzymatic protocol for various allylic alcohols. The results are summarized in Table 3. Less sterically hindered allylic alcohols are transformed into their enantiomerically pure acetates in good yields together with a small amount (5−10%) of the corresponding saturated ketone[15] (entries 1−2). In the case of the least hindered substrate **14** significant isomerization as side reaction was observed: 23% of 3-phenyl-2-butanone was formed beside the desired (*R*)-2-acetoxy-3-phenyl-3-butene **15** (entry 7). Chemoenzymatic DKR of more sterically hindered allylic alcohols (**2**, **8**, **10**, **12**, **16)** led to quantitative yields of the corresponding acetates in each case (entries 3−6 and 8). It is interesting to note that the exocyclic C−C double bond of substrate **16** remained intact during the course of the metal- and enzyme-catalyzed reaction (entry 8). The desired acetates were obtained in excellent optical purity in each case (Table 3, entries 1−8) due to the high enantioselectivity of the CALB.[16]

(15) Rearrangment to ketone is caused by ruthenium catalysis, see ref 10c and Martín-Matute, B.; Bogár, K.; Edin, M.; Kaynak, F. B.; Bäckvall, J.-E. *Chem. Eur. J.* **2005**, *11*, 5832.

Finally, we completed the synthesis of the acyl-protected acyloins by the use of a ruthenium-catalyzed oxidative cleavage of the C−C double bond of the allylic acetates obtained from the DKR reactions. Allylic acetates **3**, **11**, **13** were oxidized to acyloin acetates **18**−**20**, respectively, in high yields (96−98%) employing the Sharpless procedure[17] (eq 1; Table 4, entries 1−3). Oxidation of cyclic substrate **17** with the same procedure afforded the corresponding cyclic acylated acyloin **21** in 86% yield (Table 4, entry 4). All oxidation reactions took place under mild conditions and delivered the desired products without loss of chiral information.



3, 11, 13 18-20 (1)

Recently, Bornscheuer and co-workers reported a two-compartment chemoenzymatic DKR for the enantioselective synthesis of acylated acyloins.[14a] An acidic resin was used for the racemization, and up to 93% ee was obtained in the DKR. The present one-pot DKR of allylic alcohols has the advantage over the previous method in that it provides the acyloin esters in higher yields and higher enantioselectivity (>99% ee).

In this paper we have presented a synthetic route to acyl-protected acyloins based on a chemoenzymatic dynamic kinetic resolution under mild reaction conditions. A variety of racemic allylic alcohols were transformed into their corresponding acetates of *R*-configuration[16] in high yields and with excellent ee's. Subsequent oxidation of the allylic acetates afforded the corresponding acylated acyloins in high enantiomeric excess (>99% ee).

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Supporting Information Available: Synthesis and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The absolute configuration has been assigned on the basis of the stereoselectivity of CALB, which is known to follow Kazlauskas rule (see ref 9d) and was confirmed by comparing the optical rotations of **5** and **17** with literature values (see Supporting Information).

(17) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem*. **1981**, *46*, 3936.