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Novozym-435-catalyzed enzymatic separation of racemic propargylic alcohols. A facile route to optically active terminal aryl propargylic alcohols

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Abstract—Novozym-435 (a form of *Candida antarctica lipase B*) was found to be an effective biocatalyst for the kinetic resolution of a variety of racemic terminal aryl propargylic alcohols affording highly optically active (*S*)-propargylic alcohols and (*R*)-propargylic alcohol acetates in high yields and good ees. The advantages of this reaction are the easy availability of starting materials and the biocatalyst, simple reaction conditions, easy operation and high stereoselectivity.

Optically active propargylic alcohols are very important intermediates for the enantioselective synthesis of various natural products and precursors of otherwise difficult-to-make optically active compounds,[1] for example, eicosanoids,[2] macrolides[3] and enediyne antibiotics.[4] They are also useful starting materials for the synthesis of allenes,[5] benzo[*b*]furan (1-benzofuran) and derivatives.[6] Many methods have been reported for the synthesis of optically active propargylic alcohols;[7] however, those for terminal propargylic alcohols are limited due to the presence of the terminal proton. The optically active propargylic alcohols with terminal protons are usually prepared by the asymmetric reduction of 1-alkynyl-3-one using chiral lithium aluminum hydride reagent[8] or organoboranes,[9] the enantioselective hydrolysis of propargylic alcohol acetates using microorganisms[10] or enzymes,[11] and the kinetic esterification of propargylic alcohols.[12] Some optically active terminal 1-aryl-2-alkynols are prepared via lipase-catalyzed kinetic resolution,[12a,b] but the enantioselectivities were strongly dependent on the substitution pattern of the benzene moiety, regarding to both the type of the substituent and its position on the aromatic ring. Some of the results were unsatisfactory. The reduction protocol requires more than stiochiometric amount of enantiomerically pure chiral reagents under non-convenient reaction conditions. Some examples of terminal alkyl propargylic alcohols using *Candida antarctica* lipase B as the catalyst in organic solvent have been reported.[13]

2,3-Allenols are important starting materials for the synthesis of oxiranes,[14] 2,5-dihydrofurans,[15] α-methylenelactones,[16] α- or γ-amino alcohols,[17] and α,β-unsaturated ketones.[18] Thus, the syntheses of optically active 2,3-allenols are of current interest. Using the optically active terminal propargylic alcohols as the starting materials, the optically pure 2,3-allenols can be easily obtained.[19] During the course of our systematic study of allenes, we found that Novozym-435 (a form of *Candida antarctica* lipase B) is an efficient biocatalyst for the kinetic resolution of a series of racemic 2,3-allenols affording highly optically active (*S*)-2,3-allenols and (*R*)-2,3-allenyl acetates in high yields and excellent ees.[20] However, when it was applied to the resolution of aryl-substituted or 2-unsubstituted 2,3-allenols, the result was rather disappointing. In an attempt to develop a general and facile route to optically active 1-aryl-2,3-allenols,[19] we decided to develop an efficient route to optically active terminal 1-aryl-2-alkynols. In this paper, we wish to report the Novozym-435-catalyzed efficient kinetic resolution of racemic 1-aryl-2-alkylnols in an organic solvent.

In order to identify the best suited enzyme for the present class of compounds, extensive screening experi-

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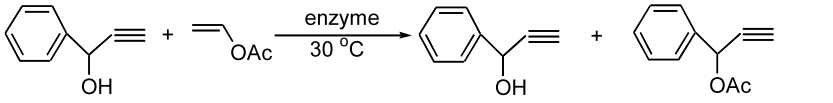
ments were performed. Some typical results listed in Table 1 show that with Lipase G (lipase from *penicillium camembertii*) and PPL (*porcine pancreatic lipase*) the occurrence of the reaction could not be observed (entries 1 and 2, Table 1). With CRL (*Candida rugosa lipase*) and Lipase Ak (lipase from *pseudomonas fluorescens*), the results are disappointing (entries 3 and 4, Table 1). In addition, with lipase Ps (lipase from *pseudomonas cepacia*), acetate **2a** was formed in a low yield with a good ee while the ee of the alcohol is very low. Fortunately, when we used Novozym-435 as the catalyst, the result is encouraging: the yields and ees of both the alcohol and the acetate are good (entry 6, Table 1). With these results in hand, we went on to optimize the reaction conditions. To our surprise, the reaction could be carried out at 60°C even with higher ees. At this temperature, the time of the reaction could be shortened from 4 days to one day (entry 1, Table 2) and the loading of the enzyme decreased from 70 mg to 18 mg (entry 4, Table 2). The absolute configuration of the major enantiomer was determined to be *S* by comparison of the sign of the specific rotation of the obtained (+)-1-phenyl-prop-2-yn-1-ol (**1a**) with the known (*R*)-(−)-**1a**.[12a] The absolute configurations of compounds in Table 3 were tentatively assigned based on this result.

In order to investigate the scope of the reaction, the standard conditions for the kinetic resolution reaction of racemic **1a** was established (entry 4, Table 2). The results of a series of racemic aryl-substituted propargylic alcohols under standard reaction conditions were summarized in Table 3. The reaction can proceed with the substrates bearing either electron-rich or electron-deficient aryl groups. In most cases of this experiment, we could obtain the expected products with high enan-

Table 1. Screening of enzymes for the resolution of **1a** with vinyl acetate[a]

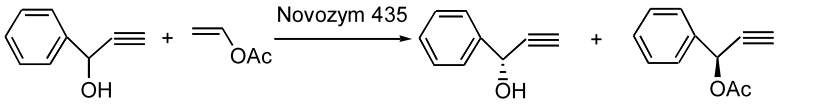


1a (racemic) **1a** (optically active) **2a** (optically active)

Entry	Enzyme	Time (days)	**1a**			**2a**			E[d]
			Absolute configuration	Yield (%)[b]	ee (%)[c]	Absolute configuration	Yield (%)[b]	ee (%)[c]	
1	Lipase G	3				NR[e]			
2	PPL	3				NR[f]			
3	CRL	3	*R*	44	5	*S*	42	5	1.2
4	Lipsase AK	3	*S*	32	69	*R*	56	40	4.5
5	Lipase Ps	3	*S*	59	31	*R*	21	92	32.5
6	Novozym 435	4	*S*	43	93	*R*	47	92	81.8

[a] The reaction was carried out at 30°C using **1a** (100 mg), vinyl acetate (5 mL), and enzyme (70 mg).
[b] Isolated yield based on **1a**.
[c] Determined by HPLC.
[d] $E=\ln[ee_P(1-ee_S)]/(ee_P+ee_S)/\ln[ee_P(1+ee_S)]/(ee_P+ee_S)$.
[e] **1a** was recovered in 94% yield.
[f] **1a** was recovered in 92% yield.

Table 2. Optimization of Novozym-435-promoted kinetic resolution of **1a**

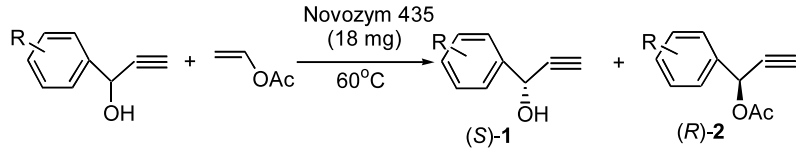


1a **(*S*)-1a** (*R*)-**2a**

Entry	Solvent (mL)	Substrate (mg)	Enzyme (mg)	T (°C)	Time (h)	(*S*)-**1a**		(*R*)-**2a**		E[a]
						Yield (%)	ee (%)	Yield (%)	ee (%)	
1	5	100	70	30	96	43	93	47	92	81.8
2	5	101	70	60	24	41	>99	50	79	>43.6
3	2.5	101	35	60	24	36	>99	35	80	>46.1
4	2.5	100	18	60	24	36	95	35	96	183.3

[a] $E=\ln[ee_P(1-ee_S)]/(ee_P+ee_S)/\ln[ee_P(1+ee_S)]/(ee_P+ee_S)$.

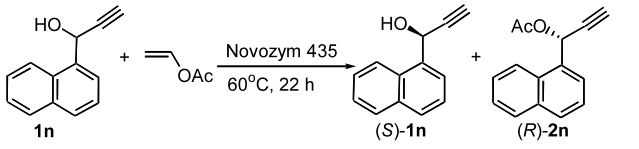
Table 3. Novozym-435-catalyzed resolution of racemic propargylic alcohols[a]



Entry	R	Time (h)	(*S*)-**1**		(*R*)-**2**		E[d]
			Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)	
1	H	24	36 (**1a**)	95	35 (**2a**)	96	183.3
2	4-CH_3	22	35 (**1b**)	>99	39 (**2b**)	ND	
3	4-F	22	39 (**1c**)	99	48 (**2c**)	66	24.2
4	4-Cl	22	30 (**1d**)	>99	52 (**2d**)	97[e]	347.7
5	3,4-Cl_2	22	42 (**1e**)	99	49 (**2e**)	98	525.0
6	2-Cl	18.5	40 (**1f**)	>99	44 (**2f**)	95[e]	>205.0
7	4-*i*-Pr	17.5	47 (**1g**)	70	47 (**2g**)	89	35.9
8	3-Cl	14.5	37 (**1h**)	>99	39 (**2h**)	88[e]	>81.6
9	4-Et	17.5	40 (**1i**)	97	48 (**2i**)	79	35.0
10	2,3-Cl_2	22.5	42 (**1j**)	99	45 (**2j**)	95	205.8
11	4-CN	24	23 (**1k**)	98	50 (**2k**)	28	6.6
12	3,4-CH_3O_2	55	44 (**1l**)	88	38 (**2l**)	75	27.6
13	2,4-Cl_2	11	40 (**1m**)	94	47 (**2m**)	98	354.3
14	4-CH_3O	21.5	42 (**1o**)	91[f]	41 (**2o**)	79	26.6

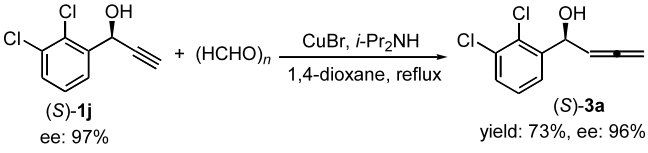
[a] The reaction was carried out at 60°C using alcohols (~100 mg), vinyl acetate (2.5 mL), and Novozym-435 (18 mg).
[b] Isolated yield.
[c] Determined by HPLC.
[d] $E = \ln[ee_P(1-ee_S)]/(ee_P+ee_S)/\ln[ee_P(1+ee_S)]/(ee_P+ee_S)$.
[e] Determined by HPLC after its conversion to the corresponding alcohol.
[f] Determined by HPLC after its conversion to the corresponding acetate.

tiomeric purity. When the substituent of the aromatic ring was a chlorine atom, the yields of the alcohols and esters were mostly good and the ees for both products were excellent (entries 4, 5, 6, 8, 10 and 13, Table 3). For some substrates, the products with very high enantiomeric purities could be obtained with only extended conversions (entries 3, 9, 11 and 12, Table 3). When we turned to 1-(2′,6′-dichlorophenyl)prop-2-yn-1-ol and 1-(2′-trifluoromethylphenyl)prop-2-yn-1-ol, the reaction did not occur. When we used 1-(1′-naphthyl)prop-2-yn-1-ol as the substrate, (*R*)-**2n** was obtained in 36% yield with 99% ee (Eq. (1)). It is notable that this reaction was carried out in organic solvents, which has made the current procedure practical for organic substrates. The crude products can be obtained by simple filtration and washing with diethyl ether.



(1)

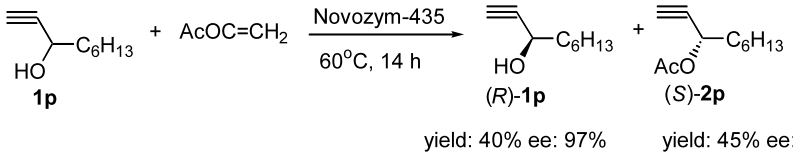
The prepared propargylic alcohol can be easily converted to the corresponding optically active 2,3-allenol (Eq. (2)).[19]



(2)

Under the current reaction conditions, the highly optically active alkyl-substituted propargylic alcohol (*R*)-**1p** can also be obtained with an extended conversion (Eq. (3)).

From the above results, we can also conclude that *Candida antarctica lipase B* has demonstrated *R* stereoselectivity toward the aryl-substituted terminal alcohols. By analogy to the conventional models[21] for the lipase-catalyzed reaction of secondary alcohols, aryl moiety is the large substituent at the hydroxymethine center as ethynyl is the medium group (Fig. 1).



(3)

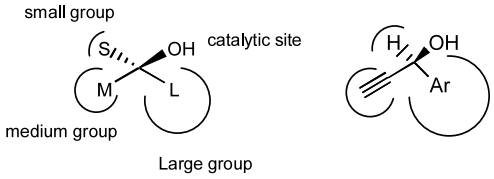


Figure 1.

In conclusion, we have developed an efficient and facile method for the preparation of optically active terminal propargylic alcohols at 60°C. Due to the easy availability of both the biocatalyst and racemic terminal propargylic alcohols, this methodology will be useful in organic synthesis. Further studies on this reaction are being carried out in our laboratory

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