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Stereoselective acylations of 1,2-azidoalcohols with vinyl acetate, catalyzed by lipase Amano PS

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Abstract—Lipase PS-catalyzed kinetic resolution of vicinal azidoalcohols was accomplished. The enzymatic reaction rates and the enantioselectivities were significantly enhanced under the ultrasonic irradiation.

1. Introduction

Chiral 1,2-aminoalcohols are very important substances as illustrated by the biologically active natural product. ephedrine, and the pharmacologically active bronchodilators, Salmeterol and Albuterol.[1a,b] In addition, they are useful chiral building blocks for the synthesis of more complex substances, such as Indinavir,[2a–c] and as chiral auxiliaries[3a,b] in asymmetric synthesis.

Chiral 1,2-azidoalcohols are immediate precursors of chiral 1,2-aminoalcohols and aziridines[4] as well as useful intermediates in carbohydrate chemistry.[5] Chiral 1,2-azidoalcohols have been prepared by three main methods: nucleophilic epoxide ring openings,[6a–d] ketone reductions[7a,b] and kinetic resolutions mediated by hydrolytic enzymes.[8a–d] In the latter case, the racemic 1,2-azidoalcohols have been most frequently resolved through lipase-catalyzed hydrolysis of the corresponding butanoates. However, kinetic resolutions via acylation have been also reported.[9]

Kinetic resolution of racemic alcohols, mediated by hydrolytic enzymes, has been widely used for the preparation of homochiral products. The main advantage of this method is the enantioselective preparation of each enantiomer. In this process, the use of enol esters such as vinyl or isopropenyl acetate as acylating agents is highly advantageous due to enol irreversible transformation in acetaldehyde or acetone. It is also known that these reactions are about ten times slower than hydrolysis of the corresponding esters.[10]

Recently, we reported the use of hydrolytic enzymes for the kinetic resolution of β-hydroxy esters.[11a,b] Now, as part of our interest in chiral 1-aryl-2-azidoethanols as precursors of biologically active natural compounds,[12a,b] we report herein our results on the efficient synthesis of enantiopure 1,2-azidoacetates from racemic vicinal 1,2-azidoalcohols via enol ester acyl transfer mediated by lipase PS, using magnetic stirring or an ultrasound bath.

2. Results and discussion

A number of commercial hydrolytic enzymes were initially screened for their ability to catalyze the acyl transfer of racemic 2-azido-1-(4-methoxyphenyl)ethanol **1a** with vinyl acetate (Scheme 1). Reactions using lipase AY Amano (*Candida rugosa*), lipase from *Candida rugosa* Sigma type VII and protease from *Aspergillus oryzae* Sigma did not proceed. On the other hand, we found that lipases Amano PS-C I (*Pseudomonas cepacia* immobilized on ceramic particles), Amano AK (*Pseudomonas fluorescens*) and Amano PS (*Pseudomonas cepacia*), were active. As the latter showed the best enantioselectivity, this was chosen for the study.

The results are summarized in Table 1. Reactions were performed without solvent and using either magnetic stirring (method A) or ultrasonification (method B). Using magnetic stirring, reaction times of 27 and 12 d for substrate **1b** and **1a**, respectively, were necessary to achieve adequate conversions (entry 2).

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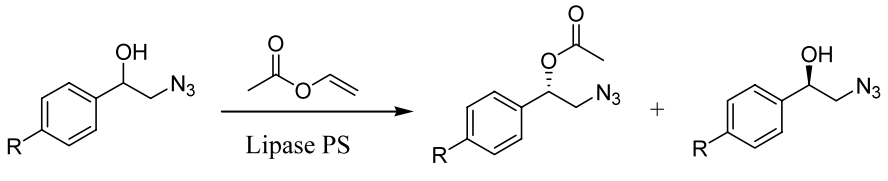


(±)-**1**

1a R = OCH_3
1b R = H

(*S*)-**2**

(*R*)-**1**

Scheme 1. Enzymatic acyl transfer of 1,2-azidoalcohols with lipase Amano PS.

As mentioned earlier, acyl transfer reactions should be slower than hydrolysis;[10] in agreement, we observed that acyl transfer to **1b** was about 37 times slower than lipase-catalyzed hydrolysis, mediated by *Pseudomonas fluorescens* and *Candida cylindracea*, of the corresponding butanoate.[8b] It has also been reported[9] that the hydrolysis of aryloxy-3-azido-2-propanol esters, mediated by *Pseudomonas* sp. lipase, was 8.5 times faster than the acyl transfer to the corresponding azidoalcohol from vinyl acetate in *t*-BuOMe.

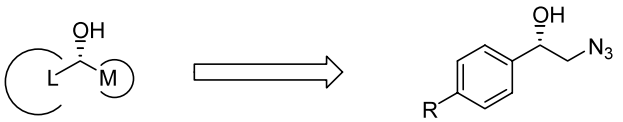
Using ultrasonification, the acyl transfer rates were greatly increased and so only 3.5 and 2.5 d were required for suitable conversions of substrates **1a**–**b**, respectively (entry 2). These findings indicate increases in reaction rates of about 3.5 and 10 times for **1a**–**b**, respectively. A reaction rate increase of 83 fold has been reported for the porcine pancreatic lipase-catalyzed acylation of naphthol derivatives using vinyl acetate, on applying ultrasonication.[14] For most nonenzymatic reactions it is generally accepted, that the rate enhancement resulting from ultrasonication arises from localised high temperatures and high pressures[15a,b] and the increase in usable surface area for catalysis.[15c] The rate enhancements from ultrasonication of enzymatic reactions have been similarly considered to arise from increases in usable catalyst surface area and to high local pressures.[14] In addition to promoting the rate enhancement of the enzymatic reactions, ultrasonication also results in an increase in the enantioselectivity of the reactions. This could be observed through the *E* values in Table 1 (entry 10). Although an increase in the enantioselectivities has been reported for hydrogenation of β-keto esters over platinum catalysts on ultrasonication,[16] no previous mention has been made for enzymatic reactions.

The absolute configurations of the unreacted azidoalcohols **1a**–**b** from the enzymatic reactions were established by comparison of their specific rotations with those published for the (*R*)-enantiomers.[7b,8b,17] Until recently[18] to the best of our knowledge, no data existed on the absolute configuration of the azidoacetates **2a**–**b**. To confirm their configurations, we prepared the corresponding acetates from the unreacted azidoalcohols **1a**–**b** from the enzymatic acylations. The signs of their specific rotations were opposed (−) to those of the azidoacetates synthesized by lipase PS (+), which confirmed that their stereochemistry to be (*S*). The selectivity of these reactions occurred according to Kazlauskas rule[19] for secondary alcohols, which states that the lipase PS enantiopreference is for the (*S*) enantiomer (Scheme 2).

Table 1. Stereoselective acylations of racemic 1,2-azidoalcohols with vinyl acetate catalyzed by lipase PS

Entry	Substrate	(±)-**1a** R = OCH_3		(±)-**1b** R = H	
1	Method[a]	A	B	A	B
2	Time (h)	288	82	659	62
3	Conversion[b] (%)	37	42	29	45
4	Yield (%) (*S*)-(+)-**2**	48	37	37	27
5	$[\alpha]_D^{25}$ (*S*)-(+)-**2**[c]	+78.6	+73.0	+62.9	+50.6
6	E.e. (%) (*S*)-(+)-**2**[d]	>95	>95	82	85
7	Yield (%) (*R*)-(−)-**1**	33	32	11	22
8	$[\alpha]_D^{25}$ (*R*)-(−)-**1**[e]	−56.9	−30.8	−66.3	−74.5
9	E.e. (%) (*R*)-(−)-**1**[f]	55	61	84	74
10	*E*[g]	68	80	14	26

[a] A, magnetic stirring; B, ultrasound bath.
[b] Determined by ^{1}H NMR from the resonances at 4.8 and 4.9 ppm (alcohols **1a** and **1b**, respectively) and 5.8 and 5.9 ppm (acetates **2a** and **2b**, respectively).
[c] *c* = 0.98; 1.3; 0.97 and 0.83 in $CHCl_3$.
[d] Determined by ^{1}H NMR in the presence of chiral shift reagent (+)-Eu(hfc)$_3$
[e] *c* = 1.1; 1.3; 0.82 and 1.1 in $CHCl_3$.
[f] Determined by ^{1}H NMR in the presence of chiral shift reagent (+)-Eu(hfc)$_3$ of the corresponding acetate.
[g] *E* = enantiomeric ratio, $E = \ln[1-c(1+\text{e.e.}_p)]/\ln[1-c(1-\text{e.e.}_p)]$, p = product.[13]



1a R = OMe
1b R = H

Scheme 2. Prefered enantiomer by lipase PS according to Kazlauskas rule for secondary alcohols.

Recently, the dynamic kinetic resolutions of 1,2-azidoalcohols, using the lipase B from *Candida antarctica* and a ruthenium catalyst, were reported.[18] The azidoacetates **2a**–**b**, which were obtained, exhibited a (+)-optical rotation, as did our products. However, Pàmies and Bäckvall,[18] attributed the absolute configuration of the azidoesters as (*R*). Assuming that this enzyme[20a–c] follows the Kazlauskas rule, these results[18] are not in agreement with the previous work of Schneider and Ader[9] and our findings.

Chiral azido alcohols **1a**–**b** are valuable biologically active natural products precursors[21a,b] and further work is currently being directed to the application of our methodology for the synthesis of such compounds. The recent publications on this subject are a measure of its importance in organic synthesis.[17,22]

3. Conclusions

In summary, we have described the kinetic resolution of vicinal azidoalcohols through lipase PS-catalyzed acyl transfer. Moderate to high enantioselectivities were obtained in the synthesis of vicinal azidoacetates. There were significant improvements in reaction rates and enantioselectivities of the enzymatic reactions using ultrasonification. The easy transformation of vicinal azidoalcohols to vicinal aminoalcohols and aziridines, as well as the simplicity and efficiency of this methodology, renders our method an attractive alternative to existing methods of obtaining homochiral aminoalcohols.

4. Experimental

4.1. General

Lipases AK (*Pseudomonas fluorescens* $\geq$20,000 u/g), PS (*Pseudomonas cepacia* $\geq$30,000 u/g), PS-C (Immobilized on ceramic particles $\geq$30,000 u/g), PS-D (Immobilized on diatomaceous earth $\geq$8,000 u/g) and AYS (*Candida rugosa* $\geq$30,000 u/g) were a gift from Amano Pharmaceutical Co., and were employed without any previous treatment. Protease from *Aspergillus oryzae* and lipase from *Candida rugosa* were purchased from Sigma. All commercially available reagent chemicals were purchased from Aldrich and Acros Organics. Solvents were distilled before use. Other chemicals were used without further purification. Reactions were monitored by TLC using silica gel Merck 60 F254 plates; purifications of products and separations of esters and alcohols after the enzymatic conversions were performed on silica gel 60 Merck with mixtures of hexane and ethyl acetate as mobile phase. IR spectra were obtained using a Perkin–Elmer Spectrum One FT IR spectrometer. ^{1}H NMR spectra were recorded on Varian Unity Plus 300 (^{1}H 300 MHz) spectrometer for solutions in $CDCl_3$ using TMS as internal standard. Optical rotations were measured at 589 nm with a Perkin–Elmer 243B polarimeter. The ultrasound bath utilized was from Cole Parmer UL-452E (47 kHz). Racemic 1,2-azidoalcohols **1a**–**b** were obtained by $NaBH_4$ reduction[23] of the corresponding 1,2-azidoketones, which in turn were prepared from the 1,2-chloroketones by procedures reported in the literature.[24a,b] Racemic 1,2-azidoacetates **2a**–**b** were prepared as reported in the literature.[8b]

4.2. Typical procedure for lipase-catalyzed acyl transfer of alcohols

The following procedure is representative. To a stirred solution of 10 mmol of racemic **1a** (1.93 g) was added 30 mmol of vinyl acetate (2.8 mL) and 0.414 g of lipase PS Amano at room temperature. The reaction progress was monitored by TLC using hexane/ethyl acetate 15% as mobile phase. A further four additions of both the enzyme and vinyl acetate were made at different times to the reaction mixture. When an adequate degree of conversion was achieved (288 h, 37%, as determined from the ^{1}H NMR spectrum using the resonances at 4.8 ppm, of the alcohol **1a**, and 5.8 ppm, of the acetate **2a**) the enzyme was filtrated, washed with CH_2Cl_2 and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel and a gradient of hexane/ethyl acetate as eluent to afford the alcohol (*R*)-(−)-**1a** 0.950 g, 48% and the acetate (*S*)-(+)-**2a** 0.797 g, 33%.

The other enzymatic resolutions were carried out in the same way. For reactions under ultrasonic irradiation, ultrasonification was applied at intervals of 30 min.

4.2.1. (*R*)-(−)-2-Azido-1-(4-methoxyphenyl)ethanol, 1a. Pale yellow oil. IR (film, cm^{-1}): 3440, 2100. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (br s, 1H), 3.36–3.50 (dd, 2H, J=4.2, 8.1, 12.6), 3.80 (s, 3H), 4.80–4.84 (dd, 1H, J=4.2, 8.1 Hz) 6.87–6.92 (d, 2H, J=6.7 Hz), 7.26–7.31 (d, 2H, J=6.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.1, 57.8, 72.8, 113.9, 127.0, 132.5, 159.4. Method A (magnetic stirring): $[\alpha]_D^{25}=-56.9$ (c 1.1, $CHCl_3$) {lit.[7b] $[\alpha]_D^{25}=-39.0$ (c 1.0, $CHCl_3$), (*R*), 97% e.e. and lit.[17] $[\alpha]_D^{20}=-117.2$ (c 1.3, $CHCl_3$), (*R*), 99% e.e.}. Method B (ultrasonic irradiation): $[\alpha]_D^{25}=-30.8$ (c 1.3, $CHCl_3$)

4.2.2. (*S*)-(+)-2-Azido-1-(4-methoxyphenyl)ethyl acetate, 2a. Pale yellow oil. IR (film, cm^{-1}): 2101, 1740. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H), 3.37–3.66 (dd, 2H, J=4.2, 8.1, 13.6 Hz), 3.80 (s, 3H), 5.85–5.89 (dd, 1H, J=4.2, 8.1 Hz) 6.88–6.92 (dd, 2H, J=8.7, 2.1 Hz), 7.26–7.31 (dd, 2H, J=8.7, 2.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 54.8, 55.1, 74.1, 114.0, 127.8, 129.0, 159.7, 169.8. Method A (magnetic stirring): $[\alpha]_D^{25}=$

+78.6 (*c* 0.98, $CHCl_3$). Method B (ultrasonic irradiation): $[\alpha]_D^{25}=+73.0$ (*c* 1.2, $CHCl_3$).

4.2.3. (*R*)-(−)-2-Azido-1-phenylethanol, 1b. Pale yellow oil. IR (film, cm^{-1}): 3409, 2106. ^1H NMR (300 MHz, $CDCl_3$): δ 2.11 (br s, 1H), 3.36–3.50 (dd, 2H, $J=4.2$, 8.1, 12.6 Hz), 3.80 (s, 3H), 4.80–4.84 (dd, 1H, $J=4.2$, 8.1 Hz) 6.87–6.92 (d, 2H, $J=6.7$ Hz), 7.26–7.31 (d, 2H, $J=6.7$ Hz). Method A (magnetic stirring): $[\alpha]_D^{25}=-66.3$ (*c* 0.82, $CHCl_3$) {lit.[7b] $[\alpha]_D^{25}=-80.1$ (*c* 0.78, $CHCl_3$), (*R*), 100% e.e., lit.[8b] $[\alpha]_D^{20}=+97.9$ (*c* 2.0 CH_2Cl_2), (*S*), >98% e.e. and lit.[17] $[\alpha]_D^{20}=+104.5$ (*c* 1.3, $CHCl_3$), (*S*), 99% e.e.}. Method B (ultrasonic irradiation): $[\alpha]_D^{25}=-74.5$ (*c* 1.1, $CHCl_3$).

4.2.4. (*S*)-(+)-2-Azido-1-phenylethyl acetate, 2b. Pale yellow oil. IR (film, cm^{-1}): 2100, 1760. ^1H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 3H), 3.42–3.68 (dd, 2H, $J=$ 3.9, 8.1, 13.2 Hz), 5.92–5.96 (dd, 1H, $J=3.9$, 8.1 Hz) 7.37 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9, 55.0, 74.4, 126.3, 128.6, 137.0, 169.7. Method A (magnetic stirring): $[\alpha]_D^{25}=+62.9$ (*c* 0.97, $CHCl_3$). Method B (ultrasonic irradiation): $[\alpha]_D^{25}=+50.6$ (*c* 0.83, $CHCl_3$).

4.3. Determination of the enantiomeric excess

The e.e. of the (*S*)-(+)-azidoesters **2a**–**b** were determined by ^1H NMR in the presence of chiral shift reagent (+)-Eu(hfc)$_3$. The e.e. of the (*R*)-(−)-azidoalcohols **1a**–**b** were determined by ^1H NMR in the presence of chiral shift reagent (+)-Eu(hfc)$_3$ after have been converted[8b] in the corresponding (*R*)-(−)-azidoacetates **2a**–**b**.

4.3.1. (*S*)-(+)-2-Azido-1-(4-methoxyphenyl)ethyl acetate, 2a. Method A (magnetic stirring): the e.e. was found to be >95% [ca. 8.4 mg of (+)-Eu(hfc)$_3$ for 5.5 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.41 ppm OAc]. Method B (ultrasonic irradiation): the e.e. was found to be >95% [ca. 10.1 mg of (+)-Eu(hfc)$_3$ for 5.0 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.37 OAc].

4.3.2. (*R*)-(−)-2-Azido-1-(4-methoxyphenyl)ethyl acetate, 2a. Method A (magnetic stirring): the e.e. was found to be 55% [ca. 10.9 mg of (+)-Eu(hfc)$_3$ for 6 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.55 ppm (*R*) and δ 2.57 ppm (*S*), OAc]; $[\alpha]_D^{25}=-59.7$ (*c* 1.3, $CHCl_3$). Method B (ultrasonic irradiation): the e.e. was found to be 61% [ca. mg of (+)-Eu(hfc)$_3$ for 5.0 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.40 ppm (*R*) and δ 2.42 ppm (*S*), OAc]; $[\alpha]_D^{25}=-62.6$ (*c* 1.1, $CHCl_3$).

4.3.3. (*S*)-(+)-2-Azido-1-phenylethyl acetate, 2b. Method A (magnetic stirring): the e.e. was found to be 82% [ca. 7.7 mg of (+)-Eu(hfc)$_3$ for 5.4 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.40 ppm (*R*) and δ 2.41 ppm (*S*), OAc]. Method B (ultrasonic irradiation): the e.e. was found to be 85% [ca. 8.0 mg of (+)-Eu(hfc)$_3$ for 5.0 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.51 ppm (*R*) and δ 2.53 ppm (*S*), OAc].

4.3.4. (*R*)-(−)-2-Azido-1-phenylethyl acetate, 2b. Method A (magnetic stirring): the e.e. was found to be 84% [ca. 9.2 mg of (+)-Eu(hfc)$_3$ for 4.7 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.50 ppm (*R*) and δ 2.52 ppm (*S*), OAc]; $[\alpha]_D^{25}=-66.4$ (*c* 1.1, $CHCl_3$). Method B (ultrasonic irradiation): the e.e. was found to be 74% [ca.9.8 mg of (+)-Eu(hfc)$_3$ for 5.1 mg of **2a** in 0.7 mL of $CDCl_3$, δ 2.47 ppm (*R*) and δ 2.50 ppm (*S*), OAc]; $[\alpha]_D^{25}=-77.1$ (*c* 0.70, $CHCl_3$).

4.4. Determination of the absolute configuration

The absolute configurations of the unreacted azidoalcohols **1a**–**b** were determined by comparison of the optical rotations with published data for the (*R*)-enantiomers. The absolute configurations of the product esters **2a**–**b** were obtained from a comparison of their optical rotations with those of the esters prepared from the unreacted (*R*)-azidoalcohols **1a**–**b**.

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