Axial Chirality

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Enantioselective Enzymatic Desymmetrization of Prochiral Allenic Diols**

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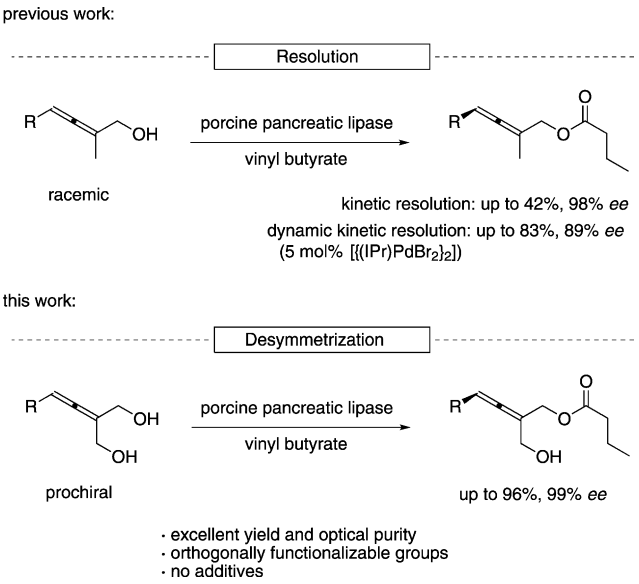
The employment of allenes as versatile synthetic building blocks represents an emerging field in modern organic chemistry.[1] Numerous novel methods, mainly based on transition metal catalysis, are opening up a toolbox for synthetic chemists to exploit the unprecedented reactivity of this class of axially chiral compounds.[2] With the increasing number of applications dealing with chiral allenes, both as synthetic intermediates and in the form of allene-based natural product target structures,[3] stereoselective methods for their preparation are becoming more and more important. Despite the fact that optically active allenes are often synthesized from enantioenriched, mainly propargylic, non-allene precursors conserving their stereochemical information,[4] there is a growing interest in the kinetic resolution of allenes.[5,6] In this context, we recently identified porcine pancreatic lipase (PPL) as an outstanding biocatalyst for the kinetic resolution of axially chiral primary allenic alcohols.[6] The crude enzyme preparation catalyzed the transesterification in organic solvents with good to excellent enantioselectivities (Scheme 1, top). However, starting from a racemic mixture, kinetic resolution is always limited to a maximum yield of 50% of the enantiopure material.[7] By means of additional racemization catalysts, allowing for a constant equilibration between both enantiomers of the starting material, dynamic kinetic resolution is obtained.[8] Using this approach, with the aid of a palladium complex we were able to further increase the yield of the allene resolution in a dynamic fashion while maintaining good optical purity of the product (Scheme 1, top).[9]

An alternative strategy to overcome yield limitations in enzyme-catalyzed transformations is to use prochiral substrates. Thus, by selective transformation of one out of two enantiotopic groups, elements of symmetry are eliminated and optically active products can be obtained in high yield.[10] Herein, we report on our investigations regarding a novel protocol for the lipase-catalyzed desymmetrization of prochiral allenic diols through selective transesterification,[11] which yields highly enantioenriched axially chiral monoesters (Scheme 1, bottom).



Scheme 1. Enantioselective biocatalytic transformations involving axially chiral allenes. IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene.

Initially, we screened a series of lipases and esterases to identify potential catalysts for the title reaction. Since good results were obtained in the kinetic resolution of allenols employing porcine pancreatic lipase, we suspected this biocatalyst to be suitable also for the stereoselective transesterification of related diol structures. And indeed, treatment of prochiral diol **1a** with vinyl butyrate in presence of PPL led to the formation of monobutyrate (*R*)-**2a** with excellent enantioselectivity, and only minor amounts of the corresponding dibutyrate **3a** from overacylation were detected (Table 1, entry 1). 1,4-Dioxane was chosen as solvent since most of the crystalline diols showed inadequate solubility in other organic solvents.

Working with lipase from porcine pancreas, inevitably the question arises whether PPL can be considered the actual catalyst or if the reaction might be influenced by hydrolase impurities present in commercial PPL preparations. As shown by Hermetter, Faber, and co-workers, both crude and pure PPL from different suppliers contain contaminations of a series of lipolytically active enzymes, typically cholesterol esterase (ChE), α-chymotrypsin (α-CT), and carboxypeptidase B.[12] Thus, we also conducted the desymmetrization reaction of **1a** in the presence of possible contaminant

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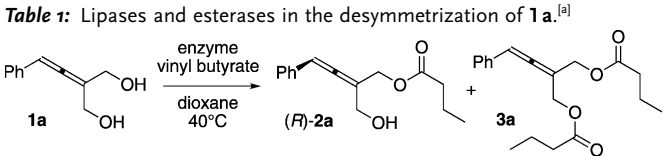
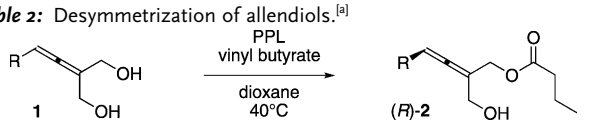
Table 1: Lipases and esterases in the desymmetrization of **1a**.[a]



Entry	Enzyme	Conv. [%]	*ee* (**2a**) [%]	**2a**/**3a**
1	porcine pancreatic lipase	96	98	98:2
2	α-chymotrypsin	<1	n.d.	n.d.
3	cholesterol esterase	36	71	92:8
4[b]	*C. antarctica* lipase B	94	91	84:16
5	*P. cepacia* lipase	78	63	97:3
6[c]	*P. fluorescens* lipase	98	68	71:29
7	*A. niger* lipase	1	n.d.	4:96
8	*C. rugosa* lipase	1	39	40:60
9	*M. javanicus* lipase	2	25	64:36
10	*P. stutzeri* lipase	4	9	87:13
11	*R. oryzae* lipase	2	11	46:54

[a] Reaction conditions: **1a** (8.8 mg, 50 μmol), vinyl butyrate (13 μL, 100 μmol), and enzyme (2.5 mg) in 1,4-dioxane (1 mL) were incubated for 72 h at 40 °C. Conversion and *ee* were determined by chiral HPLC. n.d. = not determined. [b] 1 h incubation time. [c] 16 h incubation time.

Table 2: Desymmetrization of allendiols.[a]



Entry	Diol	R	*t* [h]	Yield [%]	*ee* [%]
1	**1a**	phenyl	24	95 (**2a**)	98
2	**1b**	2-methylphenyl	96	69 (**2b**)	76
3	**1c**	3-methylphenyl	48	90 (**2c**)	98
4	**1d**	4-methylphenyl	48	78 (**2d**)	84
5	**1e**	4-chlorophenyl	30	93 (**2e**)	99
6	**1f**	4-methoxyphenyl	32	96 (**2f**)	99
7	**1g**	3,4-methylendioxyphenyl	36	92 (**2g**)	99
8	**1h**	2-naphthyl	32	93 (**2h**)	99
9	**1i**	2-trimethylsilylethynyl	46	89 (**2i**)	99
10	**1j**	*n*-heptyl	36	77 (**2j**)	92[b]
11	**1k**	cyclohexyl	96	<5 (**2k**)	n.d.

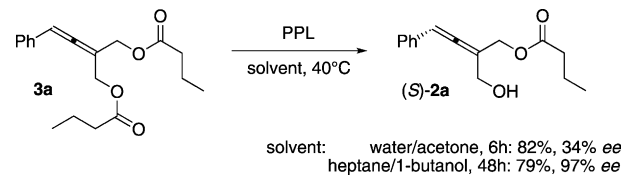
[a] Reaction conditions: allendiol **1** (0.2 mmol), vinyl butyrate (114 μL, 1.0 mmol), and PPL (20 mg) in 1,4-dioxane (1 mL) were incubated at 40 °C for 24–96 h. *ee* values were determined by chiral HPLC. n.d. = not determined. [b] *ee* value determined by chiral HPLC after derivatization to the corresponding 3,5-dinitrobenzoate.

proteins. While α-CT gave only marginal conversion (Table 1, entry 2), ChE catalyzed the transesterification with considerable effect, although with inferior selectivity (Table 1, entry 3). These results indicate that PPL does represent the catalytically active protein; however, traces of ChE might be responsible for a certain erosion of enantioselectivity.[13] Furthermore, we also tested other commercially available lipases for their ability to catalyze the transesterification of **1a**. Among the proteins tested, only lipases from *Candida antarctica* (lipase B), *Pseudomonas cepacia*, and *Pseudomonas fluorescens* showed synthetically useful conversions (Table 1, entries 4–6). The outstanding activity of *Candida antarctica* lipase B (94% conversion after 60 min), however, was qualified by a slightly lower enantioselectivity than PPL, accompanied by a significant degree of overacylation. Other lipases, namely from *Aspergillus niger*, *Candida rugosa*, *Mucor javanicus*, *Pseudomonas stutzeri*, or *Rhizopus oryzae*, did not reveal substantial catalytic activity (Table 1, entries 7–11). In all cases, the (*R*)-enantiomer was formed preferentially.[14]

To study the scope of the reaction, we conducted desymmetrizations of a variety of substituted allendiols through enzymatic transesterification. As the reaction proceeded relatively slowly under the reaction conditions used in the enzyme screening (Table 1), substrate concentration, enzyme loading, and excess of the acylating agent were further increased. Under these modified conditions, the desymmetrization of phenyl-substituted diol **1a** reached full conversion after 24 h, and monoester **2a** was isolated in 95% yield and 98% *ee* (Table 2, entry 1). Tolyl derivatives **1b**–**1d** showed an interesting phenomenon, as substitution in *ortho* or *para* position of the aryl moiety led to a considerable decrease in enantioselectivity (Table 2, entries 2 and 4), while *meta* derivative **2c** was isolated with an excellent enantiomeric excess of 98% (Table 2, entry 3). In contrast, heterosubstituents in *para* position of the arene led to improved selectivity over reference diol **1a**, and monobutyrates **2e** and **2f** were obtained in nearly enantiopure form and very high yields (Table 2, entries 5 and 6). In the same way, allenic diols bearing bicyclic (**1g** and **1h**) or acetylenic substituents (**1i**) were desymmetrized with a high degree of enantioselectivity (Table 2, entries 7–9). While alkyl-substituted allenols showed rather low selectivity in the kinetic resolution using PPL,[6] in the case of allene desymmetrization even *n*-heptyl derivative **1j** was isolated with an enantiomeric excess of 92% (Table 2, entry 10). Only cyclohexyl-substituted diol **1k** did not react under these conditions.

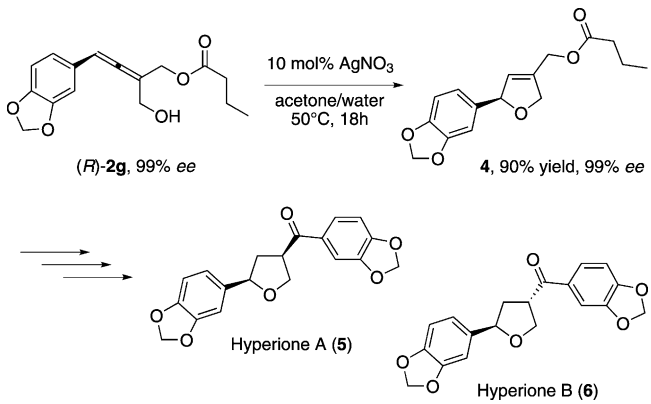
As none of the tested proteins exhibited inverse selectivity compared to PPL (see Table 1), we were also interested in the lipase-catalyzed hydrolysis of the prochiral dibutyrates **3** as an enantiocomplementary approach yielding (*S*)-configured monobutyrates **2**. To our surprise, PPL-catalyzed saponification of **3a** in aqueous buffer with acetone as cosolvent at 40 °C led to fast formation of (*S*)-**2a**, albeit at a low level of enantioselectivity (Scheme 2). This result was in sharp contrast to previous studies, where we used similar conditions for the hydrolysis of racemic allenyl butyrates with excellent stereocontrol.[9] However, treatment of **3a** with lipase from porcine pancreas under non-aqueous conditions (1-butanol in heptane) efficiently solved this selectivity issue, and highly enantioenriched (*S*)-**2a** was isolated in good yield. Thus, a single enzyme can be used to produce either (*S*)- or (*R*)-configured, axially chiral allenic monobutyrates in high enantiomeric purity by biocatalytic desymmetrization by simply choosing between synthetic or digestive reaction conditions.[15]

The spectrum of interesting reactions employing axially chiral allenols is broad; hence, these compounds are increasingly found as intermediates in the synthesis of complex natural products.[6,16] Exemplarily, the synthetic potential of the optically active monoesters formed in the allene desymmetrization is demonstrated in the silver-mediated cycloisomerization of piperonyl derivative **2g**, where dihydrofuran



Scheme 2. Enantioselective solvolysis of dibutyrate **3a**.

4 is obtained in 90% yield and with complete transfer of chirality (Scheme 3). Thus, the combination of desymmetrization and 5-*endo*-*trig*-cyclization opens up a fast asymmetric synthetic access towards the core structure of the hyperiones (**5** and **6**), two norlignanes which have recently been isolated from the roots of *Hypericum chinense*.[17]



Scheme 3. Allene cycloisomerization as access towards the core structure of the hyperiones.

In summary, a powerful chemoenzymatic protocol for the synthesis of optically active, highly functionalized allenes has been developed, combining excellent enantiopurity and high yields. Depending on the reaction conditions and prochiral allene source chosen, either enantiomer of the axially chiral allenyl monoesters is easily accessible in highly enantioenriched form. Currently, we are investigating the extended scope of this reaction as well as its implementation in natural product synthesis.

Experimental Section

Representative procedure for the desymmetrization by esterification: Allendiol **1a** (35.2 mg, 200 μmol) and vinyl butyrate (114 mg, 1.0 mmol) were dissolved in 1,4-dioxane (1.0 mL), porcine pancreatic lipase (20 mg) was added, and the reaction mixture was incubated for 24 h at 40 °C. After filtration and concentration of the filtrate in vacuo, purification by column chromatography (SiO_2, cyclohexane/ethyl acetate 8:2–6:4) delivered monoester (*R*)-**2a** (46.8 mg, 190 μmol, 95%, 98% *ee*) as colorless oil. $[\alpha]^{20}_D$: −35.6° ($c = 0.5$, $CHCl_3$). R_f (cyclohexane/ethyl acetate 7:3): 0.24. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.22$–7.33 (m 5H), 6.40 (m, 1H), 4.81 (d, $J = 2.1$ Hz, 2H), 4.26 (d, $J = 2.2$ Hz, 2H), 2.34 (t, $J = 7.4$ Hz, 2H), 1.66 (tq, $J = 7.4$ Hz, 2H), 1.28 (br s, 1H), 0.95 ppm (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.8$, 173.8, 133.3, 128.7, 127.5, 127.1, 105.1, 98.0, 62.0, 61.3, 36.1, 18.4, 13.7 ppm. FTIR (ATR): $\nu = 3402$ (br), 2964 (w), 2933 (w), 2875 (w), 1952 (w), 1732 (s), 1589 (w), 1496 (w), 1460 (w), 1415 (w), 1381 (w), 1249 (w), 1168 (s), 1024 (m), 746 (m), 692 cm^{-1} (s). Elemental analysis (%) calcd for $C_{15}H_{18}O_3$: C 73.15, H 7.37; found: C 73.02, H 7.51. HPLC (Chiralpak AD-H, hexane/2-propanol 95:5, 1.0 mL min^{-1}, 250 nm): t_R ((*R*)-**2a**) = 12.9 min, t_R ((*S*)-**2a**) = 14.2 min.

Representative procedure for the solvolytic desymmetrization: Dibutyrat **3a** (63.2 mg, 200 μmol) was dissolved in *n*-heptane (3.6 mL) and *n*-butanol (0.4 mL), porcine pancreatic lipase (100 mg) was added, and the reaction mixture was incubated for 48 h at 40 °C. Monoester (*S*)-**2a** (39.0 mg, 158 μmol, 79%, 97% *ee*) was obtained after column chromatography (SiO_2, cyclohexane/ethyl acetate 8:2–6:4) as colorless oil. $[\alpha]^{20}_D$: +34.9° ($c = 0.5$, $CHCl_3$).

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[13] "Lipase from porcine pancreas" from MP Biomedicals was used in our studies, and the results gave no indication for this effect. However, using "PPL type II" from Sigma, which was shown to contain a substantial number of contaminant proteins,[12] significantly lower enantioselectivities were obtained.

[14] The absolute configuration of the resulting monoester was confirmed by degradation to 4-methyl-2-phenyl-2,5-dihydrofuran and comparison of its optical rotation with a stereodefined sample (see the Supporting Information). All monoesters were configurationally stable, and even after storage for three month at 4 °C only marginal loss in optical purity was detected.

[15] While diester **3a** showed acceptable conversion rates in the transesterification with butanol, other allenyl dibutyrates suffered from significantly extended reaction times. Owing to the reversibility of the transesterification, full conversion was not achieved; further studies, especially with other nucleophiles, will be necessary. Nevertheless, the excellent enantioselectivity was obtained in all of the solvolytic desymmetrizations.

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