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Short communication

Lipase-catalyzed kinetic resolution of 3-phenyloxazolidin-2-one derivatives: Cascade *O*- and *N*-alkoxycarbonylations

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ABSTRACT

A lipase-catalyzed, cascade kinetic resolution protocol has been established for the synthesis of 3-phenyloxazolidin-2-one derivatives with up to excellent enantioselectivities (95% *ee*). *Candida antarctica* lipase B showed high catalytic activity and stereoselectivity in sequential *O*- and *N*-alkoxycarbonylation processes.

1. Introduction

3-Oxazolidinone-2-ones constitute a class of heterocyclic organic compounds of medical importance. These structures are commonly used as efficient antimicrobials against both Gram-positive and Gram-negative pathogens (Fig. 1) [1]. For instance, befloxatone is used clinically for the treatment of dysthymia [2], while linezolid and tedizolid are commercial drugs to treat serious infections caused by Gram-positive bacteria, especially for those resistant to many other antibiotics [3–4]. Oxazolidinone derivatives are also used as Evans auxiliaries for asymmetric synthesis [5].

To obtain enantioenriched oxazolidinone derivatives, most reported studies involve chiral transition metal catalysts, organocatalysts or chiral starting materials [6–8]. Meanwhile, biocatalysis has been gaining importance in asymmetric synthesis over the past decades for its high chemo-, regio-, and stereoselectivity, mildness of reaction conditions and environmental friendliness, thus showing advantages over other catalytic protocols [9–11]. Certain enzymes, such as lipases [12–14], have also been reported in the asymmetric synthesis of different heterocyclic structures, thus demonstrating the utility of biocatalysis for this class of compounds [15–20]. In a previous study, an enzyme-catalyzed kinetic resolution protocol using a *Burkholderia* (*Pseudomonas*) *cepacia* lipase (BCL) preparation was established for the asymmetric synthesis of 5-phenyloxazolidin-2-ones with high enantiopurities from 1,2-aminoalcohols [21]. However, 3-phenyloxazolidin-2-ones are more medically relevant structures, since the *N*-aryl group plays a crucial role in antibiotic activity [22]. This challenge has been addressed in the present study, where we present the synthesis of enantiopure 3-phenyloxazolidin-2-one structures using *Candida antarctica* lipase B (CAL-B).

2. Experimental section

2.1. General

Reagents were obtained from commercial suppliers and used as received. Lipases from *B.* (*Pseudomonas*) *cepacia* (PS-CI and PS-CII), *C. antarctica* (CAL-B), *Pseudomonas fluorescens* (PFL), *Rhizopus niveus* (RNL), *Mucor javanicus* (MJL), and porcine pancreas, type II (PPL) were purchased from Sigma-Aldrich. Lipase PS "Amano" IM (EC 3.1.1.3) was purchased from Amano Enzyme Inc. ^{1}H and ^{13}C NMR data were recorded on a Bruker Avance 400 (100) MHz and/or a Bruker Avance 500 (125) MHz, respectively. Chemical shifts are reported as δ values (ppm) with $CHCl_3/CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0) as internal standards. *J* values are given in Hertz (Hz). Analytical high performance liquid chromatography (HPLC) with chiral stationary phase was performed on an HP-Agilent 1110 Series controller and a UV detector, using Daicel Chiralpak OD-H column (4.6 × 250 mm, 10 μm)/Astec Cellulose DMP column (4.6 × 250 mm, 5 μm)/Daicel Chiralpak OJ column (4.6 × 250 mm, 10 μm). Solvents for HPLC use were of spectrometric grade. Thin layer chromatography (TLC) was performed on precoated Polygram® SIL G/UV 254 silica plates (0.20 mm, Macherey-Nagel),

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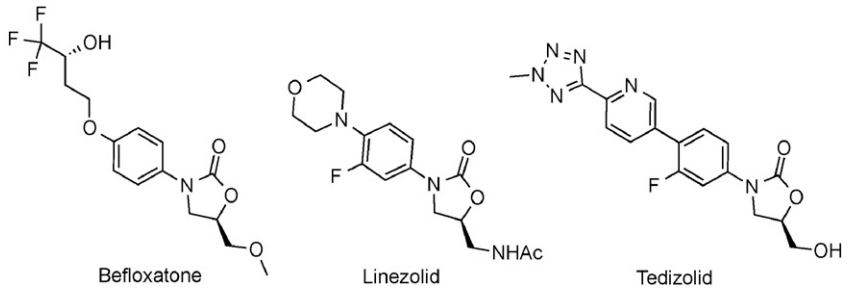
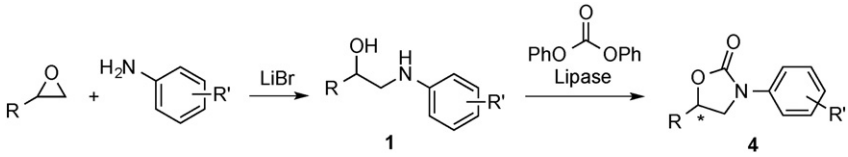


Fig. 1. Commercial drugs with 3-oxazolidinone-2-one structures.



Scheme 1. Reaction protocol.

visualized with UV-detection. Flash column chromatography was performed on silica gel 60, 0.040–0.063 mm (SDS).

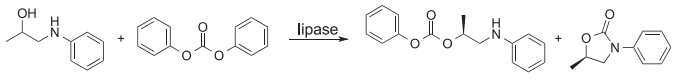
2.2. General procedure for the synthesis of 1,2-aminoalcohols (**1a**-**1k**)

LiBr (0.1 mmol) was added to a stirred mixture of respective epoxide (2 mmol) and aniline (2 mmol) under nitrogen atmosphere, and the solution was stirred at r.t. for 4 h. The reaction mixture was diluted with water (10 mL) and extracted twice with diethyl ether (15 mL each). The combined organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 3:1).

2.3. General procedure for the synthesis of racemic 3-phenyloxazolidin-2-one derivatives (**4a**-**4k**) [23–27]

1,2-Aminoalcohol **1a**-**1k** (0.08 mmol), diphenyl carbonate (0.1 mmol), NaH (0.16 mmol, 60% in oil) and THF (1 mL) were added into a 5 mL flask. The solution was stirred at r.t. for 6 h. TLC was used to monitor the reaction progress. CH_2Cl_2 was subsequently added, and the aqueous layer was extracted three times with CH_2Cl_2 (3 mL each). The combined organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 3:1).

Table 1
Screening of lipases with model reaction.[a]



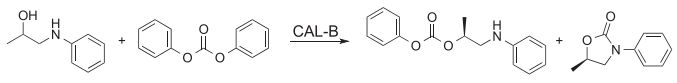
Entry	Lipase	**4a** conv. (%)[b]
1	PS-CI	52
2	PS-CII	0
3	PS-IM	32
4	CAL-B	71
5	PFL	15
6	RNL	0
7	MJL	0
8	PPL	0

[a] Determined by ^{1}H NMR.
[b] Reaction conditions: **1a** (0.05 mmol), **2** (0.15 mmol), lipase preparation (30 mg), 4 Å molecular sieves (20 mg) in TBME (0.6 mL), 30 °C for 3 d.

2.4. General procedure for kinetic resolutions of 3-phenyloxazolidin-2-one derivatives (**4a**-**4k**) [23–27]

1,2-Aminoalcohol **1a**-**1k** (0.05 mmol), diphenyl carbonate (0.15 mmol) and dry toluene (0.6 mL) were added into a 1.5 mL sealed-cap vial containing CAL-B (30 mg) and 4 Å molecular sieves (20 mg). CAL-B was dried under vacuum for at least two days before use. The vial was kept at r.t. without stirring, and ^{1}H NMR was used to monitor the reaction progress. After a specific time, the reaction mixture was filtered through a cotton-stoppered pipette. CH_2Cl_2 was subsequently added, and the aqueous layer was extracted three times with CH_2Cl_2 (3 mL each). The combined organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 3:1). Intermediates and the recovered starting materials were also collected.

Table 2
Effects of solvents and additives on the reaction rate and *ee*.[a]



Entry	Lipase	Additive	Solvent	Time	**3a** conv. (*ee*[b])	**4a** conv. (*ee*[b])
1[c]	PS-IM	SiO_2	TBME	46 h	55 (69)	45 (57)
2	CAL-B	–	TBME	48 h	15 (34)	48 (50)
3	CAL-B	–	Toluene	5 h	0	51 (77)
4	CAL-B	NEt_3	Toluene	33 h	55 (88)	45 (15)
5	CAL-B	1-methylimidazole	Toluene	5.5 h	0	50 (70)
6	CAL-B	4-methylmorpholine	Toluene	7.5 h	8 (82)	50 (71)
7	CAL-B	SiO_2	Toluene	5 h	10 (25)	46 (86)
8	CAL-B	$ZnBr_2$	Toluene	28 h	0	0

[a] Reaction conditions: Compound **1a** (0.05 mmol), compound **2** (0.15 mmol), additives (0.025 mmol), lipase preparation (PS-IM: 50 mg; CAL-B: 30 mg), 4 Å molecular sieves (20 mg) in toluene (0.6 mL), 30 °C.
[b] Determined by HPLC analysis using Chiralpak OD-H chiral column.