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Synthesis of Chiral Oxazolidinone Derivatives through Lipase-Catalyzed Kinetic Resolution

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Highlights:

- Chiral oxazolidinone derivatives were synthesized with excellent enantiopurities.
- Lipase-catalyzed kinetic resolution of two-step, cascade acylation was described.
- Carbonates were used as double acyl donors for lipase-catalyzed cyclizations.

Abstract:

The synthesis of enantioenriched oxazolidinone derivatives through lipase-catalyzed kinetic resolution is described. The synthesis comprised a two-step, cascade acylation in one pot, resulting in a range of oxazolidinone derivatives in good yields and excellent enantiopurities.

Keywords:
Lipases; kinetic resolution; oxazolidinone; asymmetric synthesis

1. Introduction

Oxazolidinone derivatives represent a class of important structures in organic and medicinal chemistry, for example constituting the core structure of Evans' auxiliaries for asymmetric synthesis [1-3]. This structural motif exists in a variety of natural products and active pharmaceutical species, such as the antidepressant drug toloxatone, the serotonin receptor agonist zolmitriptan, and the muscle relaxant metaxalone (Figure 1) [4-6]. In particular, considerable attention has been put on the development of compounds with antibacterial activity, where the oxazolidinone group of antibiotics has gained increasing interest [7-10]. For example, linezolid is a lead antibiotic against gram-positive bacteria that are resistant to other antibiotics [11-13].

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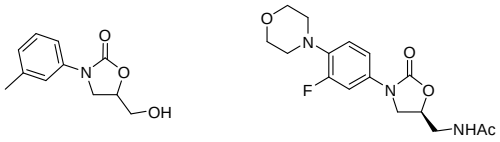


Toloxatone **Linezolid**

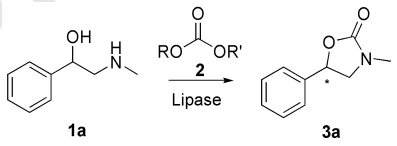
Figure 1. Structures of antidepressant toloxatone and antibiotic linezolid.

Owing to the importance of this heterocyclic structure, a variety of synthetic methods to enantioenriched oxazolidinones have been developed and studied over the years [14-18]. In most of these approaches, the resulting enantiopurity emanates from chiral starting materials or through the action of transition metal catalysts. Biocatalysis, however, one of the most efficient routes to enantiopure compounds, has not been applied in the direct synthesis of these core structures. One reason for this has been the lack of identified enzymes that catalyze these processes. Compared to other catalysts, enzymes nevertheless possess several advantages, such as environmental benignity, mild reaction conditions and high selectivity, making them attractive for synthetic processes [19-22]. Moreover, enzyme-catalyzed kinetic resolution (KR) schemes are commonly applied in asymmetric synthesis, where high enantiopurities can be obtained [23-26]. In the present study, we have taken advantage of these features and present an efficient synthesis to chiral oxazolidinone derivatives through enzyme-catalyzed kinetic resolution.

Lipases [EC 3.1.1.3], have generally evolved to catalyze the hydrolysis of triglycerides, although some lipases are known to participate in other biological processes. This family of enzymes is however also widely used in organic synthesis owing to the commercial availability, structural stability, solvent tolerance, broad substrate scope and good catalytic activity [27, 28]. In organic solvents, the enzymes generally catalyze different acylation reactions to provide esters, thiolesters and amides [26, 29-30]. In addition to intermolecular acylations, some lipases are furthermore able to catalyze promiscuous [31-33], intramolecular reactions. We have thus preciously reported different cyclization reactions catalyzed by lipases, resulting in facile synthesis of chiral 1,3-oxathiolan-5-one derivatives [34, 35], substituted Thiolanes [36], oxathiazinanones [37], and thiazolidinones [38]. The exploration of enzyme substrate- and reaction promiscuity for the synthesis of heterocycles is however an ongoing quest [39, 40], where new, efficient transformations are evaluated. In the present study, carbonate diesters were used as double acyl donors [41-42], enabling the possibility of a two-step cascade acylation in one pot.

2. Results and discussion

At the outset, different α-hydroxy, α-mercapto, and α-amino alcohols were tested for lipase-catalyzed cyclizations, all of which successfully undergoing double acylation to the respective heterocyclic products. Of these, the reactions with α-amino alcohols provided the desired oxazolidinone products, also showing promising enantiomeric excesses (*ee*s). Of the α-amino alcohols, 2-(methylamino)-1-phenylethanol (**1a**) was chosen as the model substrate for further evaluation of the lipase-catalyzed transformation (Scheme 1).



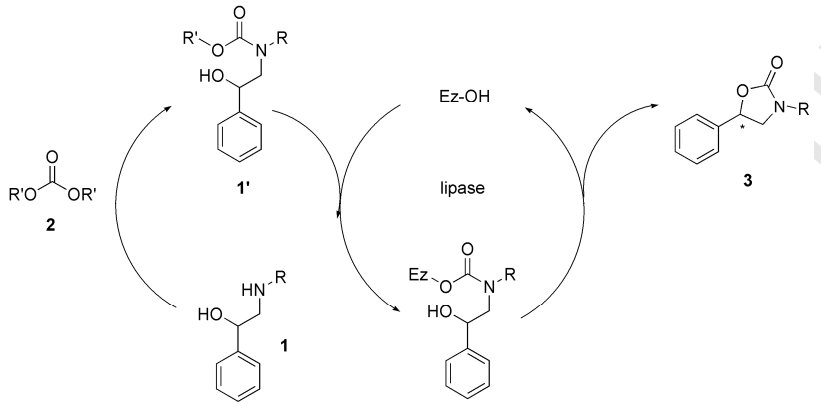
1a **3a**

Scheme 1. Synthesis of compound **3a** through lipase-catalyzed kinetic resolution.

To identify the best catalyst for the transformation, different lipase preparations were screened, including lipases from *Burkholderia* (*Pseudomonas*) *cepacia* (PS-IM and PS), *Pseudomonas fluorescens* (PFL), and *Candida antarctica* (CAL-B). Among these, PS and CAL-B did not produce any products, while both PS-IM and PFL catalyzed the reaction. PS-IM was subsequently chosen for further evaluation owing to the faster substrate transformation with this enzyme preparation compared to PFL.

The impact of the solvent on the reaction was next evaluated. Between toluene and *tert*-butyl methyl ether (TBME), the two most commonly used solvents in our previous studies, TBME was proven more efficient in the catalysis of the reaction, providing considerably better conversions within the same time scale. Different carbonate diesters (**2**), such as diphenyl carbonate and methyl phenyl carbonate were furthermore tested in reactions with compound **1a**. The results showed that the reactions with diphenyl carbonate proceeded smoothly, providing both good yields and *ee*s. Methyl phenyl carbonate, on the other hand, did not result in any products, probably due to the lipase inactivation effect of methanol released as the side product.[37]

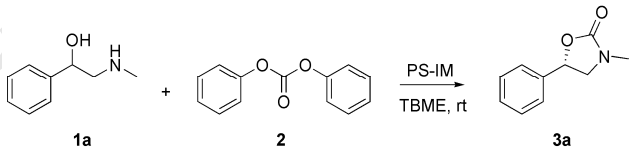
In order to elucidate the role of the enzyme in the two-step reaction process, control experiments were carried out in the absence of lipase. Under the conditions used, acylation of the amine could be detected within one hour, after which the reaction stopped without any further acylation or cyclization. This is indicative of a relatively rapid carbamation step between the carbonate diester and the α-amino alcohol, with no subsequent reaction ensuing from the resulting carbamate structure. Therefore, a kinetically controlled first-step carbamation followed by a lipase-catalyzed second-step cyclization mechanism can be proposed, leading to the enantioenriched oxazolidinone products (Scheme 2).



Scheme 2. Lipase-catalyzed, double acylation process through carbamate intermediate.

With the identified reaction conditions, the double acylation process catalyzed by PS-IM proceeded well in TBME, providing product **3a** at good yield (46%) and excellent *ee* (92%), with an absolute (*S*)-configuration of the major enantiomer according to polarimetry data [43]. In addition, starting material **1a** was fully consumed, and the carbamation intermediate (**1a'**) from the kinetic resolution process was detected with a high *ee* of 94%. However, one drawback with these conditions was the lengthy reaction times to reach full conversion of the selected enantiomer. Thus, several Lewis basic- and acidic additives were screened to improve the reaction rates (Table 1). The results showed that Et_3N had almost no effect on the process, where both the yield and the *ee* of the product remained the same as without any additives. The other two organic bases: 4-methylmorpholine and 1-methylimidazole, led to very low yields to the product, while maintaining high *ee*s. On the other hand, two of the Lewis acids tested, $ZnBr_2$ and SiO_2, increased the reaction yield in solution (entry 5 and 6), although the presence of $ZnBr_2$ resulted in substantially reduced product *ee* during the process. Fortunately, SiO_2 did not affect the enantioselectivity of the lipase-catalysis process, and the reaction was considered accelerated. The appeared reaction time was thus shortened from 4 d to 3 h, while maintaining a product *ee* of 95%.

Table 1. Effect of additives[a]



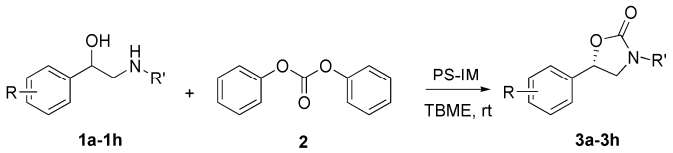
Entry	Additive	Time	Yield (%)[b]	*ee* (%)[c]
1	-	4 d	46	92
2	Et_3N	4 d	47	93
3		4 d	30	91
4		4 d	21	93
5	SiO_2	3 h	47	95
6	$ZnBr_2$	2 d	52	9

[a] Reactions were carried out with 0.05 mmol of **1a**, 3 equiv. of **2**, 0.5 equiv. of additives, 20 mg of 4 Å MS and 50 mg of PS-IM in 0.6 mL TBME at rt; [b] Determined by ^{1}H NMR spectroscopy; [c] Determined by HPLC analysis using a Daicel Chiralpak OD-H column

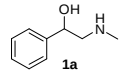
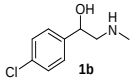
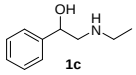
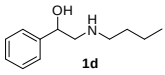
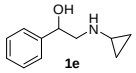
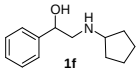
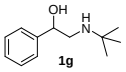
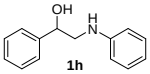
Following identification of optimized reaction conditions with respect to lipase preparation, solvent, carbonate structure and additives, a range of substrates was evaluated in the process (Table 2). Interestingly, the tested substrates resulted in different solution distributions when the reactions reached full conversions to the products. Besides the cyclized oxazolidinone products, *N*-substituted methyl, ethyl and butyl substrates gave only intermediates **1'** in the solution, while more sterically hindered substrates (**1e**, **1f** and **1g**) mainly provided starting materials **1e**-**1g**. The determined *ee*s for all constituents are shown in Table 2, where the unbalanced ratios between the enantiomers can be attributed to the irreversible interactions between the substrates and SiO_2 (*cf.* ESI). On the other hand, the benzyl-substituted substrate **1h** was not affected by the addition of SiO_2, presenting a typical pattern for kinetic resolution. In some cases, the enantioenriched intermediate **1'** was not stable under the reaction conditions, and partially reverted back to starting material **1**.

With respect to the enantioselective cyclization, the majority of the oxazolidinone products were obtained with good total yields and high enantiopurities. Changing the phenyl group for a *p*-chlorophenyl moiety (**1b**) led to a slightly lower reaction rate, but resulted in good yield and excellent *ee*. Replacing the amine methyl group for an ethyl functionality (**1c**) showed only minor effects, and the reaction rate and *ee* remained high. However, upon increasing the size of the amine substituent further by applying a butyl group (**1d**), the *ee* decreased to some extent, likely due to less optimal fit of the longer aliphatic chain into the enzyme active site. Aliphatic rings were also applied as amine substituents, including cyclopropyl (**1e**) and cyclopentyl (**1f**) groups. The reaction process proceeded well for the cyclopropyl group, resulting in good yield (50 %) and *ee* (92 %). However, increasing the ring size to the larger cyclopentyl group, led to longer reaction time and considerably lower *ee*. For the substrate with a *tert*-butyl group as amine substituent (**1g**), poor enantioselectivity and longer reaction time were recorded. In addition to the aliphatic groups, a phenyl substituent was also probed on the amine side (**1h**). Although longer time was required for this reaction to reach good yield, a high *ee* of the product was nevertheless obtained.

Table 2. Kinetic resolution of different substrates [a]



1a-1h **2** **3a-3h**

Entry	Substrate	Time	Conversion (%)[b]	*Yield (%)*[c]	ee_1 (%)[d]	$ee_{1'}$ (%)[e]	ee_3 (%)[f]
1	 **1a**	3 h	> 99	47	n.d.[g]	14	95
2	 **1b**	4.5 h	58	45	--[h]	4	> 99
3	 **1c**	3.5 h	> 99	50	n.d.	12	97
4	 **1d**	1.5 h	> 99	42	n.d.	58	88
5	 **1e**	1.5 h	50	50	44	n.d.	92
6	 **1f**	3 d	48	48	--	n.d.	28
7	 **1g**	3 d	57	57	--	n.d.	10
8	 **1h**	5 d	96	46	3	99	90

[a] Reactions were carried out with 0.05 mmol of **1**, 3 equiv. of **2**, 0.5 equiv. of SiO_2, 20 mg of 4 Å MS and 50 mg of PS-IM in 0.6 mL TBME at rt; [b] The total conversion of starting material **1**. Determined by ^{1}H NMR spectroscopy; [c] The yield from starting material **1** to product **3**. [d] *ee* of starting material **1** when the reaction reached aforementioned conversion. [e] *ee* of intermediate **1'** when the reaction reached aforementioned conversion. [f] All *ee*s were determined by HPLC analysis using a Daicel Chiralpak OD-H column. [g] No corresponding compound was detected when the reaction was quenched. [h] No chiral separation method was found.

3. Conclusions

A kinetic resolution protocol for the synthesis of enantioenriched oxazolidinone derivatives has been successfully developed using carbonate donors and lipase catalysis. Following an initial carbamation step, lipase-catalyzed cyclization provided the oxazolidinone structures in good yields and with excellent enantiopurities. The use of carbonates as double acyl donors for lipase-catalyzed cyclizations has been successfully illustrated in a cascade reaction process, representing an efficient method for chiral oxazolidinone synthesis.

4. Experimental

4.1 General methods

Reagents were obtained from commercial suppliers and used as received. Lipase PS "Amano" IM [EC 3.1.1.3] was purchased from Amano Enzyme Inc. Lipases from Pseudomonas fluorescens (PFL), Burkholderia (Pseudomonas) cepacia (PS), Candida antarctica (CAL-B) were purchased from Sigma-Aldrich. 1H and 13C 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 CDCl3 (1H NMR δ 7.26, 13C NMR δ 77.0) as an internal standard. 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 a Daicel Chiralpak OD-H 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), visualized with UV-detection. Flash column chromatography was performed on silica gel 60, 0.040-0.063 mm (SDS).

4.2 General procedure for the synthesis of α-amino alcohols (1a-1h)

Styrene oxide or 2-(4-chlorophenyl)oxirane (2 mmol), was added to a flask together with methylamine (8 mmol, 40 % aqueous solution) or other amines (8 mmol) in ethanol (2 mL). Then the solution was stirred at 60 °C for 7 h. The solvent was subsequently evaporated, and the crude product was purified using column chromatography (EtOAc, followed by EtOAc:MeOH = 10:1).

2-(Methylamino)-1-phenylethanol (1a) [44]
Light yellow solid, yield: 34 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 2.48 (s, 3H, CH_3), 2.73 (dd, J_1 = 12.1 Hz, J_2 = 8.9 Hz, 1H, CH_2), 2.84 (dd, J_1 = 12.1 Hz, J_2 = 3.7 Hz, 1H, CH_2), 4.73 (dd, J_1 = 8.9 Hz, J_2 = 3.7 Hz, 1H, CH), 7.25-7.30 (m, 1H, CH), 7.32-7.40 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 36.1, 59.3, 71.5, 125.9, 127.7, 128.5, 142.6.

1-(4-Chlorophenyl)-2-(methylamino)ethanol (1b) [44]
Yellow oil, yield: 54 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 2.44 (s, 3H, CH_3), 2.66 (dd, J_1 = 12.1 Hz, J_2 = 9.2 Hz, 1H, CH_2), 2.76 (dd, J_1 = 12.1 Hz, J_2 = 3.5 Hz, 1H, CH_2), 4.72 (dd, J_1 = 9.2 Hz, J_2 = 3.5 Hz, 1H, CH), 7.27-7.33 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 36.0, 59.1, 70.7, 127.4, 128.7, 133.3, 141.2.

2-(Ethylamino)-1-phenylethanol (1c) [44]
White solid, yield: 47 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.30-3.46 (m, 3H, CH_2CH_2), 3.92 (t, J = 8.4 Hz, 1H, CH_2), 5.49 (t, J = 8.4 Hz, 1H, CH), 7.34-7.43 (m, 5H, 5CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 12.7, 39.1, 51.8, 74.4, 125.6, 128.9, 129.1, 139.0, 157.8.

2-(Butylamino)-1-phenylethanol (1d) [45]
White solid, yield 36 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 0.93 (t, J = 7.3 Hz, 3H, CH_3), 1.31-1.40 (m, 2H, CH_2), 1.44-1.52 (m, 2H, CH_2), 2.58-2.75 (m, 3H, $CHCH_2$), 2.88 (dd, J_1 = 12.1 Hz, J_2 = 3.5 Hz, 1H, CH_2), 4.74 (dd, J_1 = 9.2 Hz, J_2 = 3.5 Hz, 1H, CH), 7.27-7.31 (m, 1H, CH), 7.34-7.41 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 14.1, 20.4, 32.5, 49.3, 57.3, 71.7, 126.0, 127.5, 128.5, 142.9.

2-(Cyclopropylamino)-1-phenylethanol (1e) [46]
Colorless oil, yield: 44 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 0.32-0.53 (m, 4H, $2CH_2$), 2.14-2.10 (m, 1H, CH), 2.80 (dd, J_1 = 12.1 Hz, J_2 = 9.1 Hz, 1H, CH_2), 3.01 (dd, J_1 = 12.1 Hz, J_2 = 3.7 Hz, 1H, CH_2), 4.73 (dd, J_1 = 9.1 Hz, J_2 = 3.7 Hz, 1H, CH), 7.25-7.30 (m, 1H, CH), 7.32-7.39 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 6.3, 7.1, 30.4, 57.3, 71.9, 126.0, 127.6, 128.5, 142.7.

2-(Cyclopentylamino)-1-phenylethanol (1f) [47]
White solid, yield: 56 %, ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 1.12 (s, 9H, $3CH_3$), 2.62 (dd, J_1 = 12.1 Hz, J_2 = 8.8 Hz, 1H, CH_2), 2.91 (dd, J_1 = 12.1 Hz, J_2 = 3.5 Hz, 1H, CH_2), 4.64 (dd, J_1 = 8.8 Hz, J_2 = 3.5 Hz, 1H, CH), 7.25-7.29 (m, 1H, CH), 7.33-7.40 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 24.0, 24.1, 33.2, 33.6, 56.0, 59.7, 72.2, 125.9, 127.6, 128.5, 142.9.

2-(*tert*-Butylamino)-1-phenylethanol (1g) [48]
Light yellow solid, yield: 9 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 1.29-1.39 (m, 2H, CH_2), 1.49-1.59 (m, 2H, CH_2), 1.63-1.73 (m, 2H, CH_2), 1.79-1.88 (m, 2H, CH_2), 2.67 (dd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, 1H, CH_2), 2.92 (dd, J_1 = 12.4 Hz, J_2 = 3.7 Hz, 1H, CH_2), 3.08-3.15 (m, 1H, CH), 4.68 (dd, J_1 = 9.2 Hz, J_2 = 3.7 Hz, 1H, CH), 7.24-7.30 (m, 1H, CH), 7.32-7.40 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 29.3, 50.4, 50.6, 72.3, 126.0, 127.5, 128.5, 143.1.

1-Phenyl-2-(phenylamino)ethanol (1h) [49]
Yellow oil, yield: 30.8 %. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 3.31 (dd, J_1 = 13.3 Hz, J_2 = 8.7 Hz, 1H, CH_2), 3.45 (dd, J_1 = 13.3 Hz, J_2 = 3.7 Hz, 1H, CH_2), 4.95 (dd, J_1 = 8.7 Hz, J_2 = 3.7 Hz, 1H, CH), 6.69 (d, J = 8.1 Hz, 2H, 2CH), 6.75 (t, J = 7.3 Hz, 1H, CH), 7.20 (t, J = 8.1 Hz, 2H, CH), 7.33 (t, J = 7.1 Hz, 1H, CH), 7.37-7.45 (m, 4H, 4CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 52.0, 72.7, 113.6, 118.2, 126.0, 128.2, 128.8, 129.5, 142.2, 148.0.

*4.3. General procedure for the synthesis of racemic oxazolidinones (**3a-3h**)*

α-Amino alcohol **1a-1h** (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. Then CH_2Cl_2 was subsequently added, and the aqueous layer was extracted three times (3 mL CH_2Cl_2 each). The combined organic layer was dried over $MgSO_4$ and removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 6:1).

*4.4. General procedure for kinetic resolution of oxazolidinones (**3a-3h**)*

α-Amino alcohol **1a-1h** (0.05 mmol), diphenyl carbonate (0.15 mmol) and dry TBME (0.6 mL) were added into a 1.5 mL sealed-cap vial containing PS-IM (50 mg), silica gel (20 mg) and 4Å molecular sieves (20 mg). PS-IM 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 certain 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 (3 mL CH_2Cl_2 each). The combined organic layer was dried over $MgSO_4$ and removed *in vacuo*. The crude products were purified using column chromatography (Hexane:EtOAc = 6:1).

(*S*)-3-Methyl-5-phenyloxazolidin-2-one ((*S*)-3a) [50]
Yield: 47%, enantiomeric excess (*ee*): 95%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:^{i}PrOH, 0.5 mL/min; t_R 38.0 min; t_R 48.6 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 2.93 (s, 3H, CH_3), 3.45 (t, J = 7.9 Hz, 1H, CH_2), 3.92 (t, J = 8.6 Hz, 1H, CH_2), 5.49 (t, J = 8.1 Hz, 1H, CH), 7.33-7.43 (m, 5H, 5CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 31.2， 54.6， 74.3， 121.9, 125.7, 128.9, 129.0, 138.9; $[\alpha]^{25}_D$ = +30 (c 1.0, $CHCl_3$, *ee*: 87%).

(*S*)-5-(4-Chlorophenyl)-3-methyloxazolidin-2-one ((*S*)-3b)
Yield: 45%, enantiomeric excess (*ee*): > 99%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:^{i}PrOH, 0.5 mL/min; t_R 41.3 min; t_R 48.3 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 2.93 (s, 3H, CH_3), 3.40 (t, J = 8.1 Hz, 1H, CH_2), 3.91 (t, J = 8.8 Hz, 1H, CH_2), 5.46 (t, J = 8.1 Hz, 1H, CH), 7.28 (d, J = 8.4 Hz, 2H, 2CH), 7.38 (d, J = 8.4 Hz, 2H, 2CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 31.3, 54.5, 73.6, 127.1, 129.3, 134.9, 137.4, 158.1; $[\alpha]^{25}_D$ = +34 (c 1.0, $CHCl_3$, *ee*: 92%); HRMS: found 212.04692, calc. for $C_{10}H_{11}C_{l1}N_1O_2$ $[M+H^+]$ 212.04728.

(*S*)-3-Ethyl-5-phenyloxazolidin-2-one ((*S*)-3c) [50]
Yield: 50%, enantiomeric excess (*ee*): 97%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:^{i}PrOH, 0.5 mL/min; t_R 31.0 min; t_R 38.1 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 1.18 (t, J = 7.2 Hz, 3H, CH_3), 3.29-3.46 (m, 3H, CH_2CH_2), 3.92 (t, J = 8.8 Hz, 1H, CH_2), 5.49 (t, J = 8.2 Hz, 1H, CH), 7.34-7.43 (m, 5H, 5CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 12.6, 38.9, 51.8, 74.3, 125.7, 128.9, 129.1, 139.0, 157.9.

(*S*)-3-Butyl-5-phenyloxazolidin-2-one ((*S*)-3d) [50]
Yield: 42%, enantiomeric excess (*ee*): 88%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:^{i}PrOH, 0.5 mL/min; t_R 25.0 min; t_R 29.8 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 0.94 (t, J = 7.5 Hz, 3H, CH_3), 1.31-1.40 (m, 2H, CH_2), 1.50-1.59 (m, 2H, CH_2), 3.23-3.38 (m, 2H, CH_2), 3.40-3.45 (m, 1H, CH_2), 3.91 (t, J = 8.8 Hz, 1H, CH_2), 5.48 (t, J = 8.1 Hz, 1H, CH), 7.33-7.43 (m, 5H, 5CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 13.8, 19.9, 29.5, 44.1, 52.3, 74.5, 125.6, 128.9, 129.0, 139.0, 158.0.

(*S*)-3-Cyclopropyl-5-phenyloxazolidin-2-one ((*S*)-3e) [50]
Yield: 50%, enantiomeric excess (*ee*): 92%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:^{i}PrOH, 0.5 mL/min; t_R 36.3 min; t_R 46.0 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 0.68-0.87 (m, 4H, $2CH_2$), 2.55-2.60 (m, 1H, CH), 3.44 (t, J = 8.5 Hz, 1H, CH_2), 3.89 (t, J = 8.7 Hz, 1H, CH_2), 5.43 (t, J = 8.1 Hz, 1H, CH), 7.31-7.43 (m, 5H, 5CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ5.7, 6.2, 26.0, 53.6, 74.6, 125.6, 128.9, 129.0, 138.7, 158.2.

(*S*)-3-Cyclopentyl-5-phenyloxazolidin-2-one ((*S*)-3f)
Yield: 48%, enantiomeric excess (*ee*): 28%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:^{i}PrOH, 0.5 mL/min; t_R 27.1 min; t_R 32.6 min. ^{1}H NMR (500 MHz, $CDCl_3$, 25 ^{o}C) δ 1.49-1.67 (m, 6H, $3CH_2$), 1.88(m, 2H, CH_2), 3.39 (t, 1H, CH_2), 3.88 (t, 1H, CH_2), 4.29(m, 1H, CH), 5.47 (t, 1H, CH), 7.26-7.41 (m, 5H, 5CH); ^{13}C NMR (125 MHz, $CDCl_3$, 25 ^{o}C) δ 24.0, 24.1, 28.8, 29.3, 48.7, 54.8, 74.6, 125.6, 128.9, 129.1, 139.1, 157.7; $[\alpha]^{25}_D$ = +3 (c 1.0, $CHCl_3$, *ee*: 26%); HRMS: found 232.1332; calc. for $C_{14}H_{17}NO_2$ $[M+H]^+$ 232.1338.

(*S*)-3-tert-Butyl-5-phenyloxazolidin-2-one ((*S*)-3g) [50]
Yield: 57%, enantiomeric excess (*ee*): 10%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:iPrOH, 0.5 mL/min; t_R 19.2 min; t_R 26.8 min. ^{1}H NMR (500 MHz, CDCl3, 25 °C) δ; 1.41 (s, 9H, 3CH3), 3.46 (t, J = 8.3

Hz, 1H, CH2), 3.96 (t, J = 8.6 Hz, 1H, CH2), 5.38 (t, J = 8.3 Hz, 1H, CH), 7.33-7.43 (m, 5H, 5CH); ^{13}C-NMR (125 MHz, CDCl3, 25 °C) δ 27.5, 51.3, 53.8, 73.7, 125.8, 128.8, 129.1, 139.1, 156.9.

(*S*)-3,5-Diphenyloxazolidin-2-one ((*S*)-3h) [50]
Yield: 46%, enantiomeric excess (*ee*): 90%, determined by HPLC analysis (Daicel Chiralpak OD-H column) 90:10 Hex:iPrOH, 0.5 mL/min; t_R 25.5 min; t_R 28.3 min. ^{1}H NMR (500 MHz, CDCl3, 25 °C) δ; 3.97 (t, *J* = 8.1 Hz, 1H, CH_2), 4.39 (t, *J* = 9.1 Hz, 1H, CH_2), 5.65 (t, *J* = 8.1 Hz, 1H, CH), 7.15 (t, *J* = 7.3 Hz, 1H, CH), 7.35-7.47 (m, 7H, 7CH), 7.56 (d, *J* = 7.7 Hz, 2H, 2CH); ^{13}C-NMR (125 MHz, CDCl3, 25 °C) δ 52.9, 74.2, 118.4, 124.3, 125.8, 129.2, 129.3, 138.2, 138.3, 154.8.

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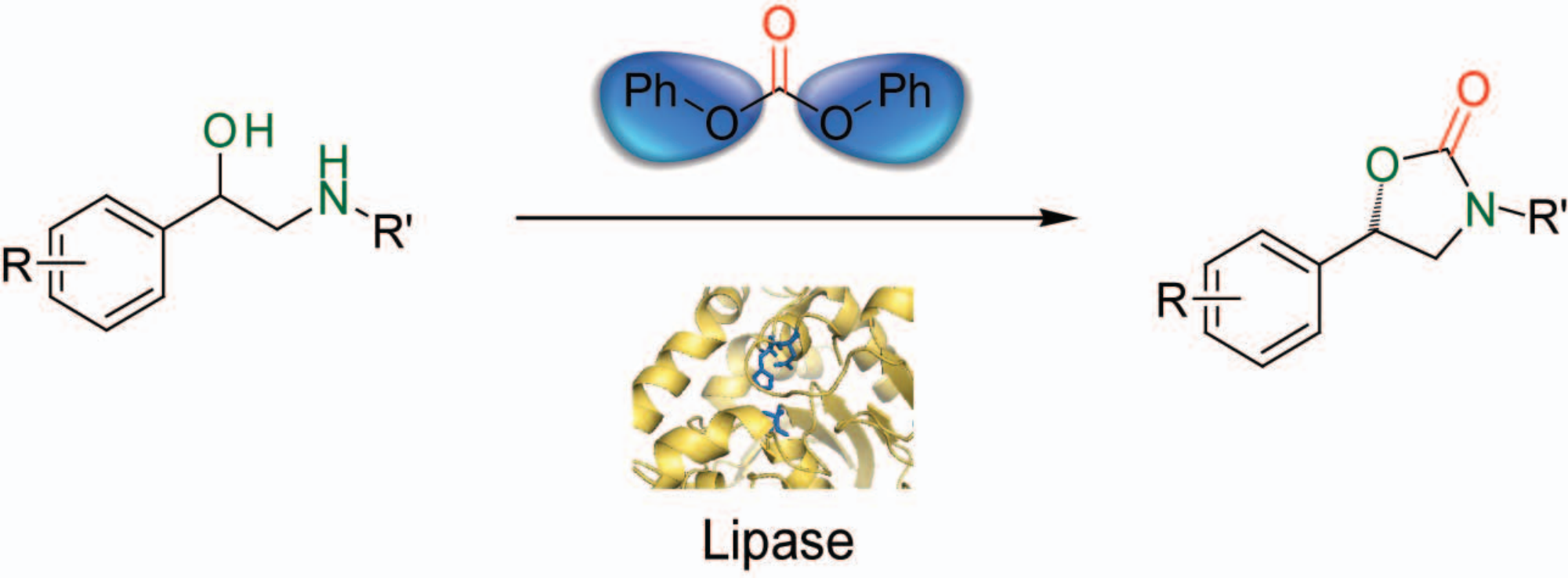
Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcatb.

[1] D. A. Evans, J. Bartroli, and T. L. Shih, J. Am. Chem. Soc., 103 (1981) 2127–2129.
[2] D. A. Evans, K. T. Chapman, and J. Bisaha, J. Am. Chem. Soc., 110 (1988) 1238–1256.
[3] A. B. Smith, Y. Qiu, D. R. Jones, and K. Kobayashi, J. Am. Chem. Soc., 117 (1995) 12011–12012.
[4] F. Moureau, J. Wouters, D. Vercauteren, S. Collin, G. Evrard, F. Durant, F. Ducrey, J. Koenig, and F. Jarreau, Eur. J. Med. Chem., 27 (1992) 939–948.
[5] G. R. Martin, A. D. Robertson, S. J. MacLennan, D. J. Prentice, V. J. Barrett, J. Buckingham, A. C. Honey, H. Giles, and S. Moncada, Br. J. Pharmacol., 121 (1997) 157–164.
[6] P. P. Toth and J. Urtis, Clin. Ther., 26 (2004) 1355–1367.
[7] M. J. Genin, D. K. Hutchinson, D. A. Allwine, J. B. Hester, D. E. Emmert, S. A. Garmon, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. Yagi, J. M. Friis, E. M. Shobe, and W. J. Adams, J. Med. Chem., 41 (1998) 5144–5147.
[8] W. A. Gregory, D. R. Brittelli, C. L. J. Wang, H. S. Kezar, R. K. Carlson, C. H. Park, P. F. Corless, S. J. Miller, and P. Rajagopalan, J. Med. Chem., 33 (1990) 2569–2578.
[9] W. A. Gregory, D. R. Brittelli, C. L. Wang, M. A. Wuonola, R. J. McRipley, D. C. Eustice, V. S. Eberly, P. T. Bartholomew, A. M. Slee, and M. Forbes, J. Med. Chem., 32 (1989) 1673–1681.
[10]J. A. Tucker, D. A. Allwine, K. C. Grega, M. R. Barbachyn, J. L. Klock, J. L. Adamski, S. J. Brickner, D. K. Hutchinson, C. W. Ford, G. E. Zurenko, R. A. Conradi, P. S. Burton, and R. M. Jensen, J. Med. Chem., 41 (1998) 3727–3735.
[11] S. J. Brickner, M. R. Barbachyn, D. K. Hutchinson, and P. R. Manninen, J. Med. Chem., 51 (2008) 1981–1990.
[12]S. J. Brickner, D. K. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, and G. E. Zurenko, J. Med. Chem., 39 (1996) 673–679.
[13]N. Selvakumar, D. Srinivas, M. K. Khera, M. S. Kumar, R. N. V. S. Mamidi, H. Sarnaik, C. Charavaryamath, B. S. Rao, M. A. Raheem, J. Das, J. Iqbal, and R. Rajagopalan, J. Med. Chem., 45 (2002) 3953–3962.
[14]S. Cacchi, G. Fabrizi, A. Goggiamani, and G. Zappia, Org. Lett., 3 (2001) 2539–2541.
[15]T. Hayashi, A. Yamamoto, and Y. Ito, Tetrahedron Lett., 29 (1988) 99–102.
[16]S. Jegham, A. Nedelec, P. Burnier, Y. Guminski, F. Puech, J. J. Koenig, and P. George, Tetrahedron Lett., 1998, 39, 4453–4454.
[17]C. Larksarp and H. Alper, J. Am. Chem. Soc., 119 (1997) 3709–3715.
[18]M. Moreno-Mañas, L. Morral, R. Pleixats, and S. Villarroya, Eur. J. Org. Chem., 1999 (1999) 181–186.
[19]K. Fesko and M. Gruber-Khadjawi, ChemCatChem, 5 (2013) 1248–1272.
[20]I. Oroz-Guinea and E. García-Junceda, Curr. Opin. Chem. Biol., 17 (2013) 236–49.
[21]M. T. Reetz, J. Am. Chem. Soc., 135 (2013) 12480–96.
[22]P. Tufvesson, J. Lima-Ramos, N. Al Haque, K. V. Gernaey, and J. M. Woodley, Org. Process Res. Dev., 17 (2013) 1233–1238.
[23]M. Ahmed, T. Kelly, and A. Ghanem, Tetrahedron, 68 (2012) 6781–6802.
[24]P. Hoyos, V. Pace, and A. R. Alcántara, Adv. Synth. Catal., 354 (2012) 2585–2611.
[25]Y. Kim, J. Park, and M.-J. Kim, ChemCatChem, 3 (2011) 271–277.
[26]P. Vongvilai, R. Larsson, and O. Ramström, Adv. Synth. Catal., 350 (2008) 448–452.
[27]W. Bonrath, R. Karge, and T. Netscher, J. Mol. Catal. B Enzym., 19-20 (2002) 67–72.
[28]V. Gotor-Fernández, R. Brieva, and V. Gotor, J. Mol. Catal. B Enzym., 40 (2006) 111–120.
[29]N. Weber, E. Klein, K. Vosmann, and K. Mukherjee, Biotechnol. Lett., 1998 (1998) 687–691.
[30]P. Vongvilai and O. Ramström, J. Am. Chem. Soc., 131 (2009) 14419–25.
[31]M. S. Humble and P. Berglund, Eur. J. Org. Chem., 2011 (2011) 3391–3401.

[32]O. Khersonsky and D. S. Tawfik, Annu. Rev. Biochem., 79 (2010) 471–505.
[33]M. Kapoor and M. N. Gupta, Process Biochem., 47 (2012) 555–569.
[34]M. Sakulsombat, Y. Zhang, and O. Ramström, Chem. Eur. J., 18 (2012) 6129–32.
[35]Y. Zhang, F. Schaufelberger, M. Sakulsombat, C. Liu, and O. Ramström, Tetrahedron, 70 (2014) 3826–3831.
[36]Y. Zhang, P. Vongvilai, M. Sakulsombat, A. Fischer, and O. Ramström, Adv. Synth. Catal., 356 (2014) 987–992.
[37]L. Hu, Y. Zhang, and O. Ramström, Org. Biomol. Chem., 12 (2014) 3572–3575.
[38]Y. Zhang and O. Ramström, Chem. Eur. J., 20 (2014) 3288–3291.
[39]L. Hu, F. Schaufelberger, Y. Zhang, and O. Ramström, Chem. Commun., 49 (2013) 10376–10378.
[40]M. Sakulsombat, P. Vongvilai, and O. Ramström, Chem. Eur. J., 20 (2014) 11322–11325.
[41]S. M. Chandrasekaran, S. Bhartiya, and P. P. Wangikar, Biotechnol. Bioeng., 94 (2006) 554–64.
[42]M. A. P. J. Hacking, F. Van Rantwijk, and R. A. Sheldon, J. Mol. Catal. - B Enzym., 9 (2000) 201–208.
[43]S. P. Tanis, B. R. Evans, J. A. Nieman, T. T. Parker, W. D. Taylor, S. E. Heasley, P. M. Herrinton, W. R. Perrault, R. A. Hohler, L. A. Dolak, M. R. Hester, and E. P. Seest, Tetrahedron: Asymmetry, 17 (2006) 2154–2182.
[44] G. Shang, D. Liu, S. E. Allen, Q. Yang and X. Zhang, Chem. Eur. J., 13 (2007) 7780–7784.
[45] M. Maheswara, K. S.V. K. Rao and J. Y. Do, Tetrahedron Lett., 49 (2008) 1795–1800.
[46] M. E. Schnute, D. J. Anderson, R. J. Brideau, F. L. Ciske, S. A. Collier, M. M. Cudahy, M. Eggen, M. J. Genin, T. A. Hopkins, T. M. Judge, E. J. Kim, M. L. Knechtel, S. K. Nair, J. A. Nieman, N. L. Oien, A. Scott, S. P. Tanis, V. A. Vaillancourt, M. W. Wathen and J. L. Wieber, Bioorg. Med. Chem. Lett., 17 (2007) 3349–3353.
[47] M. G. Siegel, A. J. Shuker, C. A. Droste, P. J. Hahn, C. D. Jesudason, J. H. McDonald, D. P. Matthews, C. J. Rito and A. J. Thorpe, Mol. Divers., 3 (1998) 113–116.
[48] M. Chini, P. Crotti and F. Macchia, J. Org. Chem., 56 (1991) 5939-5942.
[49] N. C. Mamillapalli and G. Sekar, Chem. Commun., 50 (2014) 7881-7884.
[50] Y. Du, Y. Wu, A. H. Liu and L. N. He, J. Org. Chem., 73 (2008) 4709–4712.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