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Studies on *N*-Activation for the Lipase-Catalyzed Enantioselective Preparation of β-Amino Esters from 4-Phenylazetidin-2-one

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The effect of *N*-substitution was examined for the enantioselective lipase-catalyzed ring-opening reaction of racemic 4-phenylazetidin-2-one with methanol in dry organic solvents. Marked differences in the reactivity of various *N*-protected 4-phenylazetidin-2-ones were observed. Preparative-scale reactions with *Candida antarctica* lipase B (Novozym 435 preparation) yielded *N*-acylated methyl (*R*)-3-amino-3-phenylpropanoates with enantiomeric excess (*ee*) values >99 % in up to a 49 % isolated yield, whereas *Thermomyces lanuginosus* lipase (Lipozyme TM IM) gave enantiomerically enriched methyl (*S*)-3-acetamido-3-phenylpropanoate. *Candida antarctica* lipase A catalyzed the cleavage of the *N*-chloroacetyl protective group, whereas all of the other examined lipases underwent the ring-opening reaction.

Introduction

β-Amino acids and their derivatives, including β-lactams (azetidin-2-ones), are a group of pharmaceutically important compounds and intermediates of synthetic products.[1] Various chemo- and enzyme-catalyzed synthetic routes for the preparation of these compounds in enantiomeric form have been the target of intensive studies. For instance, the transition-metal-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives and the Mannich reaction with silyl enolates along with organocatalytic approaches have been reported.[1a–1c,1e,1f] From a biocatalytic perspective, the lipase-catalyzed (EC 3.1.1.3) kinetic resolution of racemic β-lactams by an enantioselective ring-opening reaction represents a viable and extensively used approach for the preparation of β-amino acid, β-amino ester, and β-dipeptide enantiomers, leaving behind the less reactive β-lactam enantiomer.[1d,1g,2] The formation of poly(β-alanine) has even been described by the lipase-catalyzed ring-opening of azetidin-2-one.[2d] The kinetic resolution of *N*-hydroxymethylated β-lactams by lipase-catalyzed *O*-acylation followed by the removal of the *N*-methanol tail from the resolved product has allowed the simultaneous preparation of both β-lactam enantiomers.[1d,1g,3] The cascade reaction that is catalyzed by nitrile hydratase and amidase enzymes in *Rhodococcus erythropolis* AJ270 whole cells represents more recent advances in the biocatalytic preparation of β-amino acids and derivatives from the corresponding nitriles.[4]

Lipase enzymes, belonging to the serine hydrolase family, hydrolyze lipids in nature. The ability of lipases to cleave an amide bond is rare,[5] whereas serine proteases may undergo a reaction at both the amide and ester bonds. Previous studies have explained the difference between the two types of serine hydrolases by using the mechanistic details of amide hydrolysis, that is, lipases lack the transition-state stabilizing interaction between the active site and the amide nitrogen atom, which is pivotal in the amide hydrolysis by serine proteases.[6] Some lipases such as *Candida antarctica* lipase B (CAL-B, the Novozym 435 preparation) and *Burkholderia cepacia* lipase (lipase PS-D preparation) have been successfully used to cleave a β-lactam ring in a highly effective and enantioselective manner,[1d,1g,2] which can be explained by the fact that the amide bond in a β-lactam ring is less stable than a normal resonance stabilized peptide bond. However, the use of elevated temperatures or structural activation has been a prerequisite with certain β-lactam structures. Thus, in the first lipase-catalyzed β-lactam ring-opening case, *N*-benzoyl protection was used to increase the reactivity.[7] The CAL-B-catalyzed enantioselective ring-opening of many β-lactams, such as that of 4-phenylazetidin-2-one (*rac*-**1a**),[8b] with or without added water in organic solvents was previously reported to need the elevated temperature of 60 °C.[8] Fluorine-substitution allowed for the enantio- and diastereoselective ring-opening of 3-*trans*-mono- and 3,3-difluorinated *rac*-**1a** in lipase PS-D catalyzed transformations to lead to the formation of the corresponding β-amino esters and amides, β-dipeptides, and methyl α-D-glycopyranoside conjugates.[2]

In this current work, the effect of *N*-activation on the ring-opening reaction of *rac*-**1a** at room temperature (23 °C) has been studied (Scheme 1). *N*-Protecting groups

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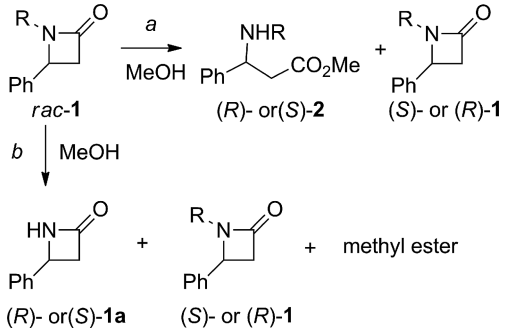
were selected on the basis of their ease of installation/removal and by varying the electron-withdrawing properties to affect the electrophilic nature of the lactam carbonyl group toward a nucleophile and decrease the stability of the ring C–N bond. Structurally the *N*-protected substrates can be grouped as *N*-acyl (i.e., *rac*-**1b**–*rac*-**1d**) and *N*-alkyl (i.e., *rac*-**1e**–*rac*-**1g**) types. Some of the *N*-protected substrates such as *N*-acetylated (*R*)-**2b** (a noncompetitive inhibitor of human α-chymotrypsin)[9] are biologically active. In practice, the lipase-catalyzed reaction of *rac*-**1a**–*rac*-**1g** has been examined by employing an alcoholysis reaction with methanol (and 1-butanol) in dry organic solvents. The main focus of the studies involved the opening of the lactam ring (Scheme 1, route a). However, the incorporation of groups such as *N*-acetyl, *N*-chloroacetyl, and *N*-*tert*-butoxycarbonyl (*N*-Boc) might introduce the possibility for an enzymatic *N*-deprotection route (Scheme 1, route b) in addition to a ring-opening route when the enzyme correctly binds the substrate. On the basis of previous work, it was found that the ring-opening reactions of *rac*-**1a**-type substrates are enantioselective to give the (*R*) isomer by using lipases such as CAL-B and lipase PS-D.[2,3,8b] If not otherwise stated, the absolute configurations in the present work are in accordance with this, as confirmed by comparing the optical rotations of products **2** to literature values and by chiral GC analysis.



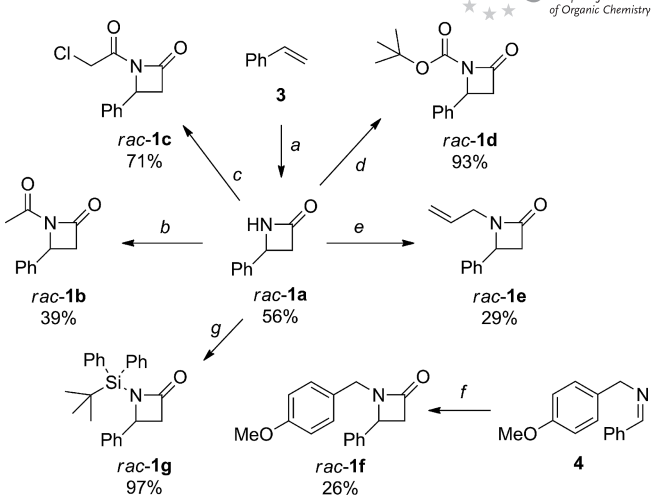
Scheme 1. Kinetic resolution of *rac*-**1**: (a) by lipase-catalyzed ring-opening of the β-lactam and (b) by lipase-catalyzed *N*-deprotection through alcoholysis.

Results and Discussion

Synthesis of Racemic *N*-Protected β-Lactams

Racemic 4-phenylazetidin-2-one (*rac*-**1a**) was obtained by the 1,2-dipolar cycloaddition of chlorosulfonyl isocyanate to styrene as described previously.[2c] The *N*-substituted analogues *rac*-**1b**–*rac*-**1d** were obtained by common reactions with the corresponding anhydride Ac_2O, $(ClCH_2CO)_2O$, and Boc_2O (Scheme 2).

The *N*-allyl derivative *rac*-**1e** was prepared by heating *rac*-**1a** at reflux with allyl bromide in the presence of K_2CO_3 in acetonitrile, whereas *tert*-butyldiphenylsilyl-protected *rac*-**1g** was synthesized by the reaction of *rac*-**1a** with *tert*-butyldiphenylsilyl chloride, triethylamine, and DMAP in acetonitrile as an adaptation of a published method.[10] The



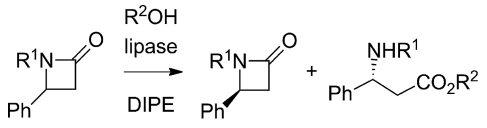
Scheme 2. Synthesis of *rac*-**1a**–*rac*-**1g**. Reagents and conditions: (a) (1) chlorosulfonyl isocyanate (CSI), dichloromethane (DCM), room temp., (2) K_2CO_3, Na_2SO_3, H_2O, room temp.; (b) Ac_2O, 4-(*N*,*N*-dimethylamino)pyridine (DMAP), DCM, room temp.; (c) $(ClCH_2CO)_2O$, DMAP, DCM, room temp.; (d) Boc_2O, DMAP, DCM, room temp.; (e) allyl bromide, K_2CO_3, acetonitrile, reflux; (f) $BrCH_2CO_2Et$, trimethylsilyl chloride (TMSCl), Zn, toluene, reflux; (g) *tert*-butyldiphenylsilyl chloride (TBDPSCl), triethylamine (TEA), DMAP, acetonitrile. See Supporting Information for further details.

N-4-methoxybenzyl-protected (*N*-PMB-protected) derivative *rac*-**1f** was obtained by a Gilman–Speeter variation of the Reformatsky reaction between *N*-(4-methoxybenzyl)-benzaldimine (**4**) and ethyl bromoacetate (2 equiv.) in the presence of zinc dust in refluxing toluene.[11] The syntheses of *rac*-**1a**–*rac*-**1g** are presented in more detail in the Supporting Information.

Enzymatic Reactions of *rac*-1a–*rac*-1g

As previously mentioned, the ring-opening reaction of *rac*-**1a** with CAL-B and water has been successful at elevated temperatures, with the (*R*) enantiomer of the β-lactam being the more reactive one.[8b] Each of the substrates *rac*-**1a**–*rac*-**1g** (50 mM) was first subjected to an alcoholysis reaction with methanol (2 equiv.) in the presence of CAL-B (30 mg mL^{-1}) in dry diisopropyl ether (DIPE) at 23 °C. The substrates can be grouped according to reactivity as those that underwent a reaction with at least one of the screened lipases (i.e., *rac*-**1a**–*rac*-**1c**) and those that did not undergo any reaction (i.e., *rac*-**1d**–*rac*-**1g**). The fact that the ring-opening reaction of *N*-Boc-protected *rac*-**1d** was not possible with methanol and CAL-B (or other lipases) is in accordance with our previous work with amines as nucleophiles.[2b] We propose that steric factors restricted the enzymatic ring-openings of *rac*-**1d**–*rac*-**1g**. As further support, CAL-B has been shown to be ineffective in previous ring-opening experiments of *N*-*para*-methoxyphenyl-substituted α-methylene-β-lactams with water, although the unprotected β-lactams were good substrates for the enzyme.[12] Compounds *rac*-**1d**–*rac*-**1f** were omitted from further studies. The results for the successful cases are given in Table 1.

Table 1. Alcoholysis of *rac*-**1a**–*rac*-**1c** (50 mM) with MeOH (2 equiv.) in the presence of a lipase preparation (30 mg mL^{-1}) in DIPE at 23 °C for 24 h (R^2 = Me).



rac-**1a–c** (*S*)-**1a–c** (*R*)-**2a–c**

Entry	Substrate	Lipase	% Conv.[a]	% $ee^{1a–1c}$	% $ee^{2a–2c}$	E[b]
1	*rac*-**1a**	CAL-B	26 (25)	35	>99	>200
2	*rac*-**1a**[c]	CAL-B	5 (18)	5	>99	>200
3	*rac*-**1b**	CAL-B	50 (54)	99	>99	>200
4	*rac*-**1c**	CAL-B	50 (57)	>99	>99	>200
5	*rac*-**1b**	TL IM	13 (13)	7	50[d]	3
6	*rac*-**1c**	TL IM	11 (18)	8	65	5
7	*rac*-**1c**	PS-C II	32 (29)	47	>99	>200
8	*rac*-**1c**	PS-D	21 (19)	27	>99	>200
9	*rac*-**1c**	RM IM	46 (46)	34	39	3
10	*rac*-**1c**	CAL-A	4 (15)	3	75[e]	7

[a] Conversion based on enantiomeric excess (*ee*) values (conversion as the disappearance of **1** against an internal standard in parenthesis). [b] E is the enantiomeric ratio value. [c] *n*BuOH (2 equiv.) was employed instead of MeOH. [d] The product is (*S*)-**2b**. [e] The product is (*S*)-**1a** through route b (Scheme 1).

In addition to the added alcohol, the supposed residual water in the seemingly dry lipase preparation in a dry organic solvent and, with *rac*-**1a**, the free amino group of the formed β-amino ester (and the acid if formed) can act as a competitive nucleophile for the ring-opening reaction of a β-lactam.[2b,2d,3a] In such a case, the conversion, which is the disappearance of a β-lactam, and the obtained enantiomeric excess values for the unreacted β-lactam should contain contributions from side reactions. Conversion values in Table 1 are based on ee^1 (unreacted substrate) and ee^2 (product) values through the equation conversion (c) = ee^1/(ee^1 + ee^2)[13] and on the disappearance of *rac*-**1** against an internal standard (in parenthesis), the latter method giving the real total conversion. Differences in the conversion values can be expected when hydrolysis and/or aminolysis are involved. Within the limits of experimental accuracy, the methods gave very similar values, which indicate the lack of or at least minimal possibility of side reactions in dry DIPE. Moreover, HPLC analysis did not give signs of side product formation. Significant differences were evident only when the ring-opening reaction of *rac*-**1a** was performed with 1-butanol (Table 1, Entry 2) and when CAL-A cleaved the *N*-chloroacetyl group (Scheme 1, route b) from *rac*-**1c** with methanol (Table 1, Entry 10).

The results of the employment of *rac*-**1a**–*rac*-**1c** as substrates in DIPE at 23 °C indicate that although *rac*-**1a** underwent the reaction slowly with CAL-B (30 mg mL^{-1}) and methanol (26% conversion after 24 h, 72 h was needed to reach 49% conversion), both *N*-acetylated *rac*-**1b** and *N*-chloroacetylated *rac*-**1c** reached 50% conversion in 24 h (Table 1, Entries 1, 3, and 4, respectively). The results under optimized conditions later revealed that the ring-opening reaction of *rac*-**1b** in *tert*-butyl methyl ether (TBME) reached the theoretical 50% conversion much faster than *rac*-**1c** (Figure 1), which demonstrates the importance of the structure of the substrate over its expected chemical reactivity in enzymatic reactions. When methanol was replaced with 1-butanol, the ring-opening reaction of *rac*-**1a** in DIPE proceeded very slowly (conversion 5% in 24 h, Table 1, Entry 2), which indicates the potential for side reactions rather than the alcoholysis. In spite of reactivity differences, the enantioselectivities of the reactions of *rac*-**1a**–*rac*-**1c** were always excellent (E > 200). Although *rac*-**1a** was only reactive with CAL-B, the use of Lipozyme TL IM (lipase from *Thermomyces lanuginosus* immobilized on granulated silica) as well as CAL-B led to the ring-opening of *rac*-**1b** (Table 1, Entries 3 and 5). Interestingly, however, Lipozyme TL IM favored the formation of (*S*)-**2b** with low enantioselectivity (Table 1, Entry 5) rather than the formation of the expected (*R*)-**2b** enantiomer. Finally, *N*-chloroacetyl-activated *rac*-**1c** was reactive with all of the investigated lipase preparations (Table 1, Entries 4 and 6–10), although the observed enantioselectivity of the ring-opening for the (*R*) isomer was negligible with enzymes other than CAL-B and the two *Burkholderia cepacia* lipase preparations (Table 1, Entries 7 and 8). Moreover, the reaction of *rac*-**1c** with *Candida antarctica* lipase A (CAL-A as the NZL-101-IMB preparation) was uncommon, as the enzymatic cleavage of the *N*-chloroacetyl group took place through route b (Scheme 1) rather than the ring-opening reaction (Table 1, Entry 10). This observation further confirms the previously discovered exceptional properties of CAL-A, which can be employed, for instance, as an *N*-acylation catalyst in the kinetic and dynamic kinetic resolution of sterically hindered heterocyclic proline as well as 2-piperidine- and 2-piperazine-substituted carboxylic acid esters.[5c,14] This interesting slow deprotection reaction was not studied further.

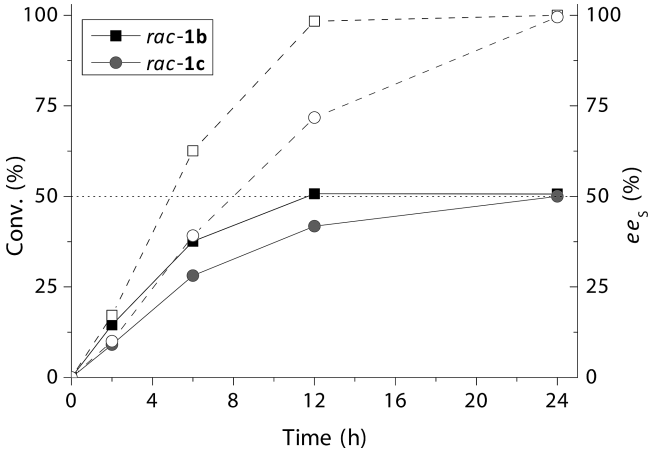
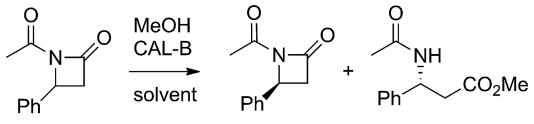


Figure 1. Alcoholysis of *rac*-**1b** (50 mM, squares) and *rac*-**1c** (50 mM, circles) with MeOH (2 equiv.) in the presence of CAL-B (10 mg mL^{-1}) in TBME at 23 °C. Conversion (solid line) and ee_S (S = unreacted substrate, dashed line), ee_P (P = formed product) always ≥99%.

The CAL-B catalyzed alcoholysis of *rac*-**1b** (50 mM) with methanol (2 equiv.) was used for further optimization studies. When the effects of the solvent were studied by carrying

out the reaction in TBME, toluene, and hexane in addition to DIPE with 30 mg mL^{-1} of the enzyme, excellent enantioselectivities and reactivities were evident in all four solvents (Table 2, Entries 1–4). These solvents are generally used in lipase-catalyzed transesterification reactions, and their applicability in many cases is substrate dependent. There are often other aspects that affect the selection of a solvent besides seeking one in which the reaction proceeds with appropriate reactivity and excellent enantioselectivity. For instance, TBME can be regarded as a safer option than DIPE because of its lower potential for peroxide formation. Substrate and product solubilities may also affect the selection of a solvent. For instance, in the present work, the low solubility of *rac*-**1b** in hexane is an obvious reason for the deviation between the conversion values after 24 h when determined on the basis of *ee* values (50%) and on the use of an internal standard (70%, Table 2, Entry 4).

Table 2. Effects of solvent and CAL-B content (5–50 mg mL^{-1}) on the alcoholysis of *rac*-**1b** (50 mM) with MeOH (2 equiv.) at 23 °C.



rac-**1b** (*S*)-**1b** (*R*)-**2b**

Entry	Solvent	CAL-B [mg mL^{-1}]	% Conv.[a]	% *ee*^{1b}	% *ee*^{2b}	*E*
1	DIPE	30	50 (54)	99	>99	>200
2	TBME	30	50 (53)	>99	99	>200
3	toluene	30	46 (46)	85	>99	>200
4	hexane[b]	30	50 (70)	>99	99	>200
5	TBME	5	47 (47)	90	>99	>200
6	TBME	10	50 (50)	>99	>99	>200
7	TBME[c]	10	50 (51)	>99	>99	>200
8	TBME[d]	10	50 (51)	>99	>99	>200
9	TBME	50	50 (56)	>99	99	>200

[a] Conversion based on *ee* values (conversion as the disappearance of **1** against an internal standard in parenthesis). [b] Poor initial solubility of *rac*-**1b**. [c] With MeOH (5 equiv.). [d] With MeOH (10 equiv.).

Finally, the optimization studies with *rac*-**1b** (50 mM) were continued by investigating the effect of CAL-B content (5–50 mg mL^{-1}) on the reactivity and enantioselectivity of the reaction in TBME (Table 2, Entries 2, 5, 6, and 9). The enzyme content did not affect enantioselectivity. The theoretical 50% conversion was reached in 24 h by using a CAL-B content of 10 mg mL^{-1} or higher (Table 2, Entries 2, 6, and 9). However, when the enzyme content was increased, the amount of the residual water in the reaction system also increased, which raised the possibility for a hydrolysis side reaction. In accordance with this, the total conversion values in parentheses gradually increased with a higher enzyme content. These values already differed by 6% when 50 mg mL^{-1} compared to 10 mg mL^{-1} of CAL-B were used (Table 2, Entry 9 vs. 6).

An increase in the methanol content from 2 equiv. with respect to *rac*-**1b** might help to favor the desired alcoholysis over the competing hydrolysis reaction. When the methanol content was increased to 5 and 10 equiv. in the reaction of *rac*-**1b** (50 mM) with 10 mg mL^{-1} of CAL-B, the result after 24 h was the same as that with only 2 equiv. (Table 2, Entries 6–8). Accordingly, we decided not to increase the amount of methanol from 2 equiv. When *rac*-**1b** (50, 100, and 200 mM) was subjected to the reaction with CAL-B (10 mg mL^{-1}) and methanol (2 equiv.), the reactivity decreased somewhat with the increasing substrate concentration. However, all of the β-lactam concentrations yielded a 50% conversion in 24 h with excellent enantioselectivity (Figure 2). Accordingly, this method provides an opportunity to widely vary both the β-lactam and methanol contents for synthetic purposes and still perform the reaction with a low enzyme content without the need for elevated temperatures.

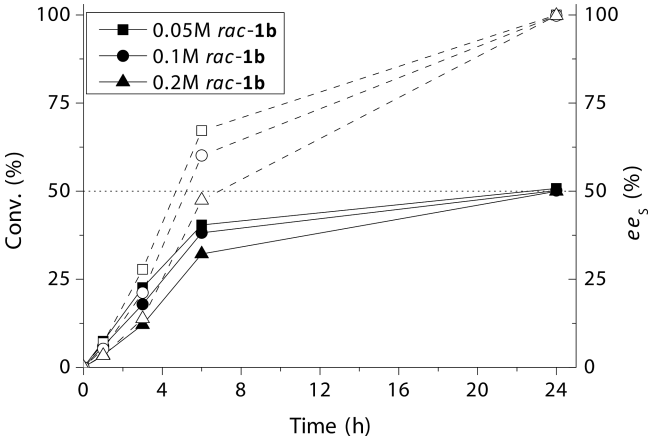


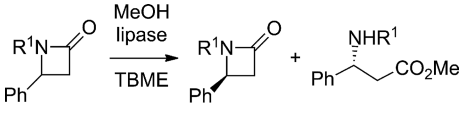
Figure 2. Effect of substrate concentration on the alcoholysis of *rac*-**1b** [50 mM (squares), 100 mM (spheres) and 200 mM (triangles)] with MeOH (2 equiv.) and CAL-B (10 mg mL^{-1}) in TBME at 23 °C [conversion (solid line) and ee_S (dashed line)].

Preparative Scale Synthesis and Product Characterization

Preparative scale reactions (reaction volume 10–20 mL) of *rac*-**1a**–*rac*-**1c** were conducted with methanol and CAL-B (10–30 mg mL^{-1}) in TBME under the conditions described in Table 3. When *rac*-**1a** (50 mM) was submitted to the reaction with methanol (2 equiv.) and CAL-B (30 mg mL^{-1}), the reaction proceeded slowly and reached 47% conversion after 4 d (Table 3, Entry 1). In accordance with an excellent enantioselectivity ($E > 200$), the ester product (*R*)-**2a** was isolated with an *ee* value of >99% and the unreacted (*S*)-**1a** with 94% *ee* at the given conversion. Although it is relatively common that preparative-scale reactions proceed slower than small-scale reactions because of factors such as different mixing conditions, the large, unexpected decrease in rate and long reaction time might increase the possibility of side reactions. The reaction between *rac*-**1a** and methanol was repeated in the presence of Boc_2O (to protect the primary amino group in situ without a catalyst)[2c,15] to rule out a possible enzymatic or chemical peptide bond formation by aminolysis.[2b,2d] In spite of the small reduction in the conversion in the presence of Boc_2O,

the reaction proceeded in a similar manner (Table 3, Entry 1 vs. 2). This together with the fact that no peptide product was isolated from the reaction mixture was taken as proof of the lack of a competing aminolysis. When *rac*-**1b** (50 mM) was treated with methanol (2 equiv.) in the presence of CAL-B (30 mg mL^{-1}), the reaction stopped at 50% conversion, and the corresponding methyl ester (*S*)-**2b** and unreacted (*R*)-**1b** were isolated in 41 and 40% yield, respectively, in enantiopure forms (Table 3, Entry 3). It was also confirmed that a substrate concentration of 200 mM and only 10 mg mL^{-1} of CAL-B content yielded an excellent outcome for a preparative-scale reaction (Table 3, Entry 4), consistent with the promise of the small-scale experiments. The production of (*R*)-**1b** and (*S*)-**2b** (Table 3, Entry 5) by using Lipozyme TL IM on a preparative scale also proceeded with a similar efficiency as the screening experiment of Table 1, Entry 5). The reaction of *rac*-**1c** (50 mM) reached only 46% conversion in 24 h (Table 3, Entry 6) to allow for the preparation of (*R*)-**2c**. We also confirmed the cleavage of the *N*-acyl group of *rac*-**1c** by using CAL-A (Scheme 1, route b) and separating and characterizing enantiomerically enriched (*S*)-**1a** (44% *ee*) and the unreacted **1c** (Table 3, Entry 7).

Table 3. Preparative-scale kinetic resolution of *rac*-**1a**–*rac*-**1c** (50 mM) with MeOH (2 equiv.) and CAL-B (30 mg mL^{-1}) in TBME at 23 °C.



rac-**1a–c** (*S*)-**1a–c** (*R*)-**2a–d**

Entry	Substrate	Lipase	Time [h]	% Conv.[a]	% Yield **1**[b]	% Yield **2**[b]
1	*rac*-**1a**	CAL-B	96	47	38 (94, *S*)	36 (>99, *R*)
2	*rac*-**1a**[c]	CAL-B	96	41	33 (70, *S*)	23 (>99, *R*)
3	*rac*-**1b**	CAL-B	24	50	40 (>99, *S*)	41 (>99, *R*)
4	*rac*-**1b**[d]	CAL-B	24	50	47 (>99, *S*)	49 (>99, *R*)
5	*rac*-**1b**	TL IM	48	57	40 (58, *R*)	34 (49, *S*)
6	*rac*-**1c**	CAL-B	24	46	26 (91, *S*)	25 (>99, *R*)
7	*rac*-**1c**	CAL-A	72	5	38 (5, *R*)	6 (44, *S*)[e]

[a] Calculated from the *ee* values. [b] Isolated yield as calculated from *rac*-**1** (% *ee* value and configuration of enantiomer are in parenthesis). [c] Kinetic resolution of *rac*-**1a** in the presence of Boc_2O (1 equiv.). Isolated product is (*R*)-**2d**. [d] *rac*-**1b** (200 mM), MeOH (500 mM), and CAL-B (10 mg mL^{-1}). [e] (*S*)-**1a** is the product instead of **2**.

Conclusions

The effect of six nitrogen protecting groups on the enantioselective ring-opening reaction of 4-phenylazetidin-2-one (*rac*-**1a**) was assessed with methanol and five lipases in immobilized form in organic solvents. We were able to show that the ring-opening reaction is sensitive to the structure of the nitrogen protecting group. Either steric effects or poor *N*-activation made the *N*-Boc-, *N*-allyl-, *N*-4-methoxybenzyl-, and *tert*-butyldiphenylsilyl-substituted substrates (i.e., *rac*-**1d**– *rac*-**1g**) unreactive towards the studied lipases, whereas the *N*-chloroacetyl-protected *rac*-**1c** underwent the ring-opening reaction with all of examined lipases except CAL-A, which resulted in an exocyclic fission of the C–N bond of the *N*-acyl moiety. Excellent enantioselectivity for the (*R*) isomer ($E > 200$) was evident by using *Candida antarctica* lipase B (CAL-B as the Novozym 435 preparation) and *Burkholderia cepacia* lipase (lipase PS-D and PS-C II preparations) as the catalysts. Preparative-scale ring-opening reactions of *rac*-**1a**–*rac*-**1c** by employing CAL-B in TBME allowed for (*R*)-**2a**–(*R*)-**2c** to be separated in enantiopure forms with conversions of 41–50%. With this method, wide variations of both β-lactam and methanol contents with a low enzyme concentration was possible without the need of elevated temperatures. We also showed that the enantiodiscrimination of Lipozyme TL IM catalyst was exceptional, preferentially giving ring-opened (*S*)-**2b** rather than the (*R*) enantiomer.

Experimental Section

General Methods: All reagents and materials were purchased from commercial sources and used as received, with the exception of the solvents, which were dried over molecular sieves (3 Å) prior to use. Powdered zinc was acid-washed prior to use.[16] Lipase preparations from Amano (*Burkholderia cepacia* lipase as Lipase PS-D and Lipase PS-C II) and Codexis [*Candida antarctica* lipase A (CAL-A) as NZL-101-IMB, *Candida antarctica* lipase B (CAL-B) as Novozym 435, *Rhizomucor miehei* lipase as Lipozyme RM IM, and *Thermomyces lanuginosus* lipase as Lipozyme TL IM] were used. The lipase-catalyzed reactions were monitored by chiral HPLC or GC analysis. HPLC analyses were performed with an HP 1090 HPLC/DAD that was equipped with a Daicel CHIRACEL-OD-H (4.6 mm × 250 mm × 5 μm) column. GC analyses were performed with a HP 6850 GC/FID that was equipped with a Chrompack CP-Chiralsil-DEX CB (25 m × 0.25 mm × 0.25 μm) capillary column. Retention times of studied compounds are presented in Table S1 (Supplementary Information). The enantiomeric ratio values E were determined by $E = \ln[(1 - ee_S)/(1 - ee_S/ee_P)]/\ln[(1 + ee_S)/(1 + ee_S/ee_P)]$, which is obtained by substituting the conversion (c) = $(ee_S)/(ee_S + ee_P)$ into the original equation of Chen and Sih (ee_S and ee_P refer to the enantiomeric excess values of the unreacted substrate and the formed product, respectively, at the point of conversion).[13] Conversion values were calculated from the *ee* values as well as from the disappearance of a β-lactam against an internal standard. Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel $^{60}F_{254}$ sheets, and the spots were visualized by UV (254 nm). Chromatographic separations were performed by column chromatography on Kieselgel 60 (0.063–0.200 μm). The ^{1}H and ^{13}C NMR spectroscopic data were recorded at 298 K in $CDCl_3$ against an internal standard (TMS) with a Bruker Avance 500 spectrometer. Mass spectra were recorded in the positive mode with a Bruker Daltonics micrOTOF-Q (ESI). Specific rotations were measured against the sodium D line (589 nm) with a Perkin–Elmer 341 Polarimeter, and the values are presented as 10^{-1} deg cm^{-2} g^{-1}. Melting points were measured with a Gallenkamp device.

Small-Scale Enzymatic Reactions with Lactams *rac*-1a–*rac*-1g: In a given small-scale experiment, *rac*-**1a**–*rac*-**1g** (50 mM) was dissolved in a solvent [1 mL, including the internal standard (5 mM dihexyl ether or methoxybenzene)], and then a lipase preparation (5–50 mg mL^{-1}) and alcohol (MeOH or 1-BuOH, 2–10 equiv.) were added. The reaction mixture was shaken (170 rpm) at room tem-

perature. Samples were taken at intervals from the reaction mixture, and these were filtered and analyzed by the developed GC and/or HPLC methods (retention times for substrates, products, and standards are presented in the Supplementary Information).

Preparative-Scale Enzymatic Reactions with Lactams *rac*-1a–*rac*-1c

Methyl (*R*)-3-Amino-3-phenylpropanoate [(*R*)-2a] and (*S*)-4-Phenylazetidin-2-one [(*S*)-1a]: Lactam *rac*-**1a** (154 mg, 1.05 mmol) was dissolved in TBME (20 mL), and then MeOH (84 μL, 2.1 mmol, 2 equiv.) and CAL-B (30 mg mL^{-1}, 600 mg) were added. The reaction mixture was shaken (170 rpm) at room temperature for 72 h before being filtered, and then the solvents were evaporated. Column chromatography (ethyl acetate/petroleum ether, 1:1) yielded (*S*)-**1a** (59 mg, 0.40 mmol, 38% yield, 94%*ee*) as an off-white solid and (*R*)-**2a** (67 mg, 0.37 mmol, 36% yield, >99%*ee*) as a thick oil. R_f = 0.37 (ethyl acetate/petroleum ether, 1:1 for **1a**); R_f = 0.05 (ethyl acetate/petroleum ether, 1:1 for **2a**). Data for (*S*)-**1a**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.87 (ddd, J = 1.0 Hz, J = 2.5 Hz, J = 14.9 Hz, 1 H, CH_aH$_b$), 3.44 (ddd, J = 2.5 Hz, J = 5.3 Hz, J = 14.9 Hz, 1 H, CH$_a$$H_b$), 4.72 (dd, J = 2.5 Hz, J = 5.3 Hz, 1 H, C*H*Ph), 6.40 (br., 1 H, N*H*), 7.32 (m, 1 H, Ar), 7.38 (m, 4 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 48.01 (*C*H$_2$), 50.39 (*C*HPh), 125.65 (Ar), 128.24 (Ar), 128.86 (Ar), 140.20 (Ar), 168.13 (*C*=O) ppm. HRMS: calcd. for C_9H_9NONa [M + Na]$^+$ 170.05764; found 170.05986. $[\alpha]_D^{22}$ = –119.2 (c = 0.5, EtOH); ref.[3b] $[\alpha]_D^{22}$ = –140.5 (c = 0.5, EtOH; 99%*ee*), m.p. 100–101 °C; ref.[17] m.p. 116–117 °C. Data for (*R*)-**2a**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.78 [br., 2 H, NH_2], 2.67 (d, J = 6.3 Hz, 2 H, CH_2), 3.69 (s, 3 H, CO_2CH_3), 4.42 (dd, J = 6.4 Hz, J = 7.3 Hz, 1 H, C*H*Ph), 7.26 (m, 1 H, Ar), 7.34 (m, 4 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 43.95 (*C*H$_2$), 51.69 (CO_2CH_3), 52.63 (*C*HPh), 126.17 (Ar), 127.46 (Ar), 128.68 (Ar), 141.61 (Ar), 172.51 (*C*=O) ppm. HRMS: calcd. for $C_{10}H_{13}NO_2Na$ [M + Na]$^+$ 202.08385; found 202.08423. $[\alpha]_D^{20}$ = +21.9 (c = 1.99, $CHCl_3$); ref.[18] $[\alpha]_D^{20}$ = +22.3 (c = 1.99, $CHCl_3$; >98%*ee*).

Methyl (*R*)-3-(*tert*-Butoxycarbonyl)amino-3-phenylpropanoate [(*R*)-2d] and (*S*)-4-Phenylazetidin-2-one [(*S*)-1a]: Lactam *rac*-**1a** (74 mg, 0.50 mmol) was dissolved in TBME (10 mL), and then Boc_2O (109 mg, 0.50 mmol, 1 equiv.), MeOH (43 μL, 1.06 mmol, 2 equiv.), and CAL-B (30 mg mL^{-1}, 300 mg) were added. The reaction mixture was shaken (170 rpm) at room temperature for 72 h before being filtered, and then the solvents were evaporated. Column chromatography (ethyl acetate/petroleum ether, 1:9–1:1) yielded (*S*)-**1a** (25 mg, 0.17 mmol. 33% yield, 70%*ee*) and (*R*)-**2d** (32 mg, 0.12 mmol, 23% yield, >99%*ee*). R_f = 0.37 (ethyl acetate/petroleum ether, 1:1 for **1a**); R_f = 0.90 (ethyl acetate/petroleum ether, 1:1 for **2e**). Data for (*S*)-**1a**: The ^{1}H NMR, ^{13}C NMR, and HRMS data were identical to that above for (*S*)-**1a**. $[\alpha]_D^{22}$ = –93.6 (c = 0.5, EtOH). Data for (*R*)-**2d**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 1.42 [s, 9 H, C(CH_3)$_3$], 2.85 (m, 2 H, CH_2), 3.62 (s, 3 H, CO_2CH_3), 5.11 (br., 1 H, C*H*Ph), 5.46 (br., 1 H, N*H*), 7.30 (m, 5 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 28.35 [C(*C*H$_3$)$_3$], 40.80 (*C*H$_2$), 51.19 (*C*HPh), 51.78 (CO_2CH_3), 79.68 [*C*(CH$_3$)$_3$], 126.12 (Ar), 127.53 (Ar), 128.67 (Ar), 141.17 (Ar), 155.05 (N*CO*t*Bu*), 171.42 (*C*=O) ppm. HRMS: calcd. for $C_{15}H_{21}NO_4Na$ [M + Na]$^+$ 302.13628; found 302.13604. $[\alpha]_D^{20}$ = +29.2 (c = 1.4, $CHCl_3$); ref.[19] $[\alpha]_D^{20}$ = +29.9 (c = 1.4, $CHCl_3$; >97%*ee*), m.p. 94–95 °C; ref.[19] m.p. 92–93.5 °C.

Methyl (*R*)-3-Acetamido-3-phenylpropanoate [(*R*)-2b] and (*S*)-*N*-Acetyl-4-phenylazetidin-2-one [(*S*)-1b]: Lactam *rac*-**1b** (100 mg, 0.52 mmol) was dissolved in DIPE (10 mL), and then MeOH (43 μL, 1.06 mmol, 2 equiv.) and CAL-B (30 mg mL^{-1}, 300 mg) were added. The reaction mixture was shaken (170 rpm) at room temperature for 24 h before being filtered, and then the solvents were evaporated. Column chromatography (ethyl acetate/hexane, 1:4; then pure acetone) yielded (*S*)-**1b** (40 mg, 0.21 mmol, 40% yield, >99%*ee*) and (*R*)-**2b** (47 mg, 0.21 mmol, 41% yield, >99%*ee*). R_f = 0.20 (ethyl acetate/hexane, 1:4 for **1b**); R_f = 0 (ethyl acetate/hexane, 1:4 for **2b**). Data for (*R*)-**1b**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.43 (s, 3 H, CH_3), 2.97 (dd, J = 3.5 Hz, J = 16.4 Hz, 1 H, CH_aH$_b$), 3.51 (dd, J = 6.5 Hz, J = 16.4 Hz, 1 H, CH$_a$$H_b$), 5.03 (dd, J = 3.4 Hz, J = 6.5 Hz, 1 H, C*H*Ph), 7.32 (m, 3 H, Ar), 7.38 (m, 2 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 24.02 (CO*C*H$_3$), 45.69 (*C*H$_2$), 52.52 (*C*HPh), 125.81 (Ar), 128.50 (Ar), 128.96 (Ar), 137.74 (Ar), 165.35 (*C*OCH$_3$), 167.51 (*C*=O) ppm. HRMS: calcd. for $C_{11}H_{11}NO_2Na$ [M + Na]$^+$ 212.06820; found 212.06721. $[\alpha]_D^{25}$ = –213.0 (c = 1.0, MeOH). Data for (*R*)-**2b**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.03 [s, 3 H, NH(CO)CH_3], 2.84 (dd, J = 5.9 Hz, J = 15.8 Hz, 1 H, CH_aH$_b$), 2.94 (dd, J = 5.8 Hz, J = 15.8 Hz, 1 H, CH$_a$$H_b$), 3.62 (s, 3 H, CO_2CH_3), 5.43 (ddd, J = 5.8 Hz, J = 5.9 Hz, J = 8.4 Hz, 1 H, C*H*NHAc), 6.58 (d, J = 7.6 Hz, 1 H, CHN*H*Ac), 7.27 (m, 3 H, Ar), 7.34 (m, 2 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 23.44 (NHCO*C*H$_3$), 39.69 (*C*H$_2$), 49.48 (*C*HPh), 51.84 (CO_2CH_3), 126.26 (Ar), 127.67 (Ar), 128.74 (Ar), 140.48 (Ar), 169.29 [NH(*C*O)CH$_3$], 171.77 (CO_2CH_3) ppm. HRMS: calcd. for $C_{12}H_{15}NO_3Na$ [M + Na]$^+$ 244.09441; found 244.09410. $[\alpha]_D^{25}$ = +62.1 (c = 1.0, MeOH); ref.[8] $[\alpha]_D^{22}$ = +60.1 (c = 0.90, $CHCl_3$), m.p. 99–100 °C; ref.[8] m.p. 94–95 °C.

Methyl (*S*)-3-Acetamido-3-phenylpropanoate [(*S*)-2b] and (*R*)-*N*-Acetyl-4-phenylazetidin-2-one [(*R*)-1b]: As above, *rac*-**1b** (95 mg, 0.50 mmol) was treated with MeOH (43 μL, 1.0 mmol, 2 equiv.) in the presence of Lipozyme TL IM (30 mg mL^{-1}, 300 mg) in TBME (10 mL) at room temp. for 48 h. Column chromatography (ethyl acetate/hexane, 1:4; then pure acetone) afforded (*R*)-**1b** (38 mg, 0.20 mmol, 40% yield, 59%*ee*) and (*S*)-**2b** (39 mg, 0.17 mmol, 35% yield, 49%*ee*). R_f = 0.23 (ethyl acetate/hexane, 1:4 for **1b**). R_f = 0 (ethyl acetate/hexane, 1:4 for **2b**). The ^{1}H and ^{13}C NMR spectra of (*R*)-**1b** and (*S*)-**2b** together with the HRMS data were identical to *rac*-**1b** and (*R*)-**2b**, respectively. Data for (*R*)-**1b**: $[\alpha]_D^{25}$ = +121.5 (c = 1.0, MeOH). Data for (*S*)-**2b**: $[\alpha]_D^{25}$ = –36.8 (c = 1.0, MeOH); ref.[20] $[\alpha]_D^{25}$ = –79.9 (c = 1.00, MeOH; >99%*ee*), m.p. 91–92 °C; ref.[20] m.p. 99–101 °C.

Methyl (*R*)-3-(Chloroacetamido)-3-phenylpropanoate [(*R*)-2c] and (*S*)-*N*-Chloroacetyl-4-phenylazetidin-2-one [(*S*)-1c]: As above, *rac*-**1c** (112 mg, 0.5 mmol) was treated with MeOH (43 μL, 1.06 mmol, 2 equiv.) in the presence of CAL-B (10 mg mL^{-1}, 100 mg) in TBME (10 mL) at room temp. for 24 h. Column chromatography (ethyl acetate/hexane, 1:4; then pure acetone) afforded (*S*)-**1c** (29 mg, 0.13 mmol, 26% yield, 92%*ee*) and (*R*)-**2c** (32 mg, 0.12 mmol, 25% yield, >99%*ee*). R_f = 0.19 (ethyl acetate/hexane, 1:4 for **1c**). R_f = 0 (ethyl acetate/hexane, 1:4 for **2c**). Data for (*S*)-**1c**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 3.07 (dd, J = 3.6 Hz, J = 16.6 Hz, 1 H, CH_aH$_b$), 3.57 (dd, J = 6.6 Hz, J = 16.6 Hz, 1 H, CH$_a$$H_b$), 4.47 (s, 2 H, C$H_2$Cl), 5.11 (dd, J = 3.6 Hz, J = 6.6 Hz, 1 H, C*H*Ph), 7.35 (m, 3 H, Ar), 7.39 (m, 2 H, Ar) ppm. ^{13}C NMR (126 MHz, $CDCl_3$, 298 K): δ = 42.99 (*C*H$_2$Cl), 45.80 (*C*H$_2$), 52.89 (*C*HPh), 125.92 (Ar), 128.84 (Ar), 129.07 (Ar), 136.78 (Ar), 163.41 (NH*C*OCH$_2$Cl), 164.79 (*C*=O) ppm. HRMS: calcd. for $C_{11}H_{10}NO_2ClNa$ [M + Na]$^+$ 246.02923; found 246.02951. $[\alpha]_D^{20}$ = –145.9 (c = 1.0, $CHCl_3$). Data for (*R*)-**2c**: ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 2.88 (dd, J = 5.8 Hz, J = 15.9 Hz, 1 H, CH_aH$_b$), 2.97 (dd, J = 5.7 Hz, J = 15.9 Hz, 1 H, CH$_a$$H_b$), 3.64 (s, 3 H, C$H_3$), 4.08 (dd, J = 15.3 Hz, J = 19.5 Hz, 2 H, CH_2Cl), 5.43 (dt, J = 5.8 Hz, J = 8.5 Hz, 1 H, C*H*Ph), 7.29 (m, 3 H, Ar), 7.35 (m, 2 H, Ar), 7.76 (d, J = 7.6 Hz, 1 H, N*H*COCH$_2$Cl) ppm. ^{13}C

NMR (126 MHz, $CDCl_3$, 298 K): δ = 39.63 (CH_2), 42.65 (CH_2Cl), 49.84 (*C*HPh), 51.98 (CO_2CH_3), 126.17 (Ar), 127.92 (Ar), 128.86 (Ar), 139.73 (Ar), 165.33 ($COCH_2Cl$), 171.40 (CO_2CH_3) ppm. HRMS: calcd. for $C_{12}H_{14}NO_3ClNa$ $[M + Na]^+$ 278.05544; found 278.05495. $[\alpha]_D^{20}$ = +15.2 (*c* = 1.0, $CHCl_3$).

(*S*)-4-Phenylazetidin-2-one [(*S*)-1a] and (*R*)-*N*-Chloroacetyl-4-phenylazetidin-2-one [(*R*)-1c]: As above, *rac*-**1c** (169 mg, 0.76 mmol) was treated with MeOH (62 μL, 1.52 mmol, 2 equiv.) in the presence of CAL-A (30 mg mL^{-1}, 450 mg) in TBME (15 mL) at room temp. for 72 h. Column chromatography (ethyl acetate/petroleum ether, 1:4–3:1) afforded (*S*)-**1a** (6 mg, 0.04 mmol, 6% yield, 44% *ee*) and (*R*)-**1c** (64 mg, 0.28 mmol, 38% yield, 5% *ee*). The ^{1}H NMR, ^{13}C NMR, and HRMS data of (*S*)-**1a** and (*R*)-**1c** were identical to the results above. Data for (*S*)-**1a**: $[\alpha]_D^{22}$ = –15.6 (*c* = 0.5, EtOH); m.p. 96–97 °C. Data for (*R*)-**1c**: $[\alpha]_D^{20}$ = +9.3 (*c* = 1.0, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): Retention times for GC and HPLC analysis, synthesis protocol for *rac*-**1a**–*rac*-**1g**, ^{1}H and ^{13}C NMR spectra for *rac*-**1a**–*rac*-**1g**, (*S*)-**1a**–(*S*)-**1c**, (*R*)-**1b**, and (*R*)-**2a**–(*R*)-**2d**.

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