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Enzymatic Dynamic Kinetic Resolution of (±)-*cis*-*N*-(Alkoxycarbonyl)cyclopentane-1,2-diamines based on Spontaneous Racemization

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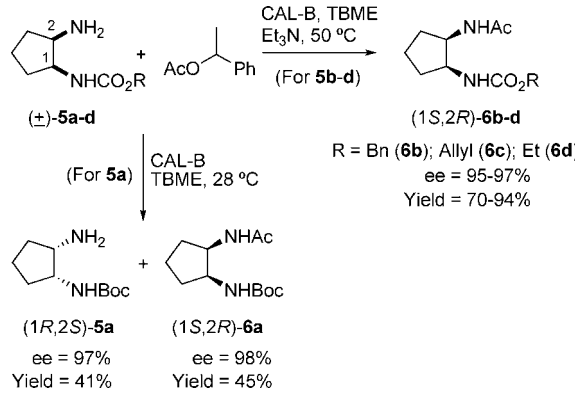
ABSTRACT



Lipase B from *Candida antarctica* is an excellent catalyst for the enantioselective acetylation of different (±)-*cis*-*N*-(alkoxycarbonyl)cyclopentane-1,2-diamines. Depending on the alkoxycarbonyl group, a simple kinetic resolution (Boc-derivative) or an interesting dynamic kinetic resolution (DKR with Cbz-, Alloc, and ethoxycarbonyl derivatives) has been developed. Racemization for the DKR occurred due to the *N*,*N*′ intramolecular migration of the alkoxycarbonyl group.

Currently, the increasing demand for both enantiomerically pure compounds and environmentally friendly procedures is being largely satisfied by the use of biocatalysts.[1] In this context, lipase-catalyzed kinetic resolution (KR) of racemic mixtures continues to be one of the easiest and most efficient methods to produce optically active alcohols, amines, and their derivatives.[2] However, in those cases in which only one enantiomer is required, dynamic kinetic resolution (DKR) is the best choice as it allows the desired enantiomer to be obtained with 100% theoretical yield, in contrast with the maximum 50% yield of KR. For successful DKR, efficient racemization of the substrate is required while its kinetic resolution is proceeding.

Although some DKRs of amines have been developed in the past decade,[3] they still remain much less explored than those of secondary alcohols. In most cases, they have been accomplished by the coupling of a highly enantioselective

(1) (a) Andrews, I.; Cui, J.; DaSilva, J.; Dudin, L.; Dunn, P.; Hayler, J.; Hinkley, B.; Hughes, D.; Kaptein, B.; Lorenz, K.; Mathew, S.; Rammeloo, T.; Wang, L.; Wells, A.; White, T.; Zhang, F. *Org. Process Res. Dev.* **2010**, *14*, 19–29. (b) Hudlicky, T.; Reed, J. W. *Chem. Soc. Rev.* **2009**, *38*, 3117–3132. For some book reviews, see: (c) *Modern Biocatalysis. Stereoselective and Environmentally Friendly Reactions*; Fessner, W.-D., Anthonsen, T., Eds.; Wiley-VCH: Weinheim, 2009. (d) *Asymmetric Organic Synthesis with Enzymes*; Gotor, V., Alfonso, I., García-Urdiales, E., Eds.; Wiley-VCH: Weinheim, 2008.

(2) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis. Regio- and Stereoselective Biotransformations*, 2nd ed.; Wiley-VCH: Weinheim, 2006.

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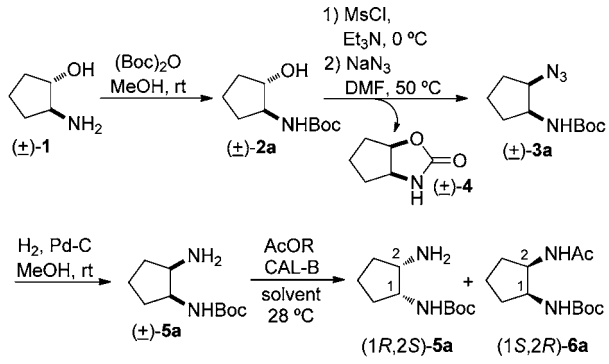
lipase-catalyzed acylation with an in situ organometallic complex (based on iridium or ruthenium)[3] or palladium-mediated[4] racemization of the starting amine. The equilibrium between both enantiomers is thus established by the metal-catalyzed reversible formation of an intermediate imine. Likewise, in a few cases, racemization of the amine is promoted by triethylamine and acetaldehyde (released in situ from the vinyl ester used as acyl donor),[5] by an alkylsulfanyl radical,[6] or even spontaneously.[7]

Here, we report the first DKR of a vicinal diamine, (±)-*cis*-*N*-(alkoxycarbonyl)cyclopentane-1,2-diamine, using lipase B from *Candida antarctica* (CAL-B) as catalyst. The interest in the chemoenzymatic method developed here lies in the great utility of optically active vicinal diamines in asymmetric synthesis and as precursors of pharmaceuticals.[8] Thus, despite the scarcity of approaches to optically active *cis*-cyclopentane-1,2-diamine derivatives, these compounds have promising applications as precursors of peptide nucleic acids (PNAs).[9]

Synthesis of racemic (±)-*cis*-*N*-Boc-cyclopentane-1,2-diamine [(±)-**5a**] was carried out from the commercial (±)-*trans*-2-aminocyclopentanol (**1**) following the sequence shown in Scheme 1. When mesylation of Boc-derivative (±)-**2a** was performed at 0 °C, the corresponding mesylate was obtained with a very high yield (94%). Subsequent reaction of the mesylate with sodium azide under the conditions described by Kumar et al.[9] (at 70 °C) yielded azide (±)-**3a** along with a significant amount of oxazolidinone (±)-**4**[10] (the ^{1}H NMR analysis of the crude material showed **3**:**4** in a 73:27 ratio). Fortunately, the amount of **4** was reduced to 18% when the reaction was conducted at 50 °C.

Scheme 1. Synthesis and Enzymatic Resolution of (±)-**5a**



entry	AcOR	time (days)	(1*R*,2*S*)-**5a** ee (%)[a] (yield, %)[b]	(1*S*,2*R*)-**6a** ee (%)[a] (yield, %)[b]	c,[c] (%)	*E*[c]
1	AcOEt[d]	0.5	42 (51)	94 (30)	31	48
2	AcOCH(Ph)CH$_3$[e]	3.5	40 (62)	98 (27)	29	146
3	AcOCH(Ph)CH$_3$[e,f]	6	97 (41)	98 (45)	50	>200

[a] Determined by chiral HPLC analysis. [b] Isolated yields. [c] Degree of conversion (c) and enantiomeric ratio (*E*) were determined from ee (ref. 12). [d] Ethyl acetate was also the solvent. [e] Solvent: TBME; the molar ratio of ester:amine was 3:1. [f] 4 Å molecular sieves were used.

Kinetic resolution of (±)-**5a** was performed by an aminolysis reaction catalyzed by CAL-B,[11] first using ethyl acetate as acyl donor and solvent (Scheme 1, entry 1). Under these conditions, the enzyme catalyzed the acetylation of the amino group of **5a**, though with moderate enantioselectivity (E = 48).[12] In an attempt to improve this result, racemic 1-phenylethyl acetate and *tert*-butyl methyl ether (TBME)[13] were employed as acyl donor and solvent, respectively. As expected, acetamide **6a** was obtained with higher enantiomeric excess and the *E* value significantly increased (entry 2). In this reaction, (*R*)-1-phenylethanol stemming from the aminolysis of the racemic ester was also produced.[14] If aminolysis were the only process catalyzed by the enzyme, identical amounts of **6a** and 1-phenylethanol should be expected. However, analysis of the ^{1}H NMR spectrum of the crude material showed a much lower percentage of acetamide than alcohol. This difference is a consequence of the competing hydrolysis of the acyl donor, also catalyzed by the enzyme.[14] Thus, acetic acid is also released to the reaction medium, which could critically affect the enantioselectivity. Effectively, by carrying out the reaction in the presence of 4 Å molecular sieves, the competitive hydrolysis of the ester drastically diminished, the enantioselectivity value increased, and both substrate **5a** and product **6a** were obtained with very high enantiomeric excesses (ee) and yields (entry 3).

(3) For some recent reviews, see: (a) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999–1015. (b) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563–1601. (c) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647–658. (d) Martín-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232. For some specific examples, see: (e) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247–1250. (f) Paetzold, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621. (g) Thalén, L. K.; Zhao, D.; Sortais, J.-B.; Paetzold, J.; Hoben, C.; Bäckvall, J.-E. *Chem.—Eur. J.* **2009**, *15*, 3403–3410.

(4) For a recent example using Pd-nanoparticles, see: Choi, Y.-K.; Kim, Y.; Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2009**, *74*, 9543–9545.

(5) DKR of secondary heterocyclic amines as proline and pipecolic acid methyl esters: Liljeblad, A.; Kiviniemi, A.; Kanerva, L. T. *Tetrahedron* **2004**, *60*, 671–677.

(6) In this case, a protease was used as catalyst for the acylation: El Blidi, L.; Nechab, M.; Vanthuyne, N.; Gastaldi, S.; Bertrand, M. P.; Gil, G. *J. Org. Chem.* **2009**, *74*, 2901–2903.

(7) DKR of 8-amino-5,6,7,8-tetrahydroquinoline: Crawford, J. B.; Skerlj, R. T.; Bridger, G. J. *J. Org. Chem.* **2007**, *72*, 669–671.

(8) For some reviews, see: (a) González-Sabín, J.; Rebolledo, F.; Gotor, V. *Chem. Soc. Rev.* **2009**, *38*, 1916–1925. (b) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140–205. (c) Douthwhite, R. E. *Coord. Chem. Rev.* **2007**, *251*, 702–717. (d) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Res.* **2006**, *67*, 101–114. (e) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627. (f) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161–3195.

(9) Govindaraju, T.; Kumar, V. A.; Ganesh, K. N. *J. Org. Chem.* **2004**, *69*, 5725–5734.

(10) This compound is the result of an intramolecular S_N2 displacement of the mesylate group by the carbonyl oxygen of the Boc group: Benedetti, F.; Norbedo, S. *Tetrahedron Lett.* **2000**, *41*, 10071–10074.

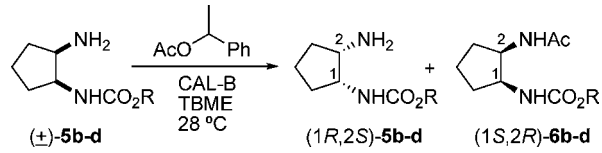
(11) Thus far, CAL-B (Novozyme SP-435) has proven to be the most effective catalyst for the aminolysis reaction in organic solvent. For a review, see: Gotor-Fernández, V.; Busto, E.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 797–812.

(12) (a) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299. (b) Program "Selectivity" by Faber, K.; Hoenig, H. http://www.cis.TUGraz.at/orgc/.

(13) González-Sabín, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2004**, *15*, 481–488.

(14) CAL-B showed very high enantioselectivity toward the *R* enantiomer of the ester (ee >97% for the produced (*R*)-1-phenylethanol). Thus, although a racemic ester was used, CAL-B only catalyzed the reaction with the *R* enantiomer.

Table 1. CAL-B-Catalyzed Resolution of (±)-**5b**−**d**



(±)-**5b-d** (1*R*,2*S*)-**5b-d** (1*S*,2*R*)-**6b-d**

			remaining substrate (1*R*,2*S*)-**5b**−**d**			product (1*S*,2*R*)-**6b**−**d**		
substrate[a]	R	time (days)	amine	ee$_s$[b] (%)	yield[c] (%)	amide	ee$_p$[b] (%)	yield[c] (%)
(±)-**5b**	benzyl	6	**5b**	60	38	**6b**	97	51
(±)-**5c**	allyl	5	**5c**	47	36	**6c**	99	50
(±)-**5d**	ethyl	5	**5d**	46	49	**6d**	99	34

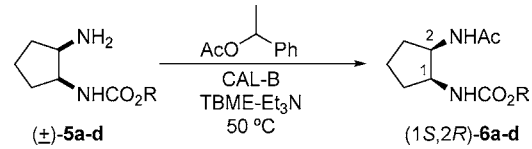
[a] For conditions, see Scheme 1, entry 3. [b] Determined by chiral HPLC analysis. [c] Isolated yields.

In order to study the scope of this chemoenzymatic method, we planned the synthesis of other racemic monocarbamates (±)-**5b**−**d** similar to that reported in Scheme 1 (see the Supporting Information). CAL-B-catalyzed resolutions of (±)-**5b**−**d** were performed under the best conditions found for (±)-**5a**; i.e., using racemic 1-phenylethyl acetate as acyl donor and TBME as solvent (Table 1). In all cases, the produced acetamides **6b**−**d** were obtained with very high ee, which correspond to reactions with high enantioselectivity values. However, some considerations should be highlighted in regard to the results obtained in the reactions of **5b** and **5c**. First, as the isolated yields for products **6b** and **6c** were 51% and 50%, respectively, the minimum degree of conversion obtained in these reactions should also be 51% and 50%. Should both processes were considered simple KRs, the expected ee for both substrates would be ≥99%. However, experimental ee for the remaining **5b** and **5c** were much lower (see Table 1). This means that optically active **5b** and **5c** are undergoing racemization, thus leading to dynamic kinetic resolutions.

The racemization of these substrates is most likely produced by an intramolecular migration of the alkoxycarbonyl group between both vicinal nitrogens.[15] As the chiral carbons supporting both nitrogen substituents have opposing absolute configurations, racemization takes place but the asymmetric centers remain unaltered throughout the entire process. To study this spontaneous racemization, enzymatic acetylation of (±)-**5b** (see Table 1) was periodically analyzed by chiral HPLC and ^{1}H NMR (see the Supporting Information for details). The most significant results are as follows: (1) the ee of acetamide **6b** remained very high (96−98%) all along the process; (2) the aminolysis of the ester ceased after 8 days (c = 56% for **6b**), but its hydrolysis continued proceeding extensively; (3) the ee for the remaining **5b** decreased until 19% after 10 days of reaction. These results indicate that slow racemization is operating, probably catalyzed by the produced acetic acid. Moreover, when the amount of acid is very high, most of amine precipitates as its acetate and the aminolysis ceases. A further addition of triethylamine allowed the amine **5b** to dissolve, the aminolysis reaction being thus restarted, and the ee of **5b** continued to decrease until it reached 8%.

Taking these results into account, we attempted the enzymatic dynamic kinetic resolution of **5b** using other solvents (1,4-dioxane and THF), Et_3N as cosolvent (a mixture 10:1 of TBME/Et_3N), and a higher reaction temperature (50 °C). Under all of the tested conditions, racemization of **5b** took place, and **6b** was obtained with very high ee (96−99%), the higher conversion value (>95%) being obtained when the reaction was conducted at 50 °C using TBME and Et_3N as cosolvent. Under these conditions, a very efficient dynamic kinetic resolution of (±)-**5b** was achieved, and **6b** was isolated with very high ee and yield (see Table 2).

Table 2. CAL-B-Catalyzed DKR of (±)-**5a**−**d**[a]



(±)-**5a-d** (1*S*,2*R*)-**6a-d**

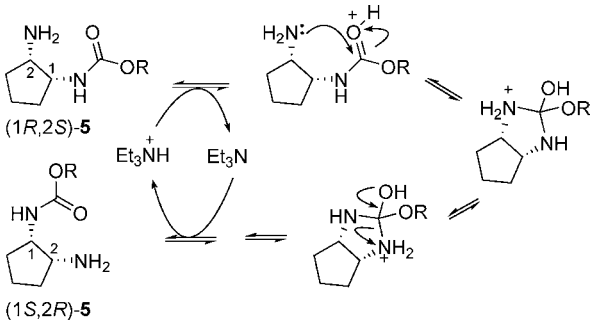
		product (1*S*,2*R*)-**6a**−**d**		
substrate	R	amide	ee (%)	yield[b] (%)
(±)-**5a**	*tert*-butyl	**6a**	96	54[c]
(±)-**5b**	benzyl	**6b**	96	94
(±)-**5c**	allyl	**6c**	97	85
(±)-**5d**	ethyl	**6d**	95	72

[a] TBME/Et_3N 10:1 was used. All reactions were carried out at 50 °C and 200 rpm for 9 days. [b] Isolated yields. [c] The remaining substrate (1*R*,2*S*)-**5a** (ee = 56%) was isolated with 24% yield.

When these DKR conditions were applied to the other monocarbamates (Table 2), good results were obtained with the *N*-allyloxycarbonyl (Alloc) and *N*-ethoxycarbonyl derivatives **5c** and **5d**, the corresponding optically active acetamides being isolated with high yields. However, in the reaction with

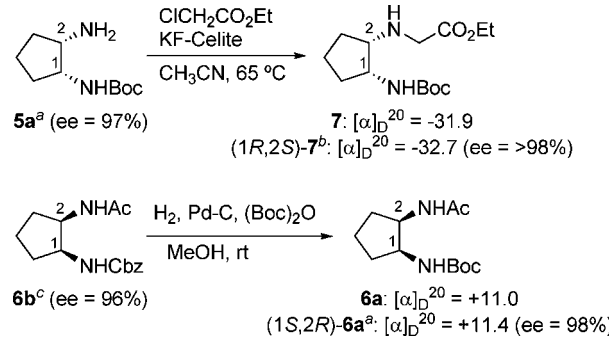
(15) For some examples in which an acyl migration in 1,2- and 1,3-diol monoacetates has been taken advantage of in dynamic asymmetric transformations, see: (a) Edin, M.; Martín-Matute, B.; Bäckvall, J.-E. *Tetrahedron: Asymmetry* **2006**, *17*, 708–715. (b) Edin, M.; Steinreiber, J.; Bäckvall, J.-E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5761–5766.

Scheme 2. Acid−base Catalyzed Migration of the Alkoxycarbonyl Group in Amino Carbamates **5**[a]



[a] AcOH + NEt_3 → $AcO^{-+}NHEt_3$.

Scheme 3. Assignment of the Configuration of the Enzymatically Prepared **5a** and **6b**



[a] Compounds isolated in the enzymatic KR of (±)-**5a**. [b] See ref 9. [c] Acetamide isolated in the enzymatic DKR of (±)-**5b**.

the *N*-Boc derivative **5a**, besides acetamide **6a**, the remaining substrate **5a** was also isolated (ee = 56%, yield = 24%). This means that migration of the *tert*-butoxycarbonyl is not favored in this case, probably due to the steric hindrance of the *tert*-butyl group. This is also the reason why the kinetic resolution of **5a** was particularly efficient (see Scheme 1).

Considering all of these observations, in Scheme 2 we propose a plausible mechanism to explain the migration of the alkoxycarbonyl group and thus the racemization of **5**. Both the acetic acid released in the reaction medium and the triethylamine could catalyze the migration.[16] This fact was also supported by additional proofs of racemization of **5b** performed in the absence of the lipase. Thus, when an enantioenriched sample of **5b** (ee = 60%) was dissolved in TBME and stored at 28 °C and 200 rpm for 7 days, **5b** was recovered with almost the same ee (58%). However, if a mixture of acetic acid (1 equiv) and triethylamine (0.5 equiv) was added, the ee of **5b** decreased to 27% after 7 days.[17]

Absolute configuration of the enzymatically prepared compounds was established as follows: amino carbamate **5a** [isolated as the remaining substrate in the KR of (±)-**5a**, see Scheme 1] was transformed into **7** (Scheme 3), and the sign of its specific rotation was compared with the reported value for (1*R*,2*S*)-**7**.[9] Thus, configuration (1*R*,2*S*) was assigned to the remaining **5a**, and hence, the produced acetamide was (1*S*,2*R*)-**6a**. In addition, configuration (1*S*,2*R*) for acetamide **6b**, obtained in the CAL-B catalyzed DKR of (±)-**5b**, was assigned by chemical correlation with (1*S*,2*R*)-**6a**. Catalytic hydrogenation of **6b** in the presence of *tert*-butyl pyrocarbonate yielded the *N*-Boc acetamide **6a** with the same sign of optical rotation as that prepared by KR of (±)-**5a** (Scheme 3). In both cases, CAL-B preferentially catalyzed the acetylation of the R enantiomer of the amine, thus following Kazlauskas' rule.[18] Taking into account the structural resemblance between the amino carbamates reported here, we have tentatively assigned the (1*S*,2*R*) configuration to the other produced acetamides **6c** and **6d**.

In conclusion, we have developed a highly efficient chemoenzymatic method to prepare optically active *cis*-cyclopentane-1,2-diamine derivatives. The key step in this strategy is the kinetic resolution or the dynamic kinetic resolution of the corresponding racemic monocarbamate. Further research work into the scope and synthetic utility of the new DKR is in progress.

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Supporting Information Available: Experimental procedures, characterization data, copies of the NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For an example of acid-promoted migration of an ethoxycarbonyl group to an aziridine nitrogen, see: Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995–3998.

(17) The addition of only acetic acid (1 equiv) caused the precipitation of the acetate of **5b**, and its ee remained unaltered.

(18) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.