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Regioselective *Pseudomonas cepacia* lipase mediated amidations of benzyl esters with diamines

Maciej Adamczyk * and Jonathan Grote

Department of Chemistry (D9NM), Abbott Diagnostics Division, Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064-3500, USA

Abstract: Novel *Pseudomonas cepacia* catalyzed amidations of benzyl esters demonstrate excellent regioselectivity with both symmetrical and unsymmetrical diamines, producing high yields of easily isolated amide products under mild conditions. © 1997 Elsevier Science Ltd

In recent years, chemoenzymatic reactions have assumed a critical importance in the regioselective modification of polyfunctional molecules.[1] In cases where increased temperatures or classical synthetic techniques fail to produce one product in good yield,[2] lipases succeed in mediating selective transformations under extremely mild (near neutral pH) conditions in a wide variety of organic solvents.[3] By combining a broad substrate recognition with a high efficiency and strong preference for a specific type of reaction, lipases provide an inexpensive source of regioselectivity useful for asymmetric transformation.

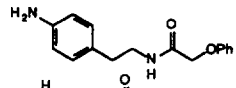
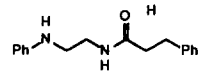
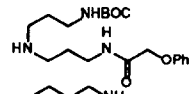
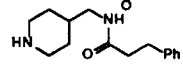
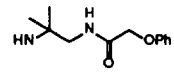
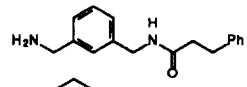
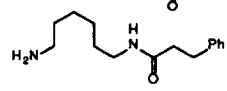
While well known as catalysts for ester hydrolysis and transesterification reactions,[4] the utility of lipases as amidation catalysts is less explored. Several *Candida antarctica* lipase catalyzed amidation reactions have been described by Gotor[5] and Conde.[6] Our recent report of *Pseudomonas cepacia* lipase catalyzed amidations of benzyl esters[7] demonstrates that benzyl esters can be regioselectively amidated. Here, we report that *Pseudomonas cepacia* lipase is capable of discriminating between different types of amines, and smoothly catalyzes regioselective amidations in molecules containing multiple amine functionalities.

Molecules containing two amine functionalities were subjected to reactions with different benzyl esters in the presence of *Pseudomonas cepacia* lipase. As shown in Table 1, both non-symmetrical (entries 1–5) and symmetrical diamines (entries 6–7) demonstrated excellent regioselectivity. Differentiation is possible between a primary and a secondary cyclic or non-cyclic amine (entries 3–4), tertiary amine (entry 5), or aniline (entries 1–2), or between two primary amines (entries 6–7). The BOC protective group (entry 5) is well tolerated. At 168 h and ambient temperature, a majority of the diamines produced excellent yields of amides.

Typically, 15 mg lipase was added to a solution of 66 μM of the benzyl ester and 132 μM (2 equivs, 4 amine equivs) of the diamine in 1.0 mL isopropyl ether, and the mixtured stirred in a 2 mL screw-cap vial at ambient temperature. Reactions were monitored by HPLC (8×100 mm C18 μBondapak column, 55% CH_3CN: 45% 0.05% CF_3COOH/H_2O, 2 mL/min, UV detection at 220 nm), and conversions to amides calculated from the integrations of the starting material and product. We ran the appropriate controls (the above reaction mixture containing no lipase),[8] which showed that lipase was essential for the amidation process. The products were identified by coelution of their HPLC peaks with the peaks from authentic samples prepared by independent synthesis, and also were independently confirmed by mass spectral analysis (electrospray mass spectrometry). The reaction described in entry 3 was scaled up, producing a good yield (89%) of isolated, purified product.[9]

* Corresponding author.

Table 1. Reactions of benzyl esters with amines catalyzed by Amano PS-30 lipase

Entry	Diamine	Ester	Product	% Conversion to Amide 24 hr	72 hr	168 hr
1	2-(4-aminophenyl) ethylamine	benzyl phenoxy-acetate		14	25	65
2	N-phenylethyl-enediamine	benzyl phenyl propionate		44	71	91
3	BOCaminopropyl propanediamine	benzyl phenoxy-acetate		76	91	>99
4	2-aminomethyl-piperidine	benzyl phenyl propionate		36	73	93
5	1,2-diamino-2-methylpropane	benzyl phenoxy-acetate		67	97	>99
6	m-phenylene-diamine	benzyl phenyl-propionate		6	12	23
7	hexanediamine	benzyl phenyl-propionate		5	18	32

In conclusion, we have demonstrated that Amano lipase PS-30, isolated from *Pseudomonas cepacia*, is an important new catalyst for the regioselective amidation of molecules containing more than one amine functionality. These amidations constitute an attractive synthetic methodology which we believe will find utility in the synthesis of natural products and their derivatives.

References

1. Waldmann, H.; Sebastian, D. *Chem. Rev.* **1994**, *94*, 911–937, and references therein.
2. Adamczyk, M.; Gebler, J. C.; Mattingly, P. G. *Tetrahedron Lett.* **1994**, *35*, 1019–1022.
3. Klibanov, A. M. *CHEMTECH* **1986**, *16*, 354–359.
4. Whitesides, G. M.; Wong, C.-H. *Angew. Chem., Int. Ed. Eng.* **1985**, *24*, 617–718; Fang, J.-M.; Wong, C.-H. *Synlett* **1994**, 393–402.
5. For recent references: Garcia, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1994**, *23*, 6935–6940; Astorga, C.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Perkin Trans. 1* **1994**, 829–832.
6. Chamorro, C.; Gonzalez-Muniz, R.; Conde, S. *Tetrahedron: Asym.* **1995**, *6*, 2343–2352.
7. Adamczyk, M.; Grote, J. *Tetrahedron Lett.* **1996**, *37*, 7913–7916.
8. Adamczyk, M.; Gebler, J. C.; Grote, J. *J. Org. Chem.* **1995**, *60*, 3557–3560.
9. A solution of 472 mg of the benzyl ester and 900 mg N-(BOCaminopropyl)diaminopropane in 6.0 mL isopropyl ether was stirred with 472 mg PS-30 lipase for 72 h. HPLC showed <5% starting ester. The reaction mixture was filtered to remove the lipase, and the lipase was washed with chloroform. The filtrate and washings were concentrated, and purified by column chromatography (10% MeOH/2% Et_3N/$CHCl_3$), producing 634 mg (89%) of the monoamide shown in Table 1 as a colorless oil: HPLC >98% (retention time 3.64 min, 40% CH_3CN/60% 0.05% CF_3COOH); ^1H NMR ($CDCl_3$) δ 7.45 (br s, 1H), 7.30 (m, 2H), 7.00 (m, 1H), 6.92 (m, 2H), 5.04 (br s, 1H), 4.48 (s, 2H), 3.44 (dt, 2H, J=6.2,5.9 Hz), 3.16 (m, 2H), 3.03 (br s, 1H), 2.67 (m, 4H), 1.74 (quin, 2H, J=6.4 Hz), 1.65 (quin, 2H, J=6.6 Hz), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.6, 157.5, 129.8, 122.1, 114.7, 67.4, 47.3, 47.0, 38.5, 37.6, 29.2, 28.5, 28.3; ESMS $(M+H)^+$ at 366.

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