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Highly enantioselective enzymatic resolution of aromatic β-amino acid amides with Pd-catalyzed racemization

Eunjeong Choi, Yunwoong Kim, Yangsoo Ahn, Jaiwook Park *, Mahn-Joo Kim *

Department of Chemistry, Pohang University of Science and Technology, San-31, Hyojadong, Pohang 790-784, Republic of Korea

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ABSTRACT

The kinetic resolution of an aromatic β-amino acid amide **3a–d** via N-acylation was explored with two lipases, *Candida antarctica* lipase A (CALA) and *Pseudomonas stutzeri* lipase (PSL). The PSL-catalyzed resolution proceeded with excellent enantioselectivity (E = >400) to give both acylated products and unreacted substrates in enantiopure forms. Three additional aromatic β-amino acid amides **3b–d** were also resolved by PSL with a high level of enantioselectivity (E = >200). The PSL-catalyzed resolution of **3a** was coupled with a Pd-catalyzed racemization to obtain enantiopure N-acylated product (*R*)-**4a** (>99% ee) in high yield (90%).

1. Introduction

β-Amino acids and their simple derivatives are an interesting class of chiral molecules due to their unique pharmacological effects and their utility as building units for biologically active peptidomimetics and natural products.[1–4] For example, taxol, a powerful anticancer agent, has β-phenylisoserine as its side chain and β-lactam antibiotics have a β-alanine unit as its four-membered ring structure. A number of chemical methods are available for the enantioselective synthesis of β-amino acids and their derivatives, including asymmetric additions of amines to α,β-unsaturated esters,[5a] asymmetric aldol-type reactions of imines,[5b] synthesis via enantiomerically pure dihydropyrimidines,[5c] and the ring opening of β-lactams.[5d] Enzymatic resolutions also provide useful routes to non-racemic β-amino acids.[6] In most of them, the substrates resolved were β-amino acid esters and *N*-acyl-β-amino acid esters. Their resolution was achieved via ester hydrolysis, transesterification, N-acylation, or deacylation.[7] To the best of our knowledge, few studies have been carried out on the resolution of β-amino acid amides. As part of our continuing efforts toward the development of procedures for the chemoenzymatic dynamic kinetic resolution (DKR) of amines[8] and amino acids,[9] we have explored the enzymatic resolution of β-amino acid amides. Herein we report that aromatic β-amino acid amides were efficiently resolved by *Pseudomonas stutzeri* lipase (PSL; trade name, lipase TL) to give both unreacted substrates and N-acylated products in highly-enantioenriched forms.[10]

2. Results and discussion

Four different aromatic β-amino acid amides **3a–d** were prepared from the corresponding acids **1a–d** via two steps: (i) the esterification of **1a–d** with methanol in the presence of thionyl chloride; and (ii) the reaction of the resulting amino esters **2a–d** with ammonium hydroxide (Scheme 1). The two-step synthesis proceeded smoothly with satisfactory yields.

The resolution of β-amino acid amides was explored first with **3a** using *Candida antarctica* lipase A (CALA), which had been previously reported to show a good enantioselectivity (E = 75) in the N-acylation of a β-amino acid ester.[7b] In a typical procedure, the CALA-mediated resolution of **3a** was carried out with a solution containing **3a** (0.3 mmol), vacuum-dried CALA (300 mg), and trifluoroethyl butanoate (2 equiv) in dry THF at room temperature. This reaction proceeded rather slowly and gave a modest resolution (Scheme 2; Table 1, entry 1).

We next examined PSL as an alternative enzyme for the resolution of **3a**. In a typical procedure, the PSL-mediated resolution of **3a** was performed with a solution containing **3a** (2 mmol), vacuum-dried PSL (400 mg), and trifluoroethyl butanoate (2 equiv) in dry THF at room temperature. The PSL-catalyzed resolution provided a perfect resolution at a synthetically useful rate (entry 2). Both the remaining substrate and acylated product were obtained in enantiopure forms (>99% ee), thus indicating that PSL is highly enantioselective (E = >400) relative to CALA. A similar level of high enantioselectivity (E = >200) was also observed in the resolutions of **3b–d** (entries 3–5). These results suggest that PSL is a perfect enzyme for the efficient resolution of aromatic β-amino acid amides.[11]

It was found that the signs of the specific rotations for the PSL-resolved products were opposite to those for the CALA-resolved

* Corresponding authors. Tel.: +82 54 279 2112; fax: +82 54 279 0654 (M.-J.K.).
E-mail address: mjkim@postech.ac.kr (M.-J. Kim).

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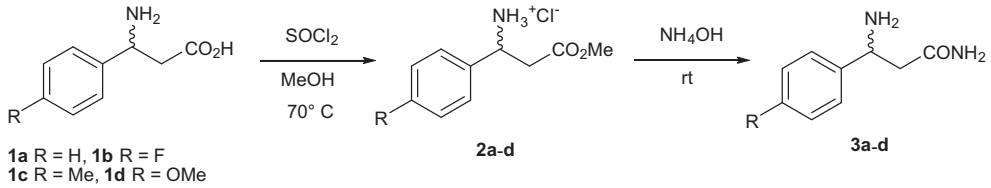
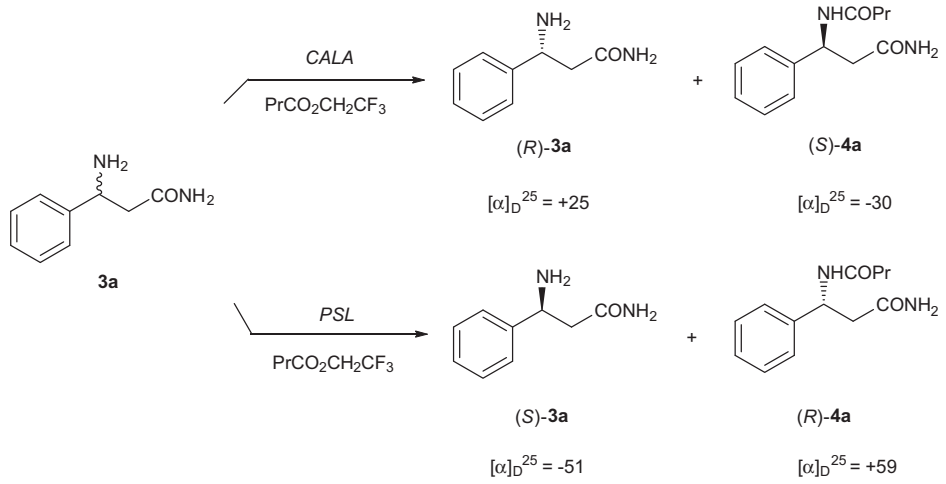


Scheme 1. Synthesis of β-amino acid amides.



Scheme 2. Lipase-catalyzed N-acylation of a β-amino acid amide.

products (Scheme 2), thus indicating that the stereopreference of PSL was opposite to that of CALA. The enantioselectivity of PSL in the resolution of **3a** should be (*R*) because CALA has been known to be (*S*)-selective in the resolution of the corresponding β-amino acid ester.[7b] The (*R*)-selectivity of PSL is in agreement with the empirical rule proposed by Kazlauskas et al. for predicting the enantioselectivity of a lipase (Fig. 1).[12,13] The enantiocomplementary relationship between PSL and CALA was also previously observed in the resolution of 1,2-diphenylethanamine and 1,2-diphenylethanol.[14,15]

The perfect enantioselectivity of PSL in the kinetic resolution of **3a** encouraged us to explore a high-yielding synthesis of enantiopure **3a** via a DKR.[16] PSL as the resolution catalyst was combined with Pd/AlO(OH),[8c] a Pd nanocatalyst entrapped in an AlO(OH) matrix, as the racemization catalyst to perform the DKR of **3a**. Since the optimum temperature for the Pd-catalyzed racemization of **3a** was 70 °C, the first DKR reaction was carried out at the same temperature but gave poor results because PSL lost its activity quickly at the elevated temperature.[17] The DKR reactions at lower temperatures (40–60 °C) were also unsuccessful due to the low thermal stability of PSL and the slow Pd-catalyzed racemization. We next carried out the PSL-catalyzed resolution and the Pd-catalyzed racemization alternatively at two different temperatures in one pot. The enzymatic resolution was first performed at room temperature for 12 h and then the Pd-catalyzed racemization at 70 °C for 12 h (Scheme 3). The sequential resolution–racemization process was repeated once with the addition of a portion of fresh enzyme. Finally, another portion of fresh enzyme was added to achieve only the enzymatic resolution at room temperature for 12 h. Overall, the whole process took 60 h with a total of 800 mg of enzyme/mmol of substrate and 5 mol % of Pd nanocatalyst to give enantiopure (*R*)-**4a** (>99% ee) with 90% isolated yield. Recently, Bäckvall et al. reported the (*S*)-selective DKR of an ester analogue of **3a** by the combination of CALA and a Ru-based racemization catalyst.[18] This and our process thus constitute as a pair of enantiocomplementary procedures for the synthesis of optically active β-amino acids and their simple derivatives.[19]

Table 1
Lipase-catalyzed N-acylation of β-amino acid amides

Entry	Substrate	Lipase	Time (h)	ee_s	ee_p	*c*	*E*
1	**3a**	CALA[a]	37	62	76	45	14
2	**3a**	PSL[b]	12	>99	>99[c]	50	>400
3	**3b**	PSL[b]	12	>99	96[c]	51	>200
4	**3c**	PSL[b]	4	96	99[c]	49	>200
5	**3d**	PSL[b]	7	88	>99[c]	47	>200

[a] 1 g enzyme/mmol of substrate.
[b] 0.2 g enzyme/mmol of substrate.
[c] The absolute configuration of the product is (*R*) according to the stereospecificity of PSL described in Figure 1.

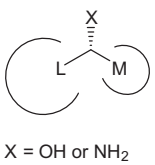
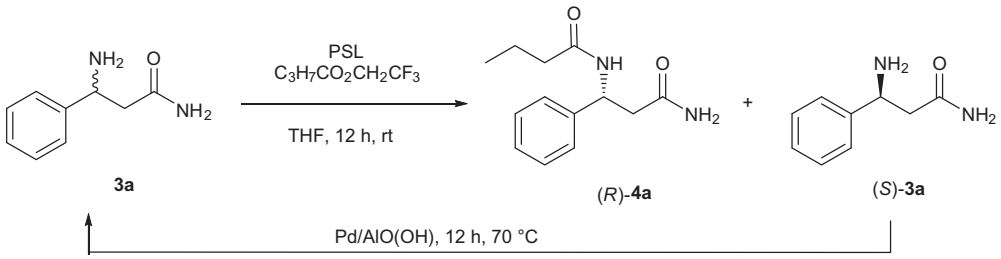


Figure 1. The enantiomer shown reacts more rapidly than the other in the lipase-catalyzed acylation if a secondary alcohol or a primary amine as its isostere has a medium-sized (M) and a relatively larger substituent (L) at the stereogenic center.



Scheme 3. PSL-catalyzed resolution of β-phenylalanine amide coupled with Pd-catalyzed racemization.

3. Conclusion

We have demonstrated that aromatic β-amino acid amides are accepted by PSL with high enantioselectivity, thus allowing for their efficient kinetic resolution. The PSL-catalyzed resolution can be coupled with a Pd-catalyzed racemization to convert racemic β-amino acid amides completely into single enantiomeric products. This process thus provides a useful alternative for the synthesis of enantioenriched β-amino acids and their derivatives.

4. Experimental

4.1. Synthesis of aromatic β-amino acid amides 3a–d

The procedure for the synthesis of **3a** is described as a representative one. Thionyl chloride (1.45 mL, 20 mmol) was dropwise added to a mixture of 3-amino-3-phenylpropanoic acid (1.65 g, 10 mmol) and dry methanol (15 mL) in a 2-neck round bottom flask connected with a condenser. After being refluxed overnight at 70 °C, the mixture was cooled to ambient temperature, and methanol was removed by evaporation. The salt precipitate was washed with ethyl acetate and then dissolved in aqueous ammonium hydroxide (20 mL). The resulting mixture was stirred at room temperature overnight and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to obtain **3a** as a white solid (1.195 g, 7.28 mmol, 73%): mp 99–101 °C (lit.[20] mp 110.1 °C); the data of ^{1}H and ^{13}C NMR were in good agreement with the literature data.[20] Compound **3b**: mp 118–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.8 (2H, br s, NH_2), 2.51–2.53 (2H, m, CH_2CH), 4.36–4.40 (1H, m, $CHNH_2$), 5.7 (1H, br s, $CONH_2$), 6.7 (1H, br s, $CONH_2$), 7.00–7.07 (2H, m, C_6H_4), 7.27–7.34 (2H, m, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 45.1, 52.2, 115.6(d), 127.5(d), 140.7(d), 160.4, 163.7, 173.5. **3c**: mp 123–126 °C; the data of ^{1}H and ^{13}C NMR were in good agreement with the literature data.[20] **3d**: mp 102–105 °C; the data of ^{1}H and ^{13}C NMR were in good agreement with the literature data.[20]

4.2. Kinetic resolution of 3a with CALA

Experimental procedure: Trifluoroethyl butanoate (92 μL, 2 equiv) was added to a solution containing **3a** (49.3 mg, 0.3 mmol) and vacuum-dried CALA (300 mg, 1000 mg/mmol) in dry THF (6 mL, 0.05 M). The resulting mixture was stirred at rt for 37 h and then the enzyme was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (methylene chloride/methanol = 15/1) to afford (*R*)-**3a** (12 mg, 0.075 mmol, 25% yield) and (*S*)-**4a** (30 mg, 0.12 mmol, 40% yield). Compound (*R*)-**3a** was acetylated by treatment with acetic anhydride to (*R*)-**4a** for the determination of its ee value by HPLC. (*R*)-**3a**: $[\alpha]_D^{25} = +25$ (*c* 0.1, THF) 62% ee. (*S*)-**4a**: $[\alpha]_D^{25} = -30$ (*c* 0.1, THF) 76% ee. See (*R*)-**4a** for its analytical data.

4.3. Kinetic resolution of 3a–d with PSL

β-Amino acid amide **3a** (328.4 mg, 2 mmol) was added to dry THF (20 mL, 0.1 M) with vacuum-dried PSL (400 mg, 200 mg/mmol). 2,2,2-Trifluoroethyl butanoate (608 μL, 2 equiv) was then added and the mixture was stirred at rt. After 12 h, the reaction was stopped by filtering off the enzyme. The solvent was evaporated off and the residue was purified by column chromatography (methylene chloride/methanol = 15/1) to afford (*R*)-**4a** (225 mg, 0.96 mmol, 48% yield) and (*S*)-**3a** (90 mg, 0.56 mmol, 28% yield). Compound (*S*)-**3a** was acetylated by treatment with acetic anhydride to (*S*)-**4a** for the determination of its ee value by HPLC: (*R,R*)-Whelk-O1, *n*-hexane/2-propanol = 80/20, flow rate = 1.5 mL/min, UV = 217 nm, (*S*)-form: 7.9 min., (*R*)-form; 13.7 min. (*S*)-**3a**: mp 105–107 °C; $[\alpha]_D^{25} = -51$ (*c* 0.5, THF) >99% ee. (*R*)-**4a**: mp 222–225 °C; $[\alpha]_D^{25} = +59$ (*c* 0.1, THF) >99% ee; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 0.95 (3H, t, *J* = 7.37 Hz, $CH_2CH_2CH_3$), 1.67 (2H, m, $CH_2CH_2CH_3$), 2.23 (2H, t, *J* = 7.49 Hz, $CH_2CH_2CH_3$), 2.78 (2H, m, $CHCH_2CO$), 5.2 and 5.7 (1H each, br s, $CONH_2$), 5.39 (1H, m, $CHCH_2CO$), 7.0 (1H, br s, $CHNHCO$), 7.27–7.35 (5H, m, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$ with a trace of methanol-d_4, ppm): δ 13.7, 19.2, 38.7, 41.2, 49.9, 126.3, 127.6, 128.8, 140.9, 173.7, 174.0; Analysis Calcd for $C_{13}H_{18}N_2O_2$: C 66.64; H 7.74; N 11.96. Found: C 66.60; H 7.58; N 11.54. (*S*)-**3b**: mp 119–122 °C; $[\alpha]_D^{25} = -41.5$ (*c* 0.24, $CHCl_3$; >99% ee). (*R*)-**4b**: mp 232–234 °C; $[\alpha]_D^{25} = +118$ (*c* 0.1, MeOH; 96% ee); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 0.81 (3H, t, *J* = 7.37 Hz, $CH_2CH_2CH_3$), 1.48 (2H, m, $CH_2CH_2CH_3$), 2.04 (2H, t, *J* = 7.2 Hz, $CH_2CH_2CH_3$), 2.46 (2H, m, $CHCH_2CO$), 5.19 (1H, m, $CHCH_2CO$), 6.8 and 7.3 (1H each, br s, $CONH_2$), 7.08–7.14 (2H, m, C_6H_4), 7.29–7.34 (2H, m, C_6H_4), 8.25 (1H, d, *J* = 8.4 Hz, $CHNHCO$). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 13.5, 18.7, 37.3, 42.1, 49.0, 114.7 (d), 128.3 (d), 139.4 (d), 159.4, 162.6, 171.0, 171.2; Analysis Calcd for $C_{13}H_{17}FN_2O_2$: C, 61.89; H, 6.79; N, 11.10. Found: C, 61.89; H, 6.86; N, 10.77. (*S*)-**3c**: mp 124–127 °C; $[\alpha]_D^{25} = -43$ (*c* 0.25, $CHCl_3$; 96% ee). (*R*)-**4c**: mp 246–248 °C; $[\alpha]_D^{25} = +92$ (*c* 0.2, MeOH; 99% ee); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 0.82 (3H, t, *J* = 7.37 Hz, $CH_2CH_2CH_3$), 1.48 (2H, m, $CH_2CH_2CH_3$), 2.04 (2H, t, *J* = 7.14 Hz, $CH_2CH_2CH_3$), 2.26 (3H, s, $C_6H_4CH_3$), 2.45 (2H, m, $CHCH_2CO$), 5.16 (1H, m, $CHCH_2CO$), 6.8 and 7.2 (1H each, br s, $CONH_2$), 7.08–7.19 (4H, m, C_6H_4), 8.2 (1H, d, *J* = 8.4 Hz, $CHNHCO$). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 14.0, 19.2, 21.1, 37.9, 42.6, 49.8, 126.8, 129.1, 136.1. 140.7, 171.4, 171.9; Analysis Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.49; H, 8.35; N, 11.23. (*S*)-**3d**: mp 102–104 °C; $[\alpha]_D^{25} = -33$ (*c* 0.29, $CHCl_3$; 88% ee). (*R*)-**4d**: mp 236–239 °C; $[\alpha]_D^{25} = +85$ (*c* 0.1, MeOH; >99% ee); ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 0.81 (3H, t, *J* = 7.37 Hz, $CH_2CH_2CH_3$), 1.48 (2H, m, $CH_2CH_2CH_3$), 2.03 (2H, t, *J* = 7.08 Hz, $CH_2CH_2CH_3$), 2.45 (2H, m, $CHCH_2CO$), 3.71 (3H, s, $C_6H_4OCH_3$), 5.15 (1H, m, $CHCH_2CO$), 6.7 and 7.2 (1H each, br s, $CONH_2$), 6.83–7.23 (4H, m, C_6H_4), 8.2 (1H, d, *J* = 8.4 Hz, $CHNHCO$). ^{13}C NMR (75 MHz, DMSO-d_6, ppm): δ 13.5, 18.7, 37.4, 42.2, 48.9, 55.0, 113.4, 127.6,

135.2, 158.0, 170.9, 171.4; Analysis Calcd for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 64.07; H, 7.83; N, 9.80.

4.4. PSL-catalyzed kinetic resolution of 3a coupled with Pd-catalyzed racemization

To a Schlenk-type flask equipped with a grease-free high vacuum stopcock were added **3a** (33 mg, 0.2 mmol), Pd/AlO(OH) (130 mg, 5 mol % Pd), vacuum-dried PSL (80 mg, 400 mg/mmol), sodium carbonate (80 mg, 400 mg/mmol), dry THF (2 mL, 0.1 M), and trifluoroethyl butanoate (61 μL, 2 equiv) in sequence. The mixture was stirred at rt for 12 h to induce the enzymatic reaction smoothly and then at 70 °C for 12 h to promote the Pd-catalyzed racemization. The reaction mixture was then cooled down to rt and a portion of fresh PSL (40 mg, 200 mg/mmol) was added. The second cycle of resolution–racemization was performed at rt for 12 h and then at 70 °C for 12 h. It should be noted that the conversion was 50% after the first cycle and increased to 80% after the second cycle. Finally, the last portion of fresh PSL (40 mg, 200 mg/mmol) was added and, after stirring at rt for 12 h, the reaction was stopped by filtering off the catalysts. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography (methylene chloride/methanol = 15/1) to afford (*R*)-**4a** (42 mg, 0.18 mmol, 90% yield; >99% ee).

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