JOC*Note*

pubs.acs.org/joc

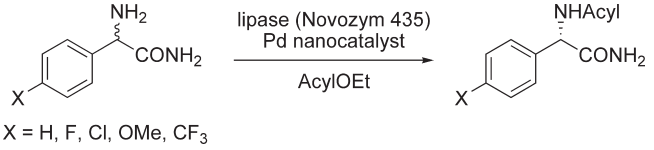
Synthesis of Optically Active Amino Acid Derivatives via Dynamic Kinetic Resolution

Yoon Kyung Choi, Yunwoong Kim, Kiwon Han, Jaiwook Park,* and Mahn-Joo Kim*

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

mjkim@postech.ac.kr

Received September 21, 2009

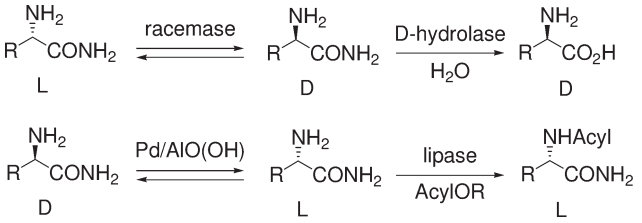


X = H, F, Cl, OMe, CF_3

The complete conversion of racemic amino acid amides to optically active amino acid derivatives was accomplished via lipase/palladium-catalyzed dynamic kinetic resolution (DKR). In the DKR, a lipase catalyzes the selective acylation of L-substrate in the presence of acyl donor while unreacted D-substrate is isomerized by a Pd nanocatalyst to L-substrate. The DKR reactions provided good yields (80−98%) and high enantiomeric excess (95−98% ee). Interestingly, the DKR reactions of phenylglycine amide in the presence of Z-Gly-OMe or Z-Gly-Gly-OMe yielded optically active di- and tripeptide .

Enantiopure amino acids and their derivatives are versatile building blocks for the asymmetric synthesis of a wide range of natural products and pharmaceuticals.[1,2] Although numerous methods have been developed for their synthesis, the resolutions of their racemic forms via enzymatic kinetic resolution or fractional recrystallization of their diastereomeric salts still provide useful routes to them. These procedures, however, suffer from the intrinsic limitation that the theoretical maximum yield for a single enantiomer cannot exceed 50%. Alternatively, dynamic kinetic resolution (DKR), in which the kinetic resolution and racemization of substrate take place simultaneously in one pot, provides high yields approaching 100%.[3] Recently, several groups have developed some useful procedures for the DKR of amino acids.[4,5] In most cases, DKR was accomplished via the enzymatic enantioselective hydrolysis of amino acid derivatives such as oxazolones[4] and hydantoins[5] which were prone to spontaneous racemization under weakly basic conditions. Lately, a purely enzymatic method was reported for the DKR of amino acid amides.[6] In this procedure, a D-selective peptide hydrolase and a racemase were coupled for the dynamic enantioselective hydrolysis of racemic amino acid amides to D-amino acids (Scheme 1, top). We herein wish to report a different approach for the DKR of amino acid amide: dynamic enantioselective acylation by the coupling of a lipase and a palladium catalyst (Scheme 1, bottom).

SCHEME 1. Two Approaches for Dynamic Kinetic Resolution of Amino Acid Amides



Previously, we reported the DKR of primary amines with a lipase−Pd couple as the catalysts.[7,8] In the lipase/Pd-catalyzed DKR, a variety of benzylic and aliphatic amines were converted to single enantiomeric products with good yields. As a part of the previous work, we also observed that phenylalanine amide was eligible as the substrate for the lipase/Pd-catalyzed DKR although a harsh condition (100 °C) was necessary for satisfactory DKR. Subsequently, we envisioned that the DKR of amino acid amides should provide a useful route to optically active amino acid derivatives.

*To whom correspondence should be addressed.

(1) (a) Williams, R. M. *Synthesis of optically active α-amino acids*; Pergamon: Oxford, UK, 1989. (b) Coppola, G. M.; Schuster, H. F. *Asymmetric synthesis: construction of chiral molecules using amino acids*; John Wiley and Sons: New York, 1987.

(2) For a recent review on catalytic asymmetric synthesis of α-amino acids, see: Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671.

(3) Reviews: (a) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647–658. (b) Martín-Matute, B.; Bäckvall, J. E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226–232. (c) Kim, M.-J.; Ahn, Y.; Park, J. *Bull. Korean Chem. Soc.* **2005**, *26*, 515–522. (d) Pàmies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247–3261.

(4) (a) Roff, G. J.; Lloyd, R. C.; Turner, N. J. *J. Am. Chem .Soc.* **2004**, *126*, 4098–4099. (b) Brown, S. A.; Parker, M.-C.; Turner, N. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1687–1690. (c) Turner, N. J.; Winterman, J. R.; McCague, R.; Parrat, J. S.; Taylor, S. J. C. *Tetrahedron Lett.* **1995**, *36*, 1113–1116.

(5) Suzuki, M.; Yamazaki, T.; Ohta, H.; Shima, K.; Ohi, K.; Nishiyama, S.; Sugai, T. *Synlett* **2000**, 189–192.

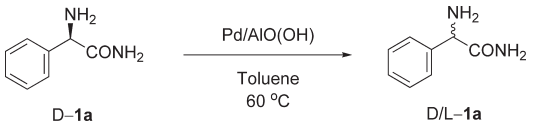
(6) Asano, Y.; Yamaguchi, S. *J. Am. Chem. Soc.* **2005**, *127*, 7696–7697.

(7) Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157–1159.

(8) The first DKR of amine by the coupling of lipaseand Pd/C was reported by the Reetz group[8l] and then more practical procedures with Pd/alkaline earth salts ($BaSO_4$ and $CaCO_3$),[8h,j] Pd/Raney metals (Ni and Co),[8d] Ru complex,[8a,j] or Ir complex[8g] as the racemization catalyst were developed. For these and additional developments, see: (a) Thalén, L. K.; Zhao, D.; Sortais, J.-B.; Pasetzold, J.; Hoben, C.; Bäckvall, J.-E. *Chem.—Eur. J.* **2009**, *15*, 3403–3410. (b) leandro, L. H.; Alexandre, A. V.; Pedrozo, E. C. *Tetrahedron Lett.* **2009**, *50*, 4331–4334. (c) Blidi, L. E.; Nechab, M.; Vanthuyne, N.; Gastaldi, S.; Bertrand, M. P.; Gil, G. *J. Org. Chem.* **2009**, *74*, 2901–2903. (d) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Adv. Synth. Catal.* **2008**, *350*, 113–121. (e) Veld, M. A. J.; Hult, K.; Palmans, R. A.; Meijer, E. W. *Eur. J. Org. Chem.* **2007**, 5416–5421. (f) Stirling, M. J.; Blacker, A. J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247–1250. (g) Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, *11*, 642–648. (h) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *13*, 2034–2043. (i) Parvulescu, A. N.; De Vos, D. E.; Jacobs, P. A. *Chem. Commun.* **2005**, 5307–5309. (j) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621. (k) Pàmies, O.; Éll, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 4699–4702. (l) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669.

DOI: 10.1021/jo902034x Published on Web 11/17/2009

TABLE 1. Racemization of Enantiopure Phenylglycine Amide by Pd Nanocatalyst[a]

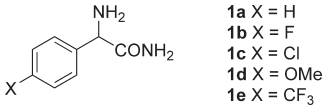


D–**1a** D/L–**1a**

entry	Pd (mol %)	time (h)	ee (%)[b]
1	1	24	70
2	3	24	33
3	5	24	16
4	5	48	< 1

[a]The reactions were carried out with a variation in the amount of Pd nanocatalyst in toluene at 60 °C. [b]Determined by HPLC with a chiral column: Chirosil (RS Tech); MeOH/10 mM aq H_2SO_4 = 80/20; flow rate = 0.5 mL/min; UV = 210 nm.

We thus examined phenylglycine amide (**1a**) and its derivatives (**1b**−**e**) as the substrates for milder DKR. It was confirmed that their DKR reactions proceeded smoothly under a milder condition (60 °C) to provide optically active amino acid derivatives including di- and tripeptides.

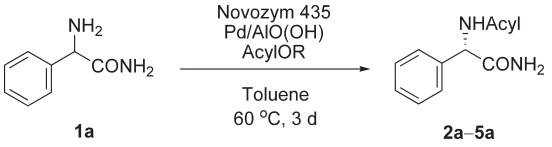


1a X = H
1b X = F
1c X = Cl
1d X = OMe
1e X = CF_3

We chose palladium nanoparticles entrapped in the AlO(OH) matrix as the catalyst for racemization and *Candida antarctica* lipase B (CALB; trade name, Novozym 435) immobilized on acrylic resin as the catalyst for enantioselective acylation. Palladium nanocatalyst (Pd/AlO(OH)) for racemization was prepared according to the procedure previously reported in the literature.[9] Its catalytic efficiency was examined with the racemization of D-**1a**, which was performed with a variation in the amount of palladium nanocatalyst in toluene at 60 °C. Complete racemization took place in the presence of 5 mol % of Pd nanocatalyst after 48 h (Table 1). Accordingly, DKR reactions were carried out in the presence of 5 mol % of Pd nanocatalyst.

First of all, the DKR reactions of phenylglycine amide (**1a**) were carried out on 0.2 mmol scale with variations in the type of acyl donor and the amount of enzyme in toluene at 60 °C for 3 days. A small amount of lipase (1 mg, 5 mg/mmol of substrate) was used with activated acyl donor, ethyl methoxyacetate, but a significantly larger amount (24 mg, 120 mg/mmol of substrate) was employed with less active acyl donors such as ethyl acetate, ethyl phenylacetate, or methyl *p*-hydroxyphenylacetate. The results from Table 2 indicate that all the reactions with different acyl donors proceeded smoothly to afford high isolated yields (90−98%) and excellent enantiomeric excesses (95−98%). Notably the DKR reaction in the

TABLE 2. Dynamic Kinetic Resolution of Phenylglycine Amide[a]

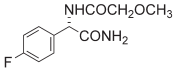
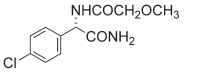
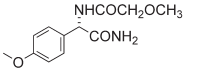
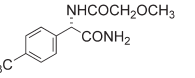


1a **2a**–**5a**

entry	AcylOR	product	yield (%)[b]	ee (%)[c]
1	$CH_3OCH_2CO_2Et$	**2a**	98	97
2	CH_3CO_2Et	**3a**	96	98
3	$PhCH_2CO_2Et$	**4a**	93	95
4	*p*-$HOPhCH_2CO_2Me$	**5a**	90	98

[a]The reactions were carried out on 0.2 mmol scale with 5 mol % of Pd nanocatalyst and 2−3 equiv of acyl donor in toluene at 60 °C for 3 days. The amount of enzyme (Novozym 435) varied according to acyl donor used: 1 mg of enzyme was used for entry 1 and 24 mg of enzyme for entries 2−4. [b]Isolated yield. [c]Determined by HPLC with a chiral column: (*R*,*R*) Whelk-O1; *n*-hexane/2-propanol = 80/20; flow rate = 2 mL/min; UV = 217 nm.

TABLE 3. Dynamic Kinetic Resolution of Phenylglycine Amide Derivatives[a]

entry	substrate	product		yield[b] (%)	ee[c] (%)
1	**1b**		**2b**	91	97
2	**1c**		**2c**	88	97
3	**1d**		**2d**	91	97
4	**1e**		**2e**	90	97

[a]The reactions were carried out on 0.2 mmol scale with 5 mol % of Pd nanocatalyst, 2 mg of Novozym 435, and 2 equiv of ethyl methoxyacetate in toluene at 60 °C for 3 days. [b]Isolated yield. [c]Determined by HPLC with a chiral column: (*R*,*R*) Whelk-O1; *n*-hexane/2-propanol = 80/20; flow rate = 2 mL/min; UV = 217 nm.

presence of ethyl methoxyacetate provided the best results (entry 1). The L-configuration of products was confirmed by comparing the optical rotation of **3a** with the literature data.[10]

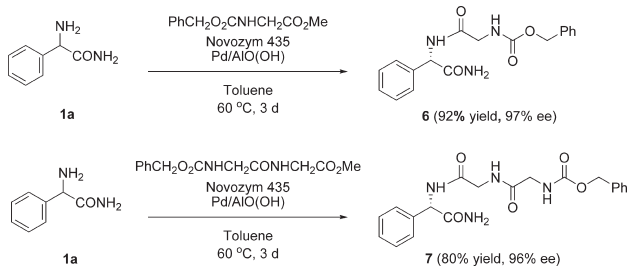
On the basis of the results from the DKR of **1a**, we chose ethyl methoxyacetate as the acyl donor for the DKR reactions of additional substrates **1b**−**e**. These DKR reactions were performed with 0.2 mmol of substrate, 0.4 mmol of ethyl methoxyacetate, 2 mg of lipase (10 mg/mmol of substrate), and 5 mol % of Pd nanocatalyst in toluene at 60 °C for 3 days. All of them afforded similarly good isolated yields (88−91%) and high enantiomeric excesses (97% ee) (Table 3).

We then thought that the synthesis of optically active peptides would be possible if amino acid esters were employed as the acyl donors for the DKR of amino acid amides (Scheme 2). We chose *N*-benzyloxycarbonylglycine methyl ester (Z-Gly-OMe) as the acyl donor for the illustrative synthesis of optically active dipeptides. The DKR reaction was performed with **1a** (0.2 mmol), acyl donor (0.3 mmol), Novozym 435 (30 mg,

(9) (a) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913–6915. (b) Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park, J. *Org. Lett.* **2005**, *7*, 1077–1079.

(10) **3a**: $[\alpha]^{25}_D$ +244.9 (*c* 0.3, $CHCl_3$, 98% ee) {lit. $[\alpha]_D$ −242 (*c* 0.3, $CHCl_3$)} for D-form: Reihlen, H.; Knoepfle, L. *Justus Liebigs Ann. Chem.* **1936**, *523*, 199–210.

SCHEME 2. Synthesis of Dipeptide and Tripeptide via DKR



150 mg/mmol of substrate), and Pd nanocatalyst (5 mol %) in toluene at 60 °C for 3 days. The reaction provided optically active dipeptide **6** in good isolated yield (92%) with high optical purity (97% ee). Interestingly, optically active tripeptide **7** (80% isolated yield, 96% ee) was prepared similarly by using *N*-benzyloxycarbonylglycylglycine methyl ester (Z-Gly-Gly-OMe) as the acyl donor in the DKR of **1a**. On the basis of these results, we believe that a wide range of optically active peptides can be prepared via DKR by varying acyl donors and amino acid amides.

In summary, we have demonstrated that racemic amino acid amides are transformed into single enantiomers via DKR catalyzed by a lipase−Pd couple, thus leading to the synthesis of optically active amino acid derivatives. The DKR reactions are straightforward and provide good isolated yields and excellent optical purities. They are also applicable to the synthesis of optically active peptides. Therefore, they should find use as new routes for the synthesis of enantiopure amino acid derivatives in organic and pharmaceutical chemistry.

Experimental Section

General Procedure. The DKR of phenylglycine amide (**1a**) in the presence of ethyl methoxyacetate is described as a representative procedure. A suspension containing **1a** (30 mg, 0.2 mmol), Novozym 435 (1 mg, 5 mg/mmol), Pd nanocatalyst (Pd/AlO(OH), 60 mg, 0.71 wt % Pd contents, 5 mol % Pd), ethyl methoxyacetate (2.0 equiv, 47 μL), and distilled toluene (2.0 mL, 0.1 M) in a 50 mL Schlenk-type flask was stirred under argon at 60 °C for 3 days. The reaction mixture was cooled to room temperature and filtered through a Celite pad to remove enzyme and Pd nanocatalyst. The filtrate was concentrated under reduced pressure and purified by chromatography on a silica gel column (eluent; CH_2Cl_2/MeOH = 10/1) to give **2a** (43.5 mg, 0.196 mmol, 98% yield, 97% ee): $[\alpha]^{25}_D$ +161.0 (*c* 0.5, MeOH, 97% ee); ^{1}H NMR (THF-d_8, 300 MHz) δ 7.84 (d, J = 6.8 Hz, 1H), 7.49 (d, J = 7.4 Hz, 2H), 7.36−7.26 (m, 3H), 7.07 (br s, 1H), 6.75 (br s, 1H), 5.57 (d, J = 7.7 Hz, 1H), 3.86 (s, 2H), 3.44 (s, 3H); ^{13}C NMR (THF-d_8, 75 MHz) δ 173.6, 170.0, 142.1, 130.5, 129.6, 74.2, 60.6, 57.7; HRMS (FAB) $C_{11}H_{14}N_2O_3 + H^+$ calcd 223.1083, found 223.1081; elemental analysis calcd C 59.45, H 6.35, N 12.61, found C 59.40, H 6.34, N 12.68; the percent ee was determined by HPLC on a (*R,R*) Whelk-O1 [*n*-hexane/2-propanol = 80/20, flow rate = 2 mL/min, UV = 217 nm; 4.5 min (D), 7.0 min (L)].

Acknowledgment. This work was supported by the National Research Foundation of Korea (R01-2006-000-10696-0 and KRF-2007-313-C00413). We thank the Korean Government for supporting our graduate program (BK21 Program).

Supporting Information Available: Analytical data of products including ^{1}H and ^{13}C NMR spectra and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.