JOC*Note*

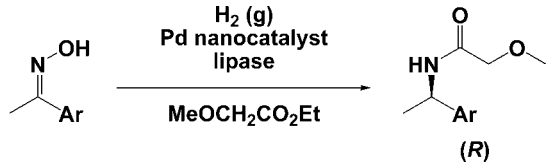
Asymmetric Reductive Acylation of Aromatic Ketoximes by Enzyme-Metal Cocatalysis

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 February 2, 2008

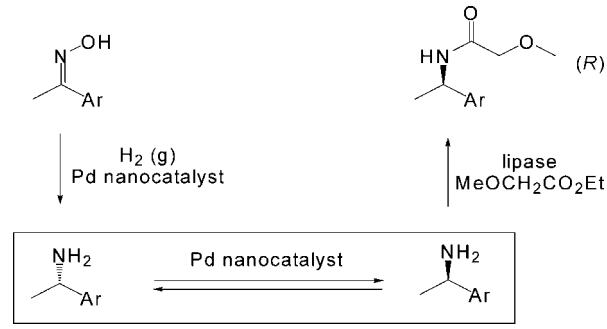


We have developed an efficient procedure for the asymmetric synthesis of chiral amides from ketoximes. This one-pot procedure employs two different types of catalysts, Pd nanocatalyst and lipase, for three consecutive transformations including hydrogenation, racemization, and acylation. Eight ketoximes have been efficiently transformed to the corresponding amides in good yields (83−92%) and high enantiomeric excesses (93−98%).

Optically active amines and their simple derivatives are an important class of chiral molecules which are useful as chiral building blocks, auxiliaries, or resolving agents in asymmetric synthesis.[1] A number of methods are currently available for their asymmetric syntheses.[2] For example, asymmetric reductive amination of ketones provides a useful route to them, particularly α-chiral amines.[3] We herein wish to report an alternative using Pd nanocatalyst and lipase in combination for the synthesis of α-chiral amides.[4,5] In this one-pot procedure, ketoximes are converted to optically active amides through three coupled reactions (hydrogenation, racemization, and enantioselective acylation) (Scheme 1).

Recently, we have developed a practical Pd nanocatalyst for use in several reactions including the reduction of olefins,[6] the oxidation of alcohols,[7] the hydrogenolysis of epoxides,[8] and the dynamic kinetic resolution (DKR) of primary amines.[9] The Pd nanocatalyst, readily prepared as palladium nanoparticles entrapped in aluminum oxyhydroxide (Pd/AlO(OH)), displayed high activity and excellent stability even at 100 °C. These superb properties encouraged us to further explore its utility as a component of catalyst for the asymmetric conversion of ketoximes to chiral amides, in which it acts as a dual catalyst for both hydrogenation and racemization (Scheme 1). Previously, we used Pd/C as such a dual catalyst, which required a long reaction time (5 days) for moderate yields.[10]

SCHEME 1. Asymmetric Reductive Acylation of Ketoximes to Amides



First, we explored the reactions of **1a** as a standard substrate to optimize the reaction conditions. In addition to the Pd nanocatalyst, thermostable *Candida antarctica* lipase B (CALB; trade name, Novozym-435) was chosen as the catalyst for the enantioselective acylation of amine intermediate with ethyl methoxyacetate. The acyl donor was chosen because it is more reactive than other acyl donors such as ethyl acetate and thus requires much smaller amounts of enzyme.[11] The reactions were carried out with 1 mol% of Pd/AlO(OH), 30 mg/mmol of Novozym-435, 1.7 equiv of ethyl methoxyacetate in toluene at 70 °C with a variation in hydrogen pressure from 0.05 to 1 bar for 48 h.

The data from Table 1 indicate that the reaction under 1 atm of hydrogen afforded unsatisfactory results (71% yield and 87% ee) with the formation of a significant amount of ethylbenzene **5** as a byproduct (entry 1). This byproduct has been known to come from a nonproductive pathway including the condensation, hydrogenation, and deamination of amines.[5b] Interestingly, the addition of molecular sieves substantially improved the enantiopurity of product to a satisfactory level with a slight increase in yield (entry 2). On the other hand, the yield was markedly enhanced by decreasing the hydrogen pressure. The best results (90% yield and 98% ee) thus were obtained in the presence of

(1) Breuer, M.; Dietrich, K.; Habicher, T.; Hauer, B.; Kessaeler, M.; Stürmer; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788–824.

(2) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203–211.

(3) (a) Nugent, T. C.; Ghosh, A. K.; Wakchaure, V. N.; Mohanty, R. R. *Adv. Synth. Catal.* **2006**, *348*, 1289–1299. (b) Nugent, T. C.; El-Shazly, M.; Wakchaure, V. N. *J. Org. Chem.* **2008**, *73*, 1297–1305.

(4) Reviews for chemoenzymatic DKR: (a) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587. (b) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3262. (c) Kim, M.-J.; Park, J.; Ahn, Y. In *Biocatalysis in the Pharmaceutical and Biotechnology Industries*; Patel, R. N., Ed.; CRC Press: Boca Raton, FL, 2007; pp 249−272.

(5) For chemoenzymatic DKRs of amines, see: (a) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669. (b) Parvulescu, A.; Vos, D. D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309. (c) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621.

(6) Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park, J. *Org. Lett.* **2005**, *7*, 1077–1079.

(7) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913–6915.

(8) Kwon, M. S.; Park, I. S.; Jang, J. S.; Lee, J. S.; Park, J. *Org. Lett.* **2007**, *9*, 3417–3419.

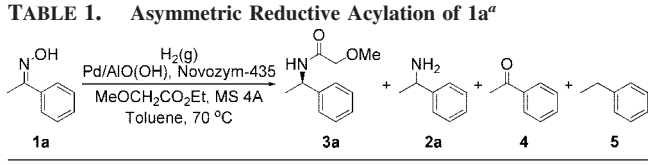
(9) Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157–1159.

(10) Choi, Y. K.; Kim, M. -J.; Ahn, Y. *Org. Lett.* **2001**, *3*, 4099–4101.

(11) For molecular modeling study of N-acylation of amine with methoxyacetate, see: Cammenberg, M.; Hult, K.; Kim, S. *ChemBioChem* **2006**, *7*, 1745–1749.

10.1021/jo800270n CCC: $40.75
Published on Web 05/03/2008

TABLE 1. Asymmetric Reductive Acylation of 1a[a]



entry	MS 4A (wt %)	H_2 (bar)	conv[b] (%)	**3a**[b] (%)	**2a**[b] (%)	**4**[b] (%)	**5**[b] (%)	ee[c] (%)
1		1	>98	71	<1	<1	29	87
2	250	1	>98	73	<1	<1	27	95
3	250	0.5	>98	80	<1	<1	20	94
4	250	0.2	>98	88	<1	<1	12	98
5	250	0.1	>98	90	<1	<1	10	98
6	250	0.05	60	42	<1	9	1	92

[a] All of the reactions were performed in a 75 mL Schlenk flask. [b] Measured by ^{1}H NMR. [c] Measured by HPLC with a chiral column.

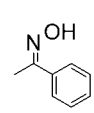
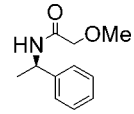
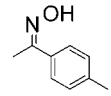
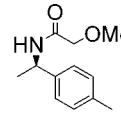
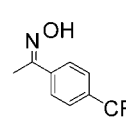
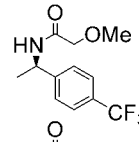
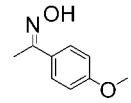
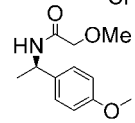
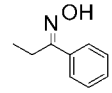
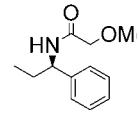
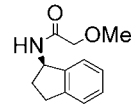
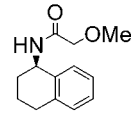
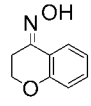
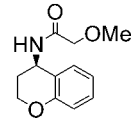
molecular sieves with 0.1 bar of molecular hydrogen (entry 5). Further decrease in hydrogen pressure resulted in slow conversion with a poor yield (entry 6).

The reactions of additional ketoximes **1b**−**h**[12] were carried out under the optimized conditions: a substrate (0.3 mmol), Pd/AlO(OH) (1 mol % of Pd), Novozym-435 (30 mg/mmol), ethyl methoxyacetate (1.7 equiv), 4Å molecular sieve (330 mg/mmol), toluene (3 mL), 0.1 bar of hydrogen, 70 °C, 48 h. After the reaction was complete, the catalysts were filtered off. The filtrate was concentrated and then subjected to column chromatography to fractionate the desired products. The enantiopurities of products were determined by HPLC using a chiral column.

The data from Table 2 indicate that all the substrates were successfully transformed into the corresponding amides with good yields (83−92%) and high enantiopurities (93−98%). It is noteworthy that the nature of substituent on benzene ring of substrate affected the yield more or less. Among acyclic substrates, **1c** was transformed with the highest yield and **1d** with the lowest yield (entries 1−4). This observation suggests that substrates with a strongly electron-attracting substituent should be less prone to the side reactions. Among cyclic substrates, **1h** was transformed with the highest yield (entries 6−8). At present, a clear rationale is not available for the highest yield. It might be a result of reduced hindrance by the presence of oxygen in the aliphatic ring.

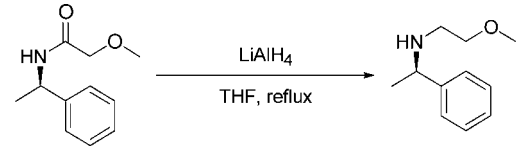
The amide products can be readily reduced to the corresponding secondary amines which should be useful as chiral building blocks, ligands, or auxiliaries for asymmetric synthesis.[13] As a representative example, amide **3a** was reduced with $LiAlH_4$ to obtain secondary amine **6** quantitatively without loss in enantiopurity (Scheme 2). This conversion thus illustrates an atom-economical use of the amide products without deacylation. In summary, we have demonstrated that achiral ketoximes are efficiently converted by the cooperation of two different types of catalysts, Pd nanocatalyst and lipase, to chiral amides in good yields.

TABLE 2. Asymmetric Reductive Acylation of Ketoximes (1a−h)[a]

entry	substrates		products		yield[b] (%)	ee (%)
1		**1a**		**3a**	88	98[c]
2		**1b**		**3b**	85	95[c]
3		**1c**		**3c**	90	95[c]
4		**1d**		**3d**	83	94[c]
5		**1e**		**3e**	84	93[d]
6		**1f**		**3f**	87	94[d]
7		**1g**		**3g**	87	96[d]
8		**1h**		**3h**	92	97[d]

[a] All of the reactions were performed in a 75 mL Schlenk flask. [b] Isolated yield. [c] Measured by HPLC with (*R*,*R*) Whelk-O1 column. [d] Measured by HPLC with a Chiralcel-OD column.

SCHEME 2. Reduction of Chiral Amide to Secondary Amine



Experimental Section

Preparation of Pd/AlO(OH). $Pd(OAc)_2$ (22 mg, 0.1 mmol), (*s*-BuO)$_3$Al (4 g, 16.2 mmol), THF (1 mL), and 2-butanol (1 mL) were added to 50 mL round-bottom flask. After the mixture was stirred at 50 °C for 20 min to give a black suspension, water (3 mL) was added for gelation. The black solid was filtered, washed with acetone, and dried in a 120 °C oven for 5 h and in vacuo at room temperature for 1 day to give Pd/AlO(OH) as dark gray powder (1.16 g, 0.9 wt % of Pd).

General Procedure for Asymmetric Reductive Acylation of Ketoximes. A suspension containing **1a** (41 mg, 0.30 mmol), Pd nanocatalyst (36 mg, 1.0 mol% Pd), Novozym-435 (9 mg, 30 mg/mmol), 4 Å molecular sieves (100 mg, 330 mg/mmol), and ethyl methoxyacetate (70 mg, 1.7 equiv) in dry and degassed toluene (3 mL, 0.10 M) was stirred at 70 °C under 0.1 bar of hydrogen pressure

(12) Ketoximes were prepared from corresponding ketones according to the general methods. See: (a) Lachman, A. *Organic Syntheses*; Wiley: New York, 1943; Collect. *Vol. II*, p 70. (b) Larock, R. C. *Comprehensive Organic Transformation*; VCH Publishers: New York, 1989; p 426.

(13) (a) Kozma, D. In *Optical Resolutions via Diastereomeric Salt Formation*; Kozma, D., Ed.; CRC Press: Boca Raton, 2002; p 690. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590. (c) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolution*; John Wiley & Sons: New York, 1981.

in a 75 mL Schlenk flask. After 48 h, the reaction mixture was cooled to room temperature and filtered through a glass filter (pore size: 20−30 μm). The filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy, indicating that all of the substrate was consumed. The mixture was subjected to flash chromatography (silica gel, *n*-hexane/ethyl acetate = 1/1) to provide **3a** (51 mg, 0.26 mmol, 88%, 98% ee).

2-Methoxy-*N*-((*R*)-1-phenylethyl)acetamide (3a). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.37−7.25 (m, 5H), 6.76 (s, 1H), 5.23−5.13 (m, 1H), 3.89 (dd, J_1 = 19.65 Hz, J_2 = 14.97 Hz, 2H), 3.39 (s, 3H), 1.51 (d, J = 6.93 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 168.6, 143.0, 128.7, 127.4, 126.1, 72.0, 59.1, 48.0, 21.9. HPLC ((*R*,*R*) Whelk-O1, *n*-hexane/2-propanol = 80/20, flow rate = 2.0 mL/min, UV 217 nm): (*S*)-**3a** = 4.97 min, (*R*)-**3a** = 11.86 min; mp 59−60 °C. $[\alpha]^{25}_D$ +84.7 (c = 0.5, $CHCl_3$). Anal. (VarioEL III CHN) Calcdfor $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.31; H, 7.82; N, 7.24.

Synthesis of (*R*)-*N*-(2-Methoxyethyl)-1-phenylethylamine (6). A suspension containing **3a** (50 mg, 0.259 mmol, 98% ee) and $LiAlH_4$ (79 mg, 2.07 mmol) in distilled THF (1.5 mL, 0.2 M) was refluxed in a 10 mL round-bottom flask equipped with a condenser. After confirming that the reaction was completed with TLC, the reaction mixture was cooled to 0 °C in ice bath, and water (75 μL, 4.14 mmol) and 1 N NaOH solution (75 μL) were added to the reaction mixture for quenching of $LiAlH_4$. The precipitate was removed by filtration followed by washing with methylene chloride (10 mL), and the filtrate was dried with Na_2SO_4 and concentrated to obtain **6** (colorless liquid, (45 mg, 97%, 98% ee)). The % ee was determined by HPLC after converting to the corresponding amide by treatment with a few drops of acetic anhydride. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.33−7.21 (m, 5H), 3.80−3.73 (m, 1H), 3.48−3.42 (m, 2H), 3.33 (s, 3H), 2.67−2.59 (m, 2H), 1.37 (d, J = 6.57 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 145.6, 128.4, 126.9, 126.6, 58.7, 58.4, 47.3, 24.4; HPLC ((*R*,*R*) Whelk-O1, *n*-hexane/2-propanol = 80/20, flow rate = 0.5 mL/min, UV 217 nm): (*S*)-**6** = 16.87 min, (*R*)-**6** = 18.02 min. $[\alpha]^{25}_D$ +36.2 (c = 1.06, MeOH). HRMS (EI): $C_{11}H_{17}NO$ calcd 179.1310 (M^+), obsd 179.1310.

Acknowledgment. This work was supported by the Ministry of Science and Technology through KOSEF (R01-2006-000-10696-0) and by the Ministry of Education and Human Resources through KRF (BK21 program).

Supporting Information Available: Characteristic data of **3b**−**h**, ^{1}H and ^{13}C NMR spectra, and HPLC chromatograms of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800270N