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Lipase/Palladium-Catalyzed Asymmetric Transformations of Ketoximes to Optically Active Amines

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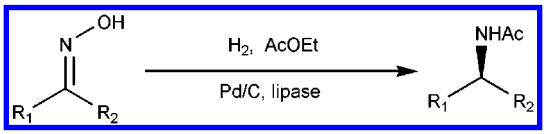
ABSTRACT



Prochiral ketoximes were asymmetrically transformed to optically active amines in the acetylated forms by coupled lipase/palladium catalysis in the presence of an acyl donor under 1 atm of hydrogen.

Optically active amines are an important class of organic compounds that can be widely used as useful chiral building blocks in asymmetric synthesis and medicinal chemistry. Some of the procedures currently available for the synthesis of optically active amines include the asymmetric catalytic hydrogenation of imines,[1] oximes,[2] or their derivatives,[3] the asymmetric borane reduction of oximes,[4] the asymmetric hydrosilylation of imines or oximes,[5] and the asymmetric hydrogenation of enamides.[6] Most of them require relatively expensive chiral catalysts such as metals with chiral ligand or chiral reagents. A useful alternative is the dynamic kinetic resolution (DKR) of racemic amines using readily available catalysts. A German group recently reported the DKR of 1-phenethylamine using lipase/palladium as the catalysts.[7] The procedure, however, required a long reaction time and provided a modest yield. We herein wish to report a better procedure employing ketoxime as the substrate with palladium and lipase as the catalysts.

On the basis of our experiences in the studies of the lipase/ruthenium-catalyzed asymmetric transformations of ketones to the esters of chiral alcohols,[8,9] we envisaged that optically active amines could be synthesized from readily available ketoximes by using two catalysts, one for reduction and racemization and one for resolution. We chose palladium as the reduction/racemization catalyst and lipase as the resolution catalyst (Scheme 1). The preliminary studies indicated that the palladium-catalyzed racemization of (*S*)-1-phenethylamine took place more efficiently in the presence of tertiary

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(2) Krsik, P.; Alper, H. *Tetrahedron: Asymmetry* **1992**, *3*, 1283.

(3) Sakio, Y.; Yoneyoshi, Y.; Suzukamo, G. *Tetrahedron Lett.* **1988**, *29*, 223.

(4) (a) Itsuno, S.; Matsumoto, T.; Sato, D.; Inoue, T. *J. Org. Chem.* **2000**, *65*, 5879. (b) Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3362. (c) Masui, M.; Shiori, T. *Tetrahedron Lett.* **1998**, *39*, 5195.

(5) (a) Brunner, H.; Becker, R. *Angew. Chem., Int. Ed.* **1984**, *23*, 222. (b) Blackwall, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921. (c) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (d) Takei, I.; Nishibayashi, Y.; Arikawa, Y.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2271.

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(8) Jung, H. M.; Koh, J. H.; Kim, M.-J.; Park, J. *Org. Lett.* **2000**, *2*, 409 and 2487.

(9) For the dynamic kinetic resolutions by lipase/ruthenium catalysis, see: (a) Persson, B. A.; Larsson, A. L. E.; Ray, M. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645. (b) Koh, J. H.; Jung, H. M.; Kim, M.-J.; Park, J. *Tetrahedron Lett.* **1999**, *40*, 6281. (c) Huerta, F. F.; Laxmi, Y. R. S.; Bäckvall, J.-E. *Org. Lett.* **2000**, *2*, 1037. (d) Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. W. *Org. Lett.* **2000**, *2*, 2377. (e) Kim, M.-J.; Choi, Y. K.; Choi, M. Y.; Kim, M. J.; Park, J. *J. Org. Chem.* **2001**, *66*, 4736.

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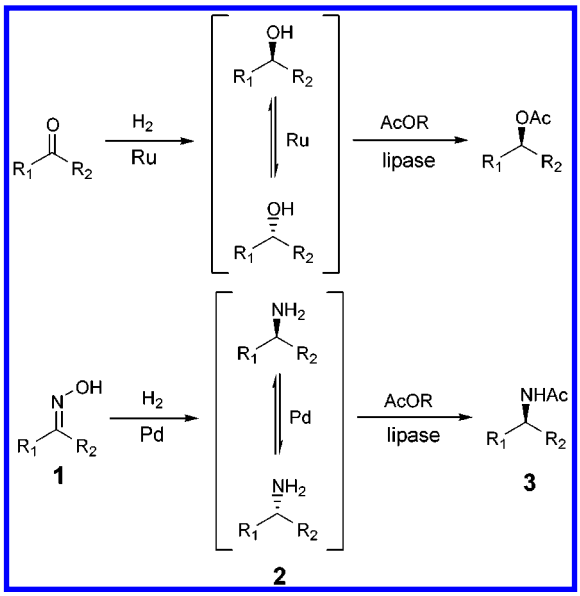
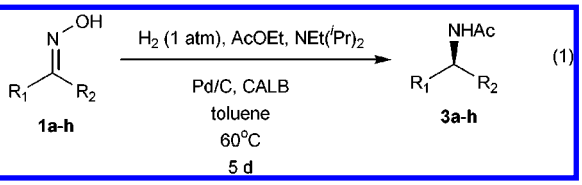
Scheme 1. Enzyme/Metal-Catalyzed Transformations of Ketones and Ketoximes



amines. In the absence of the bases, the reductive elimination of the amino group was more dominant. It was found that diisopropylethylamine was the most effective among the bases tested with enzyme.[10]

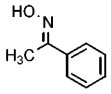
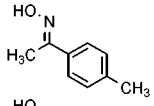
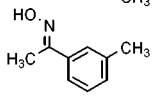
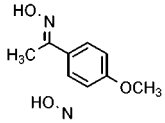
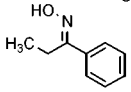
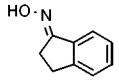
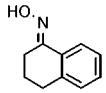
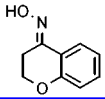
The reactions of ketoximes were explored with eight different ketoximes (**1a**−**h**),[11] *Candida antarctica* lipase B (CALB, immobilized on polyacrylamide; trade name Novozym-435) as the resolution catalyst, and palladium on carbon (Pd/C) as the reduction/racemization catalyst. Typically the reactions were performed with substrate (50 mg, 0.3−0.4 mmol), Novozym-435 (2 mass equiv), Pd/C (0.66 mass equiv), ethyl acetate (2 equiv), and diisopropylethylamine (3 equiv) in toluene (3−4 mL) at 60 °C under hydrogen gas (1 atm) for 5 days (eq 1).[12] 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 optical purities were determined by HPLC using a chiral column. The results are summarized in Table 1.

In all cases, substrates were consumed almost completely and the amounts of the remaining amine intermediates were

Table 1. Asymmetric Transformation of Ketoximes to Optically Active Amines

entry	substrate		convn[a] (%)	yield[b] (%)	ee[c] (%)
1		**1a**	> 98	80	98
2		**1b**	> 98	84	97
3		**1c**	> 98	81	94
4		**1d**	> 98	82	96
5		**1e**	> 98	76	98
6		**1f**	> 98	84	95
7		**1g**	> 98	70	97
8		**1h**	> 98	89	99

[a] On the basis of ^{1}H NMR analysis. [b] Isolated yields. [c] Enantiomeric excess on the basis of the HPLC analyses using a chiral column. Analytical conditions: Whelk-O1, *n*-hexane/2-propanol = 80/20, flow rate = 2.0 mL/min, UV 217 nm (**3a**−**d**); Chiralcel OD, *n*-hexane/2-propanol = 93/7 (**3e**), 85/15 (**3f**), 90/10 (**3g**,**h**), flow rate = 1 (**3a**−**f**), 0.5 mL/min (**3g**,**h**), UV 217 nm.

insignificant. The isolated yields of the acetylated products ranged from 70 to 89%: the highest in the reaction of **1h** and the lowest in that of **1g**. The volatile deaminated byproducts constituting the rest were removed readily during the workup. The optical purities were high (94−99% ee). The *R*-configuration was confirmed for four products (**3a**,**b**,**d**,**e**) by comparing their optical rotations with the literature data.[13] These results from Table 1 indicate that both acyclic and cyclic oximes are similarly good substrates toward the bicatalytic reductive acetylation. It is noteworthy that among

(10) In the racemization, the use of DBN (1,5-diazabicyclo[4.3.0]non-5-ene) or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the base gave the better results. However, the enzymatic acylation reaction did not proceed smoothly in the presence of the strong organic bases.

(11) Ketoximes were prepared 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.

(12) **Experimental detail**: A representative procedure is described for the reaction of **1a**. Substrate (50 mg, 0.37 mmol), Novozym-435 (100 mg), ethyl acetate (65 mg, 0.74 mmol), and diisopropylethylamine (143 mg, 1.11 mmol) were added to the suspension of Pd/C (5%, 33 mg, activated as described in the literature[7]) in toluene (3.7 mL) in a Schlenk flask. The flask was charged with dry hydrogen and heated at 60 °C for 5 days. The reaction mixture was cooled to room temperature, and the catalysts were filtered off. The resulting filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy. The residue was then subjected to a flash column chromatography (silica gel, ethyl acetate/*n*-hexane = 1/1) to obtain **3a** (48 mg, 0.29 mmol, 80%): mp 97−100 °C (lit.[6a] mp 98−100 °C).

(13) The optical rotations ($[\alpha]^{25}_D$, c = 0.1, $CHCl_3$) of the products (the literature data[6a] are given in parentheses): **3a**, +141° (−140°, c = 0.96, $CHCl_3$, (*S*)-isomer), **3b**, +146° (+144°, c = 1.03, $CHCl_3$); **3c**, +126° (−73.6°, c = 0.21, $CHCl_3$); **3d**, +145° (+51.2°, c = 0.11, $CHCl_3$); **3e**, +123° (+135°, c = 0.12, $CHCl_3$); **3f**, +72.4°; **3g**, +83.6°; **3h**, +79.2°. It is noted that our optical rotation of **3c** has an opposite sign from that of the literature value, indicating that the latter was reported incorrectly.

those examined the bicyclic substrate **1h** was the best and its deoxa analogue **1g** the poorest, indicating that the latter is more prone to reductive deamination.[14]

In summary, this work has demonstrated for the first time that prochiral ketoximes are asymmetrically converted to optically active amines by lipase−palladium bi-catalysis.[15] The procedure uses readily available substrates, catalysts, and reagents. It provides good yields and high optical purities. However, there is still some room for further improvements in yields. Particularly, the formation of side products by reductive elimination of the amino group should be more effectively reduced.[16] Further studies to overcome this limitation and broaden the scope are in progress.[17]

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(14) In this case, the steric crowdness in the cyclohexane ring increases going from oxime to amine, and thus the reductive deamination is slightly more favored.

(15) For the enantioselective synthesis of other chiral compounds such as allylic alcohols by the lipase/palladium bi-catalysis, see: (a) Allen, J. V.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 1859. (b) Choi, Y.-K.; Suh, J. H.; Lee, D.; Lim, I.; Jung, J. Y.; Kim, M.-J. *J. Org. Chem.* **1999**, *64*, 8423.

(16) The reductive elimination of amino group is particularly significant when the concentration of amine is high. That is why amines are not good substrates for lipase/ruthenium-catalzyed DKR. The side reaction can be reduced by increasing the amount of enzymes at the cost of ee.

(17) Simple imines are expected to be asymmetrically transformed to optically amines by the lipase/ruthenium bi-catalysis. However, simple imines have some disadvantages over ketoximes. They are more difficult to make and less stable.