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Dynamic Kinetic Resolution of Primary Amines with a Recyclable Pd Nanocatalyst for Racemization

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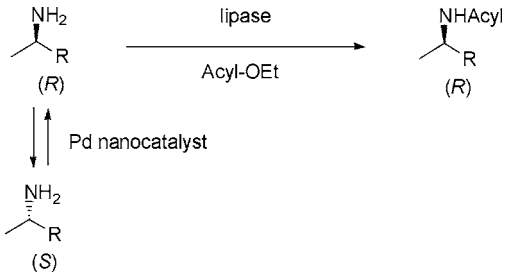
ABSTRACT



A practical procedure for the dynamic kinetic resolution (DKR) of primary amines has been developed. This procedure employs a palladium nanocatalyst as the racemization catalyst, a commercial lipase (Novozym-435) as the resolution catalyst, and ethyl acetate or ethyl methoxyacetate as the acyl donor. Eleven primary amines and one amino acid amide have been efficiently resolved with good yields (85–99%) and high enantiomeric excesses (97–99%).

The complete transformation of a racemic mixture into a single enantiomer is one of the challenging problems in chiral synthesis. Recently, a novel strategy has attracted great attention as a solution to this problem: *dynamic kinetic resolution (DKR) by the coupling of an enzymatic resolution with a metal-catalyzed racemization*.[1] Several groups including ours have developed enzyme−metal combinations as useful catalysts for such DKRs and demonstrated that racemic substrates can be efficiently transformed by them into enantiomerically enriched products with high yields and excellent enantiomeric excesses, both approaching 100%.[2] Now a pair of complementary enzyme−metal combinations, lipase−Ru and subtilisin−Ru, are available for the DKR of a wide range of racemic secondary alcohols.[3] The (*R*)-selective DKR can be performed with the former, whereas the (*S*)-selective DKR can be done with the latter. The DKR of amines including amino acids, however, is more challenging, and few practical procedures have been developed for such a DKR.[4−7] We herein wish to report for the first time a practical procedure using a palladium nanocatalyst for amine racemization, which is applicable for the DKR of primary amines as well as amino acid amides.

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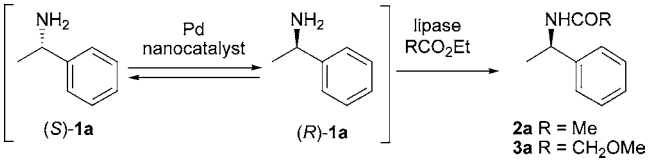
The first DKR of amine was reported by the Reetz group in 1996.[4] The DKR was done by the combination of Pd/C as the racemization catalyst and a lipase as the resolution catalyst in the presence of ethyl acetate as the acyl donor. Only one substrate, 1-phenylethylamine **1a**, was tested for DKR in this work. The reaction required a long reaction time and gave a moderate yield. Later, we reported the DKR of several amines by the lipase−Pd combination starting from ketoximes, giving better yields at shorter reaction times.[5] Lately, the Jacobs group reported an improved procedure using a modified lipase−Pd combination, in which Pd on alkaline earth metals was employed as the racemization catalyst.[6] On the other hand, the Bäckvall group introduced the use of a diruthenium complex as an alternative racemization catalyst, which displayed satisfactory activity at high temperature (90 °C).[7] Several primary amines were resolved with this catalyst and a lipase.

Our Pd nanocatalyst, Pd/AlO(OH), was prepared as palladium nanoparticles entrapped in aluminum hydroxide.[8] Its activity was examined in the racemization of optically active 1-phenylethylamine ((*S*)-**1a**, >99% ee) and compared with that of commercially available Pd/Al_2O_3. The racemization reactions were carried out with 1 mol % of palladium in toluene at 70 °C, and the change in the enantiomeric excess (ee) of the substrate was analyzed by HPLC. With the Pd nanocatalyst, the ee decreased to 29% at 12 h and reached near zero (2%) at 24 h. Meanwhile, it changed slowly to 94% and 88%, respectively, at 12 and 24 h with the commercial catalyst. These data clearly indicate that the racemization by the Pd nanocatalyst proceeds much more rapidly than by the commercial catalyst. It was also observed that the formation of some hydrolyzed and condensation products such as acetophenone and di(1-phenylethyl)amine took place in the prolonged racemization.[9] These byproducts amounted to 18% in the 24 h racemization. However, the amounts of byproducts become significantly small or negligible in DKR itself because the enzymatic acylation of amine proceeds more rapidly than the side reactions.

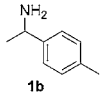
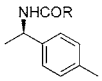
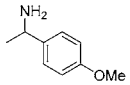
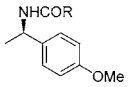
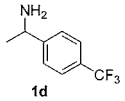
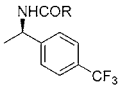
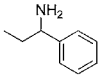
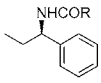
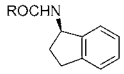
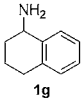
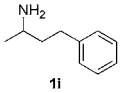
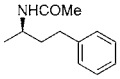
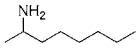
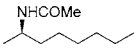
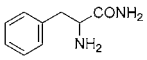
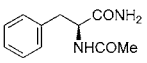
The DKR with the Pd nanocatalyst was explored with a commercial lipase (Novozym-435). First of all, **1a** was chosen as the first substrate to be resolved through the DKR. The DKR of **1a** was performed in the presence of molecular sieves with ethyl acetate as the acyl donor, 1 mol % of Pd/AlO(OH), and Novozym-435 (120 mg/mmol of substrate) in toluene at 70 °C for 3 days (Scheme 1). The DKR afforded

Scheme 1. Dynamic Kinetic Resolution of 1-Phenylethylamine



a good yield (conversion, 97%; isolated yield, 92%) and a high optical purity (98% ee). Here, molecular sieves were added to reduce the content of water mainly coming from the commercial enzyme, which could cause the hydrolysis of the imine intermediate to acetophenone. Later, it was found that the addition of molecular sieves, however, was unnecessary with the use of an activated acyl donor, ethyl methoxyacetates, and a significantly reduced amount of enzyme (15 mg/mmol of substrate). In this case, a better isolated yield (98%) was obtained with a high optical purity (>99% ee). These results encouraged us to test seven additional benzyl amines **1b**−**h** for DKR. For each substrate,

Table 1. Dynamic Kinetic Resolution of Primary Amines[a]

entry	substrate	product		yield[b] (%)	ee[c] (%)
1			**2b** R = Me	91	97
2	**1b**		**3b** R = CH_2OMe	85	99
3			**2c** R = Me	93	98
4	**1c**		**3c** R = CH_2OMe	85	98
5			**2d** R = Me	95	98
6	**1d**		**3d** R = CH_2OMe	99	99
7			**2e** R = Me	90	98
8	**1e**		**3e** R = CH_2OMe	96	99
9			**2f** R = Me	88	99
10	**1f**		**3f** R = CH_2OMe	87	97
11			**2g** R = Me	86	97
12	**1g**		**3g** R = CH_2OMe	84	99
13			**2h** R = Me	94	98
14	**1h**		**3h** R = CH_2OMe	92	99
15			**2i**	95	98
	1i				
16			**2j**	93	99
	1j				
17			**2k**	92	98
	1k				
18			**2l**	96	98
	1l				

[a] All the reactions except four cases (entries 15−18) were carried out in toluene at 70 °C under two different conditions: (1) 1 mol % of Pd nanocatalyst, 120 mg/mmol of Novozym-435, 3 equiv of AcOEt, and 700 mg/mmol of molecular sieves. (2) 1 mol % of Pd nanocatalyst, 15 mg/mmol of Novozym-435, and 1.7 equiv of ethyl methoxyacetate. In the exceptional cases, the reactions were done with 12 mol % of Pd nanocatalyst, 120 mg/mmol of Novozym-435, and 3 equiv of AcOEt in toluene at 100 °C. [b]Isolated yield. [c]Determined by HPLC using a chiral column.

two DKR reactions were carried out with a variation in the acyl donor: one with ethyl acetate and the other with ethyl methoxyacetate. The results (entries 1−14) described in Table 1 indicate that all the DKRs proceeded successfully with good isolated yields and high optical purities.

Next, we explored the DKR of aliphatic amines which are more difficult to racemize than benzyl amines. The reaction conditions were modified to facilitate racemization. Molecular hydrogen (1 atm) was employed with an increased amount of Pd/AlO(OH) (12 mol %) at higher temperature (100 °C). Here, the use of hydrogen not only enhances the racemization efficiency through the hydrogenation of the imine intermediate but also makes the addition of molecular sieves unnecessary because it reduces the level of the imine intermediate prone to the hydrolysis. Surprisingly, the DKR of **1i** in the presence of ethyl acetate as the acyl donor reached completion at a short time (4 h) and afforded the products of high optical purity in an almost quantitative yield (entry 15). Additional aliphatic amines, **1j** and **1k**, were also successfully resolved under these conditions (entries 16 and 17). For these aliphatic amines, the DKRs in the presence of ethyl methoxyacetate instead of ethyl acetate were not tried because the chemical acylation of amine by the activated acyl donor was observed at 100 °C.

The successful procedure for the DKR of aliphatic amines was then applied to the DKR of an amino acid amide, phenylalanine amide, which afforded an almost quantitative yield with high optical purities (entry 18). This is the first example for the DKR of an amino acid amide by the combination of enzyme and metal.[10]

Finally, we examined the stability of the Pd nanocatalyst through the recycling experiments. The first recycling experiment was done for the racemization of (*S*)-**1i**. The racemization reaction was performed 10 times with the recycling of the nanocatalyst (8 mol %), each time under hydrogen (1 atm) in toluene at 100 °C for 24 h. No significant decrease in racemization efficiency was observed until the 10th recycling. The second recycling experiment was done for the DKR of **1i**. The DKR reaction was carried out 11 times with the recycling of both the Pd nanocatalyst and lipase under the conditions described above. The complete conversion was achieved until the 8th recycling, and then a gradual decrease in conversion yield was observed. The conversion yield, however, was still good (89%) even for the 10th recycling and fully recovered to the completion level by the addition of some fresh enzymes (half of the initial amount) in the 11th run. On the other hand, the ee value decreased by less than 1% every recycling until the 10th recycling (from 99% to 92%) and then increased to a good level (95%) in the 11th run. These results clearly indicate that the Pd nanocatalyst is robust and sustainable. It is also noteworthy that the lipase is thermostable and recyclable even at 100 °C.

In summary, we have demonstrated that the DKR of amines can be efficiently performed by using a Pd nanocatalyst for racemization together with a lipase as the resolution catalyst. Both benzyl and aliphatic amines are transformed by these catalysts to the corresponding amides with good yields and high optical purities. The DKR of amino acid amide also proceeds equally well with the same catalysts. Because the catalysts are highly thermostable, the DKR reactions can be operated at 100 °C with the multiple recycling of these catalysts. The products from the DKR reactions can be readily deacylated to give primary amines or reduced to the corresponding secondary amines. Therefore, our DKR method provides a useful route to optically active primary and secondary amines.[11] It is concluded that this work presents an excellent illustration for the complete conversion of racemic substrates to single enantiomeric products by enzyme−metal combination.

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Supporting Information Available: Experimental procedures and data for racemization, DKR, and recycling and the analytical data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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

(9) The hydrolysis of the imine intermediate ($Ph(CH_3)C{=}NH$) from the racemization gives acetophenone, which in turn reacts with 1-phenylethyl amine, followed by hydrogenation, to yield di(1-phenylethyl)amine. The secondary amine product may be formed through the condensation of imine with 1-phenylethylamine.

(10) For the purely enzymatic DKR of amino acid amides, see: Asano, Y.; Yamaguchi, S. *J. Am. Chem. Soc.* **2005**, *127*, 7696−7697.

(11) For a chemoenzymatic deracemization route to these amines, see: (a) Alexeeva, M.; Enright, A.; Dawson, M. J.; Mahmoudian, M.; Turner, N. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3177−3180. (b) Carr, R.; Alexeeva, M.; Dawson, M. J.; Gotor-Fernández, V.; Humphrey, C. E.; Turner, N. J. *ChemBioChem* **2005**, *6*, 637−639. (c) Dunsmore, C. J.; Carr, R.; Fleming, T.; Turner, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2224−2225.