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COMMUNICATION

Dynamic Kinetic Resolution of Aromatic *sec*-Alcohols by using a Heterogeneous Palladium Racemization Catalyst and Lipase†

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Yuanfeng Xu, Meng Wang, Bo Feng, Ziyang Li, Yuanhua Li, Hexing Li and Hui Li*

Microwave-assisted one-pot dynamic kinetic resolution of aromatic secondary alcohols is successfully conducted by using a recyclable chemoenzymatic catalyst combination. This design concept will attract more attention in the foreseeable future for the synthesis of chiral drugs and their building blocks.

Enantiomerically pure alcohols are among the important key intermediates used in the pharmaceutical and agrochemical industries.[1] The enzyme-aided kinetic resolution (KR) is one of the most widely utilized methods for the production of chiral alcohols.[2] However, the resolution process is generally limited to a maximum yield of 50%. The combination of KR and in situ racemization of the remaining enantiomer results in a dynamic kinetic resolution (DKR) process, an option to tackle this problem. This modification increase the theoretical yield to 100% of a single enantiomer staring from a racemic mixture.[3] Several racemization methods have been developed those used chemocatalysts such as homogeneous transition-metal catalysts, solid acids, or supported metal catalysts.[4] In the early development of DKR processes for secondary alcohols (*sec*-alcohols), homogeneous rhodium and ruthenium catalysts played a key role. The most efficient DKR applications utilizing homogeneous Ru-based racemization catalysts have been pioneered by the groups of Bäckvall, Kim, and Park.[5] However, the Ru complexes are expensive and triggered the development of cheap transition metal catalysts. Efficient cooperative oxovanadium/lipase systems for DKR of *sec*-alcohols were prepared successfully by Akai and co-workers.[6] More recently, El-Sepelgy et al. published a study of the Knölker-type iron complexes as racemization catalysts for (*R*)-1-phenylethanol and their combination with lipase for DKR of *sec*-alcohols.[7] Heterogeneous acids are often cost effective alternatives compared to expensive transition-metal-complexes;[8] however, acid-catalyzed racemization presents numerous drawbacks, particularly including the denaturation of the enzyme suffered from the strong acidic nature and the lowering yield due to the formation of the styrene byproducts through dehydration pathway.[8a,8f] Zacceria et al. have been set up a method for the *sec*-alcohols transfer dehydrogenation catalyzed by a heterogeneous, reusable copper catalyst (Cu/Al_2O_3).[9] However, a strong inhibition of the catalyst activity was found for racemization of *sec*-alcohol due to the coordination of the oxygen in substance to the active copper sites. Accordingly, further efforts to employ a Cu-based racemization catalyst for DKR were not pursued. Up to now, several immobilized Ru^{3+} catalysts have been developed for the racemization of *sec*-alcohols.[10] Although such heterogeneous catalysts were efficient in combination with enzymes for developing DKR of *sec*-alcohols, their stability was unclear due to the lack of durability studies. Despite these advances, DKR protocols with efficient and reusable catalysts would be highly desirable.

Metallic palladium nanoparticles (NPs) have proven as excellent racemization catalysts for chiral amines;[11] however, their applications in DKR of *sec*-alcohols was rarely reported. In the present work, we report the synthesis of Pd NPs with size of approximately 2.8 nm immobilized on mesoporous silica (Pd@SBA-15), which delivers highly efficient racemization activity on optically active *sec*-alcohols. Under microwave irradiation the combination of Pd@SBA-15 and commercially available lipase (Novozym® 435) served as a powerful catalyst system for the DKR of various racemic *sec*-alcohols to give optically active esters in good yield and excellent enantioselectivity.

In general, a sufficiently high racemization rate is required to ensure the continuous feed of the faster-reacting enantiomer to the enzyme catalyst. The activity of Pd is primarily determined by its dispersion, thus the synthesis of size-controlled Pd NPs at a few nanometers scale is of great importance. The oleylamine-capped Pd NPs was synthesized in a water-in-oil microemulsion system (as described in the Experimental Section, ESI†), as we reported previously.[12] The

The Education Ministry Key Lab of Resource Chemistry and Shanghai Key Laboratory of Rare Earth Functional Materials, Shanghai Normal University, Shanghai, 200234, China. E-mail: lihui@shnu.edu.cn

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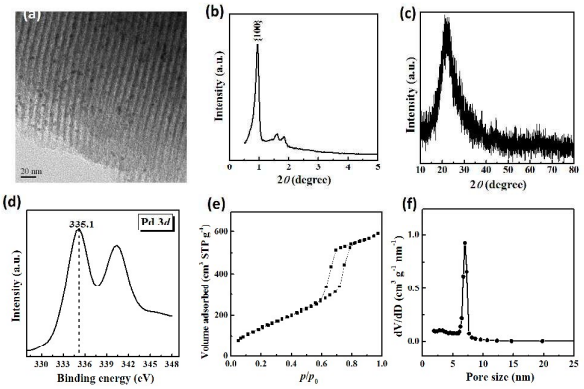
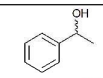
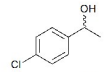
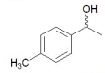
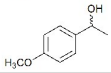
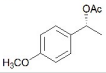


Fig. 1 (a) TEM image, (b) low-angle XRD pattern, (c) wide-angle XRD pattern, (d) XPS spectrum, (e) N_2 adsorption-desorption isotherms, and (f) pore size distribution of Pd/SBA-15.

transmission electron microscopy (TEM) image (Fig. S1a, ESI†) reveals that the as-prepared oleylamine-capped Pd was present in the form of uniformly ultrafine particles. The average particle size was about 2.8 nm. The XPS spectrum (Fig. S1b, ESI†) demonstrates that the Pd species in the as-prepared Pd were present in a metallic state, corresponding to the binding energy (BE) of 335.1 eV in Pd $3d_{5/2}$ core level.[13] Recovery of these colloidal Pd NPs following subsequent reactions was rather challenging. More importantly, the accessibility of metallic Pd to enzyme would cause denaturation. Then, we immobilized the Pd NPs onto the well-documented mesoporous silica, SBA-15 (Fig. S2, ESI†), to utilize the activity of the Pd NPs while allowing the system to behave heterogeneously. To obtain a surfactant-free Pd surface, the supported Pd sample was subjected to acetic acid at 343 K to remove the oleylamine molecules. Fourier transform infrared (FTIR) spectra of the as-prepared Pd@SBA-15 sample before and after extraction (Fig. S3, ESI†) reveal that the absorbance peaks at 2927 and 2850 cm^{-1}, assigned to asymmetric stretching and symmetric stretching vibrations of aliphatic C–H in oleylamine, disappeared completely. Thus, one could conclude that the applied template had been successfully removed from the final product after being treated with acetic acid. TEM image of Pd@SBA-15 (Fig. 1a) demonstrates that those Pd NPs were highly dispersed on the channels of support. It is to be noted that depositing of Pd NPs on the SBA-15 support caused any insignificant change in the low-angle and wide-angle XRD patterns (Fig. 1b and Fig. 1c). The presence of Pd NPs in Pd@SBA-15 was confirmed by the XPS spectrum (Fig. 1d). Further evidence comes from the N_2 physisorption. After Pd NPs loading, slight reduction in the S_{BET} (from 717 to 672 m^2/g) and D_p (from 3.3 to 3.0 nm) was observed (Fig. 1e and Fig. 1f), suggesting that Pd NPs dispersed well on the channels of SBA-15 support.

Initially, the racemization activity of Pd@SBA-15 catalyst was evaluated using (*S*)-1-phenylethanol to determine the optimal reaction conditions (Table S1, ESI†). The racemization rate was found to be highly affected by temperature (Table S1, entries 1-4, ESI†). At low temperature, the dehydrogenation of (*S*)-1-phenylethanol on the surface of Pd is not activated fully, leading to relatively higher *ee* value, whereas high temperature caused slight decrease in the selectivity because of the

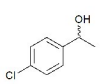
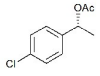
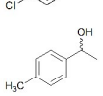
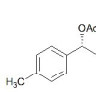
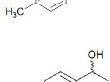
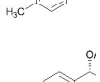
Table 1 DKR of racemic phenylethanol through Pd/lipase cocatalysis[a]

Entry	Alcohol	Product	Conversion (%)	Yield (%)	*ee* (%)
1			87	86	98
2			89	88	97
3			83	82	98
4			90	89	95

[a] Reaction conditions: a catalyst containing 2 mg of Pd, 100 mg of Novozym® 435, 0.5 mmol of *rac*-alcohol, 1.5 mmol of vinyl acetate, T = 70 ℃, P_{H2} = 0.03 MPa, 4 mL of *n*-hexane, t = 15 h.

increased desorption rate of the produced ketone. Furthermore, the enhancement of an appropriate hydrogen pressure is needed to prevent ketone formation (Table S1, entries 2, 5-7, ESI†). Nevertheless, much high hydrogen pressure could strongly slow down the racemization because the number of the gas molecules is increased during the dehydrogenation reaction of (*S*)-1-phenylethanol. Moreover, nonpolar *n*-hexane seemed to be the best solvent for racemization of (*S*)-1-phenylethanol in the presence of Pd@SBA-15 but the racemization rate slowed down in the polar *i*-PrOH and 83% ee was detected (Table S1, entries 2, 8-10, ESI†). In general, the less polar intermediate ketone is stabilized to a greater extent than the more polar starting material alcohol in the presence of nonpolar solvent, and thus the racemization proceeds faster. Prolonging the time to 15 h, Pd@SBA-15 nearly completed the racemization of (*S*)-1-phenylethanol (Table S1, entry 11, ESI†).

Table 2 Microwave-assisted DKR of racemic phenylethanol through Pd/lipase cocatalysis[a]

Entry	Alcohol	Product	*t* (h)	Conversion (%)	Yield (%)	*ee* (%)
1			2	81	80	99
2			4	89	89	99
3			4	90	89	98
4			4	88	88	97
5			4	89	89	98

[a] Reaction conditions: a catalyst containing 2 mg of Pd, 100 mg of Novozym® 435, 0.5 mmol of *rac*-alcohol, 1.5 mmol of vinyl acetate, T = 70 ℃, P_{H2} = 0.03 MPa, 4 mL of *n*-hexane.

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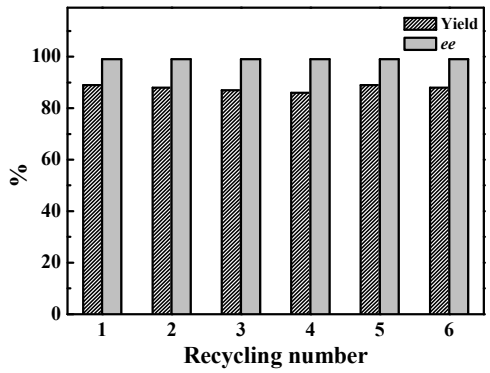

Fig.2 Recycling test of the enzyme and Pd@SBA-15 catalysts for microwave-assisted one-pot DKR of *rac*-1-phenylethanol. Reaction conditions: a catalyst containing 2 mg of Pd, 100 mg of Novozym® 435, 0.5 mmol of *rac*-1-phenylethanol, 1.5 mmol of vinyl acetate, T = 70 ℃, P_{H_2} = 0.03 MPa, 4 mL of *n*-hexane. Each run was conducted for 4 h in recycling test.

DKR of racemic *sec*-alcohols was performed in a one-pot process by combining the Pd-catalyzed dehydrogenation-hydrogenation sequence with the enzyme-aided resolution *via* acetylation using commercially available immobilized lipase B from *Candida antarctica* (Novozym® 435). Racemic 1-phenylethanol was converted to enantiopure acetate in a good yield (86%) with a high 98% *ee* value (Table 1, entry 1), thus demonstrating the excellent compatibility of Pd@SBA-15 with Novozym® 435. The DKR of racemic 1-phenylethanols with electron-withdrawing or electron-donating groups did not show obvious differences (Table 1, entries 2-4). This means that the DKR is relatively insensitive to the electronic characteristics of the substituents under the present conditions.

A separate KR experiment confirmed that the enzymatic reaction took only 2 hours (Table S2, entry 1, ESI†), much shorter than that needed in racemization. To achieve a good DKR, the rate of racemization should be at least of a similar order of magnitude as the KR. Parvulescu et al. reported microwave irradiation as heating method to increase racemization rate of amines over Pd,[11g] which provided an efficient tool for matching the Pd-catalyzed racemization of alcohols with the enzyme-aided resolution. Initial attempt to apply microwave irradiation in DKR of racemic 1-phenylethanol gave 80% yield combined with 99% *ee* within 2 hours (Table 2, entry 1). Doubling the DKR time delivered an appreciably high yield (89%) at 99% *ee* of the resulting (*R*)-1-phenylethanol (Table 2, entry 2). In general, the microwave irradiation induces local "super hot" dots on the metal surface, which can accelerate the chemical reactions.[14] To confirm the acceleration effect of microwave irradiation on Pd nanoparticles rather than other catalyst and the whole system, the racemization of (*S*)-1-phenylethanol under microwave heating conditions had been done. The results revealed that under microwave irradiation, the racemization catalyst Pd@SBA-15 gave similar performances even within shorter time (2 or 4 h) compared with the results obtained under normal heating condition after 15 h (Table S1, entries 12, 13, ESI†). Moreover, we had studied the activity of Novozym® 435 for the KR of racemic 1-phenylethanol under microwave heating condition. No differences in activity or enantioselectivity were observed between the conventional heating and microwave heating (Table S2, entries 2, 3, ESI†). Thus, the influence of microwave heating on the KR of secondary alcohol can be excluded. Apart from greatly enhanced activity, the yields in the microwave-assisted DKR of racemic 1-phenylethanols increased, as did the *ee* values (Table 2, entries 2-5). This is mainly attributed to the limitation on the unfavorable metal-enzyme interaction during the DKR with shortening time.A comparison study on the catalytic performances of our Pd@SBA-15/Novozym® 435 combination in DKR of racemic 1-phenylethanol with the reported chemoenzymatic catalyst combinations, including half-sandwich Ru complexes, $AlMe_3$/binol, Knölker-type iron complexes, zeolites, $VOSO_4$, as well as $Ru(OH)_3$, was done (Table S3 ESI†). Once homogeneous complexes were used as racemization catalysts, DKR of *rac*-1-phenylethanol can be carried out at lower temperatures; however, most of the cases needed longer reaction times relative to our chemoenzymatic catalyst combination. In comparison with the reported heterogeneous catalysts, including zeolites and $Ru(OH)_3$, the present chemoenzymatic catalyst combination gave similar yield and even more excellent enatioselectivity within shorter reaction time.

An important aspect of heterogeneous catalysis is the simple product isolation and catalyst recycling. Besides the high efficiency, both catalysts could be easily separated from the reaction solution *via* centrifugation and could be used repetitively six times without appreciable loss of yield and the *ee* of the resulting (*R*)-1-phenylethanol during the microwave-assisted DKR of 1-phenylethanol (Fig. 2). More importantly, Pd@SBA-15/Novozym® 435 combination showed much better recoverability and durability than the reported chemoenzymatic catalyst combinations (Table S3 ESI†). This result demonstrates the robustness of this chemoenzymatic catalyst combination in the present DKR conditions.

In conclusion, Pd NPs immobilized on mesoporous silica is an efficient catalyst for the racemization of phenylethanol. The racemization can be combined with enzymatic kinetic resolution in a one-pot process leading to optically pure *sec*-alcohols from racemic alcohols with good yields and excellent *ee* values. When the DKR of 1-phenylethanol was subjected to microwave heating, the induced local "super hot" dots on the Pd surface accelerated the racemization, thus greatly shortening the DKR time. Another important factor in the success of the DKR is the mutual compatibility between the immobilized lipase and Pd. Furthermore, this heterogeneous chemoenzymatic catalyst combination can be recovered and recycled several times without any loss of efficiency.

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Conflicts of interest

There are no conflicts to declare.

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SYNOPSIS TOC

Dynamic Kinetic Resolution of Aromatic *sec*-Alcohols by using a Heterogeneous Palladium Racemization Catalyst and Lipase

Yuanfeng Xu, Meng Wang, Bo Feng, Ziyang Li, Yuanhua Li, Hexing Li and Hui Li*

A novel recyclable chemoenzymatic catalyst combination has been designed which successfully converted *sec*-alcohols to chiral acetates under microwave irradiation.