Journal of Catalysis 363 (2018) 9–17

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Dynamic kinetic resolution of amines by using palladium nanoparticles confined inside the cages of amine-modified MIL-101 and lipase

Sen Xu, Meng Wang, Bo Feng, Xinchen Han, Zijie Lan, Huajun Gu, Hexing Li, Hui Li *

The Education Ministry Key Lab of Resource Chemistry and Shanghai Key Laboratory of Rare Earth Functional Materials, Shanghai Normal University, Shanghai 200234, PR China

ARTICLE INFO

Article history:
Received 28 February 2018
Revised 31 March 2018
Accepted 3 April 2018

Keywords:
Dynamic kinetic resolution
Chiral amine
Palladium
Lipase
MOFs

ABSTRACT

Dynamic kinetic resolution (DKR) of amines is an important strategy for the synthesis of chiral drugs and their building blocks; however, improving the matchability of metal-catalyzed racemization and enzymatic resolution is still a task. In this paper, Pd nanoparticles (NPs) were encapsulated inside the cages of ethylenediamine-grafted MIL-101 (ED-MIL-101), giving highly efficient catalysts (Pd/ED-MIL-101) for the racemization of primary amines. The racemization can be combined with lipase-catalyzed resolution in a one-pot DKR of *rac*-1-phenylethylamine leading to optically pure product (>99% *ee* value) with an excellent conversion and selectivity up to 99% and 93%, respectively, superior to other catalysts, such as Pd/MIL-101, Pd/MCM-41 and commercially available Pd/C. Furthermore, the heterogeneous chemoenzymatic catalyst combination can be recovered and recycled 8 times without significant loss of efficiency. The enhance catalytic performances were found to depend on the amine modification of MIL-101 that not only endows the surface of its cages with basic property, but also enables efficiently confining Pd NPs in the cages. In addition, the matchability of such chemoenzymatic catalyst combination can be further enhanced by conducting the DKR process under microwave irradiation.

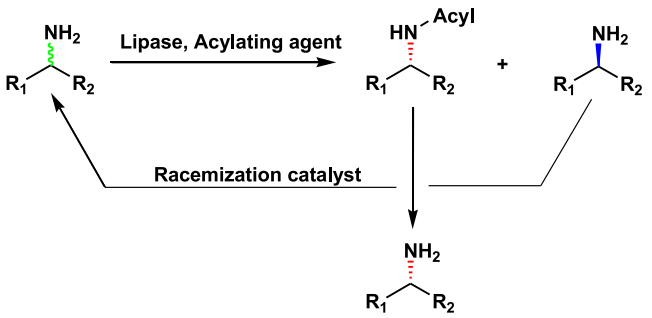
© 2018 Elsevier Inc. All rights reserved.

1. Introduction

There is an ever increasing requirement for chiral amines, primarily for use as pharmaceuticals, but also for use as important key intermediates in fine chemical and agrochemical industries [1]. Despite great achievements in catalytic asymmetric synthetic transformations [2–4], kinetic resolution (KR) of racemic starting materials is still the most common approach to obtaining enantiomerically pure amines in industrials [5]. The enzyme-aided KR is one of the most widely utilized methods for the synthesis of chiral amines [6]. 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 (Scheme 1), which is an option to tackle this problem. This modification increases the theoretical yield to 100% of a single enantiomer starting from a racemic mixture [7–11]. Furthermore, one-pot DKR that combining of racemization catalyst and enzyme into a single reaction vessel usually increases the profitability and efficiency of the process by reducing costs, time, as well as labor efforts [12]. In general, racemization of amines is difficult to achieve and requires harsh reaction conditions, resulting in the rate-determining racemization step in one-pot DKR process. To ensure the matchability of the racemization reaction with the enzyme-aided KR, a sufficiently high racemization rate is demanded for the continuous feed of the faster-reacting enantiomer to the enzyme catalyst. Several racemization methods have been developed using basic catalysts, enzymes, or transition-metal catalysts [13]. The former two kinds of racemization are relatively infrequent and thus, not applied in DKR process. In the development of one-pot DKR processes for amines, homogeneous Shvo-type ruthenium complexes played a key role. The most efficient DKR applications utilizing homogenous Ru-based racemization catalysts have been pioneered by the group of Bäckvall [14,15]. However, homogeneous transition-metal catalysis also presents a number of drawbacks, particularly including the catalyst reusability and the environmental pollution from heavy metallic ions [16,17]. The development of heterogeneous racemization catalysis system with high efficiency is preferred due to the easier work-up protocols, simple product isolation, as well as catalyst recycling [18]. The first example of heterogeneous DKR of amine was reported by Reetz and Schimossek using Pd/C for the racemization and lipase (CALB, Novozym® 435) for the enzymatic resolution [19]. This combination required long reaction time (8 days) to provide excellent *ee* value (99%) and moderate yield (75–77%) in the one-pot DKR of 1-phenylethylamine. Generally, the activity

* Corresponding author.
E-mail address: lihui@shnu.edu.cn (H. Li).

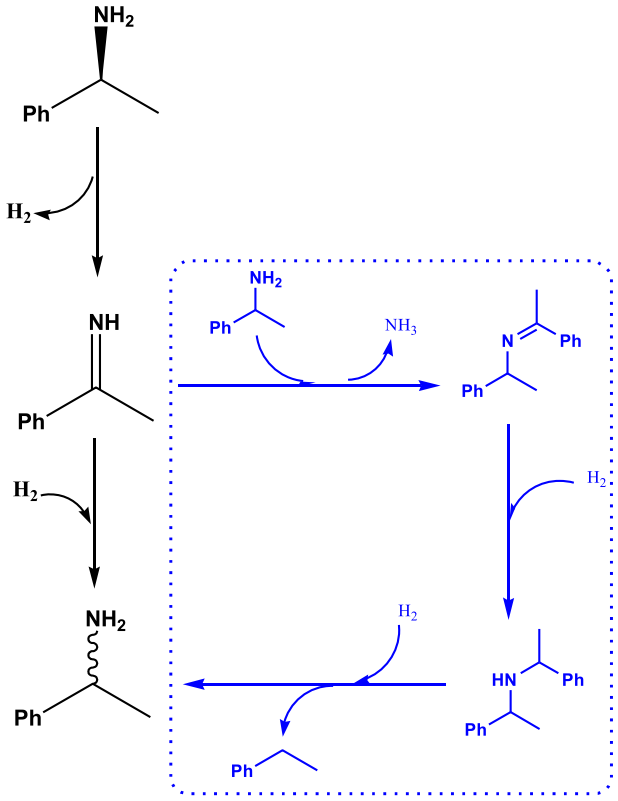
https://doi.org/10.1016/j.jcat.2018.04.006
0021-9517/© 2018 Elsevier Inc. All rights reserved.



Scheme 1. DKR of *rac*-amine.

of Pd is primarily determined by its dispersion, thus the synthesis of Pd nanoparticles (NPs) on a few nanometer scale is of great important. Kim et al. [20] reported an improved process using a modified lipase-Pd combination, in which Pd NPs in the range of 2–3 nm entrapped in aluminum hydroxide [21], Pd/AlO(OH), was employed as the racemization catalyst. The racemization of (*S*)-1-phenylethylamine by Pd/AlO(OH) proceeded much more rapidly compared to the commercially available Pd/Al_2O_3, most likely because of the high dispersion of the metallic Pd active sites. The one-pot DKR of 1-phenylethylamine was done by the combination of Pd/AlO(OH) and CALB in the presence of molecular sieves, giving a good yield (92%) and a high optical purity (98% *ee*) at shorter reaction time (3 days) [20]. Jacobs [22] and De Vos [23] utilized $Pd/BaSO_4$ in combination with CALB for the DKR of 1-phenylethylamine, obtaining good conversion (91%) and selectivity (94%) with high *ee* value (99%) of the acetylated amine product within a more shorter reaction time (24 h). Another important aspect of one-pot DKR of amines is the control of selectivity towards the target products. Jacobs and De Vos found the main byproducts in amine racemization to be a result of competing condensation reactions to secondary amine and its subsequent hydrogenolysis to ethylbenzene (EB) (Scheme 2) [22,23]. Such side product formation could be strongly suppressed when alkaline earth salts were used as supports for Pd [22,23]. In their next work, Pd on amine-functionalized silica proved to be more selective for the racemization of 1-phenylethylamine relative to Pd on bare silica [24]. They demonstrated that the acid-base properties of the supports for Pd catalysts evidently influences the formation of by-products and should be modestly basic to enable suppress the formation of byproducts [24]. By incorporating alkalic salt, Jin et al. [25] prepared K_2CO_3-modified Pd catalysts, which could efficiently suppress side reactions during the racemization and thus enhance the yield in the DKR of 1-phenylethylamine in combination with Novozym® 435; however, their stability was unclear due to the lack of durability studies. Recently, several multifunctional hybrid materials containing Pd NPs loaded on basic support and enzymes were constructed, and served as catalysts for one-pot DKR of amines [26,27], whereas the stability or efficiency is still an open task. Despite these advances, one-pot DKR protocols with efficient catalysts would be highly desirable.

Presently, metal-organic frameworks (MOFs) have drawn tremendous attention owing to their abundant diversity in structure and composition and thus specific applications [28–30]. In the domain of catalysis, besides the well-demonstrated catalytic activity of pure MOFs, these materials are also attractive candidates for catalyst supports because of their unique porous features [31–33]. In previous work, we have used MIL-101 as support to encapsulate Pd NPs in its cages and applied the as-prepared Pd/MIL-101 for one-pot indole synthesis from 2-iodoaniline and phenylacetylene in aqueous media [34]. Our results exemplified the superiority of Pd/MIL-101 over other conventional Pd catalysts,



Scheme 2. Reaction mechanism for racemization of (*S*)-1-phenylethylamine.

both in terms of activity and durability. The enhanced catalytic performances of Pd/MIL-101 were found to depend on the specifical texture of MIL-101 matrix which impeded the agglomeration of Pd NPs while maintaining efficient substrate transport owing to the porous nature of the material. Additionally, Férey and coworkers conferred basic properties to MIL-101 by grafting amine groups onto the chromium(III) coordinatively unsaturated sites (CUSs) in their mesoporous cages and, then, used the resulting modified solid as a host for further loading of Pd NPs in the internal pores [35]. In the present work, Pd NPs were encapsulated inside the cages of both the bare and the the amine-grafted MIL-101 via a facile incipient wetting procedure followed by reduction with hydrogen, giving highly efficient racemization catalysts for primary amines. The racemization can be combined with enzymatic KR in a one-pot process leading to optically pure products from racemic amines, showing superior catalytic efficiency when compared to other catalysts, such as Pd/MCM-41 and commercial Pd/C. On the basis of various characterizations, the correlation of catalytic observations to the structural characteristics has been tentatively established, especially, getting an insight into the effect of amine modification of MOFs on catalytic performances.

2. Experimental section

2.1. Catalyst preparation

All of the chemicals used in this experiment were obtained from commercial sources and used without any other treatments. Novozym® 435 (immobilized lipase B from *Candida antarctica*), (±)-1-phenylethylamines, (*S*)-1-phenylethylamines, and 1%-Pd/C were purchased from Sigma-Aldrich Inc. (USA). Other reactants were purchased from Aladdin Industrial Co., Ltd. (Shanghai, China).

MIL-101 was synthesized following the method reported by Férey et al. [36]. Ethylenediamine (ED) grafted MIL-101 were

synthesized according to the method reported by Hwang et al. [35], and designated as ED-MIL-101. All the supported Pd catalysts were achieved *via* the procedure, as we described previously [34]. First, a certain amount of $Pd(acac)_2$ was dissolved into 1.0 mL of chloroform. A calculated amount of activated MIL-101 type material was then impregnated with the Pd precursor solution. The mixture was sonicated for 20 min with an ultrasonic batch (60 W) and stirred vigorously for 24 h in Argon flow. After being dried at 423 K for 8 h, the impregnated MIL-101 samples were reduced in a 10% H_2/Ar flow at 493 K for 2 h. The as-prepared samples were designated as x%-Pd/MIL-101 or x%-Pd/ED-MIL-101, where x % denotes the nominal Pd loading. For comparison, the reference 1.5%-Pd/MCM-41 catalyst was prepared through the same incipient wet impregnation followed by the reduction method.

2.2. Catalyst characterization

Fourier transform infrared (FTIR) spectra were obtained using a Thermo Nicolet Magna 550 spectrometer. The Pd loading was analyzed by means of inductively coupled plasma optical emission spectrometry (ICP-OES; Varian VISTA-MPX). The crystalline structure was investigated by X-ray diffraction (XRD; Rigaku D/Max-RB with Cu *Ka* radiation). The material shapes and morphologies were observed by both field emission scanning electron microscopy (FESEM; HITACHI S-4800) and transmission electron microscopy (TEM, JEOL JEM2100). The surface electronic states were determined by X-ray photoelectron spectroscopy (XPS; ULVAC-PHI PHI5000 VersaProbe system using Al *Ka* radiation). All of the binding energy (BE) values were calibrated by using C 1 s = 284.6 eV as a reference. N_2 adsorption–desorption isotherms were obtained at 77 K using a Micromeritics TriStar II apparatus. By N_2 adsorption, the Brunauer–Emmett–Teller (BET) surface area (S_{BET}) was calculated by using the multiple-point BET method in the relative pressure range of P/P_0 = 0.05–0.2. The pore size distribution curve were obtained by the Barrett–Joyner–Halenda model. The active surface area (S_{Pd}) was measured by the CO chemisorption at room temperature, which was performed on a Micromeritics AutoChem II 2920 instrument using a dynamic pulse method. The sample was purged under an argon flow (purity of 99.997%, treated with an Alltech Oxy-Trap column) at 423 K for 2 h. The pretreated sample was cooled down to room temperature under argon atmosphere, and CO pulses were injected at 303 K until the calculated areas of consecutive pulses were constant. According to the CO chemisorption, S_{act} of the as-prepared catalyst was calculated assuming Pd/CO = 1 and a Pd surface density of 1.27×10^{19} atoms m^{-2}.

2.3. Catalytic performances test

Racemization reactions were carried out in 15-mL stainless steel autoclaves containing a catalyst (0.75 mg Pd), 0.13 mmol of (*S*)-1-phenylethylamine, 4 mL of solvent, and 0.005–0.030 MPa of hydrogen at 343 K. To easily obtain hydrogen pressures below 0.1 MPa, a 5% hydrogen dilution in argon was used as reactive gas. The processes were monitored on a gas chromatography (Shimadzu GC-17A) with a CP-CHIRASIL-DEX CB chiral column (25 m × 0.32 μm, CP7503) and FID detection using *n*-heptane as an internal standard. DKR reactions were performed under the same conditions as above but with 0.13 mmol of *rac*-1-phenylethylamine as reactant, 37.5 mg of Novozym® 435 as acylation catalyst and 0.13 mmol of ethyl methoxy acetate as acyl donor. In a typical experiment, the one-pot DKR of racemic 1-phenylethylamine was carried out in a 15-mL stainless steel autoclave containing 1.5%-Pd/ED-MIL-101 (0.75 mg Pd), 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, 4 mL of toluene, and 0.015 MPa of hydrogen at 343 K. The reaction system was stirred vigorously (800 rpm) to eliminate the diffusion effect. The reaction mixture was sampled at intervals for product analysis by the GC as mentioned above. After cooling to room temperature at the end of the reaction, the catalyst was separated by centrifugation and washed with toluene for further characterizations and applications. Microwave-assisted DKR was carried out in a closed glass tube by using a commercially available microwave synthesis equipment (MAS-1 SINEO). The reaction mixture was flushed with a 5% H_2/Ar flow before vial was closed. The hydrogen partial pressure inside vial was 0.015 MPa. The reaction temperature was controlled by a continuous focused microwave power delivery system with power from 0 to 1360 W and a microwave frequency source of 2450 MHz.

3. Results and discussion

3.1. Catalyst characterization

The FTIR spectra reveal that, besides those absorbance bands observed in the bare MIL-101 (Fig. 1a), the ED-grafted MIL-101 (ED-MIL-101) displays additional absorbance bands at 2950 and 2890 cm^{-1}, corresponding to the asymmetric stretching and symmetric stretching vibrations of aliphatic C—H bonds [37]. More importantly, obvious red shift can be observed for these aliphatic C-H bond stretching vibrations, as observed when the ED molecules were linked to the chromium(III) CUSs [35]. This results confirm the successful grafting of ED groups onto the Lewis acid sites at the center of mesoporous cages.

The low-angle XRD pattern of the as-prepared MIL-101 (Fig. 2a) is in excellent agreement with the simulated pattern reported by Férey et al. [36]. The ED-grafted MIL-101 also displays similar XRD pattern (Fig. 2b) to the bare MIL-101, demonstrating that the resulting ED-MIL-101 preserved the crystallinity. Compared with both the hosts, the almost unchanged XRD patterns of 1.5%-Pd/MIL-101 (Fig. 2c) and 1.5%-Pd/ED-MIL-101 (Fig. 2d) mean that the Pd NPs incorporation occurred with no apparent loss of structure integrity, but with some slight variations of the Bragg intensities. Furthermore, no significant diffraction peak characteristic of Pd species is detected from the wide-angle XRD pattern from 1.5%-Pd/MIL-101 and 1.5%-Pd/ED-MIL-101 (Fig. 3), which might be related to the embedding of Pd NPs into the cages of MOF hosts. This observation is very similar to the results reported by EI-Shall et al. [38], where the incorporation of Pd in MIL-101 produced hardly significant signals of Pd in the XRD pattern unless the Pd loading was >4.9 wt%.

ICP-OES analysis confirmed the presence of Pd species in all the supported Pd catalysts, and it also revealed that the Pd loadings in all the Pd-containing samples were very similar to the nominal Pd contents in the preparation precursors (see Table 1). XPS spectra (Fig. 4) further demonstrate that almost all the Pd species in the

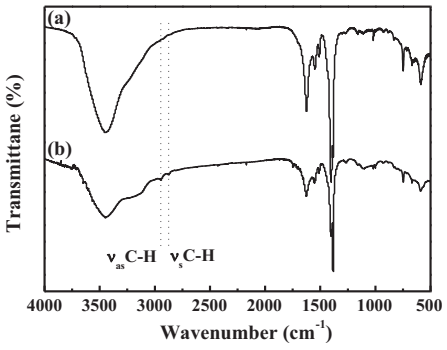


Fig. 1. FTIR spectra of (a) MIL-101 and (b) ED-MIL-101.

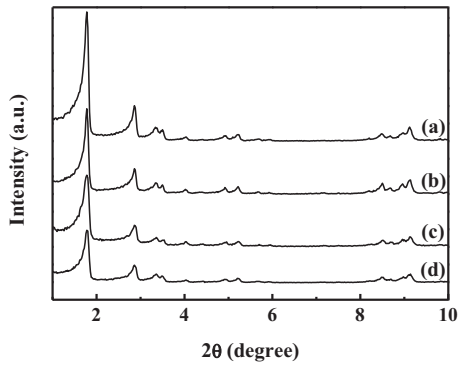


Fig. 2. Low-angle XRD patterns of (a) MIL-101, (b) ED-MIL-101, (c) 1.5%-Pd/MIL-101, and (d) 1.5%-Pd/ED-MIL-101.

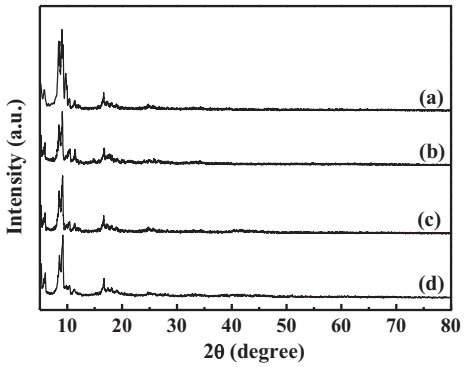


Fig. 3. Wide-angle XRD patterns of (a) MIL-101, (b) ED-MIL-101, (c) 1.5%-Pd/MIL-101, and (d) 1.5%-Pd/ED-MIL-101.

Table 1
Some structural properties of the as-prepared samples.

Sample	Pd loading (wt %)	S_{BET} (m^2/g)	S_{Pd} (m^2/g)	d_{Pd}[a] (nm)
MIL-101	–	3820	–	–
0.5%-Pd/MIL-101	0.48	3589	138	3.6
1.5%-Pd/MIL-101	1.4	3313	150	3.3
3%-Pd/MIL-101	2.9	3200	191	2.6
ED-MIL-101	–	3459	–	–
0.5%-Pd/ED-MIL-101	0.49	3256	221	2.3
1.5%-Pd/ED-MIL-101	1.4	3030	238	2.1
3%-Pd/ED-MIL-101	2.8	2730	250	2.0
1.5%-Pd/MCM-41	1.3	810	135	3.7

[a] Calculated as $6/(\rho S_{Pd})$, ρ = 12.02 g/cm^3.

x%-Pd/ED-MIL-101 were present in the metallic state with the BE about 335.1 eV in the Pd $3d_{5/2}$ core level, which is same as our previous reports on Pd/MIL-101 [34].

The N_2 adsorption-desorption isotherms and the pore size distribution profiles of the as-prepared MIL-101, ED-MIL-101, 1.5%-Pd/MIL-101, and 1.5%-Pd/ED-MIL-101 are shown in Fig. 5. The S_{BET} of MIL-101 was calculated to be 3820 $m^2\ g^{-1}$, which is close to the reported value [36,38–40]. The isotherms of MIL-101 have secondary uptakes around p/p_0 = 0.1 and 0.2 (Fig. 5a), indicating the existence of two kinds of nanopores [39]. The pore size distribution curve of MIL-101 also displays two different pore sizes, 1.7 and 2.2 nm (Fig. 4b), which is similar to the result reported by Pan et al. [40]. Compared with the bare MIL-101, ED-grafted MIL-101 exhibits significant decrease in both the S_{BET} (3459 $m^2\ g^{-1}$) and the average pore size (1.5 and 2.0 nm), which could be due to the coverage of the cage surface with the amine functionalities as reported

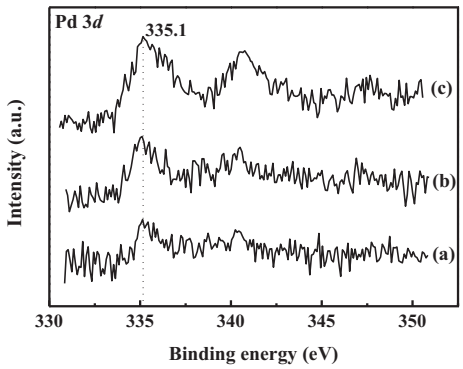


Fig. 4. XPS of (a) 0.5%-Pd/ED-MIL-101, (b) 1.5%-Pd/ED-MIL-101, and (c) 3%-Pd/ED-MIL-101.

by Hwang et al. [35]. Upon Pd loading, marked decrease in both the S_{BET} (see Table 1) and the average pore size (Fig. 4b) was noted for 1.5%-Pd/MIL-101 and 1.5%-Pd/ED-MIL-101, mainly because of the occupation of the cages of MIL-101 and ED-MIL-101 supports by the monodisperse Pd NPs.

As shown in FESEM image (Fig. 6a), the as-prepared MIL-101 is present in the form of octahedral shape on the micrometer scale, which is in agreement with the previous reports [38,39]. FESEM image of ED-MIL-101 (Fig. 6b) also displays similar octahedral morphology to the bare MIL-101. From the TEM images of the as-prepared MIL-101 (Fig. 6c) and ED-MIL-101 (Fig. 6d), the cubic symmetry of both the materials is also reflected in the shape of the crystals. These observations demonstrated that grafting of ED did not change the characteristic morphology of MIL-101. TEM images of 1.5%-Pd/MIL-101 (Fig. 6e) and 1.5%-Pd/ED-MIL-101 (Fig. 6f) reveal similar morphology and pore structure to the parent supports, further confirming that the structural integrity of MIL-101 hosts was preserved after the Pd incorporation. After deposition of 1.5 wt% Pd on both the supports, only a few NPs appear on the outside surface of the parent supports (Figs. 6e and f), demonstrating that most of the formed metallic Pd NPs were confined in the cages of the hosts [34,35]. This is in distinct contrast to the result of 1.5%-Pd/MCM-41 where much larger Pd particles were located at the external surface (Fig. S1), mainly due to the absence of the confinement effect of nanocages since MCM-41 possesses only straight channels.

It is worth noting that encapsulation of Pd NPs in the cages of MIL-101 type materials results in the difficulty measuring estimating the Pd particle size from TEM micrographs because of the poor particle-support contrast [34]. Therefore, CO chemisorption experiment was used to determine the Pd dispersion degree and subsequently calculate the Pd particle size [41]. Compared with 1.5%-Pd/MCM-41, both 1.5%-Pd/MIL-101 and 1.5%-Pd/ED-MIL-101 exhibit much higher Pd dispersion degree regardless of similar Pd loadings (Table 1). It can further verify the nanocage confinement effect on the formation of the Pd NPs in the range of 2.1–3.3 nm, in agreement with the cage diameters. For 1.5%-Pd/MCM-41, in contrast, the measured Pd size (3.7 nm) is much larger than the pore diameter of parent MCM-41 (2.4 nm), suggesting that most of Pd particles aggregated on the outer surface of MCM-41 support. This observation once again demonstrated the absence of remarkable confinement effect of straight channels in MCM-41 material. Accordingly, a portion of the formed Pd particles might emigrate out the pore channels of MCM-41, and agglomerate on the outer surface during the preparation procedure. Additionally, the CO chemisorption data (Table 1) also confirmed that, with nearly the same Pd loading, the surface amine functionalities had remarkable impact on the dispersion degree of the Pd NPs. The formation of

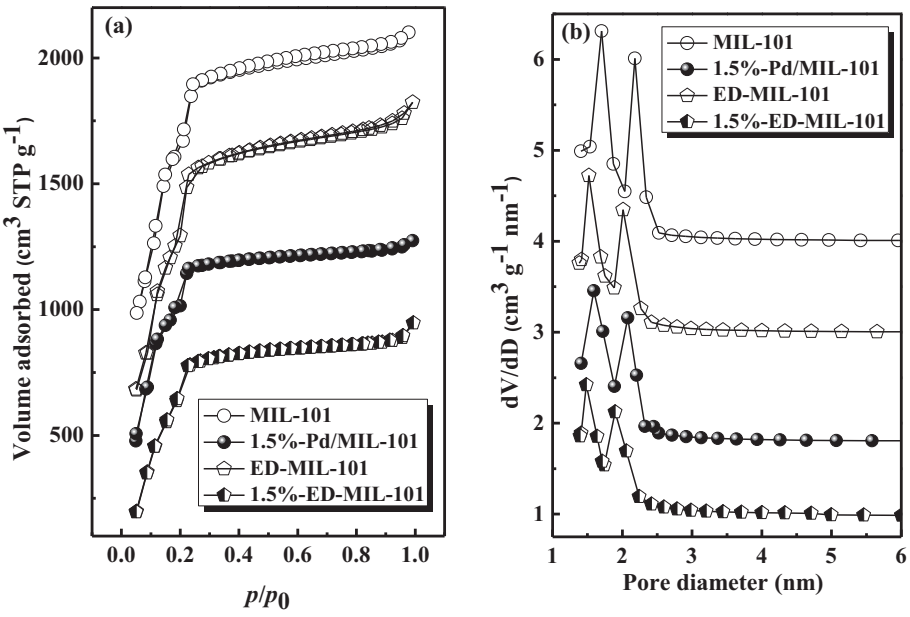


Fig. 5. (a) N_2 adsorption-desorption isotherms and (b) pore size distributions of MIL-101, ED-MIL-101, 1.5%-Pd/MIL-101, and 1.5%-Pd/ED-MIL-101.

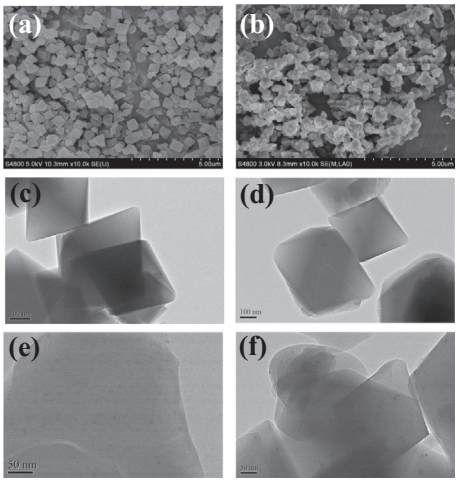


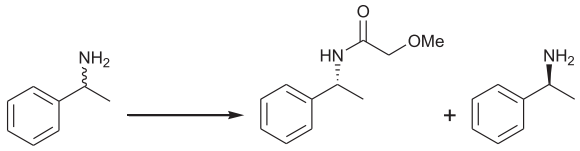
Fig. 6. FESEM images of (a) MIL-101 and (b) ED-MIL-101. TEM images of (c) MIL-101, (d) ED-MIL-101, (e) 1.5%-Pd/MIL-101, and (f) 1.5%-Pd/ED-MIL-101.

much fine Pd NPs in 1.5%-Pd/ED-MIL-101 (2.1 nm) than 1.5%-Pd/MIL-101 (3.3 nm), as observed clearly from the TEM micrographs, further demonstrates the superior influence of amine-grafting on incorporation of Pd NPs in the cages.

3.2. Catalytic performances

Initially, the racemization activity of 1.5%-Pd/MIL-101 catalyst was evaluated using (*S*)-1-phenylethylamine to determine the optimal reaction conditions. The racemization rate was found to be highly affected by temperature (Table S1, entries 1–4). At low temperature, the dehydrogenation of (*S*)-1-phenylethylamine on the surface of Pd was not activated completely, leading to a relatively higher *ee* value, whereas high temperature caused a significant decrease in the selectivity because of the increased side reaction rate. Furthermore, the decrease in an appropriate hydrogen pressure is needed to favor the dehydrogenation and suppress the formation of byproducts [23]; nevertheless, much lower hydrogen pressure could strongly slow down the racemization because the hydrogenation of intermediate imine could not proceed completely (Table S1, entries 2, 5, 6). Moreover, nonpolar toluene seemed to be the best solvent for the racemization of (*S*)-1-phenylethylamine in the presence of 1.5%-Pd/MIL-101 but the racemization rate slowed down greatly in polar solvents (Table S1, entries 2, 7–10). In general, the less polar intermediate imine is stabilized to a greater extent than the more polar starting material amine in the presence of a nonpolar solvent, and thus the racemization proceeds faster. Preliminary study also revealed that the optimal racemization of (*S*)-1-phenylethylamine was obtained on Pd catalyst with 1.5 wt% loading (Table S1, entries 2, 11, 12). The 1.5%-Pd/MIL-101 was therefore selected for the following studies. Despite similar Pd loading, 1.5%-Pd/MIL-101 was much more active than 1.5%-Pd/MCM-41 (Table S1, entry 13). Obviously, the higher reactivity over 1.5%-Pd/MIL-101 may be mainly attributed to its higher S_{Pd} (Table 1), which would provide more Pd active sites for the dehydrogenation and hydrogenation steps. Additionally, the conversion over 1.5%-Pd/MIL-101 was 20% higher than that over 1.5%-Pd/MCM-41, whereas the S_{Pd} of 1.5%-Pd/MIL-101 was only 11% larger than that of 1.5%-Pd/MCM-41. Thus, we can conclude that the larger S_{Pd} of 1.5%-Pd/MIL-101 was not the only facter responsible for its higher activity. The accessible mesoporous cages of MIL-101 may be another factor responsible for the higher activity of 1.5%-Pd/MIL-101 relative to 1.5%-Pd/MCM-41, which would favor the diffusion of the reactants into the pores reaching the Pd active sites and effectively increasing the collision frequency between reactants and Pd owing to the microreactor effect. Meanwhile, the improved selectivity over 1.5%-Pd/MIL-101 relative to 1.5%-Pd/MCM-41 may be explained as arising from the enhanced surface hydrophobicity of the MIL-101 host owing to the organic linkers (bdc), which can impede the side reactions. Moreover, side reactions are serious using commercially available Pd/C as racemization catalyst, mainly because of the presence of phenolic and carboxylic acid groups on the surface of charcoal. Meanwhile, Pd/C is known as an efficient hydrogenolysis catalyst for secondary amines at low hydrogen pressure [42]. This observation is in great agreement with Jacobs' work where no obvious improvement was found either using trimethylamine as solvent or catalyst pretreatment with base [22].

Table 2
DKR of racemic 1-phenylethylamine through Pd/lipase cocatalysis.[a]



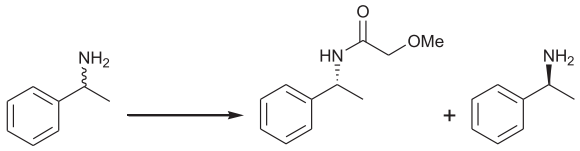
Entry	Pd catalyst	T (°C)	P_{H2} (MPa)	Solvent	Conv. (%)	Sel.$_{R\text{-amide}}$ (%)	Sel.$_{EB}$ (%)	*ee* (%)
1	1.5%-Pd/MIL-101	60	0.015	Toluene	73	83	14	>99
2	1.5%-Pd/MIL-101	70	0.015	Toluene	98	77	23	>99
3	1.5%-Pd/MIL-101	80	0.015	Toluene	97	71	29	>99
4	1.5%-Pd/MIL-101	90	0.015	Toluene	98	66	34	>99
5	1.5%-Pd/MIL-101	70	0.005	Toluene	84	68	10	>99
6	1.5%-Pd/MIL-101	70	0.030	Toluene	75	83	17	>99
7	1.5%-Pd/MIL-101	70	0.015	Methanol	79	80	19	>99
8	1.5%-Pd/MIL-101	70	0.015	Ethanol	91	76	22	>99
9	1.5%-Pd/MIL-101	70	0.015	DMF	79	79	19	>99
10	1.5%-Pd/MIL-101	70	0.015	Hexane	90	79	21	>99
11	0.5%-Pd/MIL-101	70	0.015	Toluene	90	67	20	>99
12	3%-Pd/MIL-101	70	0.015	Toluene	95	78	22	>99
13	1.5%-Pd/MCM-41	70	0.015	Toluene	82	70	30	>99
14	Pd/C	70	0.015	Toluene	85	40	38	>99

[a] Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, 4 mL of solvent, t = 18 h.

The DKR of *rac*-1-phenylethylamine 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). Apparently, the yields were far above the 50% limit and the product *ee* values exceeded 99% in all case when Pd-based catalysts were used for the one-pot DKR process (Table 2), thus demonstrating the excellent compatibility of Pd catalysts with Novozym® 435. It was also observed that the selectivity to the target products in the DKR process became greater significantly (Table 2) in comparison with that in the racemization reactions (Table S1) because the amines are generally well enzymatically acylated to the amides before it suffers irreversibly lost through condensation and hydrogenalysis [23]. Upon screening various parameters, the 1.5%-Pd/MIL-101 proved again to be the most efficient catalyst for DKR of *rac*-1-phenylethylamine when combining with Novozym® 435 (Table 2). Under optimal conditions, *rac*-1-phenylethylamine was converted to enantiopure amide in an excellent conversion (98%) and a moderate selectivity (77%) with a high *ee* value (>99%) within a shorter reaction time (18 h) (Table 2, entry 2). In comparison with the combination containing reference 1.5%-Pd/MCM-41 or commercially available Pd/C (Table 2, entries 13, 14), the present chemoenzymatic catalyst combination gave much more superior performances in the DKR of *rac*-1-phenylethylamine.

Despite this advance, efficient DKR protocols would be highly desirable, particularly the selectivity to the target product. Jin et al. have reported alkalic salt-modification of Pd catalysts to suppress side reactions during the racemization [25], which provided an efficient tool for enhance the yield in the DKR of *rac*-1-phenylethylamine. An attempt to addition Na_2CO_3 in the DKR of *rac*-1-phenylethylamine was conducted and the influence of the amount of Na_2CO_3 on the DKR performances of the combination of 1.5%-Pd/MIL-101 and Novozym® 435 was investigated (Table 3). Increasing the amount of Na_2CO_3 to 20 mg resulted in negligible change in the conversion; nevertheless, excess Na_2CO_3 dramatically decreased the catalytic activity because of the collapse of the MIL-101 matrix originating from the attack of basic Na_2CO_3 and thus the agglomeration of Pd NPs. Meanwhile, similar change in the *ee* value was observed, further confirming the collapse of the

Table 3
Effect of the amount of Na_2CO_3 on DKR of racemic 1-phenylethylamine through 1.5%-Pd/MIL-101/lipase cocatalysis.[a]



Na_2CO_3 amount (mg)	Conv. (%)	Sel.$_{R\text{-amide}}$ (%)	Sel.$_{EB}$ (%)	*ee* (%)
0	98	77	23	>99
5	97	78	22	>99
10	96	80	20	99
15	96	81	19	98
20	95	85	15	97
25	88	92	8	92
30	70	76	13	56

[a] Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, T = 70 °C, P_{H2} = 0.015 MPa, 4 mL of toluene, t = 18 h.

MIL-101 matrix at higher Na_2CO_3 content which exposed Pd NPs to lipase and thus causing unfavorable metal-enzyme interaction. Significant improvement of selectivity could be also determined with increasing the amount of Na_2CO_3 up to 25 mg, which can be primarily ascribed to the suppress effect of the basic salt on the condensation side reaction [22–25]. The distinct selectivity decrease at excess Na_2CO_3 (30 mg) was merely in connection with the agglomeration of the Pd NPs. In view of such results, 20 mg of Na_2CO_3 was selected as an effective additive to the one-pot DKR of *rac*-1-phenylethylamine catalyzed by the combination of 1.5%-Pd/MIL-101 and Novozym® 435, giving an enhanced selectivity (85%) in comparison with the Na_2CO_3-free system (77%). Industrial application of heterogeneous catalysis greatly relies on its stability [43]. Next, we investigated the durability of the combination of 1.5%-Pd/MIL-101 and Novozym® 435 during the one-pot DKR of *rac*-1-phenylethylamine in the presence of Na_2CO_3 additive. Apart from the slightly decreased *ee* value, the conversion during the recycling test decreased greatly, as did the selectivity (Fig. 7). This

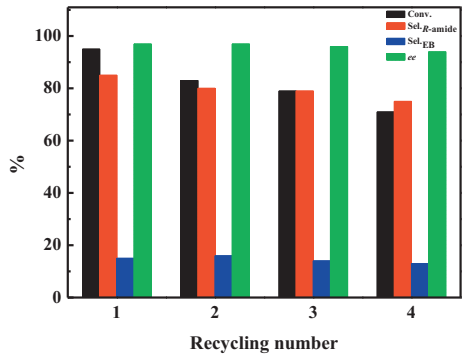


Fig. 7. Recycling test of the enzyme and 1.5%-Pd/MIL-101 catalysts for one-pot DKR of *rac*-1-phenylethylamine. Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, 20 mg of Na_2CO_3, T = 70 °C, P_{H2} = 0.015 MPa, 4 mL of toluene, t = 18 h.

undesirable stability is mainly due to the destruction of Na_2CO_3 additive on the structure of MIL-101, leading to a remarkable agglomeration of Pd NPs, as revealed by the TEM image of 1.5%-Pd/MIL-101 catalyst after 4 consecutive cycle (Fig. 8).

In an effort to favor the stability of metal-enzyme combination for the one-pot DKR of *rac*-1-phenylethylamine, MIL-101 was grafted with ED groups to afford ED-MIL-101 and then, providing 1.5%-Pd/ED-MIL-101 racemization catalyst. We first investigated the influence of the amount of ED during the preparation of ED-MIL-101 procedure on the DKR performances of *rac*-1-phenylethylamine catalyzed by Pd/lipase cocatalyst. Apparently, the selectivity to the enantiopure amide in the Na_2CO_3-free DKR process using 1.5%-Pd/ED-MIL-101 is equal to, or even higher than, that using 1.5%-Pd/MIL-101 accompanying with Na_2CO_3 additive (Table 4). More importantly, 1.5%-Pd/ED-MIL-101 with appropriate N content (1.9 mmol/$g_{cat.}$) delivered the most efficiency, an excellent conversion (99%) and a good selectivity (93%) with a high *ee* value (>99%), regardless of nearly the same Pd loading. On the basis of these observations, we could deduce that the ED-grafting on MIL-101 would render it moderate basicity and, on the other hand, favor the incorporation of Pd NPs with much small size in the cages. The Pd loading was also investigated and the 1.5%-Pd/ED-MIL-101 was screened as the most efficient catalyst for DKR of *rac*-1-phenylethylamine combining with Novozym® 435 (Table S2). It should be noted that, to keep the same Pd content, the amount of ED-MIL-101 used in the DKR process decreased with the increase of Pd loading. As a result, gradual decrease in selectivity was observed at higher Pd loading (Table S2).

Fig. 9 shows the reaction profile during the one-pot DKR of *rac*-1-phenylethylamine using the catalyst system containing both the 1.5%-Pd/ED-MIL-101 and Novozym® 435. Along with the production of amide, EB was identified as the only byproduct resulting from the hydrogenolysis of formed secondary amine. Although the content of EB was very low during the whole process of the test, the selectivity to EB increased gradually with the reaction time. Almost complete conversion of *rac*-1-phenylethylamine can be achieved within 18 h. Further prolonging the reaction time

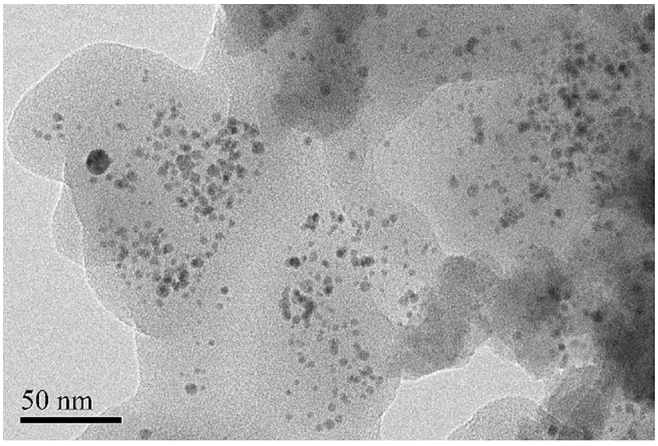


Fig. 8. TEM image of 1.5%-Pd/MIL-101 after 4 consecutive runs.

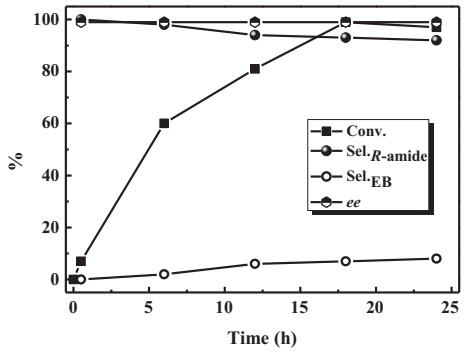
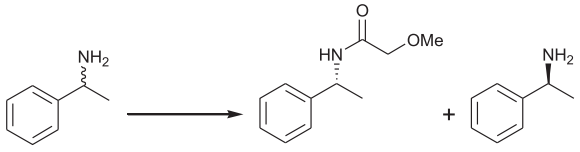


Fig. 9. Reaction profile in one-pot DKR of *rac*-1-phenylethylamine by lipase and 1.5%-Pd/ED-MIL-101. Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, T = 70 °C, P_{H2} = 0.015 MPa, 4 mL of toluene.

Table 4
Effect of the amount of ethylenediamine on DKR of racemic 1-phenylethylamine through Pd/lipase cocatalysis.[a]



Pd catalyst	ED amount (μL)	N content [b] (mmol/$g_{cat.}$)	Na_2CO_3 content (mg)	Conv. (%)	Sel.$_{R\text{-amide}}$ (%)	Sel.$_{EB}$ (%)	*ee* (%)
1.5%-Pd/MIL-101	–	–	20	95	85	15	97
1.5%-Pd/ED-MIL-101	100	0.7	0	98	86	14	>99
1.5%-Pd/ED-MIL-101	150	1.9	0	99	93	7.0	>99
1.5%-Pd/ED-MIL-101	200	3.6	0	82	89	9.0	>99

[a] Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, T = 70 °C, P_{H2} = 0.015 MPa, 4 mL of toluene, t = 18 h.
[b] Determined by elemental analysis.

resulted in the decrease of selectivity to target product owing to the side reactions. Besides the high efficiency, the 1.5%-Pd/ED-MIL-101 and Novozym® 435 combination could be easily separated from the reaction solution *via* centrifugation and could be used repetitively eight times without appreciable loss of conversion, selectivity, and *ee* value during the one-pot DKR of *rac*-1-phenylethylamine (Fig. 10). This result demonstrates the robustness of this chemoenzymatic catalyst combination under the present DKR conditions. As shown in Fig. 10, at the end of the ninth cycle, the conversion decreased by 19%. ICP-OES analysis revealed that no leaching of Pd could be detected in the reaction mixtures during the repetitive runs, implying that the metallic Pd was stable against the chelating effect of the substrates. The TEM image of the used 1.5%-Pd/ED-MIL-101 (Fig. 11) revealed that the Pd NPs aggregated to 5 nm after 9 cycles, which might be the main factor responsible for the decrease in catalytic activity.

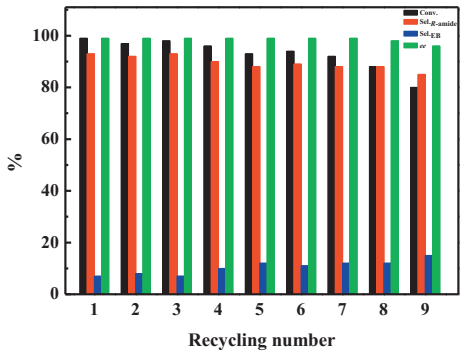


Fig. 10. Recycling test of the enzyme and 1.5%-Pd/ED-MIL-101 catalysts for one-pot DKR of *rac*-1-phenylethylamine. Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, T = 70 °C, P_{H2} = 0.015 MPa, 4 mL of toluene, t = 18 h.

Further investigations of the generality of the present strategy revealed that one-pot DKR of other several structurally different racemic benzylic amines can be also achieved by using the chemoenzymatic catalyst combination of the 1.5%-Pd/ED-MIL-101 and Novozym® 435 with good conversion (86–91%) and selectivity (86–91%), as well as excellent enatioselectivity (>99%) (Table 5).

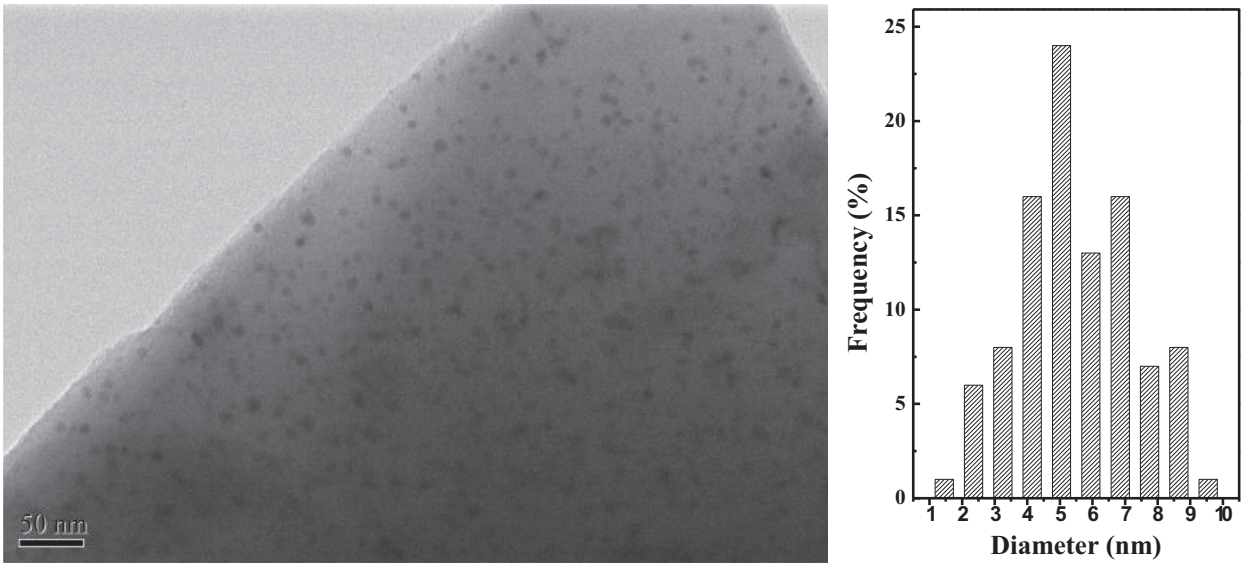
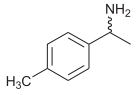
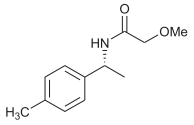
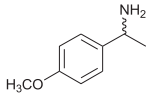
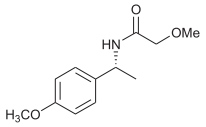
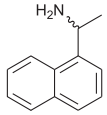
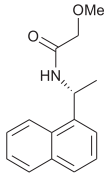


Fig. 11. TEM image (*left*) and its corresponding size distribution histogram (*right*) of 1.5%-Pd/ED-MIL-101 after 9 consecutive runs.

Table 5
DKR of racemic benzylic amine through 1.5%-Pd/ED-MIL-101/lipase cocatalysis.[a]

Entry	Amine	Product	Conv. (%)	Sel.$_{R\text{-amide}}$ (%)	Sel.$_{EB}$ (%)	*ee* (%)
1			90	90	10	>99
2			86	91	9.0	>99
3			91	86	14	>99

[a] Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-benzylic amine, 0.13 mmol of ethyl methoxy acetate, T = 70 °C, P_{H2} = 0.015 MPa, 4 mL of toluene, t = 18 h.

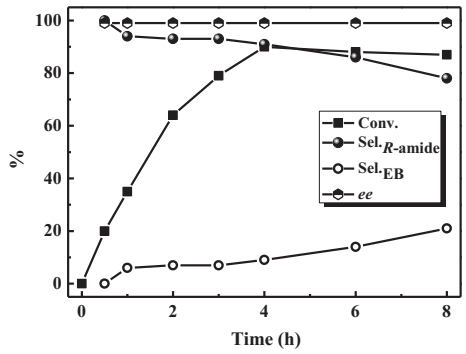


Fig. 12. Reaction profile in microwave-assisted one-pot DKR of *rac*-1-phenylethylamine by lipase and 1.5%-Pd/ED-MIL-101. Reaction conditions: a catalyst containing 0.75 mg of Pd, 37.5 mg of Novozym® 435, 0.13 mmol of *rac*-1-phenylethylamine, 0.13 mmol of ethyl methoxy acetate, $T = 70$ °C, $P_{H2} = 0.015$ MPa, 4 mL of toluene.

To achieve a matchable metal-lipase cocatalysis, further enhancing the racemization rate of amines over the present 1.5%-Pd/ED-MIL-101 catalyst is desired. Parvulescu et al. reported microwave irradiation as a heating method to increase the racemization rate of amines over Pd [44]. Very recently, we also successfully conducted microwave-assisted one-pot DKR of aromatic secondary alcohols by using the chemoenzymatic catalyst combination of Pd@SBA-15 and Novozym® 435, greatly shortening the DKR time [45]. These works proved microwave irradiation to be an efficient tool for matching the Pd-catalyzed racemization reaction with the enzyme-aided resolution, and inspirited us to conducted the one-pot DKR of *rac*-1-phenylethylamine under microwave heating conditions. Notably, when the one-pot DKR of *rac*-1-phenylethylamine using 1.5%-Pd/ED-MIL-101 and Novozym® 435 combination was subjected to microwave heating, the reaction time was shortened greatly to 4 h with similar performances (Fig. 12) to those under normal heating (Fig. 9). This mainly attributed to the local "super hot" dots on the Pd surface induced by microwave irradiation, which can accelerate the chemical reactions[46] and thus, greatly shortening the DKR time.

4. Conclusions

In summary, Pd NPs confined in the cages of ethylenediamine-grafted MIL-101 could be employed as an efficient racemization catalyst, and exhibited excellent matchability with immobilized lipase B for one-pot DKR of *rac*-1-phenylethylamines. Meanwhile, the present chemoenzymatic catalyst combination possessed better stability and could be used repetitively for at least 9 times, showing great promise for practical application. Our findings highlight the advantages of amine modification of the surface of the cages in MIL-101 in terms of conferring basic property to the material and locating Pd NPs inside its cages. Additionally, microwave irradiation proved to be a highly efficient tool for matching the Pd-catalyzed racemization with the enzyme-aided resolution. This recyclable chemoenzymatic catalyst combination also might provide a preferable method for the one-pot cascade reactions.

Acknowledgement

This work is supported by the Ministry of Education of China (PCSIRT_IRT_16R49).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jcat.2018.04.006.

References

[1] M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keβeler, R. Stürmer, T. Zelinski, Angew. Chem. Int. Ed. 43 (2004) 788.
[2] G. Liu, D.A. Gogan, J.A. Ellman, J. Am. Chem. Soc. 119 (1997) 9913.
[3] J.R. Porter, J.F. Traverse, A.H. Hoveyda, M.L. Snapper, J. Am. Chem. Soc. 123 (2001) 10409.
[4] A.A. Boezio, J. Pytkowicz, A. Côté, A.B. Charette, J. Am. Chem. Soc. 125 (2003) 14260.
[5] H. Pellissier, Adv. Synth. Catal. 353 (2011) 1613.
[6] K. Faber, Biotransformations in Organic Chemistry, fourth ed., Springer-Verlag, Berlin, 2000.
[7] O. Pàmies, J.E. Bäckvall, Chem. Rev. 103 (2003) 3247.
[8] B. Martín-Matute, J.E. Bäckvall, Curr. Opin. Chem. Biol. 11 (2007) 226.
[9] A. Kamal, M.A. Azhar, T. Krishnaji, M.S. Malik, S. Azeeza, Coordin. Chem. Rev. 252 (2008) 569.
[10] P. Hoyos, V. Pace, A.R. Alcántara, Adv. Synth. Catal. 354 (2012) 2585.
[11] O. Lågvik, T. Saloranta, D.Y. Murzin, R. Leino, ChemCatChem 7 (2015) 4004.
[12] C.M.R. Volla, I. Atodiresei, M. Rueping, Chem. Rev. 114 (2014) 2390.
[13] E.J. Ebbers, G.J.A. Ariaans, J.P.M. Houbiers, A. Bruggink, B. Zwanenburg, Tetrahedron 53 (1997) 9417.
[14] O. Pàmies, A.H. Éll, J.S.M. Samec, N. Hermanns, J.E. Bäckvall, Tetrahedron Lett. 43 (2002) 4699.
[15] J. Paetzold, J.E. Bäckvall, J. Am. Chem. Soc. 127 (2005) 17620.
[16] B. Bhanage, M. Arai, Catal. Rev. 43 (2001) 315.
[17] C.J. Welch, J. Albaneze-Walker, W.R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D.J. Mathre, S. Spencer, X. Bu, T. Wang, Org. Process Res. Dev. 9 (2005) 198.
[18] M.J. Climent, A. Corma, S. Iborra, Chem. Rev. 111 (2011) 1072.
[19] M.T. Reetz, K. Schimossek, Chimia 50 (1996) 668.
[20] M.J. Kim, W.H. Kim, K. Han, Y.K. Choi, J. Park, Org. Lett. 9 (2007) 1157.
[21] M.S. Kwon, N. Kim, C.M. Park, J.S. Lee, K.Y. Kang, J. Park, Org. Lett. 7 (2005) 1077.
[22] A. Parvulescu, D. De Vos, P. Jacobs, Chem. Commun. (2005) 5307.
[23] A.N. Parvulescu, P.A. Jacobs, D.E. De Vos, Chem. Eur. J. 13 (2007) 2034.
[24] A.N. Parvulescu, P.A. Jacobs, D.E. De Vos, Appl. Catal. A 368 (2009) 9.
[25] Q. Jin, G. Jia, Y. Zhang, C. Li, Catal. Sci. Technol. 4 (2014) 464.
[26] K. Engström, E.V. Johnston, O. Verho, K.P.J. Gustafson, M. Shakeri, C.W. Tai, J.E. Bäckvall, Angew. Chem. Int. Ed. 125 (2013) 14256.
[27] X. Zhang, L. Jing, F. Chang, S. Chen, Y. Yang, Q. Yang, Chem. Commun. 53 (2017) 7780.
[28] A. Corma, H. García, F.X.L. Xamena, Chem. Rev. 110 (2010) 4606.
[29] B.Y. Guan, X.Y. Yu, H.B. Wu, X.W.D. Lou, Adv. Mater. 29 (2017) 1703614.
[30] Q. Yang, Q. Xu, H.L. Jiang, Chem. Soc. Rev. 46 (2017) 4774.
[31] J. Lee, O.K. Farha, J. Roberts, K.A. Scheidt, S.T. Nguyen, J.T. Hupp, Chem. Soc. Rev. 38 (2009) 1450.
[32] D. Farrusseng, S. Aguado, C. Pinel, Angew. Chem. Int. Ed. 48 (2009) 7502.
[33] J. Gascon, A. Corma, F. Kapteijn, F.X. Llabrés, i Xamena, ACS Catal 4 (2013) 361.
[34] H. Li, Z.H. Zhu, F. Zhang, S.H. Xie, H.X. Li, P. Li, X.G. Zhou, ACS Catal. 1 (2011) 1604.
[35] Y.K. Hwang, D.Y. Hong, J.S. Chang, S.H. Jhung, Y.K. Seo, J. Kim, A. Vimont, M. Daturi, C. Serre, G. Férey, Angew. Chem. Int. Ed. 47 (2008) 4144.
[36] G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé, I. Margiolaki, Science 309 (2005) 2040.
[37] S.L. Wang, W. Wei, Y. Zhao, H.X. Li, H. Li, Catal. Today 258 (2015) 327.
[38] M.S. El-Shall, V. Abdelsayed, A.E. Rahman, S. Khder, H.M.A. Hassan, H.M. El-Kaderi, T.E. Reich, J. Mater. Chem. 19 (2009) 7625.
[39] S.H. Jhung, J.H. Lee, J.W. Yoon, C. Serre, G. Férey, J.S. Chang, Adv. Mater. 19 (2007) 121.
[40] Y. Pan, B. Yuan, Y. Li, D. He, Chem. Commun. 46 (2010) 2280.
[41] S. Ichikawa, H. Poppa, M. Boudart, J. Catal. 9 (1985) 1.
[42] B. Török, G.K. Surya Prakash, Adv. Synth. Catal. 345 (2003) 165.
[43] R.A. Sheldon, Adv. Synth. Catal. 349 (2007) 1289.
[44] A.N. Parvulescu, E. Van der Eycken, P.A. Jacobs, D.E. De Vos, J. Catal. 255 (2008) 206.
[45] Y.F. Xu, M. Wang, B. Feng, Z.Y. Li, Y.H. Li, H.X. Li, H. Li, Catal. Sci. Technol. 7 (2017) 5838.
[46] N.J. Yoshikawa, Microw. Power Electromagn. Energy 44 (2010) 4.