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# Modification of supported Pd catalysts by alkalic salts in the selective racemization and dynamic kinetic resolution of primary amines<sup>†</sup>

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Supported Pd nanoparticles (PdNPs) were modified with various alkalic salts by incipient wetness impregnation method. The effect of the salts on the catalytic activity and selectivity behavior of Pd catalysts for the racemization of (*S*)-1-phenylethylamine was investigated. The presence of alkalic salts can greatly enhance the selectivity of Pd catalysts, without significantly decreasing the catalytic activity. This modification method is suitable for PdNPs supported on various supports, such as micro/mesoporous silica and activated carbon. Combined with the immobilized lipases (Novozyme 435), this catalyst system can efficiently catalyze the dynamic kinetic resolution (DKR) of 1-phenylethylamine with yield and enantioselectivity up to 97% and 99%, respectively.

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#### 1. Introduction

Enantiomerically pure amines are widely used as building blocks for the synthesis of various biologically active compounds in the pharmaceutical and agrochemical industries, and therefore it is of considerable importance to develop their preparation methods.<sup>1</sup> Kinetic resolution (KR) of racemic amine mixtures by enzyme catalysis has been employed in the preparation of chiral amines for a long time.<sup>2,3</sup> However, the major drawback of KR is that the theoretical maximum yield cannot exceed 50% for either enantiomer. Dynamic kinetic resolution (DKR) (Scheme 1) that combines enzyme-catalyzed KR with *in situ* racemization of the undesired enantiomer can overcome the limitation of KR and theoretically increase the yield up to 100%.<sup>4–7</sup> To achieve this goal, an efficient racemization catalyst compatible with the enzymatic KR is prerequisite.<sup>8</sup>

Palladium on carbon (Pd/C) was first used as a racemization catalyst for the DKR of amines in 1996.<sup>9</sup> Using triethylamine as solvent, racemic 1-phenylethylamine was transformed to the corresponding (R)-amide with 64% yield but a long reaction time (8 days) was necessary. Since then, no significant development has been reported for nearly a decade because racemization of amines is difficult and usually needs harsh reaction conditions.<sup>10</sup> Until 2005, several successful catalyst systems for

the racemization and DKR of amines were developed.11-15 For example, Paetzold and Bäckvall developed an efficient ruthenium (Ru) catalyst. By combining Ru-catalyzed racemization and lipase-catalyzed resolution, a wide range of primary amines were transferred into one enantiomer of amides with good yield and selectivity.<sup>11,16</sup> As an alternative to homogeneous racemization catalysts, palladium nanoparticles (PdNPs) supported on alkaline earth salts, aminofunctionalized silica, layered double hydroxide (LDH) and aluminum hydroxide [AlO(OH)] exhibited at least the same or better performance than the Ru catalyst in the racemization of chiral aromatic amines.<sup>12,13,17</sup> Besides, Parvulescu and co-workers found that RANEY® nickel and cobalt catalysts, as an alternative to noble metals such as Pd or Ru, are able to racemize various chiral amines with high selectivity.14 Recently, Shakeri and co-workers reported that PdNPs supported in aminopropyl-modified mesocellular foam (Amp-MCF) showed higher activity than other racemization catalysts reported so far.15

Porous carbon and silica with high specific surface area are ideal supports for the immobilization of PdNPs, but the



Scheme 1 Dynamic kinetic resolution (DKR) of racemic 1-phenylethylamine.



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acid property of the supports could promote side reactions during the racemization of chiral amines.<sup>12</sup> The previous reports regarding SiO<sub>2</sub> supported PdNPs indicate that aminofunctionalization can effectively modify the surface property of SiO<sub>2</sub> and enhance the selectivity of the racemization reaction, which is mainly ascribed to the basicity of the amino groups.<sup>15,17</sup> However, most amino-modified SiO<sub>2</sub> cannot resist high temperature, which may limit its application in catalysis. Recently, incorporation of metal salts has been demonstrated to modify the surface acid-base properties and the active component of catalysts in such ways that are beneficial to their catalytic activity and selectivity.<sup>18-22</sup> For example, Groppo et al.<sup>19</sup> reported that K-doping on a Pd/SiO<sub>2</sub>-Al<sub>2</sub>CO<sub>3</sub> catalyst had a great influence on the starting Pd<sup>2+</sup> precursor phase, the fraction of truly available Pd surface sites and the lifetime of Pd catalysts. Liu et al.21 reported that incorporation of K<sub>2</sub>CO<sub>3</sub> into cinder could enhance the surface alkalinity and catalytic performance of catalysts. Zhu et al.22 reported that modification of the Cu/SiO<sub>2</sub> catalyst with alkaline earth metals could catalyze the conversion of 1.4-butanediol to  $\gamma$ -butyrolactone with high selectivity. Thus it is of great interest to explore the effect of incorporated salts on the catalytic activity and selectivity behavior of supported Pd catalysts for the racemization of primary amines.

In the present work, we report that the addition of alkalic salts to supported PdNPs could eliminate the surface acidity of the supports to some extent and improve the selectivity towards racemization of (*S*)-1-phenylethylamine. Moreover, their ability to suppress side reactions is related to the basic strength of inorganic salts. Pd catalysts modified with  $K_2CO_3$  show excellent catalytic activity and selectivity for the racemization and DKR of primary amines, irrespective of the type of support material.

#### 2. Experimental section

#### 2.1 Materials and instruments

Lipase acrylic resin from *Candida antarctica* ( $\geq 10\,000$  U g<sup>-1</sup>, Novozyme 435), pluronic P123 (EO20PO70EO20) and F127 (EO106PO70EO106) copolymer were purchased from Sigma-Aldrich; silicon(v) oxide (amorphous fumed), mesitylene, tetraethoxysilane, ( $\pm$ )-1-phenylethylamine, (*S*)-1-phenylethylamine and tetraamine palladium( $\pi$ ) chloride monohydrates were obtained from Alfa Aesar. Bromothymol blue, phenolphthalein, NH<sub>4</sub>F, Cs<sub>2</sub>CO<sub>3</sub>, Rb<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, Li<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, Na<sub>3</sub>PO<sub>4</sub>, CH<sub>3</sub>COOK, CH<sub>3</sub>COONa, KCl and NaCl were obtained from the Shanghai Chemical Reagent Company by the Chinese Medicine Group and dried before use.

Transmission electron microscopy (TEM) images were recorded on an FEI Tecnai  $G^2$  Spirit at an accelerating voltage of 120 kV. High-resolution TEM (HRTEM) images and energy dispersive X-ray (EDX) spectroscopy were taken using an FEI Tecnai  $G^2$  F30 Spirit microscope operating at an accelerating voltage of 300 kV. N<sub>2</sub> sorption isotherms of mesoporous and microporous materials were measured on a Quantachrome NOVA 4200e and Autosorb-1 at 77 K, respectively. Before measurements, the samples were outgassed at 393 K for 6 h. The X-ray diffraction (XRD) patterns were recorded on a D/Max2500V/PC powder diffractometer (Rigaku), using Cu K $\alpha$  radiation that operated at 40 kV and 100 mA. Infrared spectra were recorded on a Thermo-Nicolet Nexus 470 Fourier transform infrared (FT-IR) spectrometer. All the samples, with KBr, were pressed into self-supporting wafers and mounted in an IR cell for FT-IR spectroscopy.

The amount of Pd loading was measured using a sequential inductively coupled plasma atomic emission spectrometer (ICPS-8100 made by SHIMADZU). The samples were prepared as follows: appropriate amounts of supported Pd catalysts were successively dissolved in *aqua regia* and hydrofluoric acid, then this solution was diluted with pure water to a final volume of 100 mL.

X-ray photoelectron spectroscopy (XPS) was performed on an ESCALAB 250Xi (Thermo Scientific) with Al K $\alpha$  radiation at 7.1 × 10<sup>-5</sup> Pa, calibrated internally by silica Si (2p) binding energy at 103.4 eV. The binding energy of Pd 3d<sub>5/2</sub> and Pd 3d<sub>3/2</sub> peaks were separated by 5.25 eV with peak ratios of 3/2. The binding energies of Pd 3d<sub>5/2</sub> were set as thus: Pd<sup>0</sup>: 335.2 eV; PdO: 336 eV; Pd(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub>: 338.4 eV.

#### 2.2 Catalyst preparation procedure

Support materials such as MCF, SBA-15 and FDU-12 were synthesized according to the procedures reported previously.<sup>23–25</sup> Supported Pd catalysts were prepared by employing SiO<sub>2</sub> (800 mg) for the adsorption of Pd(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> precursor solution (5 mM, 40 mL).<sup>26</sup> Before adsorption, the pH of the precursor solution was adjusted to 11.0 with ammonia. After stirring for 6 h, the light yellow solid was centrifuged from the slurry and then dried at 80 °C overnight. Then, the Pd<sup>2+</sup>/SiO<sub>2</sub> complex was reduced in flowing hydrogen at 200 °C for 3 h. The resultant Pd catalysts were denoted as Pd/R (R = MCF, SBA-15, FDU-12 and SiO<sub>2</sub>).

A series of salt-modified Pd catalysts were prepared by the incipient wetness impregnation method using 1 mL of 0.5 M salt solution and 200 mg of supported Pd/R catalysts (Pd/R = Pd/MCF, Pd/FDU-12, Pd/SBA-15, Pd/SiO<sub>2</sub> and 5% Pd/C). After shaking for 6 h, the resultant mixtures were lyophilized for 10 h on a 2.5 L Labconco Freeze Dry at a condenser temperature of -49 °C and a pressure of 20 Pa. The amounts of incorporated K<sub>2</sub>CO<sub>3</sub> were adjusted by varying the concentration of K<sub>2</sub>CO<sub>3</sub> solution. The resultant catalysts were denoted as R'-Pd/R (R' = Li<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Rb<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, Na<sub>3</sub>PO<sub>4</sub>, CH<sub>3</sub>COOK, CH<sub>3</sub>COONa, KCl, and NaCl).

### 2.3 Procedure of racemization and dynamic kinetic resolution of 1-phenylethylamine

Typically, 0.50 mmol of (*S*)-1-phenylethylamine (65  $\mu$ L), 0.22 mmol of hexadecane (65  $\mu$ L) as internal standard, 4 mL of toluene and 0.01 mmol of supported Pd catalysts (43.4 mg, 2.45 wt.%) were added into a 10 mL Schlenk tube. After freezing with liquid nitrogen and removing air under vacuum, the

racemization reaction was performed under stirring at 70 °C with a 5 L hydrogen balloon (10% H<sub>2</sub> and 90% N<sub>2</sub>). 100  $\mu$ L of the mixture were removed from the reaction system at intervals of 1 h and acylated by acetic anhydride. After a high speed centrifugation, the supernatant liquor was used to monitor the enantiomeric excess (ee%) and selectivity on an Agilent 7890 gas chromatograph with a Supelco- $\beta$ -DEX<sup>TM</sup> 225 chiral column (0.25 mm × 30 m × 0.25  $\mu$ m). The oven temperature was firstly kept at 160 °C for 25 min and then 180 °C for 30 min. The injector (split 1:50) temperature was 250 °C and the detector FID temperature was 280 °C. The flow rates of the carrier gases nitrogen, hydrogen and air were 10, 40 and 400 mL min<sup>-1</sup>, respectively.

Dynamic kinetic resolution (DKR) was performed similarly, with 0.50 mmol of racemic 1-phenylethylamine (65  $\mu$ L), 1.0 mmol of ethyl methoxyacetate (120  $\mu$ L), 4 mL of toluene, 0.01 mmol of Pd source and 100 mg of immobilized *Candida antartica* lipase B (Novozyme 435) as a resolution catalyst. After the reaction was completed, the reaction mixture was evaporated and then separated on a silica gel column to give an isolated yield of product.

#### 2.4 Basicity characterization

The basic strength (H<sub>-</sub>) of inorganic salts and salt-modified Pd/MCF catalysts were determined using the Hammett indicator. Generally, 0.20 mmol of inorganic salts or 0.01 mmol of salt-modified Pd/MCF were suspended in 2 mL of an indicator solution (0.1 mg of bromothymol blue or phenolphthalein per mL of toluene) and then left to equilibrate for 2 h until no further color changes were observed. According to the literature,<sup>21</sup> the basic strength of samples is defined as being stronger than a weaker indicator that exhibits a color change, and weaker than a stronger indicator that produces no color change. The basicity values (mol/mol) of inorganic salts were determined by the method of Hammett indicator-benzene carboxylic acid (0.1 mol L<sup>-1</sup> anhydrous toluene solution) titration until the color changed back to the original color.

#### 3. Results and discussion

#### 3.1 Textural properties of supported Pd catalysts

Siliceous mesocellular foam (MCF) with high surface area and continuous 3-D pore structure was chosen as a model support to immobilize PdNPs. ICP results indicate that Pd loading of Pd/MCF increases with increasing the concentration of Pd(NH<sub>3</sub>)<sub>4</sub>Cl<sub>2</sub> precursor and reaches the maximum 8 wt.% (Fig. S1†). The XRD patterns of Pd/MCF catalysts are shown in Fig. 1. Besides the typical diffraction peak due to MCF, the additional peaks at  $2\theta = 40.14^\circ$ ,  $46.69^\circ$  and  $68.17^\circ$ are ascribed to PdNPs (according to the ICDD PDF databases). The intensity of Pd diffraction peaks is enhanced gradually with increasing the Pd loading, indicating the growth of PdNPs. Pd/MCF with Pd loading of 2.45 wt.% was selected for further study.

The oxidation states of Pd on the reduced Pd/MCF catalysts were investigated by XPS and the fitting result



Fig. 1 XRD pattern of MCF and Pd/MCF with different Pd loading.

reveals that the ratio of  $Pd^0$  and  $Pd^{2+}$  is 1:1 (Fig. S2†). Although nearly half of the Pd species exist as  $Pd^{2+}$ , there is no obvious diffraction peak of PdO in the XRD pattern of Pd/MCF. The metal dispersion and mean particle diameter estimated from CO adsorption is 47.5% and 2.4 nm, respectively.

No aggregation of PdNPs is observed in the TEM image of Pd/MCF (Fig. 2a), indicating that PdNPs are uniformly dispersed into the nanopores of MCF. However, it is difficult to discriminate PdNPs from the disordered pore structure of MCF. The dark field image was also captured at the same position (Fig. 2b) and a large number of light spots indicate the presence of PdNPs. The PdNPs in the specific area labelled 1 were analysed by EDX and the characteristic peaks at around 2.84 KeV are ascribed to Pd species. Moreover, individual PdNPs can be observed in the enlarged TEM images (Fig. 2c). Indeed the PdNPs shows obvious crystalline character, which is evidenced by the presence of the lattice fringes (Fig. 2d). However, it seems that the particle diameter of PdNPs estimated from TEM images is larger than that from CO adsorption.

## 3.2 The effect of salts on the catalytic activity and selectivity of supported Pd catalysts for racemization of (*S*)-1-phenylethylamine

Using Pd/MCF as a racemization catalyst, the racemization of (S)-1-phenylethylamine proceeded in toluene at 70 °C and the enantiomer excess (ee) decreased to below 5% in 2 h (Entry 2, Table 1). However, the selectivity for 1-phenylethylamine was 69% and further decreased upon prolonging the reaction time. Taking the advantage of salt effect in modulating the basicity of catalyst,<sup>20-22</sup> various alkalic salts were introduced into pores of Pd/MCF by the incipient wetness impregnation method and then the salt-modified Pd catalysts were applied to racemize (S)-1-phenylethylamine. After the addition of inorganic salts, there is a slight decrease in the catalytic activity of Pd/MCF, which is partly ascribed to the pore blockage by inorganic salts. Despite this slight decrease, the addition of alkalic potassium salts significantly improves the reaction selectivity, such as 97% selectivity for K<sub>3</sub>PO<sub>4</sub>-Pd/MCF (Entry 4, Table 1), 96% selectivity for K<sub>2</sub>CO<sub>3</sub>-Pd/MCF (Entry 6, Table 1), and 91% selectivity for CH<sub>3</sub>COOK-Pd/MCF (Entry 8, Table 1), while the effect of neutral KCl and NaCl on the selectivity of the racemization reaction is not obvious. It seems that their ability to



Fig. 2 TEM images and EDX spectrum of Pd/MCF, (a: light field TEM; b: dark field TEM; c and d: enlarged PdNPs).

**Table 1** Salt-modified Pd/MCF catalyzed the racemization of (S)-1-phenylethylamine<sup>a</sup>

(S)-1-phenylethylamine racemic 1-phenylethylamine					
		$ee^b$	Conversion <sup>b</sup>	Selectivity <sup>b</sup>	
Entry	Catalyst	(%)	(%)	(%)	
1	Ideal	0	50	100	
2	Pd/MCF <sup>c</sup>	5	64	69	
3	Pd/MCF	1	79	42	
4	K <sub>3</sub> PO <sub>4</sub> -Pd/MCF	25	39	97	
5	Na <sub>3</sub> PO <sub>4</sub> -Pd/MCF	9	50	91	
6	K <sub>2</sub> CO <sub>3</sub> -Pd/MCF	4	53	96	
7	Na2CO3-Pd/MCF	1	68	65	
8	CH <sub>3</sub> COOK-Pd/MCF	6	51	91	
9	CH <sub>3</sub> COONa-Pd/MCF	4	75	48	
10	KCl-Pd/MCF	14	56	78	
11	NaCl-Pd/MCF	7	68	60	
12	$Li_3PO_4 + Pd/MCF^d$	20	45	91	
13	Li2CO3-Pd/MCF	2	63	73	
14	Rb <sub>2</sub> CO <sub>3</sub> -Pd/MCF	5	48	98	
15	$Cs_2CO_3$ -Pd/MCF	13	45	98	

<sup>*a*</sup> Standard reaction conditions: (*S*)-1-phenylethylamine (0.50 mmol), Pd/MCF (2.45 wt.%, 0.01 mmol of Pd), incorporated salt (2.5 mmol g<sup>-1</sup> catalyst), hexadecane (0.22 mmol), toluene (4 mL), 0.01 MPa H<sub>2</sub>, 70 °C, 4 h. <sup>*b*</sup> Determined as corresponding acetamide using chiral GC. <sup>*c*</sup> 2 h. <sup>*d*</sup> Mechanical mixing.

suppress side reactions is related to the dissociation constant of conjugated acids of incorporated salts, with an order  $PO_4^{3-}$  (p $K_a$ : 12.38)  $\approx CO_3^{2-}$  (p $K_a$ : 10.33) > CH<sub>3</sub>COO<sup>-</sup>  $(pK_a: 4.76) > Cl^- (pK_a: -7)$ . It is noteworthy that, except Na<sub>3</sub>PO<sub>4</sub>, the addition of alkalic sodium salts (Na<sub>2</sub>CO<sub>3</sub> and CH<sub>3</sub>COONa) to Pd/MCF cannot result in obvious improvement in the selectivity of the racemization reaction. This suggests that their ability to suppress side reactions is also related to the counter cations of inorganic salts.

Then the addition of  $Li_3PO_4$  to Pd/MCF by mechanical mixing was tested and it could indeed effectively suppress the formation of side products with 91% selectivity (Entry 12, Table 1). Pd/MCF was also modified with other carbonates of group I and the catalytic results are summarized in Table 1. The addition of  $Li_2CO_3$  can not effectively suppress the side reactions during the racemization and  $Li_2CO_3$ -Pd/MCF exhibits poor selectivity (about 73%). On the contrary, the presence of Rb<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> significantly improves the performance of Pd/MCF and high selectivity up to 98% is obtained. Based on the research result of references,<sup>12,15,17</sup> we speculate that the basicity of inorganic salts is the main cause of higher selectivity for 1-phenylethylamine.

### 3.3 Basicity characterization of incorporated inorganic salts and Pd catalysts

The acid–base properties of salt-modified Pd catalysts strongly depend on the basic strength (H\_) of inorganic salts in organic solvent. Using Hammett indicators, the basic strength of inorganic salts was determined. Bromothymol blue is a common Hammett indicator for weak bases and its basic strength (H\_) is 7.2. It acts as a weak acid in organic solvent and can thus be in protonated or deprotonated form, appearing yellow in acid solution or blue in basic solution, respectively. In neutral solution it is bluish green.

Fig. 3 shows the color of bromothymol blue in toluene solution suspended with various alkalic salts. Pristine bromothymol blue appears yellow in toluene solution (middle). The addition of inorganic salts leads to the color change of bromothymol blue solution, which is related to the basicity of inorganic salts, and indicates that their basic strength (H\_) is above 7.2. According to the depth of blue, the basicity of inorganic salts can be expressed as  $K_2CO_3 \approx K_3PO_4 \approx Na_3PO_4 >$ CH<sub>3</sub>COOK > Na<sub>2</sub>CO<sub>3</sub> > CH<sub>3</sub>COONa. This basicity trend is in accordance with that of the selectivity of salt-modified Pd/MCF in the racemization of (*S*)-1-phenylethylamine (Table 1), suggesting that high selectivity for amine is mainly ascribed to the basicity of inorganic salts. In addition, Li<sub>3</sub>PO<sub>4</sub>, Na<sub>3</sub>PO<sub>4</sub> and K<sub>3</sub>PO<sub>4</sub> can convert bromothymol blue from yellow to dark blue (Fig. S3<sup>†</sup>), indicating their similar basicity in toluene solution.



Fig. 3 The color of bromothymol blue in toluene solution suspended with alkalic salts.

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However, carbonate salts with different counter ions have different basicity in toluene solution. This can explain why the counter ion in the carbonate of group I influences the selectivity of the racemization reaction.

The basic strength of inorganic salts was also determined using phenolphthalein ( $H_{-} = 9.8$ ) as Hammett indicator. Among them,  $K_2CO_3$ ,  $K_3PO_4$ ,  $Na_3PO_4$ , and  $CH_3COOK$  can convert phenolphthalein from colorless to purple and their basic strengths ( $H_{-}$ ) are above 9.8.  $Na_2CO_3$  and  $CH_3COONa$  fail to change the color of phenolphthalein and their basic strengths ( $H_{-}$ ) are between 7.2 and 9.8. In view of such results, as well as the observation on the selectivity of salt-modified Pd/MCF, it permits us to conclude that inorganic salts with basic strength above 9.8 can be used as an effective additive to selectively catalyze the racemization of (*S*)-1-phenylethylamine.

Furthermore, the basicity values (mol/mol) of inorganic salts were determined by the common method of Hammett indicator-benzoic acid titration.<sup>18</sup> As shown in Table 2, the basicity value of these alkalic salts decreases in the order of  $K_3PO_4 > K_2CO_3 > Na_3PO_4 > CH_3COOK > Na_2CO_3 > CH_3COONa$ , which also is in accordance with that of the selectivity of salt-modified Pd/MCF and further confirms that their ability to suppress side reactions is related to the basicity of inorganic salts.

Using Hammett indicator, the basic strength (H<sub>-</sub>) of saltmodified Pd/MCF was also determined. Pristine and halitemodified Pd/MCF are weakly acidic and their basic strengths (H<sub>-</sub>) are below 7.2. After the addition of salts with strong basicity, such as K2CO3, K3PO4, and Na3PO4, the saltmodified Pd/MCF become alkalescent and can change the color of bromothymol blue from yellow to blue but fail to convert phenolphthalein from colorless to purple, so their basic strengths (H<sub>-</sub>) are between 7.2 and 9.8. The addition of Na<sub>2</sub>CO<sub>3</sub> and CH<sub>3</sub>COONa to Pd/MCF cannot convert the color of bromothymol blue solution from yellow to blue, so their basic strengths (H<sub>-</sub>) are below 7.2. These results indicate that the addition of Na<sub>2</sub>CO<sub>3</sub> and CH<sub>3</sub>COONa is not enough to effectively eliminate the surface acidity of MCF. The basicity values of salt-modified Pd/MCF cannot be exactly determined by the Hammett method because the color changes of titration endpoints are seriously disturbed by black catalyst powder.

### 3.4 The effect of K<sub>2</sub>CO<sub>3</sub> on the selective racemization of (*S*)-1-phenylethylamine

Among the salts tested,  $K_3PO_4$  and  $K_2CO_3$  are found to be the most effective additives in the selective racemization of

**Table 2** The basicity values of various alkalic salts in the toluene<sup>*a*</sup>

Salt	Total basicity (mol/mol)	Salt	Total basicity (mol/mol)
K <sub>2</sub> CO <sub>3</sub>	0.85	Na <sub>2</sub> CO <sub>3</sub>	0.30
$K_3PO_4$	1.0	$Na_3PO_4$	0.60
CH <sub>3</sub> COOK	0.40	CH <sub>3</sub> COONa	0.03

<sup>*a*</sup> Conditions: 0.2 mmol salts in 2 mL of bromothymol blue solution, 0.1 M benzoic acid, stirring.

(*S*)-1-phenylethylamine, and therefore  $K_2CO_3$  was selected for further study. Single  $K_2CO_3$  or  $K_2CO_3$ -impregnated MCF shows no catalytic activity, suggesting  $K_2CO_3$  merely serves as a modifier to eliminate the surface acid of MCF.

The amount of  $K_2CO_3$  is an important parameter which affects the activity and selectivity of supported Pd catalysts. As illustrated in Fig. 4, the catalytic activity decreases with increasing the amount of  $K_2CO_3$  and nearly disappears when  $K_2CO_3$  content reaches up to 30 mmol g<sup>-1</sup>. Here the decreased catalytic activity of Pd/MCF is mainly ascribed to the combined effect of pore blockage and basicity of  $K_2CO_3$ . On the other hand, reaction selectivity is significantly improved and maintained enduringly at around 99% when  $K_2CO_3$  content is higher than 5 mmol g<sup>-1</sup>. Therefore, the amount of  $K_2CO_3$  was set at 5 mmol g<sup>-1</sup> in the following discussion.

The effect of adding method of  $K_2CO_3$  to Pd/MCF was also investigated. From the time courses for racemization of (*S*)-1phenylethylamine (Fig. 5), the addition of  $K_2CO_3$  to Pd/MCF by incipient wetness impregnation or mechanical mixing can significantly suppress the consumption of amines and a high selectivity (>98%) is maintained even after complete conversion. However, when  $K_2CO_3$  is added directly to the reaction mixture, side reactions take place and the selectivity of the racemization reaction decreases to 72%.

The FT-IR and XRD results (Fig. S4 and S5<sup>†</sup>) indicate that  $K_2CO_3$  species can be successfully introduced into Pd/MCF catalyst by incipient wetness impregnation or mechanical mixing. The reproducibility of catalyst preparation was evaluated by comparing the catalytic performance of  $K_2CO_3$ -Pd/MCF catalysts with different batches and scales in the racemization of (*S*)-1-phenylethylamine and the results are summarized in the Tables S1 and S2.<sup>†</sup> From these results, it seems that our reported preparation method of Pd catalysts has high reproducibility.

The fact that the addition of  $K_2CO_3$  to Pd/MCF can significantly improve the selectivity of the racemization reaction might be related to the basicity of  $K_2CO_3$ . As reported previously in the literature,<sup>12,17</sup> a basic support is necessary in the Pd-catalyzed racemization of primary amines, which can



Fig. 4 Effect of  $K_2CO_3$  content on the activity and selectivity of Pd/MCF in the racemization of (S)-1-phenylethylamine.



**Fig. 5** Time courses for the racemization of (*S*)-1-phenylethylamine catalyzed by Pd/MCF in the presence of  $K_2CO_3$ , (ee%: solid line; selectivity%: dotted line. Standard reaction conditions: a: the addition of  $K_2CO_3$  by incipient wetness impregnation; b: mechanical mixing of Pd/MCF and  $K_2CO_3$ ; c:  $K_2CO_3$  was added into reaction system directly).

suppress the formation of side products. Moreover, Pd on amino-functionalized silica is proved to be more selective for the racemization of (*S*)-1-phenylethylamine, mainly due to the basicity of aminopropyl group.  $K_2CO_3$  has similar base strength with propylamine, which can create a basic microenvironment for PdNPs to suppress the acid-promoted side reactions of imine intermediate with 1-phenylethylamine, resulting in an enhanced selectivity in the racemization reaction.

#### 3.5 Expanding support scope

To examine the generality of  $K_2CO_3$  addition for improving the selectivity of immobilized PdNPs in the racemization of chiral amines, three other porous silica materials were also chosen as support materials to immobilize PdNPs. Among them, MCF and FDU-12 silica are composed of large spherical cells that are connected by windows to create a 3D system, while hexagonal one-dimensional mesoporous SBA-15 and commercial SiO<sub>2</sub> possess no cagelike pore structure (Fig. S6†). N<sub>2</sub> sorption isotherms of MCF, FDU-12 and SBA-15 (Fig. S7†) possess obvious hysteresis loops, which further confirm the presence of mesoporous structures. Commercial SiO<sub>2</sub> mainly has micropores with surface area of 227 m<sup>2</sup> g<sup>-1</sup> and pore volume of 1.61 cm<sup>3</sup> g<sup>-1</sup> (Table S3†). All these support materials have different mesoporous structures, surface areas and pore volumes.

As shown in Table 3, all the supported Pd catalysts exhibit similar high activity and poor selectivity in the racemization of (*S*)-1-phenylethylamine. The modification of Pd catalysts by  $K_2CO_3$  impregnation can result in a significant enhancement of the reaction selectivity, irrespective of the kind of supports. We optimized the amount of  $K_2CO_3$  for each support (shown in Fig. S8†) and it turned out that 5 mmol g<sup>-1</sup> was prerequisite. It is known that side reactions are serious using Pd/C as racemization catalyst, and in Jacobs' work no obvious improvement was found either using triethylamine as solvent or catalyst pretreatment with base.<sup>12</sup> Surprisingly, the addition of  $K_2CO_3$  to Pd/C by incipient wetness impregnation method increases the selectivity of the racemization reaction up to 90%. However, mechanical mixing of Pd/C and

**Table 3** The effect of  $K_2CO_3$  on the activity and selectivity of Pd catalysts immobilized on different supports for the racemization of (S)-1-phenylethylamine<sup>*a*</sup>

Entry	Catalyst	$\begin{array}{c} K_2 CO_3 \\ (mmol \ g^{-1}) \end{array}$	ee <sup>b</sup> (%)	Conversion <sup>b</sup> (%)	Selectivity <sup>b</sup> (%)
1	Pd/MCF	0	1	79	42
		5	1	49	99
2	Pd/SBA-15	0	2	78	42
		5	10	45	99
3	Pd/FDU-12	0	2	88	25
		5	6	48	98
4	$Pd/SiO_2^c$	0	1	88	23
		5	3	49	99
5	$Pd/C^{c}$	0	3	89	22
		5	11	48	90
	$\mathrm{Pd/C}^d$	10	5	62	74

<sup>*a*</sup> Standard reaction condition. <sup>*b*</sup> Determined as corresponding acetamide using chiral GC. <sup>*c*</sup> Commercial. <sup>*d*</sup> Mechanical mixing of Pd/C and K<sub>2</sub>CO<sub>3</sub>.

 $K_2CO_3$  only increases the selectivity to 74%. Then we tested the recyclability of the  $K_2CO_3$ -Pd/C catalyst (Table S4†). It can be reused at least 4 times without obvious loss in reaction selectivity. However, there is a slight decrease in the catalytic activity of  $K_2CO_3$ -Pd/C, which is probably due to the aggregation of PdNPs. These results indicate that the addition of  $K_2CO_3$  to supported Pd catalysts by incipient wetness impregnation is an efficient way for improving the selectivity of the racemization reaction.

#### 3.6 Expanding substrate scope

Besides (S)-1-phenylethylamine, other substrates were also tested. As shown in Table 4, Pd/MCF can catalyze the racemization of functionalized chiral aromatic amines, such as (S)-1-(4-MeO-phenyl)ethylamine, (S)-1-(4-tolyl)ethylamine and (S)-1-(4-F-phenyl)ethylamine, but the selectivity is very poor. After the addition of  $K_2CO_3$  (5 mmol g<sup>-1</sup>) to Pd/MCF, the reaction selectivity for all the functionalized chiral aromatic amines is improved. For example, the selectivity for 1-(4-MeO-phenyl)ethylamine and 1-(4-tolyl)ethylamine are increased to 99% and 92%, respectively. Compared with 1-phenylethylamine, the selectivity of K<sub>2</sub>CO<sub>3</sub>-Pd/MCF for (S)-1-(4-F-phenyl) ethylamine is decreased. It seems that the presence of an electron withdrawing group in amines can affect the reaction selectivity. In addition, K<sub>2</sub>CO<sub>3</sub>-Pd/MCF can successfully catalyze the racemization of (S)-1-phenylpropyl-amine with selectivity up to 99%. Unfortunately, aliphatic chiral amine, such as (S)-1-cyclohexylethylamine and (S)-2-hexyl-amine cannot be racemized with Pd/MCF or K<sub>2</sub>CO<sub>3</sub>-Pd/MCF as a catalyst, even at high temperature (100 °C) and long reaction time (3 days).

#### 3.7 Dynamic kinetic resolution of racemic 1-phenylethylamine

With K<sub>2</sub>CO<sub>3</sub>-modified Pd catalysts in hand, DKR of racemic 1-phenylethylamine was attempted using Novozyme 435 as the resolution catalyst and ethyl methoxyacetate as the acyl agent (Table 5). When PdNPs are supported on mesoporous

Table 4 Racemization of functionalized chiral aromatic amines catalyzed by Pd/MCF<sup>a</sup>

Substrate	$K_2CO_3 \text{ (mmol g}^{-1}\text{)}$	T (°C)	t (h)	ee <sup>b</sup> (%)	Conversion <sup>b</sup> (%)	Selectivity <sup>b</sup> (%)
NH2	0	70	12	3	81	36
$\hat{\mathbf{D}}$	5	90	12	19	44	92
NH <sub>2</sub>	0	70	10	-	96	07
OH <sub>3</sub> C	5	70 90	12	5	49	27 99
$\underline{N}H_2$						
$\bigwedge$	0	90	24	56	71	37
F	5	90	24	57	42	74
NH2						
$\bigwedge \\$	0	70	4	0	70	61
$\checkmark$	5	70	8	1	50	99

<sup>*a*</sup> Standard reaction conditions: substrate (65  $\mu$ L), Pd/MCF (2.45 wt.%, 0.01 mmol of Pd), hexadecane (120  $\mu$ L), toluene (4 mL), 0.01 MPa H<sub>2</sub>. <sup>*b*</sup> Determined as corresponding acetamide using chiral GC.

 Table 5
 Dynamic kinetic resolution of 1-phenylethylamine<sup>a</sup>



Entry	Catalyst	Time (h)	Conversion (%)	Yield <sup>b</sup> (%)	ee (%)
1	K <sub>2</sub> CO <sub>3</sub> -Pd/MCF	9	97	96	99
2	K <sub>2</sub> CO <sub>3</sub> -Pd/SBA-15	9	97	96	99
3	K <sub>2</sub> CO <sub>3</sub> -Pd/FDU-12	9	98	97	99
4	K <sub>2</sub> CO <sub>3</sub> -Pd/SiO <sub>2</sub> <sup>c</sup>	9	97	90	98
5	K <sub>2</sub> CO <sub>3</sub> -Pd/C	6	98	82	98
6	$K_2CO_3$ -Pd/C <sup>d</sup>	6	99	96	99

<sup>*a*</sup> Reaction conditions: 0.50 mmol of racemic 1-phenylethylamine, 120 μL of ethylmethoxyacetate, 0.01 mmol of Pd source, 100 mg of Novozyme 435, 4 mL of toluene, 0.01 MPa H<sub>2</sub>, 70 °C. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Commercial. <sup>*d*</sup> Multiple incipient wetness impregnations.

silicate, such as MCF, FDU-12 and SBA-15, the yield of (*R*)-1-phenylethylamide exceeds 95% and the enantioselectivity of product is 99% ee (Entries 1–3, Table 5). When PdNPs are supported on commercial SiO<sub>2</sub>, the yield of (*R*)-1-phenylethylamide decreases to 90% (Entry 4, Table 5). Commercial Pd/C affords the lowest yield of the corresponding (*R*)-amide (82%). However, the yield can be further enhanced up to 97% by multiple incipient wetness impregnations of Pd/C with K<sub>2</sub>CO<sub>3</sub>. To the best of our knowledge, this is the first case that DKR of amines can be efficiently performed with the catalyst based on commercial Pd/C.

#### 4. Conclusion

In summary, incorporation of alkalic salts ( $H_{-} > 9.8$ ) into supported Pd catalysts is found to be an efficient method for improving the selectivity for the racemization of (*S*)-1-phenylethylamine. These alkalic salts supported on Pd catalysts can efficiently suppress side reactions during the racemization and enhance the yield of chiral amines. Combined with immobilized lipases (Novozyme 435), these salt-modified Pd catalysts can catalyze the DKR of racemic 1-phenylethylamine with good yield and selectivity. Noteworthily, modification of Pd/C with  $K_2CO_3$  by multiple incipient wetness impregnations has successfully achieved the high yield (97%) of the product from racemization and DKR of primary amines.

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