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Enantioselective hydrogenation of isophorone and kinetic resolution of 3,3,5-trimethylcyclohexanone over Pd catalysts in the presence of (*S*)-proline

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Abstract

Enantioselective hydrogenation of isophorone and kinetic resolution of 3,3,5-trimethylcyclohexanone (TMCH) over Pd catalysts in the presence of (*S*)-proline revealed that the enantioselectivity for hydrogenation of isophorone was mainly originated from the kinetic resolution of TMCH. The rapid hydrogenation of isophorone primarily yielded racemic TMCH, and the followed kinetic resolution consumed the (*R*)-TMCH enantiomer, leaving the (*S*)-TMCH enantiomer in excess. The kinetic resolution of racemic TMCH is closely related to the acidic/basic properties of the support, and the addition of K_2CO_3 to Al_2O_3 provided more enantio-differentiating environment through the enhanced adsorption of (*S*)-proline on the catalyst surface. As a result, the Pd/Al_2O_3-K_2CO_3 catalyst with finely dispersed Pd particles and enhanced adsorption of (*S*)-proline gave very high enantioselectivities (e.e. value up to 98%) for the enantioselective hydrogenation of isophorone.

Keywords: Isophorone; TMCH; (*S*)-Proline; Enantioselective hydrogenation; Kinetic resolution

1. Introduction

Due to the significantly increased interest in practical applications, chiral heterogeneous hydrogenations over supported metal catalysts in the presence of chiral modifiers were extensively investigated with the aim to improve the enantioselectivity and to elaborate the reaction mechanism in recent years. Since the original works by Izumi et al. [1] and Orito et al. [2], the chiral heterogeneous hydrogenations of α, β-ketoesters over Pt/cinchona and Raney Ni/tartaric acid systems, respectively, are now the well-established reactions. It is generally recognized that the enantioselectivity in the hydrogenation of C=O bond containing compounds is originated from the chiral modifier involved in the enantio-differentiation step which occurs on the surface of the metal [3–5]. However, the enantioselective hydrogenation of the equally important C=C bond has received very little attention and still remains as an open challenge [6,7]. The most promising example is the hydrogenation of isophorone to (*S*)-3,3,5-trimethylcyclohexanone (TMCH) over Pd catalysts with the presence of (*S*)-proline as a chiral auxiliary. The essential work was reported by Tungler et al. [8,9] with relatively moderate enantioselectivities and further studies were conducted by Török and co-workers [10–12]. (*S*)-Proline has been proved to be a good chiral auxiliary in enantioselective hydrogenation of isophorone and the enantiomeric excesses (e.e.) value can be as high as 99% for TMCH [10,11]. But it was also noted that that the role of (*S*)-proline in the hydrogenation of isophorone was quite different from other modifiers in heterogeneous enantioselective hydrogenations. The enantioselective hydrogenation of isophorone does not work through a chiral modified reaction mechanism, and the (*S*)-proline acts as a chiral auxiliary which has to be used in stoichiometric amount with respect to the substrate [6]. It was previously proposed that (*S*)-proline was initially condensed with isophorone to form an iminium salt, and the subsequent hydrogenation of this intermediate generated the enantioselectivity of the product [9]. Hydrogenation of the C=C bond in the iminium salt led to the formation of (*S*)-TMCH, while hydrogenation of the C=N bond in the iminium salt would cause the formation of undesired byproducts. Török and co-workers [10,11] observed that the acidic/basic property of the support in Pd catalysts remarkably influenced the

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adsorption of (*S*)-proline and thus affected the reaction performance. Accordingly, they proposed a refined version of the reaction mechanism, in which the key step is the adsorption of (*S*)-proline on the support and the followed steps (mainly involves the kinetic resolution of TMCH) occur through the surface linked proline [10]. For example, $BaCO_3$, $SrCO_3$ and $CaCO_3$ supported Pd catalysts showed very high enantioselectivities (e.e. value up to 99%) due to the enhanced adsorption of (*S*)-proline on the basic supports [10]. However, these higher e.e. values were also accompanied by the lower yields of TMCH (about 50%) due to the formation of byproducts (fully hydrogenated compounds), which left in the solution [10,13]. Quite recently, Lambert and co-workers [13] reported that the enantioselectivity is merely the result of kinetic resolution process that occurs homogeneously in the solution. Racemic TMCH is produced by the initial rapid hydrogenation of isophorone, (*S*)-proline then reacts homogeneously and preferentially with the (*R*)-TMCH enantiomer, leaving the (*S*)-TMCH enantiomer in excess. According to this reaction scheme, the role of the metal surface is to catalyze the hydrogenation of isophorone, but it is not involved in the enantio-differentiation step. Hence, it seems that the originality of enantioselectivity as well as the reaction mechanism in the hydrogenation of isophorone over Pd catalysts with (*S*)-proline as chiral auxiliary is still under debate.

We recently investigated enantioselective hydrogenation of isophorone in the presence of (*S*)-proline over Pd catalysts with respect to the acidic/basic features of the supports and the particle sizes of Pd. It was found that the Pd/MgO catalyst with enhanced adsorption of proline and moderate Pd particle size resulted in high enantioselectivity (e.e. of 95%) and 43% yield of TMCH [14]. In this work, we comparatively studied the hydrogenation of isophorone and the kinetic resolution of racemic TMCH on Pd/Al_2O_3 and Pd/Al_2O_3-K_2CO_3 catalysts in the presence of (*S*)-proline to explore the role of (*S*)-proline adsorption and the contribution of kinetic resolution of TMCH to the enantioselectivity.

2. Experimental

2.1. Materials

Isophorone, TMCH, (*S*)-proline, K_2CO_3, $Pd(OAc)_2$ and ethanol used in this work were all in analytical grade. Al_2O_3 is a commercial product (SINOPEC, 298 m^2/g).

2.2. Preparation of Pd catalysts

Al_2O_3 was calcined at 500 °C for 3 h prior to use. K_2CO_3–Al_2O_3 mixture was prepared by grinding K_2CO_3 and Al_2O_3 (24/76 in weight) with the addition of distilled water of 0.5 ml/g. The paste was then dried at 110 °C for 12 h and crushed into particles (200 mesh).

Sixty-three milligrams $Pd(OAc)_2$ and 1 g of the support (with the nominal Pd content of 3%) were added to 20 ml ethanol in a 50 ml stainless steel autoclave, the mixture was kept at 30 °C for 30 min under stirring. After flushing with hydrogen, the suspension was further stirred for 2 h under hydrogen pressure of 3.0 MPa. The catalyst was then centrifuged and washed with ethanol, and dried in vacuum at 30 °C for 4 h.

2.3. Catalyst characterization

The actual Pd loading in the catalysts was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES), using a Plasma-Spec-I spectrometer. The samples were dissolved in acidic solutions, and then diluted to concentrations within the detection range of the instrument.

Transmission electronic microscope (TEM) images were taken on a Philips Tecnai $G^2$20 instrument operated at 200 kV. Specimens were prepared by ultrasonically suspending the sample in ethanol. A drop of the suspension was then applied onto a clean copper grid and dried in air.

2.4. Hydrogenation of isophorone and kinetic resolution of TMCH

Hydrogenation of isophorone and kinetic resolution of TMCH were conducted in a stainless steel autoclave with quartz inner at 25 °C and hydrogen pressure of 3.0 MPa. The typical reaction system includes catalyst, (*S*)-proline, isophorone (or TMCH), ethanol as solvent, which were mixed with desirable amounts in a quartz tube. The tube was placed in a 50 ml stainless steel autoclave with magnetic stirrer. Before reaction, the mixture was initially stirred for 40 min and flushed with hydrogen for three times. The products were analyzed by using an off-line GC (Agilent 6890N) equipped with β-cyclodextrin capillary column (Chirasil-Dex CB, Varian) at a temperature of 110 °C and a flame ionization detector. Conversion of isophorone, selectivity of TMCH and e.e. were calculated according to the following equations, using *n*-octane as an external standard:

$$\text{Conversion}\,(\%) = 100 \times \frac{\text{isophorone}_{\text{initial}} - \text{isophorone}_{\text{final}}}{\text{isophorone}_{\text{initial}}}$$

$$\text{Selectivity}\,(\%) = 100 \times \frac{\text{TMCH}}{\text{isophorone}_{\text{initial}} - \text{isophorone}_{\text{final}}}$$

$$\text{Yield}\,(\%) = 100 \times \frac{\text{TMCH}_{\text{final}}}{\text{TMCH}_{\text{initial}}}$$

$$\text{e.e.}\,(\%) = 100 \times \frac{[S]-[R]}{[S]+[R]}.$$

3. Results and discussion

3.1. Hydrogenation of isophorone

Table 1 summarizes the reaction results of isophorone hydrogenation over the Pd/Al_2O_3 and Pd/Al_2O_3-K_2CO_3 catalysts. Without the presence of (*S*)-proline, isophorone was rapidly hydrogenated into TMCH, and no enantioselectivity could be detected. When (*S*)-proline was present in the

Table 1
Isophorone hydrogenation over the Pd catalysts with and without (*S*)-proline

Catalyst	(*S*)-Proline (mmol)	Conversion (%)	Selectivity (%)	e.e. (%)
Pd/Al_2O_3[a]	–	53	>99	–
Pd/Al_2O_3-K_2CO_3[a]	–	94	>99	–
Pd/Al_2O_3[b]	0.39	29	51	14
Pd/Al_2O_3-K_2CO_3[b]	0.39[a]	61	62	27

Reaction conditions: 16 mg catalyst, 1.18 mmol isophoronel and 4.4 ml ethanol.

[a] Data were taken after running the reaction for 30 min.

[b] Data were taken after running the reaction for 60 min.

reaction media, the hydrogenation of isophorone showed enantioselectivity towards TMCH, but the reaction rate and the selectivity of TMCH were greatly decreased. It can be further noted that the addition of K_2CO_3 to Al_2O_3 support resulted in about two-fold increase in both the e.e. values (from 14% to 27%) and the conversion of isophorone (from 29% to 61%). Moreover, the selectivity of TMCH was also significantly promoted (from 51% to 62%). It has been reported that the nature of the support strongly affected the catalytic hydrogenation of isophorone and basic supports considerably enhanced the adsorption of (*S*)-proline on the catalyst surface and provided a better chiral environment, leading to higher e.e. values [10]. This phenomenon was also observed in the proline mediated asymmetric hydrogenation of exocyclic unsaturated ketones and interpreted in terms of the increased proline adsorption on the more basic catalyst surface [15]. Therefore, it can be proposed that the addition of potassium carbonate to alumina increased the basic property of the support, and thus provided a better kinetic resolution environment through the enhanced adsorption of (*S*)-proline.

3.2. Kinetic resolution of TMCH

Kinetic resolution is regarded as a process in which the chiral source reacts with one of the enantiomer, leaving the other enantiomer in excess, and thus the e.e. value increases as the process goes on [7]. The kinetic resolution of TMCH on Pd catalysts was conducted under the same reaction conditions as the hydrogenation of isophorone. Table 2 summarizes the reaction results of kinetic resolution of TMCH over the Pd catalysts. Obviously, the Pd/Al_2O_3-K_2CO_3 catalyst exhibited better performance than the Pd/Al_2O_3 catalyst with respect to the e.e. value. After running the reaction for 1 h, the e.e. value reached 51% and it was further increased to more than 98% when the reaction was operated for 10 h. While the corresponding values over the Pd/Al_2O_3 catalyst were only 24% and 90%, respectively. Fig. 1 shows the effect of the reaction time on the kinetic resolution of TMCH over the Pd/Al_2O_3-K_2CO_3 catalyst. Rapid increase in the e.e. value was observed during the initial 5 h, and the e.e. value of about 100% was achieved after running the reaction for 15 h. This implied that the (*R*)-TMCH was almost completely consumed by (*S*)-proline, leaving the (*S*)-TMCH in excess. Fig. 1 also presents the (*S*) and (*R*)-TMCH contents in the solution with the reaction time during the kinetic resolution of TMCH over the Pd/Al_2O_3-K_2CO_3 catalyst. It is clear that the amount of (*R*)-TMCH decreased dramatically to practical zero within 10 h, while the amount of (*S*)-TMCH only moderately decreased in the initial 10 h and very slight decrease occurred in the followed reaction course. These results clearly demonstrated that the kinetic resolution process played an important role in obtaining higher e.e. values.

Table 2
Kinetic resolution of racemic TMCH on the Pd catalysts

Reaction time (h)	Pd/Al_2O_3		Pd/Al_2O_3-K_2CO_3	
	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)
1	88	24	61	51
10	52	90	27	>98

Reaction conditions: 16 mg catalyst, 0.40 mmol (*S*)-proline, 0.56 mmol TMCH and 4.4 ml ethanol.

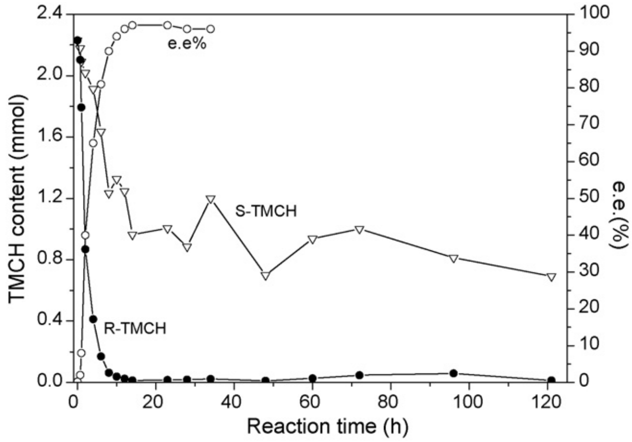

Fig. 1. The e.e. values and changes of (*S*) and (*R*)-TMCH contents in the solution as a function of reaction time during the kinetic resolution of TMCH over the Pd/Al_2O_3-K_2CO_3 catalyst. Reaction conditions: 128 mg catalyst, 3.83 mmol (*S*)-proline, 4.46 mmol TMCH and 35 ml ethanol.

Our primary experiments showed that (*S*)-proline did not react with any enantiomer of TMCH without the presence of Pd catalysts, and only the supports like Al_2O_3, K_2CO_3 and their mixture, also could not catalyze the reaction between (*S*)-proline and TMCH. This evidenced that the reaction between (*S*)-proline and (*R*)-TMCH is a kinetic resolution process, in which the adsorption of (*S*)-proline on the catalyst surface might be a critical step. The Pd/Al_2O_3-K_2CO_3 system exhibited significantly promoted performance, compared with the Pd/Al_2O_3 catalyst, either in the short reaction period of 1 h or in a long period of 10 h. The addition of K_2CO_3 to Al_2O_3 greatly increased the basic feature of the support which could enhance the adsorption of (*S*)-proline on the catalyst surface, favoring the kinetic resolution of TMCH. This implies that the e.e. value obtained in hydrogenation of isophorone mainly originated from the kinetic resolution process, which is affected by the acidic/basic properties of the catalysts. The reaction between (*S*)-proline and (*R*)-TMCH could be promoted on the Al_2O_3–K_2CO_3 basic support, due to the enhanced adsorption of (*S*)-proline on the catalyst surface,

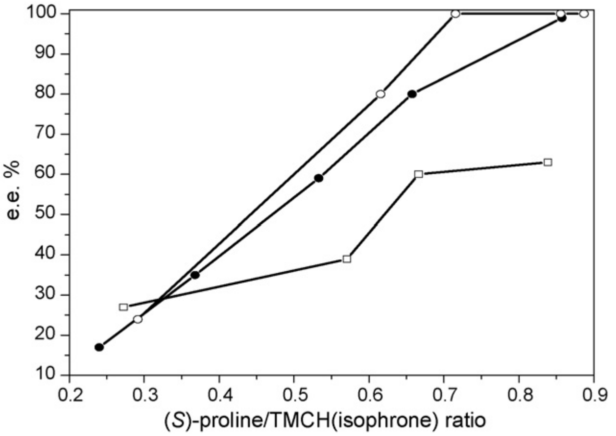

Fig. 2. Effect of (*S*)-proline/TMCH (or isophorone) ratio on the e.e values during kinetic resolution of TMCH (or hydrogenation of isophorone) over the Pd catalysts. Reaction conditions: 16 mg catalyst, 0.56 mmol TMCH (or isophorone) and 4.4 ml ethanol. (○) Kinetic resolution of TMCH over the Pd/Al_2O_3-K_2CO_3 catalyst, data were taken after running the reaction for 10 h; (□) kinetic resolution of TMCH over the Pd/Al_2O_3 catalyst, data were taken after running the reaction for 10 h; (●) hydrogenation of isophorone over the Pd/Al_2O_3-K_2CO_3 catalyst, data were taken after running the reaction for 12 h.

which provided more enantio-differentiating environment. Namely, the kinetic resolution of racemic TMCH is closely related to the acidic/basic properties of the catalysts. This phenomenon is also in good accordance with the recent observations [10,15].

3.3. Effect of (S)-proline amount

As mentioned above, the enantioselective hydrogenation of isophorone does not work through a modified reaction, but the (*S*)-proline is a chiral auxiliary which has to be used in stoichiometric amount with respect to the substrate [6]. Fig. 2 compares the influence of (*S*)-proline amount in the kinetic resolution of TMCH and the hydrogenation of isophorone over the Pd catalysts. The e.e. values increased linearly with increasing of the molar ratio of (*S*)-proline/TMCH during the kinetic resolution of TMCH, but relatively higher e.e. values were obtained over the Pd/Al_2O_3-K_2CO_3 catalyst. With a molar ratio of (*S*)-proline/TMCH of 0.7, the e.e. value of 100% was achieved on the Pd/Al_2O_3-K_2CO_3 catalyst, while the corresponding e.e. value was only about 60% on the Pd/Al_2O_3 catalyst. This indicates again that the kinetic resolution of TMCH is associated with the acidic/basic properties of the catalysts, and the presence of basic potassium carbonate provided more enantio-differentiating environment through the enhanced adsorption of (*S*)-proline.

Interestingly, the e.e. values of isophorone hydrogenation over the Pd/Al_2O_3-K_2CO_3 catalyst also increased monotonously with increasing the (*S*)-proline/isophorone molar ratio, and it followed almost the same trend as that of the kinetic resolution of TMCH. This phenomenon confirmed that the observed e.e. value for isophorone enantioselective hydrogenation is mainly resulted from the kinetic resolution of racemic TMCH, primarily produced by hydrogenation of isophorone.

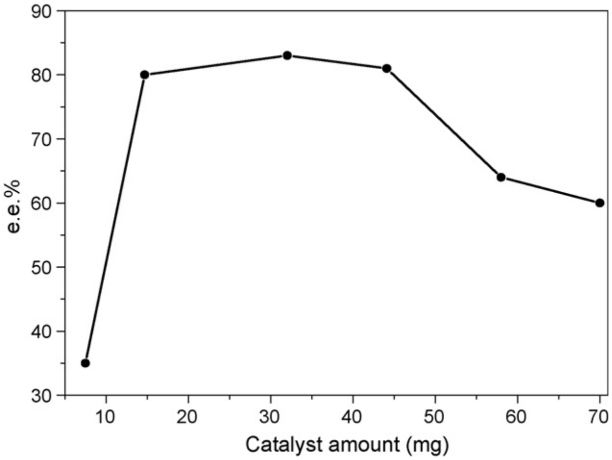

Fig. 3. Effect of the catalyst amount on the kinetic resolution of TMCH over the Pd/Al_2O_3-K_2CO_3 catalyst. Reaction conditions: 0.49 mmol (*S*)-proline, 0.56 mmol TMCH, 4.4 ml ethanol and reaction time 2 h.

3.4. Effect of catalyst amount

Fig. 3 shows the effect of the amount of the Pd/Al_2O_3-K_2CO_3 catalyst on the kinetic resolution of TMCH. When the catalyst amount increased from 8 mg to 15 mg, the e.e. value dramatically increased from 35% to 80%. Then, the e.e. value kept stable around 80% with further increasing the catalyst loading to 45 mg. However, the e.e. value remarkably decreased to 55% with increasing the catalyst to 70 mg. Since the reaction between (*R*)-TMCH and (*S*)-proline is much faster than the reaction between (*S*)-proline and (*S*)-TMCH, as shown in Fig. 1, this catalyst loading dependence can be explained by the fact that the excess amount of the catalyst in the reaction media would accelerate the reaction of (*S*)-TMCH with (*S*)-proline, which caused significant decrease in the e.e. value.

3.5. Recycle of the Pd catalysts in kinetic resolution of TMCH

Table 3 summarizes the results of recycle tests of the Pd catalysts in kinetic resolution of TMCH. After five recycles, the catalytic performances of the catalysts were significantly decreased. The e.e. value over the Pd/Al_2O_3-K_2CO_3 catalyst dropped from 98% to 56%, while it drastically decreased from

Table 3
Recycle tests of the Pd catalysts for kinetic resolution of TMCH

Recycle times	e.e. (%)	
	Pd/Al_2O_3	Pd/Al_2O_3-K_2CO_3
1	90	>98
2	70	>98
3	70	74
4	43	62
5	13	56

Reaction conditions: 16 mg catalyst, 0.49 mmol (*S*)-proline, 0.56 mmol TMCH and 4.4 ml ethanol. Reaction time for each run was set for 10 h. After each run, the mixture was centrifuged and the catalyst was washed with ethanol, dried in air at room temperature.

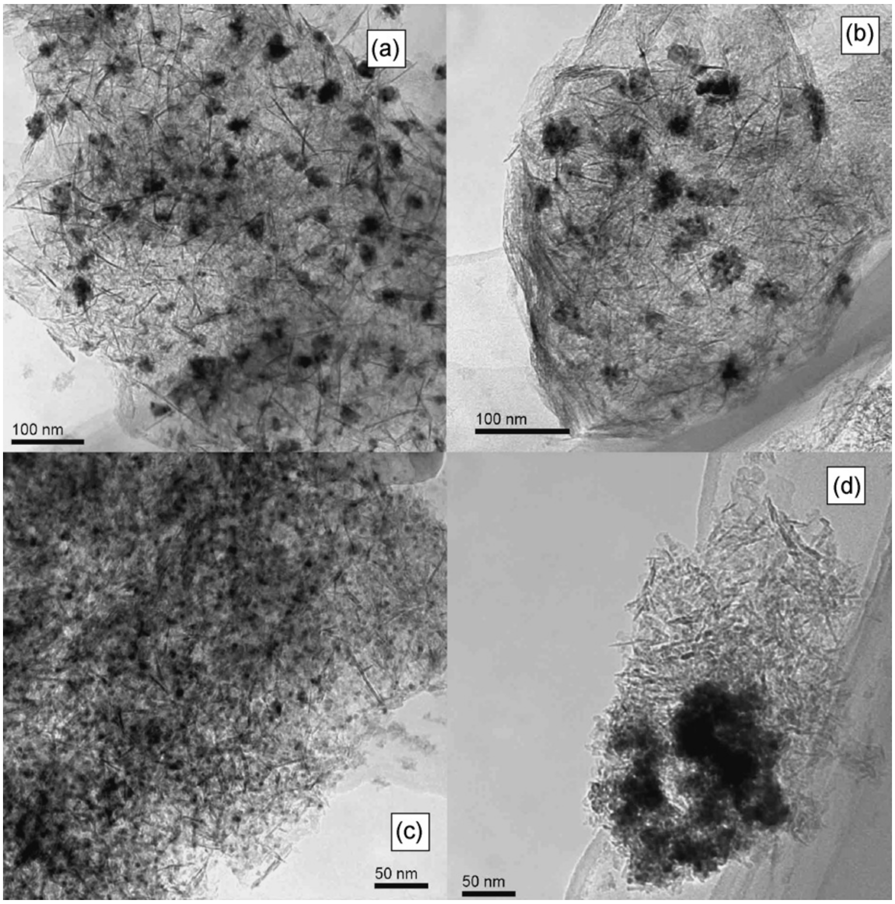

Fig. 4. TEM images of the Pd/Al_2O_3 catalysts: (a) fresh, (b) used and the Pd/Al_2O_3-K_2CO_3, (c) fresh and (d) used.

90% to 13% on the Pd/Al_2O_3 catalyst. Thus, it is clear that the Pd/Al_2O_3-K_2CO_3 catalyst could exhibit relatively better catalytic stability.

ICP analysis revealed that leaching of Pd during the reaction course could be one reason. The Pd loading was 2.48 wt.% in both of the fresh catalysts. After five cycles, the Pd contents were 1.49 wt.% for Pd/Al_2O_3 and 1.89 wt.% in Pd/Al_2O_3-K_2CO_3, respectively. Fig. 4 shows the TEM images of the fresh and the used Pd catalysts. It appears that the Pd particle size in the fresh Pd/Al_2O_3-K_2CO_3 catalyst was about 5–10 nm, which is smaller than that of the fresh Pd/Al_2O_3 catalyst (10–15 nm). Moreover, after running for five recycles, the Pd particle in both catalysts aggregated into relatively large sizes (40–60 nm), which is more pronounced in the case of Pd/Al_2O_3. This indicated that the presence of potassium carbonate favors the formation of small Pd particles and also could stabilize the Pd particles during the reaction course, in addition to enhance (*S*)-proline adsorption.

4. Conclusion

Hydrogenation of isophorone and kinetic resolution of racemic TMCH over Pd catalysts in the presence of (*S*)-proline were comparatively studied, and it was found that the enantioselectivity was originated mainly from the kinetic resolution of TMCH, which is the primary product of isophorone hydrogenation. The kinetic resolution of racemic TMCH was closely associated with the acidic/basic properties of the support, and the addition of K_2CO_3 to Al_2O_3 significantly enhanced the adsorption of (*S*)-proline on the Pd/Al_2O_3-K_2CO_3 catalyst, resulting in high enantioselectivities (e.e. value up to 98%) by promoting the enantio-differentiation reaction between (*S*)-proline and (*R*)-TMCH.

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