

### Article

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# Chemoselective Continuous-Flow Hydrogenation of Aldehydes Catalyzed by Platinum Nanoparticles Dispersed in an Amphiphilic Resin

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Supporting Information Placeholder

**ABSTRACT:** A chemoselective continuous-flow hydrogenation of aldehydes catalyzed by a dispersion of platinum nanoparticles in an amphiphilic polymer (ARP-Pt) has been developed. Aromatic and aliphatic aldehydes bearing various reducible functional groups, such as keto, ester, or amide groups, readily underwent flow hydrogenation in aqueous solutions within 22 seconds in a continuous-flow system containing ARP-Pt to give the corresponding primary benzylic or aliphatic alcohols in up to 99% yield with excellent chemoselectivity. Moreover, the long-term continuous-flow hydrogenation of benzaldehyde for eight days was realized, and the total turnover number of the catalyst reached 997. The flow hydrogenation system provides an efficient and practical method for the chemoselective hydrogenation of aldehydes bearing reducible functional groups.

**KEYWORDS**: continuous-flow reactor, platinum nanoparticles, amphiphilic polymer support, chemoselectivity, hydrogenation, aldehydes, alcohols

## INTRODUCTION

The reduction of carbonyl compounds is a fundamental and essential organic reaction that has been widely used in the syntheses of various chemicals and pharmaceutical compounds.1 In particular, the chemoselective reduction of aldehydes in the presence of reducible functional groups, especially keto groups, has been recognized as a major challenge. Conventional methods for the chemoselective reduction of aldehydes in the presence of ketone functionalities require the use of stoichiometric amounts of hydride reagents such as NaBH<sub>4</sub>, NaBH(OR)<sub>3</sub>, LiAlH(OR)<sub>3</sub>, or Bu<sub>3</sub>SnH.<sup>2</sup> However, the use of such reagents in stoichiometric amounts results in the production of large amounts of waste, which is a problem for these reactions.

Catalytic hydrogenation using molecular hydrogen would be a more desirable method from the viewpoint of green sustainable chemistry.<sup>3</sup> However, differentiation of the selectivity between

aldehydes and ketones is usually difficult in catalytic hydrogenations, because the energy of the hydrogenation of aldehydes  $(-\Delta H^{0}_{298} = 16-20)$ kcal/mol) is close to that of ketones  $(-\Delta H^{0}_{298} = 14)$ kcal/mol).<sup>4</sup> Consequently, aldehydes and ketones are both readily reduced under most hydrogenation conditions involving conventional transition-metal catalysts. Recent significant progress in this research field has provided some excellent homogeneous Fe,5a-d Ru,5e-g Rh,5h Ir,5i and Au5j,k catalysts that permit chemoselective catalytic hydrogenation of aldehydes in the presence of ketone groups. Although hydrogenation on heterogeneous catalysts has considerable advantages for green sustainable chemistry and in applications,<sup>3c,6</sup> industrial the range of chemoselective heterogeneous hydrogenations of aldehydes by using molecular hydrogen in the presence of ketone groups is guite limited.7

#### **ACS Catalysis**

Continuous-flow organic reactions have recently attracted much attention because they can permit efficient. practical. and green sustainable transformations.<sup>8,9</sup> Continuous-flow reactions provide significant advantages in terms of improved safety, high efficiency, precise control of reaction conditions, and simple scale-up. The continuous-flow hydrogenations of olefins, nitroarenes, and carbonyl compounds by using have heterogeneous catalysts been widely investigated, because of their numerous applications in the synthesis of valuable organic compounds.9 However, to our best knowledge, there is no available continuous-flow system that permits the exclusive hydrogenation of aldehyde groups while leaving ketone groups intact. Therefore, the development of new continuous-flow systems to realize efficient and practical flow chemoselective hydrogenation of aldehydes is highly desirable.

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We have previously developed a continuous-flow reaction system containing supported platinum nanoparticles dispersed in an amphiphilic polystyrene-poly(ethylene glycol) resin (PS-PEG) (Amphiphilic Resin-supported nanoParticles of Platinum; ARP-Pt), prepared by treatment of a PS-PEG supported platinum-ethylene complex with benzyl alcohol in water at 80 °C (Scheme 1).10 This continuous-flow system was effective for the aqueous aerobic oxidation of alcohols<sup>11</sup> and the hydrogenation of olefins and nitroarenes.<sup>12</sup> Both reactions were completed within 73 seconds. The flow system was also applied to gram-scale oxidation and hydrogenation reactions. These successful results prompted us to expand the substrate scope for the flow hydrogenation. Here, we report a continuous-flow hydrogenation of aldehydes with molecular hydrogen catalyzed by ARP-Pt. The continuous-flow hydrogenation of various aromatic and aliphatic aldehydes was completed within 22 seconds to give the corresponding benzylic or primary aliphatic alcohols in up to 99% isolated yield. Notably, aldehydes bearing other reducible carbonyl substituents, such as ketone, ester, or amide groups, were selectively converted into primary alcohols with these reducible substituents intact. Our flow hydrogenation system containing ARP-Pt can reduce aldehyde, alkenes, alkynes, or nitro groups and can not reduce ketone, ester, or amide groups.<sup>12</sup> The flow hydrogenation system provides a green, sustainable, efficient, and practical method for the chemoselective hydrogenation of aldehydes bearing reducible functional groups.



Scheme 1. Preparation of ARP-Pt.

### **EXPERIMENTAL SECTION**

#### General

All chemicals were sourced commercially and used as received without purification, unless otherwise mentioned. Substrates 1p, 1q, 1t, 3j, and 3k were prepared according to the reported procedure.<sup>13</sup> Water was deionized with a Millipore system (Milli-Q grade). The flow hydrogenation was carried out with an H-Cube Pro reactor system (ThalesNano Nanotechnology Inc., Budapest). <sup>1</sup>H and <sup>13</sup>C{<sup>1</sup>H} NMR spectra were recorded on a JEOL JNM-ECS 400 spectrometer. GC analyses were performed with an Agilent 6850 GC system. Mass spectra were recorded on an Agilent 6890/5973 or an Agilent 7820A/5977E GC/MS system (GC EI-MS). ICP analysis was performed on a Leeman Labs Profile plasma spectrometer. TEM analyses were carried out with a JEOL JEM-2100F transmission electron microscope.

### Batch Hydrogenation; General Procedure

A Schlenk reaction tube was charged with the appropriate substrate (0.2 mmol) and ARP-Pt (2 mol% Pt). The solvent was added and the atmosphere inside the reaction tube was replaced with  $H_2$ . The contents of the reaction tube were then stirred at 25 °C. When the reaction was complete, the catalyst was collected by filtration and the filtrate was analyzed by GC and MS.

## Flow Hydrogenation; Typical Procedure

A 12.5 mM aqueous solution of benzaldehyde (1a) was pumped at a flow rate of 1.0 mL/min into the H-Cube Pro reactor system equipped with an ARP-Pt catalyst cartridge (300 mg; 0.073 mmol Pt). The flow hydrogenation of 1a with H<sub>2</sub> gas (30 vol% of nanobubbles) was conducted at 40 °C under a system pressure of 30 bar. The resulting solution was collected for 20 min (20 mL) and then extracted with ethyl acetate ( $3 \times 40$  mL). The organic phases were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and carefully concentrated by evaporation to afford benzyl alcohol (2a) as a colorless oil (89% yield) without any further purification.

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## ICP analysis of the catalyst after flow hydrogenation

After the continuous-flow hydrogenation of benzaldehyde (**1a**) for 7852 min, the used catalyst was removed from the catalyst cartridge. A portion of this catalyst (20 mg) was added to aqua regia (5 mL), and the mixture was heated at 100 °C for two hours. The resulting solution was diluted with water to a total volume of 50 mL, and the aqueous solution was analyzed by ICP.

### **RESULTS AND DISCUSSION**

## Hydrogenation of Aldehydes and Ketones with ARP-Pt under Batch Conditions

Initially, the catalytic activity of ARP-Pt in the hydrogenation of aldehydes and ketones was evaluated under batch conditions. Batch hydrogenation of benzaldehyde (1a) was carried out in the presence of ARP-Pt (2 mol% Pt) in H<sub>2</sub>O (0.6 M) at 40 °C under  $H_2$  (1 atm) for 12 hours (Scheme 2a). Benzaldehyde (1a) was consumed with 97% conversion under these conditions, but the desired benzyl alcohol (2a) was obtained in only 59% GC yield (61% selectivity), along with overreduced products such as cyclohexanecarbaldehyde and cyclohexylmethanol. When the hydrogenation of benzaldehyde (1a) was conducted in EtOH, the yield of benzyl alcohol (2a) improved to 79%, but overreduction occurred similarly. When the batch hydrogenation of decanal (3a) was investigated under the same catalytic conditions (Scheme 2b), although hydrogenation occurred with 43-56% conversion, the desired decan-1-ol (4a) was obtained in poor yield (15-17%) with low selectivity (27–40%). Decanoic acid and *n*-decane were generated as the major side products. Acetophenone (5) was fully consumed in H<sub>2</sub>O and EtOH under the batch-catalytic conditions (2 mol% of ARP-Pt, 1 atm of  $H_2$ , 40 °C, 12 h) to give 1-phenylethanol (6) in 42-52% yield, along with the overreduced products 1-cyclohexylethanone (16 - 10%)and 1-cyclohexylethanol (9-16%)(Scheme 2c). The batch hydrogenation of aldehydes and aromatic ketones therefore proceeded in the presence of ARP-Pt, but often suffered from low selectivity toward the desired alcohols due to overreduction. In contrast, ARP-Pt was ineffective in the hydrogenation of aliphatic ketones: batch hydrogenation of decane-2-one (7) did not proceed under the catalytic conditions, even at 100 °C (Scheme 2d).



**Scheme 2.** Batch Hydrogenation of Aldehydes and Ketones with ARP-Pt.

## Optimization of Conditions for Flow Hydrogenation of Aldehydes

The unsatisfactory results obtained in the batch hydrogenation prompted us to investigate the flow hydrogenation of aldehydes catalyzed by ARP-Pt in the belief that the precise control of the reaction achievable in the flow system might improve the selectivity of the hydrogenation and prevent undesired overreduction.



**Figure 1.** Photographs of (a) the H-Cube Pro reactor and (b) a catalyst cartridge ( $\phi$  4.0 × 70 mm).



**Figure 2.** Plot of the GC yield of benzyl alcohol (**2a**) versus time (min) for the flow hydrogenation of benzaldehyde (**1a**) in various solvents, catalyzed by ARP-Pt: EtOH: circles;  $H_2O$ : squares; toluene: upward-pointing triangles; 1,4-dioxane: downward-pointing triangles. *Reaction conditions*: benzaldehyde (**1a**; 25 mM solution), ARP-Pt (1 cartridge; 300 mg, 0.073 mmol Pt),  $H_2$  (30 vol% in flow stream), system pressure: 5 bar, flow rate: 1 mL/min; contact time: 22 s.

The continuous-flow hydrogenation of benzaldehyde (1a) catalyzed by ARP-Pt was carried out in various solvents in a flow reactor (H-Cube Pro. Figure 1a) for five hours. A 25 mM solution of **1a** was introduced into the reactor at a flow rate of 1.0 mL/min and passed through a catalyst cartridge (internal diameter: 4 mm; length: 70 mm, Figure 1b), charged with ARP-Pt (300 mg, 0.073 mmol Pt) at a system pressure of 5 bar at 40 °C. The solution stream contained 30 vol% of nanosized bubbles of  $H_2$ . The contact time of the solution with the catalyst was 22 seconds. The flow hydrogenation of **1a** in EtOH proceeded efficiently during an initial 90 minutes, giving benzyl alcohol (2a) in over 83% yield, without formation of overreduced products (Figure 2). After 90 minutes, the catalytic activity gradually decreased. At 290 minutes, 2a was obtained in 42% yield. The flow hydrogenation of benzaldehyde in H<sub>2</sub>O, toluene, or 1,4-dioxane proceeded well during the initial a few minutes, but the activity rapidly decreased and benzaldehyde was obtained in yields of 34, 30, and 7%, respectively, at 100 min. Under these reaction conditions, rapid aggregation of the platinum nanoparticles would occur to decrease the catalytic activity (See also the section of Long-term Flow hydrogenation of benzaldehyde).

We then attempted further optimization of the reaction conditions in EtOH (Figure 3). When the concentration of the substrate **1a** was reduced from 25 mM to 12.5 mM, the yield of benzyl alcohol (2a) fell within 50 minutes in flow hydrogenation under 5 bar pressure. A large amount of EtOH would promote aggregation of the platinum nanoparticles to decrease the catalytic activity because the resulting platinum(II) intermediate in the hydrogenation would be reduced with alcohol. Therefore, the concentration of benzaldehyde in EtOH significantly affected the catalytic activity (25 mM vs. 12.5 mM). Increasing the system pressure to 10 bar did not ameliorate this problem. Unfortunately, the activity of APR-Pt could not be improved in the flow hydrogenation of benzaldehyde (1a) in EtOH.



**Figure 3.** Plot of the GC yield of benzyl alcohol versus time (min) for the flow hydrogenation of benzaldehyde (**1a**) in EtOH catalyzed by ARP-Pt under various conditions: 25 mM and 5 bar: white circles; 25 mM and 10 bar: blue circles; 12.5 mM and 5 bar: black circles. *Reaction conditions*: benzaldehyde (**1a**), EtOH (12.5 or 25 mM), ARP-Pt (1 cartridge; 300 mg, 0.073 mmol Pt),  $H_2$  (30 vol% in flow stream), system pressure: 5 or 10 bar, flow rate: 1 mL/min; contact time: 22 s.

In an attempt to improve the catalytic activity of ARP-Pt, we revisited the flow hydrogenation of benzaldehyde (1a) in  $H_2O$  and carried out an optimization of this reaction (Figure 4). Reduction of the concentration of the substrate solution from 25 mM to 12.5 mM enhanced the catalytic activity in the flow hydrogenation at 5 bar, although a low yield of benzyl alcohol (2a) was observed during the initial 50 min (Figure 4; blue squares versus white squares). The yield of 2a improved from 19% to 34% after 270 min. When the system pressure

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was increased, a further improvement of the catalytic activity was observed in the flow hydrogenation of **1a** in  $H_2O$  (12.5 mM). The flow hydrogenation at 30 bar provided optimal, maintaining the yield of benzyl alcohol (**2a**) at more than 90% yield during 270 minutes, without a significant drop in the catalytic activity. We therefore decided to apply these conditions (12.5 mM, 30 bar) for the flow hydrogenation of various aldehydes in aqueous solution.



**Figure 4.** Plot of the GC yield of benzyl alcohol (1a) versus time (min) for the flow hydrogenation of benzaldehyde in H<sub>2</sub>O catalyzed by ARP-Pt under various conditions: 25 mM, 5 bar: blue squares; 12.5 mM, 5 bar: white squares; 12.5 mM, 10 bar: green upward-pointing triangles; 12.5 mM, 20 bar: brown upward-pointing triangles; 12.5 mM, 30 bar: red diamonds. *Reaction conditions*: benzaldehyde (2a), H<sub>2</sub>O (12.5 or 25 mM), ARP-Pt (1 cartridge; 300 mg, 0.073 mmol Pt), H<sub>2</sub> (30 vol% in flow stream), system pressure: 5–30 bar, flow rate: 1 mL/min; contact time: 22 s.

## Substrate Scope for the Flow Hydrogenation of Aldehydes Catalyzed by ARP-Pt

With the optimized conditions in hand, we investigated the substrate scope for the flow hydrogenation in aqueous solution (Scheme 3). When substrates that were insoluble in  $H_2O$  were used, the flow hydrogenation was carried out in a mixture of  $H_2O$  and EtOH (9:1 to 4:6). We also confirmed that the catalytic activity of ARP-Pt in the flow hydrogenation of benzaldehyde (**1a**) in a 1:1 mixture of  $H_2O$  and EtOH was maintained for

300 minutes. Benzaldehydes **1b-f** bearing the para-substituents methoxy, methyl, hydroxy, chloro, and trifluoromethyl, respectively, underwent aqueous flow hydrogenation to afford the corresponding benzvl alcohols **2b**-**f** in 86–99% isolated yield without recovery of the starting aldehydes and formation of side products (100% selectivity). When 4-nitrobenzaldehyde was exposed to the flow conditions, both the aldehyde group and the nitro group were reduced, to afford (4-aminophenyl)methanol (2g) in 95% yield with 100% selectivity.<sup>12</sup> The presence of substituents in the ortho- or meta-positions (**1h** and **1i**) did not affect the reaction. 1,3-Benzodioxol-5-carbaldehyde (1j), 2-naphthaldehyde (1k), and pyridine-2carbaldehyde (11) were also fully reduced to the corresponding primary alcohols **2k**-**l** without any side products. In case of 2-furaldehyde (1m), decomposition of 2-furaldehyde was observed. Therefore the desired alcohol (2m) was obtained in 52% vield. In the hydrogenation of cinnamaldehyde (1n), both the carbonyl group and the unsaturated bond were hydrogenated to give 3phenylpropan-1-ol (2n) in 99% yield. Notably, the carbonyl groups of ester 10 and carbamates 1p and 1q (BocNH and CbzNH) remained intact under the flow conditions in a mixture of H<sub>2</sub>O and EtOH, while the aldehyde groups were efficiently converted into hydroxy groups to give alcohols 20-2q without any side products. Furthermore, the flow hydrogenation of 4-acetylbenzaldehyde (1r) in 7:3 H<sub>2</sub>O-EtOH gave 1-[4-(hydroxymethyl)phenyl]ethanone (2r) in 82% yield without recovery of the starting aldehydes and formation of side products. The catalytic flow hydrogenation process on ARP-Pt, in aqueous solution therefore realized selective hydrogenation of aromatic aldehydes, without reduction of keto substituents.



**Scheme 3.** Substrate scope for benzaldehyde derivatives **1** in the aqueous flow hydrogenation. *Reaction conditions*: **1**, H<sub>2</sub>O (12.5 mM), ARP-Pt (1 cartridge, 300 mg, 0.073 mmol Pt), H<sub>2</sub> (30 vol% in flow stream), 40 °C, system pressure: 30 bar, flow rate: 1 mL/min; contact time = 22 s. Isolated yields are reported unless stated otherwise. <sup>*a*</sup> In 8:2 H<sub>2</sub>O-EtOH. <sup>*b*</sup> In 7:3 H<sub>2</sub>O-EtOH. <sup>*c*</sup> **2g** was obtained from 4-nitrobenzaldehyde. The resulting product contained ~6% of the imine derivative. <sup>*d*</sup> In 9:1 H<sub>2</sub>O-EtOH. <sup>*e*</sup> NMR yield. <sup>*f*</sup> In 6:4 H<sub>2</sub>O-EtOH (6:4). <sup>*g*</sup> In 4:6 H<sub>2</sub>O-EtOH.

Although the batch hydrogenation of aliphatic aldehydes 3 was sluggish in the presence of ARP-Pt (see above), the flow hydrogenation of linear alkyl aldehydes **3a–e** proceeded efficiently at 100 °C in a 1:1 mixture of H<sub>2</sub>O and EtOH (Scheme 4). The corresponding aliphatic alcohols 4a–e were obtained excellent vields. in Cyclohexyl-, cycloheptyl-, and cyclooctylacetaldehyde (3f-h) also underwent flow hydrogenation at 40–80 °C to afford the corresponding alcohols **4f-h** in 87–95% vield. The sterically hindered aldehyde 3,3dimethylbutanal (3i) was also efficiently converted into 3,3-dimethylbutan-1-ol (4i) in 78% yield.



**Scheme 4.** Substrate scope for aliphatic aldehydes **3** in the aqueous flow hydrogenation. *Reaction conditions*: Substrate **3**, H<sub>2</sub>O–EtOH (12.5 mM), ARP-Pt (1 cartridge, 300 mg, 0.073 mmol Pt), H<sub>2</sub> (30 vol% in flow stream), system pressure: 30 bar, flow rate: 1 mL/min; contact time: 22 s. Isolated yields are reported unless stated otherwise. <sup>*a*</sup> In 5:5 H<sub>2</sub>O–EtOH. <sup>*b*</sup> In H<sub>2</sub>O. <sup>*c*</sup> In 6:4 H<sub>2</sub>O–EtOH. <sup>*d*</sup> In 7:3 H<sub>2</sub>O–EtOH. <sup>*e*</sup> In 8:2 H<sub>2</sub>O–EtOH. <sup>*f*</sup> At 100 °C. <sup>*g*</sup> At 60 °C. <sup>*h*</sup> At 40 °C. <sup>*i*</sup> At 80 °C. <sup>*j*</sup> Yield by GC using an internal standard.

### Investigation on Selective Flow Hydrogenation of Aldehydes

As mentioned above, we found that the aldehyde group was selectively hydrogenated without reduction of the keto group in the catalytic flow hydrogenation of 4-acetylbenzaldehyde (1r). This result encouraged us to investigate further the scope for the selective hydrogenation of aldehydes (Scheme 5). The flow hydrogenation of 3acetylbenzaldehyde (1s) and 4'-acetylbiphenyl-4carbaldehyde (1t) in various mixtures of H<sub>2</sub>O and EtOH (7:3 to 4:6) provided the corresponding keto alcohols 2s and 2t in 89 and 97% yield, respectively, without reduction of the ketone groups. The selective hydrogenation was also effective for aliphatic keto aldehydes. The flow hydrogenation of 5-oxohexanal (3j) and 6oxoheptanal (3k) in a 7:3 mixture of  $H_2O$  and t-BuOH (7:3) gave 5-oxohexanol (4j) and 6oxoheptanol (4k) in 71% and 87% yield, respectively. These results clearly demonstrate that the flow system with ARP-Pt is effective in the selective catalytic hydrogenation of aldehydes.

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**Scheme 5.** Chemoselective catalytic hydrogenation on ARP-Pt of aldehydes bearing ketone groups. Isolated yields are reported unless stated otherwise. *<sup>a</sup>* Yield by GC with an internal standard.

#### Long-Term Flow Hydrogenation of Aldehydes

To check the stability of ARP-Pt under flowhydrogenation conditions, we examined a longterm flow hydrogenation (Figure 5). When the flow hydrogenation of benzaldehyde (1a) was conducted at 40 °C at a flow rate of 1 mL/min (contact time 22 s) under a system pressure of 30 bar, the yield of benzyl alcohol (2a) was maintained at over 90% during about four days (4000 min). Subsequently, the activity of ARP-Pt gradually decreased, and at 7852 minutes, the yield eventually fell to 5%. In the hydrogenation process, the total turnover number (TON) reached 997.<sup>14</sup> We also performed long-term hydrogenations of 1a at flow rates of 2 and 3 mL/min. At a flow rate of 2 mL/min, a significant decrease in the yield of 2a was observed after 500 minutes, and at 2800 minutes, the yield had fallen to 30%. The total TON of ARP-Pt also dropped to 664. Rapid flow therefore facilitated deactivation of ARP-Pt. In the flow hydrogenation at a flow rate of 3 mL/min, the catalytic activity of ARP-Pt was almost lost after 1500 minutes, and a lower TON (472) was observed.

ICP analysis of the used catalyst after long-term flow hydrogenation of **1a** for 7850 min (flow rate: 1 mL/min) revealed that the Pt content was identical to that of the fresh catalyst. No leaching of Pt from the catalyst had occurred during the longterm flow reaction, although the deactivation of ARP-Pt was observed. TEM analysis of the used ARP-Pt catalyst after the long-term hydrogenation reaction (Figure 6) showed the presence of large aggregates and enlargement of the platinum nanoparticles during the flow reaction (Figure 6b). Therefore, a change in the size of the nanoparticles is probably responsible for the deactivation of ARP-Pt. Under rapid-flow conditions (flow rate: 2–3 mL/min), more-rapid formation of large aggregates of the platinum nanoparticles occurs, resulting in faster deactivation of the catalyst.



Figure 5. Plot of the GC yield of benzyl alcohol (2a) versus time (min) for the long-term flow hydrogenation of benzaldehyde (1a; 12.5 mM) in  $H_2O$  at 40 °C catalyzed by ARP-Pt. Flow rate 1 mL/min (contact time 22 s): red downward-pointing triangles; 2 mL/min (contact time 11 s): green downward-pointing triangle; 3 mL/min (contact time 7.3 s): blue squares.



**Figure 6.** TEM images of ARP-Pt (a) before the reaction and (b) after long-term hydrogenation of benzaldehyde (**1a**) at 40 °C at a flow rate of 1 mL/min for 7852 minutes.

#### CONCLUSION

In conclusion, we have developed an efficient aqueous continuous-flow system for the selective hydrogenation of aldehydes by using a continuousflow reactor containing platinum nanoparticles dispersed on an amphiphilic polystyrenepoly(ethylene glycol) resin (ARP-Pt). Aromatic and aliphatic aldehydes bearing various substituents such as ketone, ester, or amide groups were selectively hydrogenated under the aqueous flow conditions (40–100 °C, 30 bar) to give the corresponding primary alcohols in up to 99% yield, leaving the other substituents intact. Moreover long-term continuous-flow hydrogenation of benzaldehyde was realized. The total turnover number reached 997 during eight days. This flow system therefore provides an efficient and practical method for the selective catalytic hydrogenation of aldehydes bearing reducible functional groups, such as ketone, ester, or amide groups.

#### ASSOCIATED CONTENT

#### **Supporting Information**

Analytical data for products **2** and **4**, (<sup>1</sup>H, and <sup>13</sup>C{<sup>1</sup>H} NMR spectra, MS data). This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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of benzaldehyde using heterogeneous catalysts are available. In the batch hydrogenation of benzaldehyde with heterogeneous palladium catalyst showing the similar chemoselectivity of aldehydes toward ketones (ref 7), the total TON after the reuse experiment (5 times) was 485.

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**Chemoselective Flow Hydrogenation of Aldehydes** 

