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Recoverable, Reusable, Highly Active, and Sulfur-Tolerant Polymer Incarcerated Palladium for Hydrogenation

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Abstract: A new type of immobilized palladium, PI (polymer incarcerated) Pd (**2b**), from $Pd(PPh_3)_4$ and copolymer (**1b**) has been developed. The excellent activity of PI Pd has been demonstrated in hydrogenation of various olefins, benzyl ethers, and nitro and aromatic compounds. PI Pd is tolerant under high pressure and high temperature and can be recovered and reused several times without loss of activity even under harsh conditions. Moreover, PI Pd is highly resistant to poisoning by sulfur.

Palladium-catalyzed hydrogenation is frequently used not only in laboratories but also in industry. While immobilized palladium catalysts such as Pd/C and Pd/Al_2O_3, etc. have been often employed, leaching of the palladium from the supports, moderate yields of recovery, contamination of the palladium to products, and poisoning by sulfur are sometimes serious problems especially in the manufacture of pharmaceuticals.[1]

We have recently developed the polymer-incarcerated (PI) method[2] to immobilize metal catalysts onto polymers.[3] The method is based on microencapsulation[4] and cross-linking, and $Pd(PPh_3)_4$ was immobilized using this method to form polymer-incarcerated palladium (PI Pd). It was revealed that PI Pd (**2a**) derived from polymer (**1a**) consisted of phosphine-free palladium(0) and effectively catalyzed hydrogenation of olefins in THF under atmospheric pressure. Moreover, the catalyst was recovered completely by simple filtration and could be reused several times without loss of activity. On the other hand, it was assumed that the benzyl ether moieties of PI Pd (**2a**) would be cleaved in the hydrogenation under harsh conditions, such as high hydrogen pressure and high temperature. We decided to modify the structure of PI Pd (**2a**) and now report here a new type of highly active and versatile PI Pd, which has high resistance to harsh conditions and poisoning by sulfur in various hydrogenations.

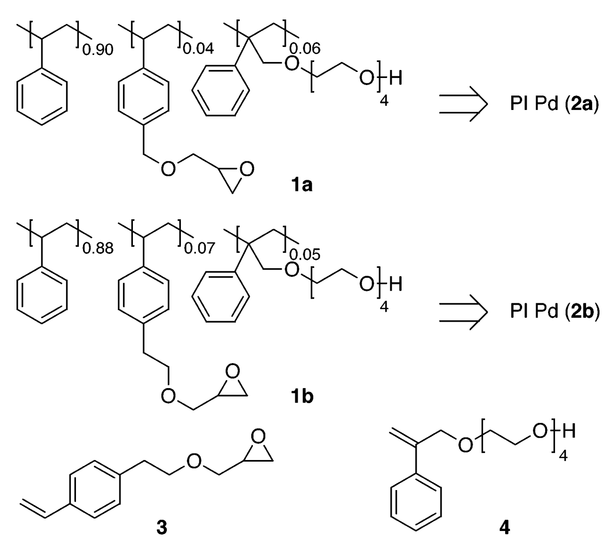

FIGURE 1. Compounds **1**−**4**.

We designed a new copolymer (**1b**) for higher resistant PI Pd (**2b**), which has no benzylic ether moiety. Copolymer (**1b**) was synthesized by radical copolymerization of styrene, epoxide monomer (**3**), and tetraethyleneglycol monomer (**4**) (Figure 1).[5] PI Pd (**2b**) was prepared from $Pd(PPh_3)_4$ and polymer (**1b**) according to the method for the preparation of **2a**.[2,5] First, we examined the catalytic activity and the effect of loading levels[5,6] of **2a** and **2b** in the hydrogenation of benzalacetone and cholesterol under atmospheric pressure (Tables 1 and 2). It was revealed that the activity of **2b** was almost the same as that of **2a** in the hydrogenation of benzalacetone, while **2b** exhibited higher activity than **2a** in the reduction of cholesterol, a more hindered substrate. We also confirmed that the loading level of the palladium did not affect the activity of either PI Pd catalyst.

Several other substrates were hydrogenated using PI Pd (**2b**), and the results are summarized in Table 3. In addition to normal C−C double and triple bonds, benzyl ethers, nitrobenzene, and quinoline were easily hydrogenated under atmospheric pressure at room temperature. We also applied PI Pd (**2b**) to the reduction of less reactive substrate **7**, which is the intermediate for the synthesis of an antidiabetic agent, pioglitazone (**8**). This agent is expected to effectively ameliorate the abnormal glucose and lipid metabolism associated with noninsulin dependent diabetes mellitus or obesity.[7] It is known that the yields of the hydrogenation of **7** using conventional

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[1] (a) Trimm, D. L. *Design of Industrial Catalysts*; Elsevier: Amsterdam, 1980. (b) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985. (c) Satterfield, C. N. *Heterogeneous Catalysis in Industrial Practice*, 2nd ed.; McGraw-Hill: New York, 1991.

[2] Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3412.

[3] For recent reviews of polymer-supported metal catalysts, see: (a) Corain, B.; Centomo, P.; Lora, S.; Kralik, M. *J. Mol. Catal. A: Chem.* **2003**, 755. (b) Karakhanov, E. A.; Maximov, A. L. *Met. Complexes Met. Macromol.* **2003**, 457. (c) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217. (d) Stefan, B.; Johannes, K.; Nils, G. *Handb. Organopalladium Chem. Org. Synth.* **2002**, *2*, 3031. (e) Kralik, M.; Biffis, A. *J. Mol. Catal. A: Chem.* **2001**, *177*, 113.

[4] (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985. (b) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org Chem.* **1998**, *63*, 6094. (c) Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229. (d) Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649. (e) Akiyama, R.; Kobayashi, S. *Angew.* Chem., Int. Ed. **2001**, *40*, 3469. (f) Akiyama, R.; Kobayashi, S. *Angew.* Chem., Int. Ed. **2002**, *41*, 2602.

[5] Details are shown in the Supporting Information.

[6] The loading level of the palladium was determined by XRF analysis.

[7] (a) Sohda, T.; Momose, Y.; Meguro, K.; Kawamatsu, Y.; Sugiyama, Y.; Ikeda, H. *Arzneim-Forsch.* **1990**, *40*, 37. (b) Sugiyama, Y.; Taketomi, S.; Shimura, Y.; Sohda, T.; Meguro, K.; Fujita, T. *Arzneim-Forsch.* **1990**, *40*, 253. (c) Sugiyama, Y.; Shimura, Y.; Ikeda, H. *Arzneim-Forsch.* **1990**, *40*, 436.

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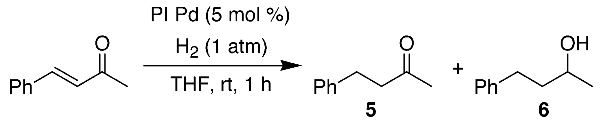
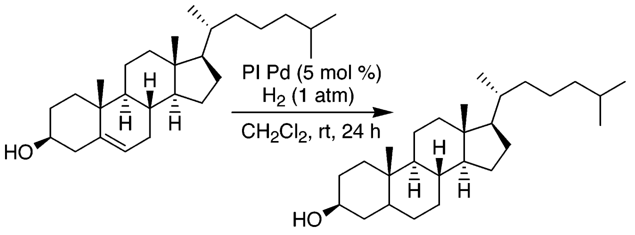
TABLE 1. Hydrogenation of Benzalacetone Using PI Pd



entry	PI Pd	loading level of Pd (mmol/g)	yield[a] (%)
1	**2a**	0.108	85
2	**2b**	0.091	85
3	**2b**	0.707	87

[a] Isolated yield (the ratio of **5**/**6** = 95/5).

TABLE 2. Hydrogenation of Cholesterol Using PI Pd

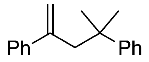
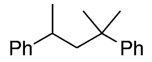
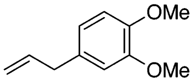
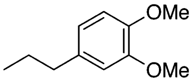
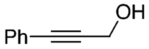
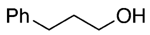
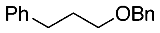
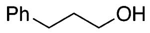
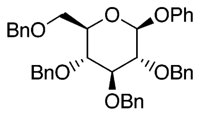
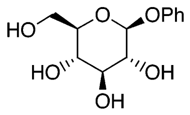
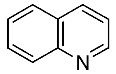
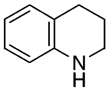


entry	PI Pd	loading level of Pd (mmol/g)	yield[a] (%)
1	**2a**	0.108	63
2	**2a**	0.813	69
3	**2b**	0.090	85
4	**2b**	0.593	85

[a] Determined by ^1H NMR analysis.

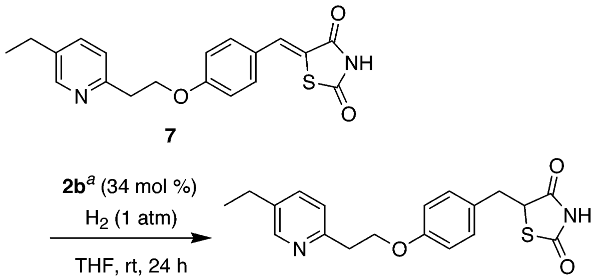
catalysts are not satisfactory probably because this substrate has catalytic poisonous nitrogen and sulfur moieties in the molecule.[8] The hydrogenation of **7** using PI Pd (**2b**) under atmospheric pressure proceeded smoothly to afford **8** quantitatively (Scheme 1). No contamination of the palladium was detected by X-ray fluorescence (XRF) analysis,[9] and PI Pd (**2b**) could be recovered and reused. On the other hand, phenanhrene and 2-methoxynaphthalene were hydrogenated under 70 atm of hydrogen pressure at 50 °C (Scheme 2 and Table 4). PI Pd (**2b**) was successfully recovered and reused even under high hydrogen pressure at elevated temperature without loss of activity, and leaching of the palladium was not detected by XRF analysis in all runs.

TABLE 3. Hydrogenation of Several Substrates Using 2b[a]

entry	substrate	time (h)	product	yield (%)[b]
1		1		quant
2		1		quant
3		1		93
4	PhOBn	18	PhOH	89[c]
5		5		98
6		72		87
7	PhNO₂	18	PhNH₂	93[c]
8		24		quant

[a] All reactions were carried out using 5 mol % of **2b** (the loading level of the palladium was 0.707 mmol/g) in THF under atmospheric H_2 pressure at rt. The leaching of the palladium to reaction mixture was measured by XRF analysis. No peaks of the palladium were detected in all entries. [b] Isolated yield. [c] Determined by GC analysis.

SCHEME 1. Hydrogenation for Antidiabetic Agent Using 2b[a]



Pioglitazone (**8**)
quant[b]

[a] (a) The loading level of the palladium was 0.593 mmol/g. (b) Isolated yield.

Furthermore, a remarkable result was obtained in the hydrogenation of benzothiophene. In the petrochemical industry, the hydrotreating of petroleum feedstocks is conducted in refineries, and sulfur compounds are converted to hydrocarbons and H_2S via a hydrodesulfurization (HDS) process. Among the sulfur compounds, thiophenes are quite abundant and benzothiophene is one of the most difficult to degrade.[10] The HDS process is typically performed at high hydrogen pressures (>200 atm) and temperatures (300−450 °C) in the presence of sulfided metal-based catalysts such as nickel- and cobalt-promoted MoS_2 and WS_2 supported on alumina, and benzothiophene is hydrogenated to dihydrobenzothiophene during the HDS process.[11] It is noted that the hydrogena-

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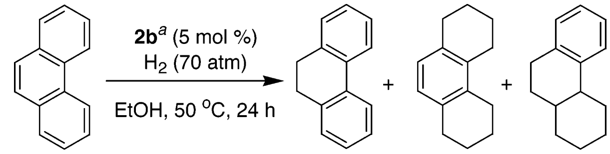
(8) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Shoda, T. *Chem. Pharm. Bull.* **1991**, *39*, 1440.

(9) The lower limit is <5 ppm.

(10) Highly active homogeneous ruthenium catalysts for HDS have been reported. (a) Borowski, F. A.; Sabo-Etienne, S.; Donnadieu, B.; Chaudret, B. *Organometallics* **2003**, *22*, 4803. (b) Bianchini, C.; Meli, A.; Moneti, S.; Oberhauser, W.; Vizza, F.; Herrera, V.; Fuentes, A.; Sanchez-Delgado, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 7071. (c) Rojas, I.; L. Linares, F.; Valencia, N.; Bianchini, C. *J. Mol. Catal*, **1999**, *144*, 1.

(11) (a) Topsφe, H.; Clause, B. S.; Massoth, F. E. *Hydrotreating Catalysis*; Springer-Veralag: Berlin, 1996. (b) Scherzer, J.; Gruia, A. J. *Hydrocracking Science and Technology*; Marcel Dekker: New York, 1996. (c) Gates, B. C.; *Catalytic Chemistry*; John Wiley: New York, 1992; Chapter 5, p 390. (d) Whitehurst, D. D.; Isoda, T.; Mochida, I. *Adv. Catal.* **1998**, *42*, 345. (e) van den Berg, J. P.; Lucien, J. P.; Germaine, G.; Thielemans, G. L. B. *Fuel Process Technol.* **1993**, *35*, 119. (f) Prins, R.; de Beer, V. H. J.; Somorjai, G. A. *Catal. Rev.-Sci. Eng.* **1989**, *31*, 1.

SCHEME 2. Hydrogenation of Phenanthrene Using 2b[a]

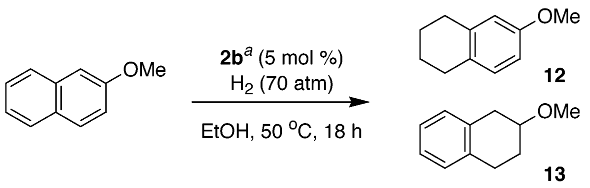


9 **10** **11**

conv. 80% (**9**/**10**/**11** = 81/14/5)[b]

[a] (a) The loading level of the palladium was 0.707 mmol/g. (b) The ratio of **9**/**10**/**11** was determined by ^{1}H NMR. No leaching of the palladium to the reaction mixture was detected.

TABLE 4. Reuse of 2b under Harsh Conditions



12

13

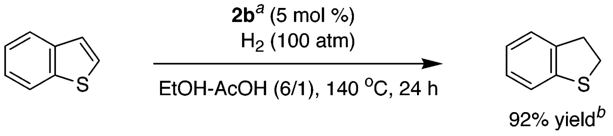
run	yield[b] (%)	ratio of **12/13**[c]	recovery of **2b** (%)
1	100	73/27	quant
2	100	74/26	quant
3	100	74/26	quant
4	99	74/26	quant
5	100	74/26	quant

[a] All reactions were carried out using 5 mol % of **2b** (the loading level of the palladium was 0.707 mmol/g) in THF under atmospheric H_2 pressure at rt. The leaching of the palladium to reaction mixture was measured by XRF analysis. No peaks of the palladium were detected in all entries. [b] Isolated yield. [c] Determined by GC analysis.

tion of benzothiophene using PI Pd (**2b**) under milder conditions compared to HDS conditions proceeded in excellent yield (Scheme 3).[12] The excellent activity of PI Pd (**2b**) is possibly due to the highly dispersed palladium in the polymer, and the surrounding benzene rings of the polymer may protect the palladium from poisoning by sulfur.

In summary, we have prepared a new type of PI Pd (**2b**) from $Pd(PPh_3)_4$ and **1b**. The excellent activity of PI Pd (**2b**) has been shown in hydrogenation of various olefins, benzyl ethers, and nitro and aromatic compounds. PI Pd (**2b**) was tolerant under high pressure and high temperature and could be recovered and reused several times without loss of activity even under harsh conditions. It is noted that PI Pd is highly resistant to poisoning by sulfur.

SCHEME 3. Hydrogenation of Benzothiophene Using 2b[a]



[a] (a) The loading level of the palladium was 0.707 mmol/g. (b) Isolated yield. No leaching of the palladium to the reaction mixture was detected.

Experimental Section

A Typical Experimental Procedure for the Hydrogenation. PI Pd (**2b**, 0.025 mmol, 5 mol %) and 2-methoxynaphthalene (79.1 mg, 0.50 mmol) were combined in ethanol (7 mL). The mixture was stirred for 18 h at 50 °C under 70 atm of hydrogen pressure. The catalyst was filtered and washed with tetrahydrofuran, and the solvents of the filtrate were removed under reduced pressure. The residue was purified by PTLC to afford a mixture of 5,6,7,8-tetrahydro-2-methoxynaphthalene (**12**) and 1,2,3,4-tetrahydro-2-methoxynaphthalene (**13**) (81.1 mg, conversion 100%, **12**/**13** = 73/27). Recovered PI Pd was dried under reduced pressure and reused.

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Supporting Information Available: General experimental information and experimental details and spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) It was confirmed that catalytic activity of **2b** was higher than that of Pd/C (5% Pd/C gave the reduced product in 14% yield, 54% yield was obtained using PI Pd (**2b**) under the same conditions (10 atm, 140 °C for 24 h in THF).