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Development of Carbon-Neutral Cellulose-Supported Heterogeneous Palladium Catalysts for Chemoselective Hydrogenation

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Abstract: Palladium catalysts immobilized on cellulose particles (Pd/CLP) and on a cellulose-monolith (Pd/CLM) were developed. These composites were applied as hydrogenation catalysts and their catalyst activities were evaluated. Although both catalysts catalyzed the deprotection of benzyloxycarbonyl-protected aromatic amines (Ar-N-Cbz) and aromatic benzyl esters (Ar-CO_2Bn), only Pd/CLM could accomplish the hydrogenolysis of aliphatic-N-Cbz and aliphatic-CO_2Bn protective groups. The difference in the physical structure of the cellulose supports induced unique chemoselectivity. Aliphatic-N-Cbz and aliphatic-CO_2Bn groups were tolerated under the Pd/CLP-catalyzed hydrogenation conditions, while Ar-N-Cbz, Ar-CO_2Bn, alkene, alkyne, azido and nitro groups could be smoothly reduced.

Introduction

Chemoselective hydrogenation is an essential subject in the field of organic synthesis for the development of novel short-step synthesis pathways.[1] The use of heterogeneous palladium catalysts offers advantages such as easy removability of the catalyst by simple filtration, reusability, and less metal residue compared to homogeneous catalysis.[2] It is well known that the activity of heterogeneous palladium catalysts is affected mainly by the unique characteristics of the supports; thus, a wide variety of organic and inorganic materials are utilized as efficient supports.[3] We previously developed many heterogeneous and chemoselective Pd catalysts immobilized on various functionalized supports, such as polyethyleneimine (Pd/PEI),[4] silk fibroin (Pd/Fib),[5] molecular sieves (Pd/MS),[6] boron nitride (Pd/BN),[7] ceramics (Pd/ceramic),[8] monolithic ion-exchange resins (Pd/monolith),[9] and so on.

Cellulose is an Earth-abundant, ubiquitous, and environmentally friendly biomass (biopolymer).[10] The use of cellulose results in carbon neutrality and circulates carbon dioxide;[11] thus, it has attracted attention as an alternative to industrially synthesized polymers derived from fossil fuels, such as bio-ethanol,[12] bio-methanol,[13] hydrogen gas,[13,14] hydrocarbons,[15] lactic acid,[12a,16] pentenoic acid,[17] and bio-coal.[18] Several types of cellulose-derived functional materials have also been utilized in filters for water purification,[19] sensors,[20] and biomedicine.[21] Because cellulose is resistant to heat and highly acidic and basic conditions and is a cheap, renewable, and biodegradable material,[23] various functionalized and unmodified cellulose derivatives have also been widely utilized as efficient supports for metal catalysts[24–29] for organic reactions, such as coupling reactions,[24,26,28e] reduction,[25] oxidation,[26] hydrogen evolution reactions,[27] hydrogenations[28] and so on.[29] While some cellulose derivative-supported palladium catalysts have been applied for hydrogenation,[29] the effect of the physical structure of cellulose as a catalyst support on the catalyst activity for hydrogenation, has not been sufficiently investigated.
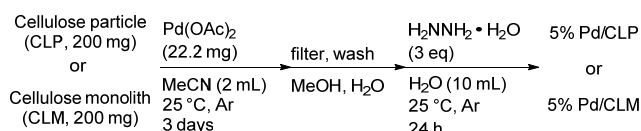
Herein, we developed two types of new heterogeneous palladium catalysts, [Pd/CLP (cellulose particle) and Pd/CLM (monolithic cellulose)], using cellulose particles (CLP) and monolithic cellulose (CLM) as supports, and applied these catalysts as hydrogenation catalysts for a wide variety of reducible functionalities. Both catalysts exhibit novel chemoselective catalyst activity under batch reaction conditions. Furthermore, continuous-flow chemoselective hydrogenation using a 5% Pd/CLM packed cartridge as a catalyst was demonstrated.

Results and Discussion

Preparation and catalyst activity of 5% Pd/CLP and 5% Pd/CLM

A colorless, bulky, lump-shaped cellulose monolith (CLM) polymer was finely cut into small pieces (ca. 2 mm) using scissors before preparation of the CLM-supported Pd catalyst. For the congener, colorless cellulose particle (CLP) powder was used without further treatment. Pd species were embedded in CLP and CLM via the impregnation metal-immobilizing method developed by our group (Scheme 1).[3,8,9] CLP and CLM were added to an acetonitrile (MeCN) solution of Pd(OAc)$_2$ at 25 °C and stirred for 3 d under argon atmosphere. The colorless CLP and CLM turned yellow, and the dark orangish solution was

gradually decolorized to a slightly pale yellow. The filtered Pd(OAc)$_2$-adsorbed CLP and CLM were washed with MeOH and H$_2$O, dried in vacuo, and subsequently stirred in an aqueous solution of hydrazine monohydrate at 25 °C under argon atmosphere for 24 h. The resulting solution was filtered through a Hirsch funnel, washed with MeOH and H$_2$O, and dried in vacuo to afford Pd/CLP and Pd/CLM as pale gray particles and cubes, respectively. The Pd content of Pd/CLP and Pd/CLM was 5 wt.% in both cases based on the concentration of the residual Pd species in the filtrate from each metal-immobilizing and Pd reduction step, determined by atomic absorption spectrophotometry (AAS, Pd detection limit: 1 ppm). 5% Pd/CLP and 5% Pd/CLM were also prepared in EtOAc and MeOH via a preparation method similar to that in MeCN.

Cellulose particle (CLP, 200 mg) or Cellulose monolith (CLM, 200 mg) → Pd(OAc)$_2$ (22.2 mg), MeCN (2 mL), 25 °C, Ar, 3 days → filter, wash, MeOH, H$_2$O → H$_2$NNH$_2$ • H$_2$O (3 eq), H$_2$O (10 mL), 25 °C, Ar, 24 h → 5% Pd/CLP or 5% Pd/CLM

Scheme 1. Preparation of 5% Pd/CLP and 5% Pd/CLM in CH$_3$CN.

With five different kinds of heterogeneous Pd catalysts immobilized on CLP and CLM prepared in MeCN, EtOAc, and MeOH, respectively, in hand, we evaluated the catalyst activity of each species for the hydrogenation of 4-ethylnitrobenzene (Table 1). The 5% Pd/CLP and 5% Pd/CLM catalysts prepared in MeCN demonstrated higher catalyst activity than the congeners that were prepared in EtOAc and MeOH (Entries 2 vs. 1, and 5 vs. 3 and 4). Among the five different kinds of heterogeneous Pd catalysts, 5% Pd/CLM prepared in MeCN showed the highest catalyst activity for the hydrogenation of 4-ethylnitrobenzene. The use of an H$_2$ balloon (hydrogen pressure about 1.04 atm) instead of a gas sampling bag (no positive pressure, 1.00 atm) did not affect the hydrogenation efficiency. Therefore, the H$_2$ balloon was used in subsequent experiments because of its high versatility and ease of use (Entry 5, in parentheses).Based on these results, 5% Pd/CLP and 5% Pd/CLM prepared in MeCN were chosen as catalysts for subsequent studies.

Table 1. Comparison of the catalyst activity for the hydrogenation of 4-ethylnitrobenzene in the presence of 5% Pd/CLP and 5% Pd/CLM catalysts prepared in MeCN, EtOAc, and MeOH

Catalyst (1 mol%), H$_2$ (gas sampling bag), MeOH (1 mL), 25 °C, 2 h; 0.25 mmol
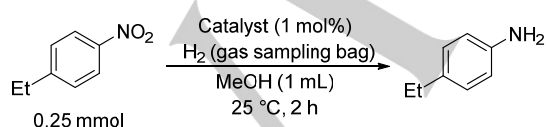
Entry	Catalyst type	^{1}H NMR ratio (substrate : product)	Conversion
1	5% Pd/CLP (EtOAc)	100 : 0	0%
2	5% Pd/CLP (MeCN)	68 : 32	35%
3	5% Pd/CLM (EtOAc)	77 : 23	23%
4	5% Pd/CLM (MeOH)	64 : 36	44%
5	5% Pd/CLM (MeCN)	7 : 93 (10 : 90)[a]	93% (90%)[a]

[a] H$_2$ balloon was used instead of gas sampling bag.

Physical properties of 5% Pd/CLP and 5% Pd/CLM

The 5% Pd/CLP and 5% Pd/CLM catalysts were analyzed in detail using scanning transmission electron microscopy (STEM), scanning electron microscopy (SEM), energy dispersive X-ray spectrometry (EDX), and X-ray photoelectron spectroscopy (XPS), as shown in Figure 1. The particle size of a significant number of the Pd clusters in both 5% Pd/CLP and 5% Pd/CLM before the hydrogenation reaction was estimated to be ca. 1–5 nm from the STEM images. Significant aggregation of the Pd species of 5% Pd/CLP was revealed by a comparison of the STEM images in a and b, suggesting a reason for the lower catalyst activity of 5% Pd/CLP compared with that of 5% Pd/CLM (Table 1). Namely, the large specific surface area of CLM for Pd distribution based on the monolithic structure could avoid aggregation of Pd species to result in the higher catalyst activity of 5% Pd/CLM in comparison to 5% Pd/CLP. The surfaces of both catalysts before and after the hydrogenation reaction were not significantly structurally different on the macroscopic level based on the SEM images (5% Pd/CLP; c-1 vs. c-2, 5% Pd/CLM; d-1 vs. d-2). The EDX images indicated that the Pd clusters were uniformly distributed in all regions of both the CLP and CLM supports before and after hydrogenation (5% Pd/CLP; e-1 vs. e-2, 5% Pd/CLM; f-1 vs. f-2). X-ray photoelectron spectroscopy (XPS) revealed that most of the Pd species on both catalysts were present was as Pd(0) (g-1 and h-1). The characteristic peaks of Pd (0) for 5% Pd/CLP and 5% Pd/CLP were observed at ca. 341.0 and 335.7 eV, corresponding to Pd 3d3/2 and Pd 3d5/2, respectively, (g-1 and h-1). Furthermore, the ratios of Pd (0) and Pd (II) were largely maintained before and after hydrogenation (g-1 vs. g-2, and h-1 vs. h-2; the detailed ratio is presented in Supporting Information). These results strongly suggest the efficient and stable immobilization of Pd(0) clusters on CLP and CLM.
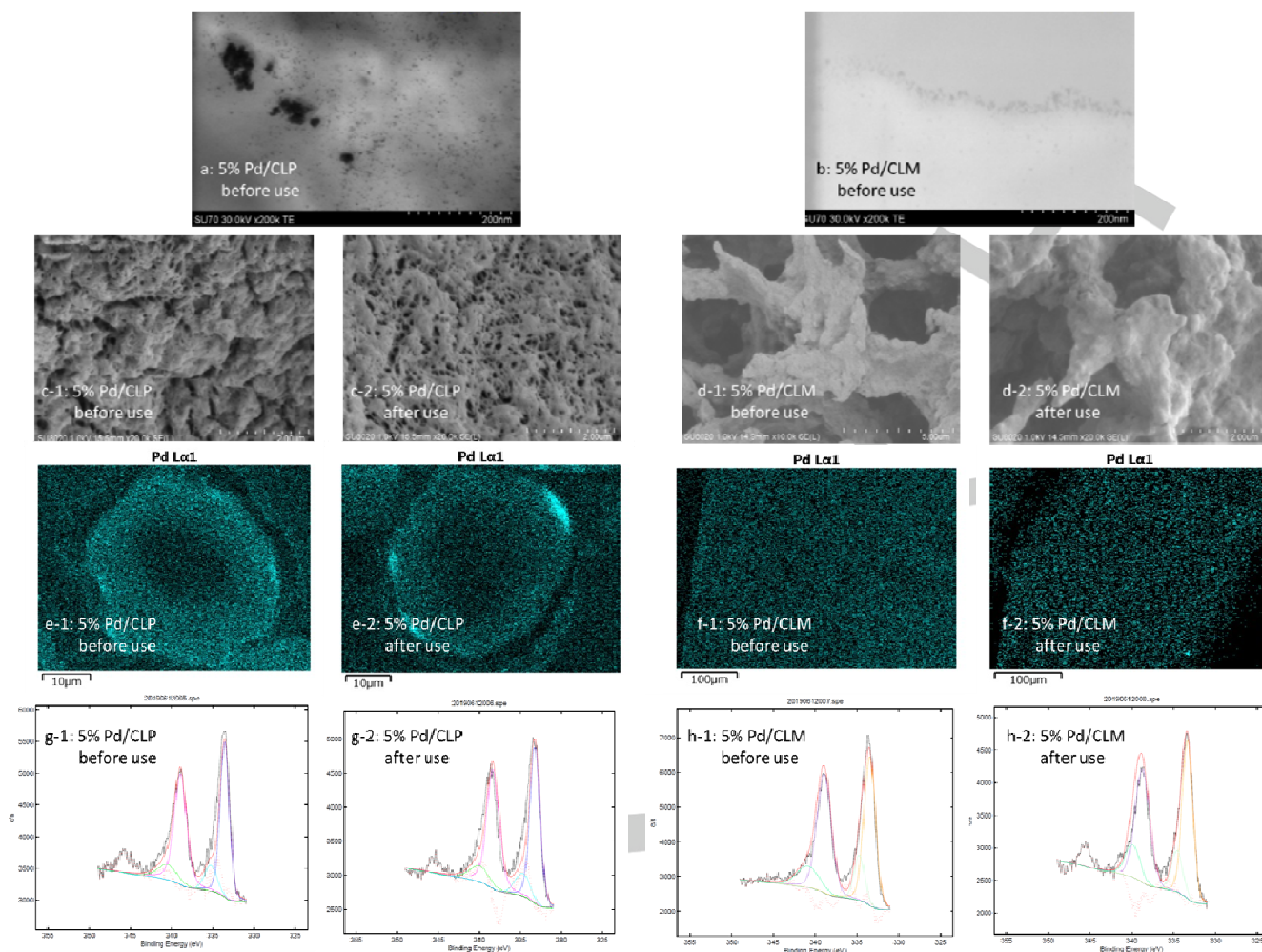
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Figure 1. a, c, e, and g: STEM, SEM, EDX, and XPS data for 5% Pd/CLP, respectively. b, d, f, and h: STEM, SEM, EDX, and XPS data for 5% Pd/CLM, respectively.

5% Pd/CLP- and 5% Pd/CLM-catalyzed chemoselective hydrogenation

The catalyst activity of 5% Pd/CLP and 5% Pd/CLM for the hydrogenation of various reducible functionalities was evaluated in MeOH as a solvent. Alkynes (Table 1, entries 1 and 2), alkenes (entries 7, 8, 15, 16, 25, and 26), nitro (entries 3 and 4), and azido (entries 5, 6, 33, and 34) were readily hydrogenated in the presence of each catalyst to give the corresponding reduced products in excellent yields. These catalysts could also catalyze the deprotection of *aromatic N*-Cbz and CO$_2$Bn (entries 7, 8, 11, and 13). However, only 5% Pd/CLM catalyzed the hydrogenation of *aliphatic N*-Cbz and CO$_2$Bn (entries 10 and 16). Aromatic ketones could be partially hydrogenated in the presence of both catalysts to give the corresponding *sec-*

alcohols as chemoselectively reduced products (entries 21 and 22), and further hydrogenolysis of benzyl alcohol did not occur (entries 21, 22, 31, and 32). On the other hand, both aromatic and aliphatic benzyl ethers (entries 17, 18, 19, 20, 33, and 34) were stable under both 5% Pd/CLP- and 5% Pd/CLM-catalyzed hydrogenation conditions, and the benzyl ether functionalities remained unchanged. Although styrene oxide (entries 23 and 24) was smoothly reduced to the corresponding 2-phenylethyl alcohol, the aliphatic epoxide ring of glycidyl methacrylate (entries 25 and 26) was not reduced, and only methacrylic alkene was hydrogenated. Furthermore, the aromatic chloride and *tert*-butyldimethylsilyl (TBS) ether were tolerated under both 5% Pd/CLP- and 5% Pd/CLM-catalyzed hydrogenation conditions (entries 27, 28, 29, and 30).

Table 2. 5% Pd/CLP- and 5% Pd/CLM-catalyzed hydrogenation of various reducible functionalities[a]

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	substrate $\xrightarrow[\text{MeOH, 25 °C, time}]{\substack{\text{[A] (1 mol\%) or [B] (1 mol\%)}\\ \text{H}_2 \text{ (balloon)}}}$ product	[A] = 5% Pd/CLP [B] = 5% Pd/CLM			
entry	substrate	product	catalyst	time	yield
1	Ph——Ph	Ph⌒Ph	[A]	6 h	quant.
2			[B]	6 h	quant.
3	Et-C6H4-NO2	Et-C6H4-NH2	[A]	6 h	98%
4			[B]	6 h	97%
5	Et-C6H4-N3	Et-C6H4-NH2	[A]	6 h	93%
6			[B]	6 h	97%
7[c]	Ph-N(Cbz)-allyl	Ph-NH-propyl	[A]	24 h	92%
8[c]			[B]	24 h	86%
9	Ph⌒⌒NHCbz	Ph⌒⌒NH2	[A]	24 h	0 (quant.)[b]
10[c]			[B]	12 h	86%
11	Ph⌒CO2Bn	Ph⌒CO2H	[A]	24 h	quant.
12[d]			[B]	3 h	0 (quant.)[b]
13			[A]	24 h	quant.
14[d]			[B]	3 h	0 (quant.)[b]
15	Ph⌒CO2Bn	Ph⌒⌒CO2Bn	[A]	24 h	0 (quant.)[b]
16		Ph⌒⌒CO2H	[B]	5 h	99%
17	Me-C6H4-OBn	Me-C6H4-OH	[A]	24 h	0 (quant.)[b]
18			[B]	6 h	0 (quant.)[b]
19	⌒9-OBn	⌒9-OH	[A]	6 h	0 (quant.)[b]
20			[B]	24 h	0 (quant.)[b]
21[c]	Ph-C(O)-iPr	Ph-CH(OH)-iPr	[A]	24 h	99%
22[c]			[B]	24 h	97%
23	Ph-epoxide	Ph⌒OH	[A]	24 h	99%
24			[B]	24 h	83%
25	methacrylate glycidyl ester	isobutyrate glycidyl ester	[A]	24 h	89%
26			[B]	24 h	93%

Table 2. Continued

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substrate → product

[A] (1 mol%) or [B] (1 mol%)
H₂ (balloon)
MeOH, 25 °C, time

[A] = 5% Pd/CLP
[B] = 5% Pd/CLM

entry	substrate	product	catalyst	time	yield
27	Ph⌇OTBS	Ph⌇OTBS	[A]	24 h	79%
28			[B]	24 h	99%
29	Cl (1-chloronaphthalene)	naphthalene	[A]	24 h	0 (quant.)[b]
30			[B]	24 h	0 (96%)[b]
31	Ph⌇OH (1-phenyl-3-buten-1-ol)	Ph⌇OH	[A]	24 h	94%
32			[B]	24 h	quant.
33	N₃⌇OBn	H₂N⌇OBn	[A]	24 h	99%
34			[B]	24 h	99%

[a] Substrate (0.25 mmol) and 1 mol% of 5% Pd/CLP or 5% Pd/CLM (5.32 mg) in MeOH (1 mL) stirred under hydrogen atmosphere. [b] Recovery yield of the substrate. [c] Reaction was carried out at 50 °C. [d] Ethyl acetate was used as the solvent instead of methanol.

Figure 2 summarizes the hydrogenation activity of 5% Pd/CLP and 5% Pd/CLM in comparison with commercial Pd/C and some heterogeneous hydrogenation catalysts previously developed by our research group.[3,8,9] The corresponding catalysts could hydrogenate the reducible functionalities within each frame. Therefore, novel chemoselective hydrogenation catalyst activity was established using 5% Pd/CLP and 5% Pd/CLM.

The reuse of 5% Pd/CLP and 5% Pd/CLM under the hydrogenation conditions was examined using diphenylacetylene as a substrate (Table 3). The catalysts could be readily recovered and reused at least three times without any loss of activity. No reaching of the Pd species was detected in the filtrates of the reaction mixture after hydrogenation using inductively coupled plasma-atomic emission spectroscopy (ICP-AES; detection limit: < 1 ppm; eq. 1).[30]

Catalyst activity / **Reducible functionalities**

	Reducible functionalities	Novel Chemoselectivities
Pd/C, Pd/HP20, Pd/CM	R-O-TBS, Benzyl alcohol, Aliphatic-O-Bn	
Pd/WA30, Pd/AM	Epoxide	**Pd/CLM**
Pd/CR	Aromatic-O-Bn	Aliphatic-CO₂Bn, Aliphatic-N-Cbz
	Ar-Cl	RCOR **Pd/CLP**, Aromatic-N-Cbz, Aromatic-CO₂Bn
Pd/Fib		R-NO₂
Pd/MS3A, Pd/BN		Alkene
Pd/PEI		R-N₃
Pd/BN+pyridine		Alkyne

Figure 2. Comparison of the hydrogenation catalyst activity of 5% Pd/CLP, and 5% Pd/CLM with that of previously developed chemoselective heterogeneous Pd catalysts.

Table 3. Reuse of 5% Pd/CLP and 5% Pd/CLM

Ph—≡—Ph (0.25 mmol) →
5% Pd/CLP (1 mol%) or 5% Pd/CLM (1 mol%)
H₂ (balloon)
MeOH (1 mL), 25 °C, 6 h
→ Ph⌇Ph
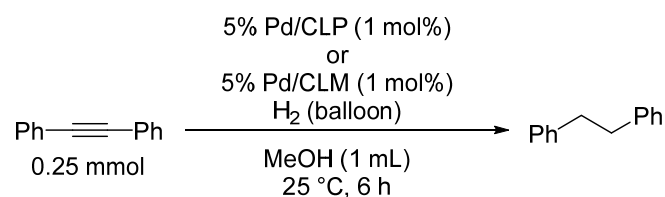
	5% Pd/CLP		5% Pd/CLM	
run	yield (%)	catalyst recovery yield (%)	yield (%)	catalyst recovery yield (%)
1	quant.	95	quant.	quant.
2	quant.	94	97	quant.
3	quant.	95	quant.	quant.

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eq. (1) scheme:

Ph━━━Ph
0.25 mmol

5% Pd/CLP or CLM (1 mol%)
(Pd: 5.32 mg)

MeOH (1 mL)
H₂, r.t., 600 rpm, 6 h

Ph⌒Ph   (eq. 1)

97% yield

Without Pd leaching
: below detection limit
of the AAS analysis
(< 1 ppm order)
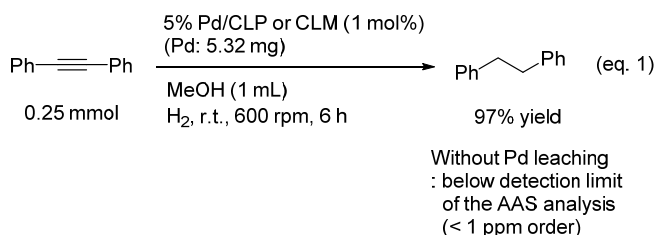
Catalytic hydrogenation employing 5% Pd/CLM was employed under continuous-flow conditions. Diphenylacetylene in 10 mL MeOH was quantitatively reduced to diphenylethane in a 5% Pd/CLM-packed cartridge at 50 °C at a flow rate of 0.1 mL/min under hydrogen at a flow rate of 10 mL/min in a one-pass manner, as shown in Table 4, entry 1. Benzyl benzoate was hydrogenolyzed to benzoic acid in quantitative yield (entry 2). Deprotection of mefenamic acid benzyl ester also proceeded smoothly to give the nonsteroidal anti-inflammatory drug (NSAID), mefenamic acid in 98% isolated yield (entry 3).

Table 4. Application of 5% Pd/CLM to continuous flow reaction.

entry	substrate	product	yield (%)
1	Ph━━━Ph	Ph⌒Ph	quant.
2[a]	Ph⌒CO₂Bn	Ph⌒CO₂H	quant.
3[a]	(2-methylphenyl)amino benzyl ester	(2-methylphenyl)amino acid	98%

[a] The reaction was carried out using 100 mg of 5% Pd/CLM under the 0.5 MPa of back pressure.

Conclusion

Two types of cellulose-supported palladium catalysts (5% Pd/CLP and 5% Pd/CLM) was developed for novel chemoselective hydrogenation based on the unique structure of CLP and CLM as supports. The Pd nanoparticles were strongly immobilized on CLP and CLM with negligible leaching after the hydrogenation reactions; thus, both catalysts could be reused at least three times after simple filtration without degradation of the catalyst activity. The 5% Pd/CLM catalyst, which exhibit the highest catalyst activity under batch conditions, could be applied to the continuous-flow hydrogenation reaction based on its high durability.

Experimental Section

Materials All reagents and solvents were obtained from commercial sources and used without further purification. Cellulose particle (CLP) and cellulose monolith (CLM) were obtained from JNC Corporation (Tokyo, Japan). Pd(OAc)₂ was obtained from N.E. Chemcat Corporation (Tokyo, Japan). The ¹H NMR and ¹³C NMR spectra were recorded on JEOL JNM ECA-500 (500 MHz for ¹H NMR and 125 MHz for ¹³C NMR) and ECZ-400 (400 MHz for ¹H NMR and 100 MHz for ¹³C NMR) spectrometers. CDCl₃ was used as the solvent for the NMR measurements. The chemical shifts (d) are expressed in parts per million and internally referenced (0.00 ppm for tetramethylsilane and 2.50 ppm for DMSO-d_6 for ¹H NMR and 77.0 ppm for CDCl₃ and 39.5 ppm for DMSO-d_6 for ¹³C NMR). KeyChem-H (YMC) was used for the continuous-flow hydrogenation reactions. Hitachi SU-70, ULVAC-PHI PHI QuanteraSXM, Hitachi SU8020, Horiba E-max, and Shimadzu AA-7000 instruments were used for scanning transmission electron microscopy (STEM) analysis, X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM) analysis, energy dispersive X-ray spectrometry (EDX), and atomic absorption spectrometry (AAS), respectively. All of the ¹H NMR spectra of the known products were identical to those reported in the literature.

Preparation of 5% Pd/CLP (MeCN) A suspension of dry CLP (200 mg, colorless particle) in an MeCN solution (2 mL) of Pd(OAc)₂ [22.2 mg, 989 µmol (10.5 mg, palladium quantity)] was stirred under argon atmosphere at 25 °C for 3 d. The resulting yellow solid was collected by filtration (1 mm filter paper), washed with H₂O (10 mL × 3), and MeOH (10 mL × 3), and dried in vacuo for 24 h. The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH, and 4.0 ppm (0.4 mg) of palladium species was observed in the diluted filtrate by using atomic absorption spectrometry (SHIMADZU AA-7000). The collected solid was then stirred with hydrazine monohydrate (NH₂NH₂·H₂O) (14.4 µL, 297 µmol) in H₂O (15 mL) under argon atmosphere at 25 °C for 16 h. The pale gray solid was collected by filtration (1 mm filter paper), washed with H₂O (10 mL× 3) and MeOH (10 mL × 3), and dried in vacuo for 48 h to give Pd/CLP (200 mg). The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with H₂O and palladium species was not observed in the diluted filtrate. The total palladium species that was not absorbed on the CLP was 0.4 mg; thus, the palladium content of Pd/CLP (MeCN) was estimated to be approximately 5% [(10.5 – 0.4)/200 × 100].

Preparation of 5% Pd/CLP (EtOAc), 5% Pd/CLM (MeCN), and 5% Pd/CLM (EtOAc) 5% Pd/CLP prepared in EtOAc [5% Pd/CLP (EtOAc)] and 5%Pd/CLM prepared in MeCN [5% Pd/CLM (MeCN)] and EtOAc [5% Pd/CLM (EtOAc)] were also prepared using CLP (200 mg, colorless particle) or CLM (200 mg, colorless cube), which was cut into ca. 2 mm cubes using scissors, and Pd(OAc)₂ [22.2 mg, 989 µmol (10.5 mg, palladium quantity)] in a method similar to that used prepare 5% Pd/CLP in MeCN. In these processes, 201 mg of 5% Pd/CLP (EtOAc), 210 mg of 5% Pd/CLM (MeCN), and 197 mg of 5% Pd/CLP (EtOAc) were obtained, respectively. The total free palladium species in each filtrate after the palladium absorption and subsequent reduction process was 0.6 mg, 0.3 mg, and 0.5 mg; thus, the palladium content of these palladium catalysts was estimated to be approximately 5%.

Preparation of 5% Pd/CLM (MeOH) A suspension of colorless small pieces of CLM (200 mg, ca. 2 mm) in a MeOH solution (2 mL) of Pd(OAc)₂ [22.2 mg, 989 µmol (10.5 mg, palladium quantity)] was stirred under argon atmosphere at 25 °C for 3 d. The resulting gray solid was collected by filtration (1 mm filter paper), washed with H₂O (10 mL× 3) and MeOH (10 mL × 3), and dried in vacuo for 24 h to give Pd/CLM (210 mg). The filtrate was transferred to a 100 mL volumetric flask and diluted to 100 mL with MeOH; 6 ppm (0.6 mg) of palladium species was observed in the diluted filtrate by using atomic absorption spectrometry (SHIMADZU AA-7000). The total palladium species that was not

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absorbed on CLM was 0.6 mg; thus, the palladium content of Pd/ CLM (MeOH) was estimated to be 5% [(10.5 – 0.6)/210 × 100].

General procedure for chemoselective hydrogenation under batch conditions (Table 2) A mixture of the substrate (250 µmol) and 5% Pd/CLP or 5% Pd/CLM (5.3 mg, 2.5 µmol) in MeOH or EtOAc (1 mL) was stirred at 25 or 50 °C using a test tube equipped with a H_2 balloon. The reaction was continuously monitored by thin-layer chromatography. After a specific time, as indicated in Table 2, the mixture was filtered through a membrane filter (pore size: 0.45 µm). The catalyst on the filter was washed with ethyl acetate (5 mL × 3). The combined filtrates were concentrated in vacuo to afford the corresponding analytically pure product. If necessary, the product was further purified by silica-gel column chromatography (hexane/EtOAc or hexane/diethyl ether). (^{1}H and ^{13}C spectra are presented in the Supporting Information).

General procedure for hydrogenation under continuous-flow conditions (Table 4) A solution of the substrate (250 µmol) in MeOH (10 mL, 0.05 M) was pumped into the catalyst-packed cartridge [5% Pd/CLM (50.0 mg or 100 mg); φ 4.6 × 50 mm, stainless] at 0.1 mL/min using hydrogen gas at a flow rate of 10 mL/min at 50 °C after introducing a flow of MeOH and hydrogen gas into the cartridge under the same conditions for ca. 5 min. The whole reaction mixture was collected and concentrated in vacuo to give the corresponding hydrogenated product. If necessary, the product was further purified by silica-gel column chromatography (hexane/EtOAc).

Acknowledgements

Keywords: Heterogeneous catalyst • Cellulose • Chemoselective hydrogenation • Continuous-flow reaction • Carbon-neutral support

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[30]   Hot-filtration experiments of 5% Pd/CLP and 5% Pd/CLM for
        investigation of Pd leaching were conducted. See Supporting
        Information for experimental details.

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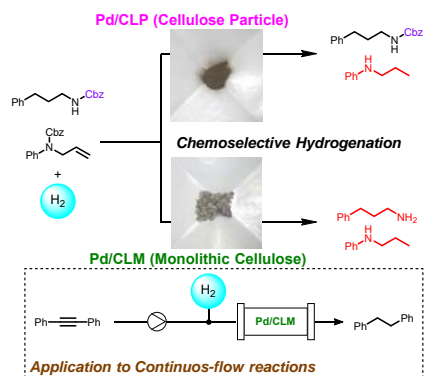
Newly developed palladium catalysts immobilized on cellulose particle (Pd/CLP), and cellulose-monolith (Pd/CLM) efficiently catalyzed chemoselective hydrogenation of various reducible functionalities including deprotection of an aromatic *N*-benzyloxycarbonyl protective group. Although limited to Pd/CLM, the hydrogenolysis of an aliphatic-*N*-Cbz protective group could also accomplish, and it was applicable to continuous-flow hydrogenation reactions.