Current Topics

Reversal or Control of the Innate Reactivity of Functional Groups

Recent Development of Palladium-Supported Catalysts for Chemoselective Hydrogenation

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Received February 16, 2016

This paper describes practical and selective hydrogenation methodologies using heterogeneous palladium catalysts. Chemoselectivity develops dependent on the catalyst activity based on the characteristic of the supports, derived from structural components, functional groups, and/or morphologies. We especially focus on our recent development of heterogeneous palladium catalysts supported on chelate resin, ceramic, and spherically shaped activated carbon. In addition, the application of flow technology for chemoselective hydrogenation using the palladium catalysts immobilized on molecular sieves 3A and boron nitride is outlined.

Key words　chemoselectivity; hydrogenation; heterogeneous palladium catalyst; support; selective deprotection; flow reaction

1. Introduction

The development of catalysts for chemoselective hydrogenation, which can achieve the selective reduction of specific reducible functionalities alone within molecules, is one of the most important topics in organic chemistry because it could create novel, straightforward synthetic routes.[1,2] Heterogeneous palladium catalysts immobilized on insoluble materials have been widely employed for the hydrogenation of a variety of reducible functionalities as well as the deprotection of protective groups, such as *N*-benzyloxycarbonyl (Cbz), *O*-benzyl, and *O-tert*-butyldimethylsilyl (TBS) protective groups, from amines, alcohols, and carboxylic acids, due to their simple, easy handling under neutral conditions.[3–6] However, widely available catalysts, such as palladium on carbon (Pd/C), possess markedly high catalyst activities so that their uses for hydrogenation basically lead to the complete reductions of most reducible functionalities, including protective groups, in the molecule.

Two basic types of strategy for chemoselective hydrogenation using heterogeneous palladium catalysts are available. The first method is the application of adequate catalyst poisons, such as sulfur- or nitrogen-containing compounds, as additives, which causes the appropriate deactivation of persisting palladium catalysts based on their ability to coordinate with palladium species[7–18]; *e.g.*, Lindlar's hydrogenation enables the semihydrogenation of alkynes to the corresponding alkenes using lead acetate and quinoline as catalyst poisons under Pd/CaCO$_3$-catalyzed hydrogenation conditions.[7,8] We have also developed Pd/C-ethylenediamine [Pd/C(en) (Wako Pure Chemical Industries, Ltd., Osaka, Japan; 169-21443)][19–27] and Pd/C-diphenylsulfide [Pd/C(Ph$_2$S) (N.E. Chemcat Corporation, Tokyo, Japan; SGS-10DR)][28] as chemoselective hydrogenation catalysts. The second method is a strategy based on the characteristics of catalyst supports, such as special functionalities

on the material of the support, structural components, surface area, and pore volume[29–53]; *e.g.*, the group of Cheon reported the selective hydrogenation of aliphatic benzyl ether in the presence of a trisubstituted alkene using a palladium catalyst supported on a type of mesoporous silica, MCM-48.[30] We previously reported palladium catalysts for chemoselective hydrogenation, which were immobilized on oxygen- and/or nitrogen-containing materials, such as molecular sieves 3A (MS3A)[54,55] and boron nitride (BN).[56–59] The 0.5% Pd/MS3A and 0.3% Pd/BN exhibit relatively similar catalyst activities, and thus the hydrogenation of alkynes, alkenes, and azides proceeds, while other reducible functionalities including nitro groups remain intact under atmospheric hydrogen conditions.

In this paper, we describe our recent progress in the development of heterogeneous palladium catalysts for chemoselective hydrogenation depending on the characteristics of the catalyst supports: 1) chelate resin, which bears iminodiacetate partial moieties within the molecule as the chelating functionalities[60,61]; 2) ceramic, which consists of a variety of mineral-derived elements[62]; and 3) spherically shaped activated carbon (SC).[63] Chemoselective and continuous hydrogenation under flow reaction conditions using Pd/MS3A and Pd/BN initially developed in our laboratory is also outlined.[64]

2. Pd/CR11-Catalyzed Hydrogenation[60,61]

Pd/C has been widely employed as a highly active catalyst for the hydrogenation of a variety of reducible functionalities.[3–6] However, the catalyst activity often differs depending on the vendor, product number, and even lot number, because the activated carbon for the catalyst support is derived from natural resources, such as plants and peat; thus, the difference in the catalyst activity comes from the type and source of the raw materials as well as the diverse preparation methods of activated carbon, which affect the characteristics as a sup-

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port, such as impurity contents including heavy metals and inorganic materials, surface areas, and pore size structures. On the other hand, a palladium catalyst (Pd/HP20) supported on a synthetic adsorbent, DIAION HP20 (HP20, Mitsubishi Chemical Corporation, Tokyo, Japan),[65,66] which is a polystyrene–divinylbenzene polymer (Fig. 1), has been developed as a reliable catalyst that exhibits specific, guaranteed activity based on the industrial production of the support under strict regulations.[67,68] Pd/HP20 could be used as an alternative active catalyst to Pd/C for hydrogenation and cross-coupling due to its hydrophobic property with a large surface area (*ca.* 590 m^2/g), facilitating efficient contact with organic substrates. However, the high catalyst activity of Pd/HP20 leads to poor chemoselectivity in hydrogenation, because almost all reducible functionalities are hydrogenated in the same manner as with Pd/C.

DIAION CR11 (CR11, Mitsubishi Chemical Corporation) is a chelate resin bearing iminodiacetate moieties on the benzene rings of the polystyrene–divinylbenzene polymer backbone as a chelating functionality[69–72] (Fig. 1). The palladium catalyst on DIAION CR11 (Pd/CR11) was designed with the expectation of the appearance of chemoselectivity in hydrogenation based on the weakened palladium catalyst activity due to the

ability of the aromatic rings and iminodiacetate functionalities of CR11 to coordinate with palladium metals.[61]

A two-step method was conducted for the preparation of Pd/CR11: the incorporation of palladium(II) ions onto CR11; and the reduction of Pd(II) to Pd(0). CR11 was immersed in a solution of Pd(OAc)$_2$ in EtOAc at room temperature, and the yellowish Pd(II)/CR11 was collected by filtration; washed with EtOAc, H$_2$O, and MeOH; and dried *in vacuo* (Figs. 2a–c). The collected Pd(II)/CR11 was then treated with NH$_2$NH$_2$ in H$_2$O at room temperature, filtered, washed with MeOH and H$_2$O, and dried *in vacuo* to give the black Pd(0)/CR11, on which 8 wt% of palladium was included (Fig. 2d). The estimated average diameter of the palladium clusters of 8% Pd/CR11 was *ca.* 15 nm (high-angle annular dark-field scanning transmission electron microscopy; HAADF-STEM).

The 8% Pd/CR11 (1 mol%) was used for the hydrogenation of a variety of reducible functionalities in MeOH (Table 1). Alkyne (Table 1, entries 1, 7), alkene (entries 4, 6, 8, 11, 12), azide (entry 2), nitro (entry 3), benzyl ester (entry 4), and aryl benzyl ether (entry 5) functionalities could be readily reduced, while alkyl benzyl ether (entry 6) and TBS ether (entry 11) were tolerated under atmospheric hydrogen conditions. The deprotection of Cbz groups was achieved by heating at 50°C or pressurizing with hydrogen to 3 atm to afford the corresponding aromatic and aliphatic deprotected amines in quantitative yields (entries 7, 8). Although aromatic aldehydes and ketones were comparatively stable, the corresponding benzyl alcohols were obtained under 2 atm hydrogenation pressure without any formation of overreduced (hydrogenolysis) products (entries 9, 10). While the epoxide was partially hydrogenolyzed in MeOH to afford the ring-opening products in *ca.* 15% yield, the reaction could be completely suppressed by the use of 1,4-dioxane as a solvent, leading to the chemoselective hydrogenation of only the alkene (entry 12). The complete
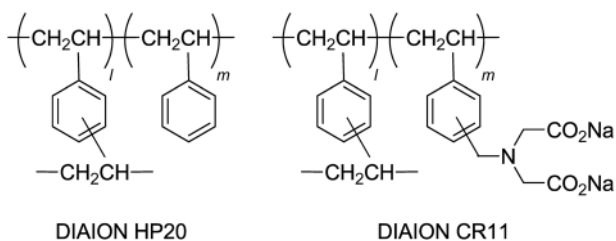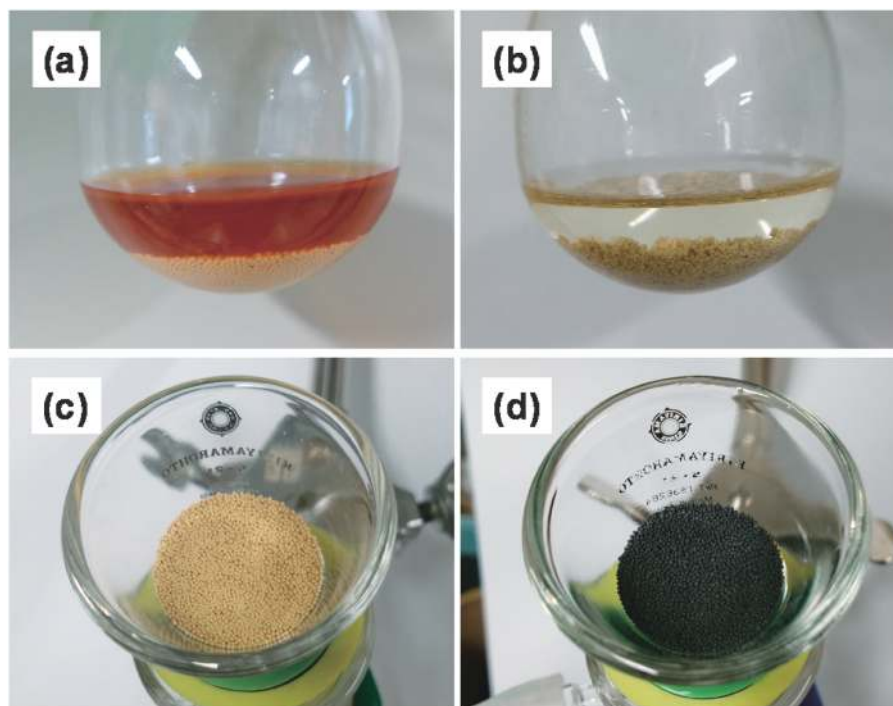

Fig. 1. Structure of DIAION HP20 and CR11

Fig. 2. Preparation of 8% Pd/CR11

a) Initial step in the adsorption process of Pd(II) onto CR11; b) Final step in the adsorption process of Pd(II) onto CR11; c) Collected Pd(II)/CR11; d) Collected Pd(0)/CR11.

Table 1. Eight Percent Pd/CR11-Catalyzed Hydrogenation[a)]

entry	substrate	time (h)	product	yield (%)[b]
1	Ph——Ph	6	Ph⁀Ph	100
2	EtO₂C—⟨⟩—N₃	6	EtO₂C—⟨⟩—NH₂	100
3	MeO—⟨⟩—NO₂	4.5	MeO—⟨⟩—NH₂	93
4	⟋⟍CO₂Bn	24	Me⟍CO₂H	100[c]
5	HO—⟨⟩—OBn	18	HO—⟨⟩—OH	100
6	Ph⟍⟋OBn	24	Ph⟍⟋OBn	100
7[d]	≡—⟨⟩—NHCbz	24	Et—⟨⟩—NH₂	100
8[e]	⟍N⟋, Cbz	24	Pr–N–Pr, H	100[c]
9[e]	MeO—⟨⟩—CHO	24	MeO—⟨⟩—CH₂OH	86
10[f]	⟨⟩—Ac	24	⟨⟩—OH Me	96
11	Ph⟍⟋⟍OTBS	24	Ph⟍⟋⟍OTBS	100
12[g]	⟍(⟍)₆ epoxide	9	Me(⟍)₆ epoxide	97

a) Conditions: All reactions were carried out using a substrate (0.25 mmol) and 8% Pd/CR11 (1 mol%) in MeOH (1 mL) at rt under H₂ (balloon) unless otherwise noted. b) The starting material in all entries was completely consumed, and the desired reduced product could be obtained as the sole product without any by-products. c) The reaction was carried out in CD₃OD, and the yield of the reduced product was confirmed by ¹H NMR due to the volatile nature of the product. d) 50 °C. e) 3 atm. f) 3 atm, 50 °C. g) The reaction was carried out in 1,4-dioxane.

suppression by 1,4-dioxane could be achieved by the mild bulk coordination effect of its oxygen atoms with palladium metal in cooperation with the chelation of the iminodiacetate function on CR11. Another remarkable feature of Pd/CR11 is its reusability: it can be reused for at least five runs without any palladium leaching.

3. Pd/Ceramic-Catalyzed Hydrogenation[62)]

While clay, a raw material of ceramics, has been used for a support of the heterogeneous palladium catalyst for the hydrogenation of various functionalities,[31–44,73–83)] the use of a ceramic as a catalyst support is very limited.[84)] Although the components of the ceramic that we used for catalyst support are very similar to those of molecular sieves 3A and 5A, the ceramic contains a variety of elements, such as magnesium, titanium, iron, sulfur, and zirconium, in addition to the common elements oxygen, silicon, aluminum, potassium, and sodium. The ingredients of the ceramic were expected to result in some unique catalyst activities in hydrogenation.

The immobilization of palladium metal on the ceramic was achieved by simply immersing the ceramic in MeOH solution of Pd(OAc)₂ at room temperature; palladium(II) ions were effectively adsorbed on the ceramic and successively reduced to palladium(0) by MeOH as the solvent and reducing agent in the same flask, affording the corresponding 5% Pd/ceramic.[62)] The particle size of palladium metal in the construction of 5% Pd/ceramic is estimated to be approximately 10 nm based on transmission electron microscope (TEM) images.

As shown in Table 2, 5% Pd/ceramic catalyzed the hydrogenation of alkyne (entries 1, 4), alkene (entries 5–7, 9, 12, 13), azide (entry 2), and nitro (entry 3) functionalities to give the corresponding reduced products. The *N*-Cbz group could be readily deprotected to the aromatic (entry 4) and aliphatic (entry 5) amines, while the benzyl ester (entries 6, 7) and benzyl ether (entries 8, 9) did not undergo deprotection. The present chemoselectivity is one of the noteworthy features of Pd/ceramic-catalyzed hydrogenation. The hydrogenation of the aromatic aldehyde (entry 10) to the benzyl alcohol proceeded under pressurized hydrogen conditions (5 atm, 80°C), but further hydrogenolysis of the resulting benzyl alcohols did not occur. On the other hand, the aromatic ketone was barely reduced even under 5 atm hydrogen conditions (entry 11). *O*-TBS and epoxide functionalities were stable under 5% Pd/ceramic-catalyzed hydrogenation conditions, and the selective hydrogenation of alkene moieties was achieved in the presence of these functionalities (entries 12, 13). The 5% Pd/ceramic is a reusable catalyst without deactivation for at least five runs.
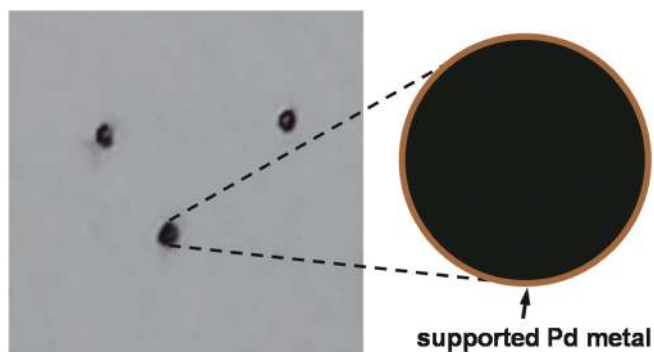
4. Pd/SC-Catalyzed Hydrogenation[63)]

The palladium(0) catalyst supported on SC (0.5% Pd/SC, *ca.* 0.36 mm in diameter), which is commercialized as a continuous-flow hydrogenation catalyst (YMC Co., Ltd., Kyoto, Japan), was found to exhibit a distinguishing chemoselectivity in hydrogenation under batch conditions, unlike the high catalyst activity of commonly used powdered Pd/C. The palladium species of 0.5% Pd/SC are localized only on the spherical surface as clusters 5.6 nm in mean diameter (Fig. 3).

As shown in Table 3, 0.5% Pd/SC could be used for the

Table 2. Five Percent Pd/Ceramic-Catalyzed Hydrogenation[a)]

entry	substrate	time (h)	product	yield (%)[b]
1	Ph—≡—Ph	6	Ph⌒Ph	98
2	EtO$_2$C—⟨⟩—N$_3$	9	EtO$_2$C—⟨⟩—NH$_2$	97
3	HOH$_2$C—⟨⟩—NO$_2$	5	HOH$_2$C—⟨⟩—NH$_2$	100
4	≡—⟨⟩—NHCbz	24	Et—⟨⟩—NH$_2$	98
5	⌒N(⌒)Cbz	24	Pr⌒N(H)Pr	100[c]
6	Ph⌒CO$_2$Bn	6	Ph⌒CO$_2$Bn	97
7	�—⟨⟩—CO$_2$Bn	6	Et—⟨⟩—CO$_2$Bn	99
8	HO—⟨⟩—OBn	24	Recovery	—[d]
9	⌒OBn	7	Me⌒OBn	100[c]
10[e]	MeO—⟨⟩—CHO	24	MeO—⟨⟩—CH$_2$OH	100
11[e]	⟨⟩—Ac	24	⟨⟩—CH(OH)Me	11
12	Ph⌒OTBS	24	Ph⌒OTBS	100
13	⌒(CH$_2$)$_6$epoxide	24	Me⌒(CH$_2$)$_6$epoxide	100

a) Conditions: All reactions were carried out using a substrate (0.5 mmol) and 5% Pd/ceramic (1 mol%) in MeOH (1 mL) at rt under H$_2$ (balloon) unless otherwise noted. b) The starting material in all entries only except for entries 8 and 11 was completely consumed, and the desired reduced product could be obtained as the sole product without any by-products. c) The reaction was carried out in CD$_3$OD, and the yield was confirmed by ^{1}H NMR due to the volatile nature of the product. d) The starting material was quantitatively recovered. e) 5 atm, 50 °C.

Fig. 3.   Localization of Palladium Species on 0.5% Pd/SC[63)]

hydrogenation of azide (entry 1), nitro (entry 2), alkene (entries 3, 5, 7, 9), and alkyne (entry 6) functionalities with the benzyl ester (entries 1, 3, 4), benzyl ether (entry 4), and *N*-Cbz (entries 6, 7) functional groups untouched. A notable property of 0.5% Pd/SC under batch conditions is the discriminable deprotection between alkyl (entry 8) and aryl TBS ethers (entry 9). The 0.5% Pd/SC could be used without any leaching of palladium species into the reaction media. The only negative aspect of 0.5% Pd/SC is its friable property, which causes poor reusability based on the loss of the active palladium spe-

cies localized on the spherical surface by their abrasion due to mechanical damage during the reaction process.

5. Pd/MS3A- and Pd/BN-Catalyzed Hydrogenation under Flow Conditions[64)]

Hydrogenation catalyzed by heterogeneous catalysts under continuous-flow conditions has attracted great attention in organic and process chemistry due to a number of advantages over corresponding batch conditions using flasks or reaction vessels, such as high reaction efficiency based on the secure contact of the substrate and hydrogen with the catalyst packed in a cartridge inserted into a narrow channel, avoidance of the ignition risk of the metal catalyst separated from air, and simple application to large-scale synthesis.[85–108)] When 10% Pd/C or 10% Pd/HP20 was used as the catalyst for flow hydrogenation, most reducible functionalities, such as alkynes, alkenes, azides, nitro groups, benzyl esters, benzyl ethers, and *N*-Cbz groups, could be completely reduced by only a single pass of the substrate solution in MeOH through the catalyst cartridge. A new development of chemoselective hydrogenation as well as a complete hydrogenation method under flow reaction conditions would be practically important. The application of the above-mentioned catalysts, 0.5% Pd/MS3A and 0.3% Pd/BN, to continuous-flow hydrogenation using various reducible functionalities in a single-pass manner was investigated in

Table 3. Half Percent Pd/SC-Catalyzed Hydrogenation[a)]

entry	substrate	product	yield (%)[b]
1	BnO$_2$C—⟨⟩—N$_3$	BnO$_2$C—⟨⟩—NH$_2$	96
2	MeO—⟨⟩—NO$_2$	MeO—⟨⟩—NH$_2$	95
3[c]	Ph∼CO$_2$Bn	Ph∼CO$_2$Bn	99
4[d]	BnO—⟨⟩—CO$_2$Bn	Recovery	—[e]
5[d]	HO—⟨⟩—Ac (allyl)	HO—⟨⟩—Ac (Pr)	92
6	≡—⟨⟩—NHCbz	Et—⟨⟩—NHCbz	100
7[f]	allyl-N(Cbz)-allyl	Pr-N(Cbz)-Pr	93
8[g]	Ph∼∼OTBS	Ph∼∼OH	91
9[h]	⟨⟩(vinyl)—OTBS	⟨⟩(Pr)—OTBS	94

a) Conditions: All reactions were carried out using a substrate (1 mmol) and 0.5% Pd/SC (0.05 mol%) in MeOH (1 mL) at rt under H$_2$ (balloon) for 24 h unless otherwise noted. b) The starting material in all entries only except for entry 4 was completely consumed, and the desired reduced product could be obtained as the sole product without any by-products. c) The reaction was carried out in MeCN. d) The reaction was carried out in 1,4-dioxane. e) The starting material was recovered in 93% yield. f) 3 h. g) 72 h. h) 48 h.

greater detail (Table 4).

Alkyne, alkene, and azide functional groups underwent hydrogenation using either catalyst to give the corresponding reduced products, as is the case under batch hydrogenation conditions (Table 4, entries 1–8, 11, 12, 19). A sharp difference in chemoselectivity caused by the application of flow conditions is a slight but clear-cut extension of the reducible functionalities. Nitro groups join the ranks of reducible functionalities (entries 7, 8), while aromatic carbonyls (entries 5, 6, 9, 10), benzyl esters (entries 11, 12), benzyl ethers (entries 13–16), and aliphatic *N*-Cbz groups (entries 17, 18) are all irreducible.

All chemoselective hydrogenation reactions could be completed within approximately 15 s during a single pass through the catalyst cartridge (30 mm long, *ca*. 0.3 mL interior volume) at a 1-mL/min flow rate of the substrate solution. Both catalysts packed in the cartridge could be repeatedly used without replacement over the course of the study (more than 1.5 years) because the palladium species never leached out. Not only these features but also chemoselectivity in hydrogenation would be advantages for practical use.

6. Conclusion

Figure 4 summarizes the chemoselectivities among a wide variety of reducible functionalities in hydrogenation using heterogeneous palladium catalysts, which were developed by our research group except for Pd/C. Reducible functionalities within the framework could be reduced using each corresponding catalyst. Pd/CR11 possesses catalyst activity similar to that of Pd/C appropriately deactivated by the addition of ammonium acetate as a catalyst poison (Fig. 4, solid frame-

work). The chemoselectivity of Pd/CR11 is probably achieved by a moderate deactivation of the catalyst activity based on the mild chelation effect of the iminodiacetate moiety on CR11 to palladium metal. Pd/ceramic clearly discriminates between the *O*-benzyl (both ether and ester) and *N*-Cbz protective groups, which cannot be achieved by other catalysts (Fig. 4, dashed framework). Pd/SC catalyzes the hydrogenation not only of the alkyne, alkene, azide, and nitro functionalities but also of the alkyl TBS ether, functionalities that are relatively tolerant of the usual hydrogenation conditions (Fig. 4, dashed-dotted framework).

Continuous-flow technology could also be applied to chemoselective hydrogenation using Pd/BN and Pd/MS3A as catalysts, and the catalyst activities were slightly and selectively enhanced in comparison with batch hydrogenation conditions. The nitro group could also be hydrogenated in addition to alkyne, azide, and alkene functionalities under the Pd/BN- and Pd/MS3A-catalyzed flow hydrogenation conditions (Fig. 5).

In this review, we described our recent progress in the development of heterogeneous palladium catalysts possessing unique chemoselective catalyst activities, which are based on the characteristics of the catalyst supports derived from constituent elements and functional groups and the supporting morphology of palladium metal. These palladium catalysts would be useful over a wide range of organic chemistry fields, including medicinal and process chemistry, due to their easy preparation and handling, clear-cut selectivity, and non-palladium-leaching properties.

Table 4.   Half Percent Pd/MS3A and 0.3% Pd/BN-Catalyzed Hydrogenation under the Flow Conditions[a)]

entry	substrate	cat.	Pressure (bar)	Temp. (°C)	product	yield (%)[b]
1	Ph—≡—Ph	A	1	25	Ph⌒Ph	97
2		B	1	25		99
3	MeO / MeO—⟨⟩—/=—Me	A	1	25	MeO / MeO—⟨⟩—Pr	91
4		B	1	25		89
5	O / Ph—C—⟨⟩—N₃	A	1	50	O / Ph—C—⟨⟩—NH₂	90
6		B	1	25		94
7	O₂N—⟨⟩—/=⌒OH	A	1	75	H₂N—⟨⟩—⌒⌒OH	77
8		B	1	25		93
9	MeO—⟨⟩—CHO	A	1	100	No reaction	100[c]
10		B	1	100	No reaction	100[c]
11	Ph⌒=⌒CO₂Bn	A	50	100	Ph⌒⌒CO₂Bn	100
12		B	50	100		100
13	HO—⟨⟩—OBn	A	1	100	No reaction	100[c]
14		B	1	100	No reaction	100[c]
15	BnO⌒⌒OBn	A	80	100	No reaction	90[c]
16		B	80	100	No reaction	88[c]
17	Me⌒(⌒)₉NHCbz	A	50	100	No reaction	100[c]
18		B	50	100	No reaction	100[c]
19	≡—⟨⟩—NHCbz	A	1	100	Et—⟨⟩—NHCbz	78

a) Conditions: All reactions were carried out by allowing a MeOH solution of a substrate (1 mmol, 20 mL) at 1 mL/min to flow through the catalyst-packed cartridge [30 mm long, ca. 0.3 mL volume; 0.5% Pd/MS3A (**A**) (99.6 mg) or 0.3% Pd/BN (**B**) (99.7 mg)] under 1, 50, or 80 bar H₂ gas using an H-Cube (ThalesNano Nanotechnology Inc.) in a single-pass manner. b) The starting material in all entries except for entries 9, 10, and 13–18 was completely consumed, and the desired reduced product could be obtained as the sole product without any by-products. c) Yield of the recovered starting material.
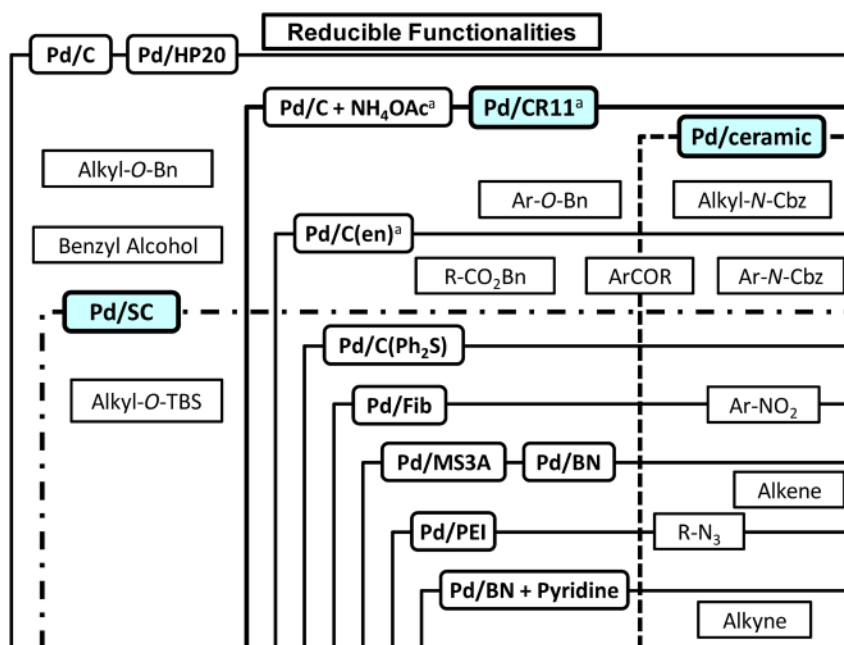

Fig. 4.   Catalyst Activities of 8% Pd/CR11, 5% Pd/Ceramic, and 0.5% Pd/MS for Hydrogenation

ᵃ The hydrogenolysis of epoxides could be suppressed under the Pd/CR11-catalyzed hydrogenation conditions, while the use of Pd/C(en) or combined use of Pd/C and NH₄OAc leads to the formation of ring-opening products.
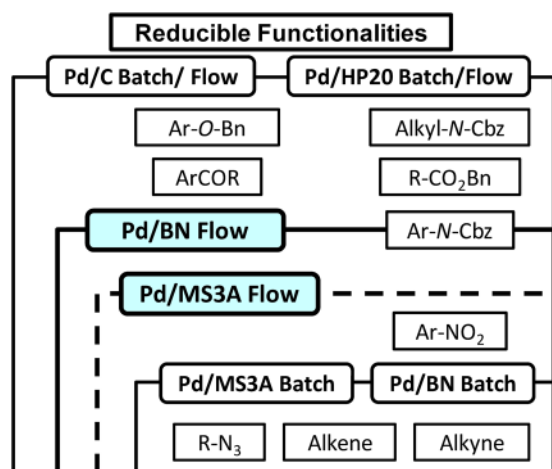
Fig. 5. Catalyst Activities of 0.5% Pd/MS3A and 0.3% Pd/BN for Hydrogenation under Batch and Flow Conditions

Conflict of Interest   The authors declare no conflict of interest.

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