



# Systematic evaluation of the palladium-catalyzed hydrogenation under flow conditions



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## ABSTRACT

Four types of heterogeneous Pd catalysts (10% Pd/C, 10% Pd/HP20, 0.5% Pd/MS3A, and 0.3% Pd/BN) were applied to the flow hydrogenation to systematically evaluate the appropriate conditions for the reduction of a wide variety of reducible functionalities. The use of 10% Pd/C and 10% Pd/HP20 allowed the hydrogenation of various reducible functionalities by a single-pass of the substrate–MeOH solution through the catalyst cartridge, while 0.5% Pd/MS3A and 0.3% Pd/BN catalyzed a novel chemoselective hydrogenation; only alkene, alkyne, azide, and nitro functionalities could be reduced with other coexisting reducible functionalities intact.

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## 1. Introduction

The continuous flow system for hydrogenation is a technology that significantly achieves high reaction efficiency compared to the batch (non-flow) system in a flask or reaction vessel, etc., by the secure communication of hydrogen gas and the substrate solution with a solid catalyst inserted in a narrow channel.<sup>1,2</sup> The catalyst, which is generally packed in a cartridge, can be reused without its replacement by a new one after each reaction. The danger of the ignition of flammable catalysts could also be avoided because of no contact with air. Furthermore, a simple concentration of the resulting solution (reaction mixture), which is passed through the catalyst, is only required to obtain the desired product. Therefore, the continuous flow hydrogenation using solid catalysts has drawn a great deal of attention in the synthetic organic chemistry community over the past decade from practical points of view.<sup>1–3</sup>

The hydrogenation reactions using a variety of supported catalysts under continuous flow conditions have been applied for the reduction of various reducible functionalities.<sup>1,2</sup> However, no systematic evaluation of each catalyst for the hydrogenation of the functionalities based on optimization of the reaction conditions has ever been investigated due to a lot of variable parameters, such as solvent, concentration of the substrate solution, flow rate of the

liquid (or length of catalyst cartridge), reaction temperature, and hydrogen pressure.

We have recently developed a variety of palladium catalysts immobilized on macromolecules, such as a synthetic adsorbent (DIAION HP20),<sup>4</sup> molecular sieves (MS3A and MS5A),<sup>5</sup> and boron nitride (BN).<sup>6</sup> The catalyst activity of 10% Pd/HP20, 0.5% Pd/MS3A, and 0.3% Pd/BN for the hydrogenation under batch conditions was found to be significantly dependent on the characteristic features of the supports; i.e., 10% Pd/HP20 has a strong catalyst activity comparable to 10% Pd/C, while 0.5% Pd/MS3A and 0.3% Pd/BN were useful for the chemoselective hydrogenation of alkynes, alkenes, and azides, while leaving the other functionalities including nitro groups intact. The chemoselectivity of 0.5% Pd/MS3A is achieved by the partial suppression of palladium catalyst activity based on the chemical properties of MS3A, such as a coordination ability of oxygen atoms on the surface of the support (MS3A) to the palladium metal. The specific catalyst activity of 0.5% Pd/BN would be attributed to the moderate interaction of palladium metal with BN surface by the conjugation effect between unoccupied orbital of boron atoms and nitrogen lone pairs of BN.<sup>7</sup> In this paper, we report a systematic study of the hydrogenation of a variety of reducible functional groups using 10% Pd/C, 10% Pd/HP20, 0.5% Pd/MS3A, and 0.3% Pd/BN as catalysts under continuous flow reaction conditions using a flow hydrogenation reactor, H-Cube<sup>®</sup> (ThalesNano Nanotechnology, Inc.) that can control the temperature and hydrogen pressure up to 100 °C and 100 bar, respectively.

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## 2. Results and discussion

We first investigated the solvent effect of the 10% Pd/C-catalyzed hydrogenation of benzophenone (**1**, 1 mmol) at a concentration of 0.05 M and flow rate of 1 mL/min under 1 bar hydrogen (Table 1). The reactions in MeOH, EtOH, cyclopentyl methyl ether (CPME), cyclohexane, and EtOAc were carried out at 25 °C, 50 °C, 75 °C, and 100 °C in a single-pass manner, in which a substrate solution passes through the catalyst cartridge (ca. 0.3 mL inside volume) only once (the transit time of the reaction solution in the cartridge was ca. 15 s; entries 1–8). MeOH was found to be the most appropriate solvent, and diphenylmethane (**3**) was obtained as the sole product via hydrogenolysis of the intermediary diphenylmethanol (**2**) at 50 °C (entry 2) under ordinary pressure. The increase in the substrate concentration to 0.1 M and higher markedly reduced the conversion ratio of **1** (entries 2 vs 9 and 10). Therefore, the following investigation was performed in MeOH as the solvent at the substrate concentration of 0.05 M.

**Table 1**  
Solvent effect on hydrogenation of the benzophenone under the flow conditions

Entry	Solvent	Temp (°C)	Concentration (M)	Ratio <b>1</b> : <b>2</b> : <b>3</b> <sup>a</sup>
1	MeOH	25	0.05	2:16:82
2	MeOH	50	0.05	0:0:100
3	EtOH	25	0.05	25:64:11
4	EtOH	100	0.05	3:9:88
5	CPME	25	0.05	100:0:0
6	CPME	100	0.05	91:1:8
7	Cyclohexane	100	0.05	98:0:2
8	EtOAc	100	0.05	100:0:0
9	MeOH	50	0.1	55:0:45
10	MeOH	50	0.5	88:0:12

<sup>a</sup> Determined by GC–MS. CPME: cyclopentyl methyl ether.

**Table 2**  
Scope of substrate catalyzed by 10% Pd/C or Pd/HP20

Entry	Substrate	Catalyst	H <sub>2</sub> pressure (bar)	Temp (°C)	Product	Ratio <sup>a</sup>	Yield (%) <sup>b</sup>
1		<b>A</b>	1	25		—	100
2		<b>B</b>	1	25		—	100
3		<b>A</b>	1	25		—	88
4		<b>B</b>	1	25		—	84
5		<b>A</b>	1	25		—	79
6		<b>B</b>	1	25		—	79

(continued on next page)

We next investigated the catalyst activity of the 10% Pd/C (Catalyst A) and 10% Pd/HP20 (Catalyst B) for the hydrogenation of various reducible functionalities in MeOH under continuous and single-pass flow reaction conditions (1 mL/min) (Table 2). The resulting reaction solution was concentrated in vacuo and its <sup>1</sup>H NMR was measured to determine the product ratio. As the reaction was incomplete at 25 °C, the temperature was raised to 50 °C, 75 °C, and 100 °C. When the reaction was still incomplete, the hydrogen pressure was then increased to 50 or 80 bar, and the reaction was monitored again at 25 °C, 50 °C, 75 °C, and 100 °C under each hydrogen pressure. Alkynes (Table 2, entries 1, 2 and 27–30), alkenes (entries 3, 4 and 23–26), azides (entries 5–10), nitro groups (entries 11–14), and aromatic carbonyl groups (entries 15–22) were readily hydrogenated to the corresponding reduced products at 25 °C or by a minor tuning of the temperature in some instances. When benzaldehyde was used as a substrate (entries 15–18), the corresponding benzyl alcohol was selectively obtained as a single product, and further hydrogenolysis to form the toluene derivative never took place (entries 16 and 18). The hydrogenation has been generally employed for the efficient removal of the protecting groups, such as the benzyl ether for alcohols, benzyl ester for carboxylic acids, and benzylcarbamate (*N*-Cbz) for amines. Therefore, the development of quick and reliable deprotection methods is demanded. When 10% Pd/C was used as a catalyst for the reduction of benzyl cinnamate at 25 °C under 1 bar hydrogen gas, only the alkene moiety was selectively hydrogenated without the hydrogenolysis of the benzyl ester (Entry 23), while the selectivity could not be achieved by the use of 10% Pd/HP20, which led to the formation of a mixture with dihydrocinnamic acid by the partial removal of the benzyl group (entry 25). The benzyl ester was completely cleaved with an increase in temperature using either 10% Pd/C (100 °C) or 10% Pd/HP20 (50 °C) as a catalyst (entries 24 and 26). Although the 10% Pd/C-catalyzed chemoselective hydrogenation of the alkyne moiety of *N*-Cbz-4-ethynylaniline was difficult to achieve even under ordinary temperature and pressure (entry 27), 10% Pd/HP20 smoothly and selectively catalyzed the reaction at 25 °C under 1 bar hydrogen pressure to give *N*-Cbz-4-ethylaniline probably due to the slightly low catalyst activity for

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