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Fine-Bubble-Based Strategy for the Pd-Catalysed Hydrogenation of Nitro Groups: Measurement of Ultrafine Bubbles in Organic Solvents

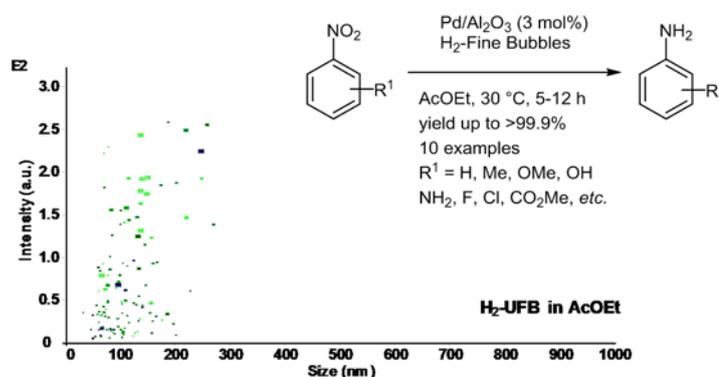
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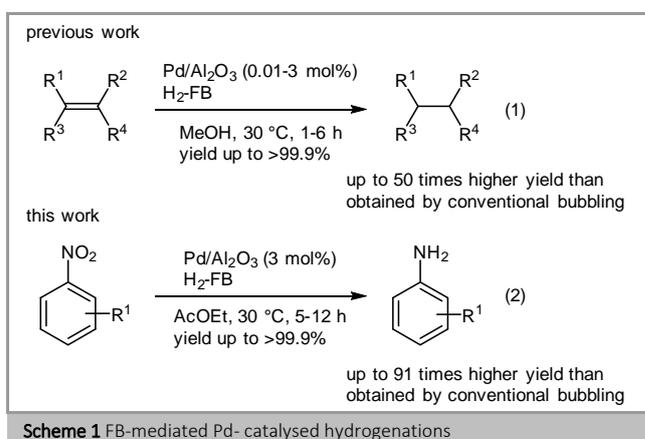
Abstract Hydrogen fine bubbles were employed as a new reaction medium for the autoclave-free, gas-liquid-solid multiphase hydrogenation of nitro groups on the multigram scale. Furthermore, ultrafine bubbles were examined by nanoparticle tracking analysis in organic solvents.

Key words fine bubble, microbubble, ultrafine bubble, hydrogenation, heterogeneous catalysis, green chemistry

The development of new chemical reactor technology that practically improves the efficiencies of gas-liquid multiphase reactions for industrial production, as well as academic research, has been a long-standing demand.¹ In recent years, fine bubbles (FBs)^{2,3} have been used for gas-liquid reactions during the Cu/TEMPO-catalysed aerobic oxidation of primary alcohols to aldehydes, with a simple, safe, and user-friendly protocol.⁴ This methodology has been further applied to gas-liquid-solid multiphase Pd-catalysed hydrogenations of carbon-carbon unsaturated bonds in an autoclave-free environment under atmospheric pressure (Scheme 1-1).⁵ Although the behaviour of FBs in organic solvents still remains unclear,⁶ in principle, the FB-mediated method can generally be applied to gas-related multiphase reactions.⁷ Herein, we report a Pd-catalysed gas-liquid-solid multiphase hydrogenation of nitroarenes (Scheme 1-2), and disclose that the H₂-FB method overcomes the drawbacks of the conventional bubbling method. Furthermore, the existence of H₂-ultrafine bubbles (H₂-UFB) has been confirmed by nanoparticle tracking analysis⁸ (NTA) in organic solvents.

Aromatic amines are important intermediates in the industrial production of materials like urethane monomers, pharmaceuticals, herbicides, dyes, and rubber processing chemicals. Consequently, many studies on the gas-liquid-solid multiphase heterogeneous catalytic hydrogenation of nitroarenes to anilines have been reported.⁹ However, existing

problems need to be addressed in order to improve reactivity and chemical yield. A pressure-resistant reaction vessel under high-pressure conditions and/or vigorous bubbling and mechanical stirring is required. Finely powdered Pd/C is required to improve the chemical yield;¹⁰ however, the removal of Pd/C by filtration often necessitates a batch system and long operation times, and careful monitoring to prevent clogging of the filter is required in continuous flow systems. These problems can be solved by increasing the concentration of the dissolved gas at atmospheric pressure, without vigorous bubbling and stirring, with a non-powdery supported Pd catalyst. Therefore, we investigated the hydrogenation of nitroarenes under H₂-FB conditions using Pd on alumina spheres (Pd/Al₂O₃, 0.5% Pd, approx. 2–4 mm) despite its lower reactivity compared to Pd/C powder.



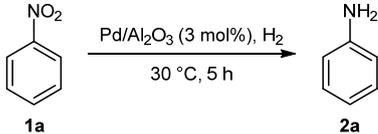
Hydrogenation of nitrobenzene (**1a**, 10 mmol, 1.2 g) on the gram scale was chosen as a model reaction for the evaluation of reaction efficiency (Table 1). To determine an appropriate solvent for the FB-mediated hydrogenation, solvent screening was carried out. Water and DMF were less reactive solvents

(Table 1, entries 1 and 2), while *N*-methylaniline was obtained as a by-product in methanol, which is often used as the solvent in hydrogenation reactions (entry 3).¹¹ In frequently used solvents such as ethanol, THF, acetic acid and ethyl acetate, the desired aniline (**2a**) was obtained in yields of over 90% (entries 4–7). Ethyl acetate was chosen as the optimized solvent due to its low miscibility with water and the lack of co-products generated during hydrogenation. The superiority of the FB method was examined by comparison with conventional methods. Using a balloon (1 atm), or by bubbling H₂ through the solution with a conventional gas dispersion tube fitted with a porous fritted glass tip, at the same H₂ flow rate as used in the FB method, resulted in low yields (entries 8–9). The yield was not improved even when a pressure-resistant reaction vessel at high pressure (0.3 MPa) was used (entry 10). Although it is possible to forcibly improve the yield by vigorous stirring, it is not possible to reuse the catalyst under these conditions due to the damage caused by the vigorous stirring. Since three hydrogen molecules are involved in the hydrogenation of the nitro group,¹² the concentration of dissolved hydrogen greatly influences the reaction rate. In fact, hydrogenation was greatly promoted under FB conditions, since the solution is rapidly saturated with H₂.⁵

Next, the scope of the substrate in the FB-method was examined in comparison with the conventional bubbling method (Table 2). In the case of electron-donating substituents such as methyl and methoxy, aniline derivatives **2** were produced in quantitative yields (entries 2 and 3). Similarly, hydrogenation of unprotected hydroxyl and amino-substituted nitroarenes proceeded smoothly (entries 4 and 5). In the case of 4-aminonitrobenzene (**1e**), the difference in reactivity between

conventional bubbling and FB conditions was remarkable (91 times faster, entry 5). During the hydrogenation of the nitro group, the aniline product is adsorbed onto the catalyst and may decrease its catalytic activity.¹⁴ However, the exchange of the product with hydrogen at the catalytic active site is considered

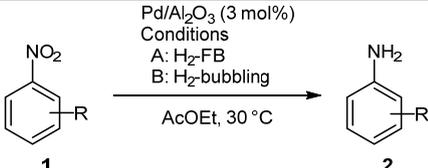
Table 1 Comparison of hydrogenation conditions^a

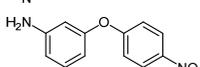


Entry	Conditions	H ₂ (mL/min)	Solvent	Yield (%) ^b
1	FB	5	H ₂ O	69.0
2	FB	5	DMF	41.0
3	FB	5	MeOH	68.6 ^c
4	FB	5	EtOH	93.0
5	FB	5	THF	96.1
6	FB	5	AcOH	>99.9
7	FB	5	AcOEt	>99.9
8	Balloon	-	AcOEt	1.6
9	Bubbling	5	AcOEt	5.2
10	Autoclave ^d	-	AcOEt	1.0

^a Reaction conditions: aniline (**1a**, 10 mmol), Pd/Al₂O₃ (3 mol%), solvent (80 mL, 0.125 M), H₂-FB or bubbling (5 mL/min), or balloon, 30 °C, for 5 h. ^b Determined by GC-analyses (column: GL Sciences TC-17). ^c *N*-Methylaniline was formed as a by-product in 20% yield. ^d This reaction was carried out at 0.3 MPa.

Table 2 Substrate scope in FB-mediated hydrogenation of nitroarenes^a



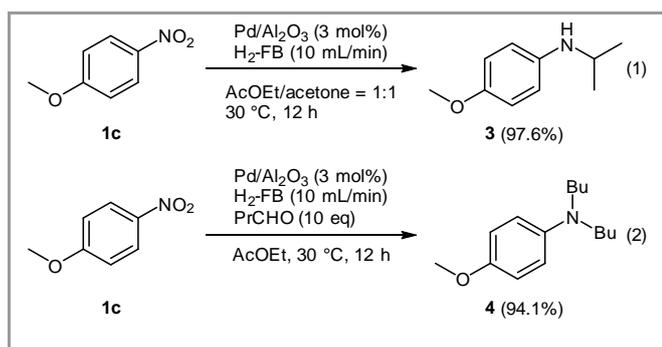
Entry	Substrate	R	Time (h)	Yield A/B (%) ^b	Ratio ^c	Product
1	1a	H	5	>99.9/5.2	19	2a
2	1b	4-Me	12	>99.9/8.7	11	2b
3	1c	4-OMe	5	>99.9/4.2	24	2c
4	1d	4-OH	9	91.6/14.0	7	2d
5	1e	4-NH ₂	6	91.0/<1.0	91	2e
6	1f	4-F	7	>99.9/6.1	16	2f
7	1g	4-Cl	7	86.7/3.1 ^d	28	2g
8	1h	4-CO ₂ Me	12	90.4/3.7	24	2h
9	1i		10	97.0/3.4	29	2i
10 ^e	1j		7	>99.9/48.0	2	2j

^a Reaction conditions: nitroarene (**1**, 10 mmol), Pd/Al₂O₃ (3 mol%), solvent (80 mL, 0.125 M), H₂-FB or bubbling (5 mL/min), 30 °C (see also reference 13). ^b Yield A represents data obtained under FB conditions; yield B under bubbling conditions. Yields were determined by GC-analyses (column: GL Sciences TC-17). ^c Ratio = Yield A/Yield B. ^d Dehalogenation product **2b** was obtained in 13% yield. ^e The reaction was carried out in DMF.

to be rapid under FB conditions in which hydrogen is dissolved at high concentrations. As a result, deactivation of the catalyst is suppressed even in the case of 4-aminoaniline (**2e**), which is easily adsorbed onto the catalyst. Although nitroarenes substituted with electron-withdrawing groups are readily hydrogenated in high yields, simultaneous partial dehalogenation of 4-chloronitrobenzene (**1g**) was observed to proceed in 13% yield (entries 6–8). The heterocyclic 5-nitroquinoline (**1i**) was efficiently hydrogenated under FB conditions (entry 9).

Since FB-mediated hydrogenations can efficiently and easily be performed at atmospheric pressure, this method is expected to be applied to the industrial production of 3-(4-aminophenoxy)aniline (**2j**); the reduced product **2j** is a monomer used in the preparation of a man-made high-performance aramid fibre. Monomer **2j** has been prepared on an industrial scale by the hydrogenation of 3-(4-nitrophenoxy)aniline (**1j**) in DMF under high temperature and pressure conditions.¹⁵ The amount of catalyst was increased to 4 mol% to compensate for the low hydrogenation reactivity in DMF (Table 1, entry 2); the desired diamine monomer **2j** was obtained twice as efficiently when compared to the conventional bubbling conditions (entry 10).

Considering that *N*-methylaniline was obtained as a by-product during nitro group reduction in methanol (Table 1, entry 3),¹¹ reductive amination reactions are expected to occur in the presence of ketones or aldehydes. Indeed, the secondary and tertiary amines **3** and **4**, in the presence of acetone and butyraldehyde, respectively, were produced in one-pot operations in yields of over 90% (Schemes 2-1 and 2-2). Not only are nitro and imino groups smoothly reduced by the FB-method, carbonyl groups are also efficiently reduced in a synthetically useful manner; for example benzaldehyde is quantitatively reduced using 3 mol% Pd/Al₂O₃ and H₂-FB (5 mL/min) to give benzyl alcohol (see Supporting Information).



Scheme 2 FB-mediated reductive aminations

The UFBs are too small to be observed by visual inspection or optical microscopy; consequently the solutions appear to be clear because of the presence of extremely small dispersed particles. However, it has recently become possible to examine UFBs through technological innovations in nanoparticle analysis equipment. Thus, the behaviour of UFBs in water is gradually being revealed. On the other hand, analysis of UFBs in organic solvents has hardly been studied. We reported preliminary analytical results of UFBs in methanol produced using an FB-generator (MA3-FS), in which the H₂-UFB number (2.7×10^7 particles/mL) and average size (158 nm) have been determined

using the NanoSight LM10-HS nanoparticle tracking analysis (NTA) instrument, fitted with a red (638 nm) laser.⁵ To understand the behaviour of UFBs in more detail, we chose to use the NanoSight LM10-VHST instrument, with a purple (405 nm) laser that increases the intensity the light scattered by the UFBs. H₂-UFBs were observed in the 50–200 nm size range in water, with an average of 148.5 ± 6.4 nm (Figure 1, left). The number of UFBs per mL was determined to be $(1.35 \pm 0.17) \times 10^8$; purple lasers can visualize more UFBs than red lasers. Despite the small numbers of visually observable micro-scale bubbles in the ethyl acetate used during the hydrogenation of nitroarenes, the number and sizes of the H₂-UFBs in this solvent were confirmed to be similar to those in H₂O (average size: 134.1 ± 10.8 nm, number of H₂-UFB: $(2.17 \pm 0.38) \times 10^7$, Figure 1, right).¹⁶

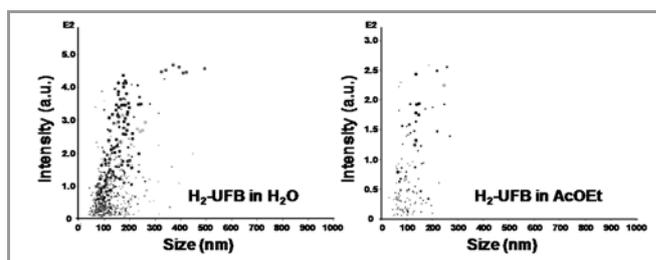


Figure 1 Intensity as a function H₂-UFB size in H₂O (left), and AcOEt (right)

Next, air-UFBs were examined in conventional organic solvents (Figure 2); UFBs was observed in all of the organic solvents, except hexane. The microbubble (MB) rising speed depends on the viscosity (η) of the liquid in accordance with the Stokes equation, and the surface zeta potential of the MB depends on the permittivity (ϵ) of the liquid in accordance with the Smoluchowski equation.² Consequently, viscosity and permittivity of the liquid should not only affect the stability of MBs, but also UFBs. We observed no clear correlation between viscosity or permittivity and UFB number. In contrast, the calculated value (CV) obtained by multiplying the normalized viscosity and permittivity, based on the values of water, correlate linearly with the number of UFBs (Figure 2). In hexane, having low viscosity (0.3 mPa·s) and permittivity (1.9 ϵ), UFBs are hardly observed under our measurement conditions. When the calculated value is larger than 0.01, the UFB number can be determined. As viscosity and/or permittivity increases, more UFBs are detected. For example, 2-propanol ($\eta = 2.0$, $\epsilon = 19.9$, CV = 0.58) produces an air-UFB number of 6.2×10^7 particles/mL. Water ($\eta = 0.9$, $\epsilon = 78.5$, CV = 1.00) and DMSO ($\eta = 2.0$, $\epsilon = 46.5$, CV = 1.32) contain more than 10^8 UFBs per mL of liquid.

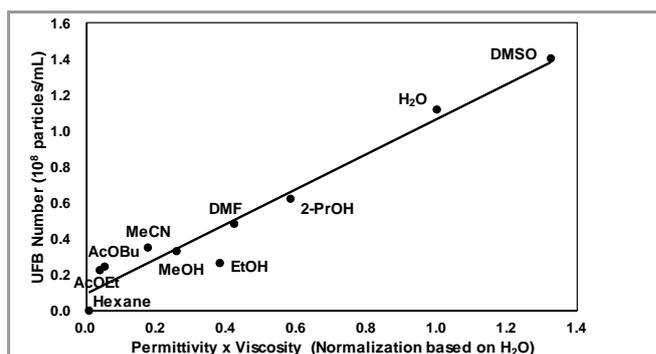


Figure 2 Plot of air-UFB number as a function of solvent permittivity x viscosity

(normalization based on H₂O)

In principle, the FBs of various gases can be generated; indeed, UFBs of various gases were observed not only in water but also in ethyl acetate (Figure 3). The number of UFBs in water ranged from $(1-1.6) \times 10^8$, and $(2-2.6) \times 10^7$ were counted for ethyl acetate. Interestingly, the UFB number depends on the solvent but is largely independent of the gas.

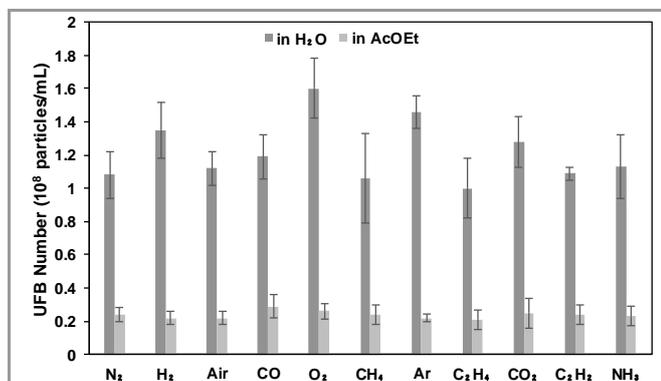


Figure 3 UFB numbers of various gases in H₂O and AcOEt

For example, when less water-soluble nitrogen gas was used, 1.08×10^6 UFBs were observed; for highly soluble ammonia gas in water, 1.13×10^6 UFBs were observed. It is apparent that the average UFB size does not depend on the kind of gas or the solvent under any conditions. The average UFB sizes of various gases in H₂O or AcOEt lie in the 100–200 nm range (Figure S1 in Supporting Information). With our current level of understanding, the reason why the numbers of UFBs and their average sizes are largely independent of gas or solvent remains unclear. However, the rate of gas dissolution into the liquid, and saturation, depends on the type of gas and liquid, but UFB numbers and sizes are about the same in their gas-liquid-saturated equilibrium states.

In conclusion, H₂-FBs were used as a new reaction medium for gas-liquid-solid multiphase reactions in autoclave-free, multi-gram-scale hydrogenations of nitro groups. In addition, several kinds of UFB were examined by NTA in organic solvents. FBs were generated using various gases and liquids; therefore, the FB method is widely applicable. This environmentally friendly FB-mediated gas-related reaction system has the potential to contribute to the synthesis of various fine chemicals, as well as bulk chemicals.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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- (13) **The typical procedure for hydrogenation of nitroarens using the H₂-FB-based strategy**
The hydrogenation was carried out in a 100 mL vial equipped with an FB-generator without additional stirring. Nitroarene **1** (10 mmol) was dissolved in ethyl acetate (80 mL), and then warmed to 30 °C. Using the FB-generator (MA3-FS), H₂-FB was introduced into the reactor in the presence of palladium on alumina spheres (0.5%Pd, 2–4 mm, 0.3 mmol, 3 mol%) at an H₂-flow rate of 5 mL/min. The samples of the reaction mixture were taken out periodically to monitor the reaction progress using the GC analysis. After the completion of the hydrogenation reaction, ethyl acetate was evaporated in vacuo to afford the desired aniline **2** with good to excellent purity.
GC analyses (SHIMADZU GC-2010, capillary column GL Sciences TC-17, He = 0.80 MPa, H₂ = 0.50 MPa, Air = 0.50 MPa, Flow Rate: 1.4 mL/min, T_{inj} = 250 °C, T_{det} = 250 °C, T₁ = 100 °C, T_r = 250 °C, Rate

= 10 °C/min): Nitrobenzene (**1a**, CAS: 98-95-3, t_R = 5.3 min), aniline (**2a**, CAS: 62-53-3, t_R = 5.5 min) (see Supporting Information).

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7). Since the reaction rate of the hydrogenation was proportional to the concentration of dissolved hydrogen, the reactivity was decreased in H₂O which had low solubility of H₂ gas. In addition, the solubility of the hydrophobic substrate should affect the reaction rate, therefore, the reactivity in H₂O would be reduced.