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Micro and Nanobubble-Based Strategy for Gas-Liquid-Solid Multiphase Reactions: Palladium-Catalysed Hydrogenation of Carbon-Carbon Unsaturated Bonds

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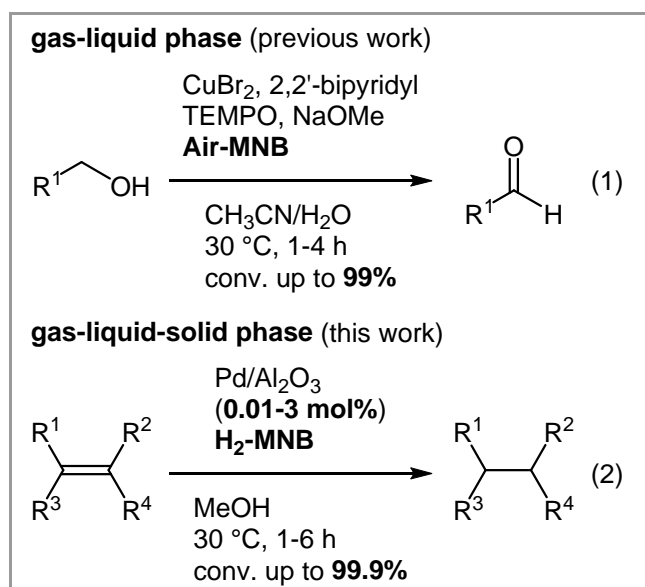
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Abstract: We have developed an autoclave-free gas-liquid-solid multiphase hydrogenation of carbon-carbon unsaturated bonds using hydrogen micro and nanobubbles (MNBs) that enables the liquid phase of the reaction mixture to maintain a high concentration of hydrogen gas.

Key words: gas-liquid-solid multiphase reactions, heterogeneous catalysis, homogeneous catalysis, hydrogenation, micro and nanobubble

A gas-liquid-solid multiphase reaction is one of the most important categories of reactions in organic synthesis, as it is used for the production of diverse fine chemicals via hydrogenation, hydroformylation, carboxylation, and biochemical processes.¹ However, it is difficult to handle such reactions because it often involves the use of high-pressure gases in pressure-resistant reaction vessels for increasing the reaction yields. The development of novel reactor technologies to improve the efficiency in gas-liquid multiphase reactions is a longstanding challenge, not only in industrial manufacturing but also in academic research. In the late 1990s, for example, microreactors emerged as smaller and safer reactors for performing “flash chemistry.”² Recently, we used micro and nanobubbles (MNBs) to develop a new experimental methodology for a gas-liquid multiphase reaction in organic synthesis, and significantly improved the efficiency of the aerobic oxidation of primary alcohols to aldehydes in the presence of copper/TEMPO catalysts (Scheme 1-1).³ Because, in principle, MNBs could potentially be used for conducting gas-liquid multiphase reactions other than aerobic oxidation, we believe that this new methodology is an important contribution to general gas-liquid multiphase reactions with simple, safe, and environment-friendly protocols. In order to further develop this methodology, the gas-liquid-solid multiphase palladium-catalysed hydrogenation of carbon-carbon unsaturated bonds was evaluated (Scheme 1-2). In this study, the yields of reactions using H₂-MNBs were found to be superior to those with conventional methods involving vigorous stirring.

In collaboration with Asupu Company Limited, we developed a stainless-free Teflon[®]-generator (MA3-FS, pumping rate 120–150 mL/min, Figure 1-a). Thus, H₂-MNBs were generated and passed into methanol to prepare a slightly turbid mixture (Figure 1-b).



Scheme 1 MNB-based strategy for aerobic oxidation and hydrogenation

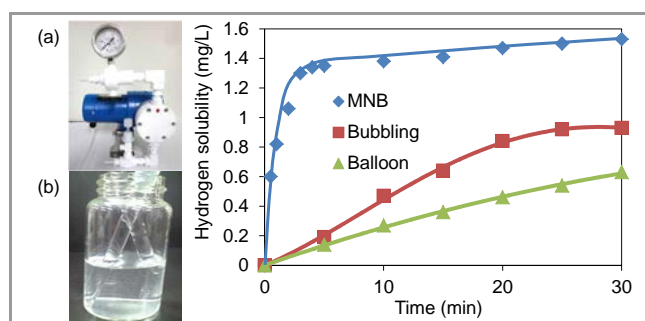
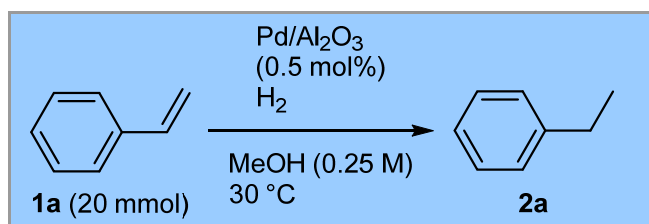


Figure 1 MNB-generator and degree of hydrogen in distilled water

The measurement of dissolved H₂ gas levels in distilled water showed that the Teflon[®]-MNB generator rapidly saturated the solution with H₂ gas under an H₂-flow rate of 5 mL/min even without stirring (Figure 1, right). On the other hand, the bubbling of H₂ at the same H₂-flow rate using a conventional gas dispersion tube with porous fritted glass tip under vigorous stirring (500 rpm) resulted in lower H₂ concentration. This finding is similar to that under general H₂ balloon condition. Although the mole fraction of H₂ (0.141×10^4) is lower than that of O₂ (0.230×10^4),⁴ these results indicate that a Teflon[®]-

MNB generator is an effective and well-assembled instrument to dissolve H₂ gas into distilled water.

Table 1 Comparison between reaction conditions^a



Entry	Conditions	H ₂ -Flow Rate (mL/min)	Temp. (°C)	Time (h)	Yield (%) ^b
1	MNB	3	30	5	99.9
2	MNB	5	30	2	99.9
3	MNB	10	30	45 min	99.9
4	MNB	5	50	2	99.9
5	MNB	5	70	3	99.9
6 ^c	MNB	5	30	5	99.9
7 ^c	MNB	5	30	6	99.9
8	Balloon	^d	30	2	4.4
9	Bubbling	5	30	2	38.3
10	Bubbling	10	30	2	76.0
11	Bubbling	5	50	3	16.6
12	Bubbling	5	70	3	4.0
13	Autoclave	^e	30	2	35.0

^a Conditions: See references (5) and Supporting Information. No stirring in Entries 1–7; 500 rpm stirring in Entries 8–13.

^b Determined by GC-analyses (column: GL Sciences TC-17).

^c Pd/Al₂O₃ (entry 6: 0.05 mol%, entry 7: 0.01 mol%) was used.

^d Atmospheric pressure.

^e 0.6 MPa pressure



Figure 2 Hydrogenation: apparatus and different methods

The hydrogenation of styrene (**1a**, 20 mmol, 2 g) was selected as the model reaction to evaluate the reaction efficiency (Table 1). Palladium on activated carbon (Pd/C) powder is usually employed for hydrogenation; however, it sometimes takes a long operation time to remove Pd/C in filtration process. Moreover, operators have to prevent the filters from clogging during operation in flow reactors. Therefore, palladium on alumina spheres (Pd/Al₂O₃, 0.5% Pd, 2–4 mm) was used, which have excellent abrasion resistance; but this system is less reactive compared to Pd/C powder.

The hydrogenations were carried out using three different methods (Figure 2). Our initial attempts

using H₂-MNBs (Figure 2-a, H₂-flow rate: 3 mL/min) afforded the desired ethylbenzene (**2a**) in quantitative yield after 5 h in the presence of 0.5 mol% Pd/Al₂O₃ at 30 °C (entry 1). The hydrogenation was completed within 1 h by increasing the H₂-flow rate to 10 mL/min (Entries 2 and 3). On the other hand, general H₂-balloon method under vigorous stirring (Figure 2-b) resulted in very low reaction yield (entry 8). Similarly, H₂-bubbling (H₂-flow rate: 5 mL/min) using a conventional gas dispersion tube resulted in 38% yield (entry 9).

Even when the reactions were carried out at a high H₂-flow rate up to 10 mL/min and/or high-pressure up to 0.6 MPa, the reaction yields were lower than that obtained with the MNB-based procedure (entry 2 vs. 10 and 13). Although reflux condensers and/or stainless autoclave must be used when reactions are performed at high-gas-flow rates and/or high-pressure conditions; the MNB-based procedure does not require such engineering controls. Furthermore, a very interesting temperature effect was observed. The reaction yields significantly decreased with increasing temperature under general H₂-bubbling condition, whereas high reactivities were still observed under the MNB-based conditions (Entries 4 and 5 vs. 11 and 12). According to Henry's law, the solubility of gases usually decreases with increasing temperature; however, the catalytic activity did not substantially affected by increasing temperature under the MNB-based conditions due to high H₂-concentration. Furthermore, the catalyst loading could also be decreased to 0.01 mol% (entries 6 and 7).

Encouraged by these results, the scope of this type of MNB-based hydrogenation was studied with compounds **1** bearing carbon-carbon unsaturated bonds under the optimised reaction conditions (Table 2).⁵ Hydrogenated products **2** were obtained in almost quantitative yields within 12 h at 30 °C in the presence of 0.5–3 mol% catalyst. Monosubstituted, 1,1-disubstituted, and 1,2-disubstituted alkenes **1** were smoothly hydrogenated within 3 h, where the ratio of yield (MNB)/yield (bubbling) was up to 50 (Table 2, Entries 1–8). The MNB-based method was found to be effective for less reactive trisubstituted and tetrasubstituted alkenes **1** in yield ratios up to 30 times higher (Entries 9–16). Moreover, the hydrogenation of the triple bonds afforded saturated compounds in quantitative yields (Entries 17–20).

The MNB-based hydrogenation system is quite simple. The inlet and outlet tubes were simply connected to the reaction vessel (Figure 2-a). Therefore, MNB-based hydrogenation method may offer significant advantages for pharmaceutical and industrial processes. To study a multigram-scale synthesis (100 mmol, >10 g), styrene (**1a**, 10.4 g), (*E*)-3-phenylprop-2-en-1-ol (**1d**, 13.4 g), or citronellal (**1e**, 15.4 g) was placed in the reaction vessel in MeOH (1.25 M) in the presence of 0.3 mol% Pd/Al₂O₃. H₂-MNBs were introduced by MNB-generator for 6–20 h, and

methanol was simply evaporated to give the saturated product **2** (Table 3). Extraction, washing, filtration, or

column chromatography was not needed to obtain the product with excellent purity in multigram-scale.

Table 2 Hydrogenation of unsaturated compounds **1** to alkanes **2**^a

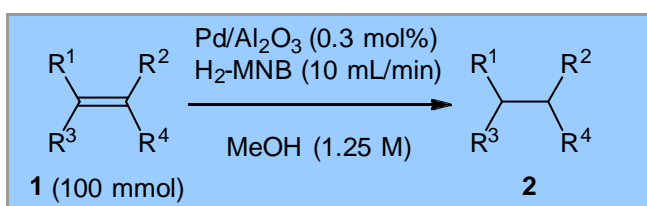
Entry	Substrate	Method	Catalyst (mol%)	Time (h)	Yield (%) ^b	Ratio ^c	Product
1		MNB	0.5	2	99.9		
2	1a	Bubbling	0.5	2	38.3	2.6	2a
3		MNB	0.5	3	99.9		
4	1b	Bubbling	0.5	3	12.2	8.2	2b
5		MNB	0.5	3	96.0		
6	1c	Bubbling	0.5	3	29.3	3.3	2c
7		MNB	1	2	99.9		
8	1d	Bubbling	1	2	2.0	50	2d
9		MNB	0.5	6	99.9		
10	1e	Bubbling	0.5	6	24.0	4.2	2e
11		MNB	1	12	99.9		
12	1f	Bubbling	1	12	24.0	4.2	2f
13		MNB	1	9	93.2		
14	1g	Bubbling	1	9	3.1	30	2g
15		MNB	3	6	99.9		
16	1h	Bubbling	3	6	12.0	8.3	2h
17		MNB	0.5	3	99.9		
18	1i	Bubbling	0.5	3	2.1	48	2a
19		MNB	0.5	4	99.9		
20	1j	Bubbling	0.5	4	4.1	24	2j

^a Conditions: See references (5).

^b Determined by GC-analyses (column: GL Sciences TC-17).

^c Yield (MNB)/Yield (bubbling)

Table 3 Multigram-scale hydrogenation under MNB-based method^a



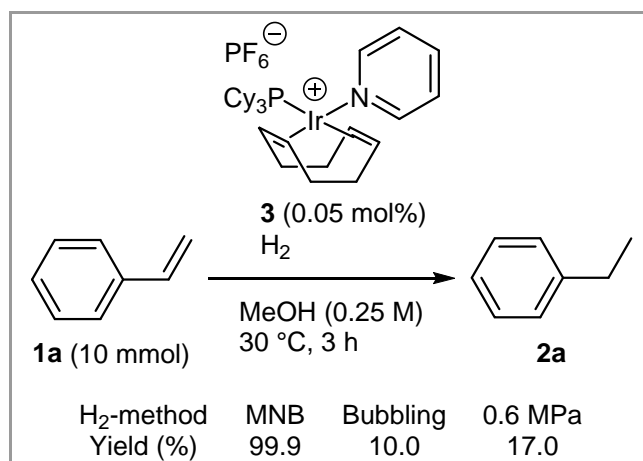
Entry	Substrate	Quantity (g)	Temp. (°C)	Time (h)	Yield (%) ^b	Product
1	1a	10.4	30	6	99.9	2a
2	1d	13.4	50	10	99.9	2d
3	1e	15.4	50	20	97.2	2e

^a Conditions: See references (5).

^b Determined by GC-analyses (column: GL Sciences TC-17).

Finally, the application of this MNB-based method to homogeneous catalytic system was studied (Scheme 2). Iridium complex **3** of 1,5-cyclooctadiene, tricyclohexylphosphine, and pyridine, known as Crabtree's catalyst, is an air-stable homogeneous catalytic system for hydrogenation reactions.⁶ A low catalyst loading (0.05 mol%) was found to be

sufficient for catalysing the hydrogenation of **1** to **2** (Scheme 2).



Scheme 2 Homogeneous hydrogenation

In summary, H₂-MNBs were employed to develop a novel experimental methodology for autoclave-free, gas-liquid-solid multiphase hydrogenation in organic synthesis. A significant improvement in the reaction

efficiency was achieved by virtue of this new MNB-based technique for the reduction of unsaturated carbon-carbon bonds. Further, studies focusing on the full scope of this unique MNB-based reaction system are in progress and will be reported in due course.^{7,8}

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

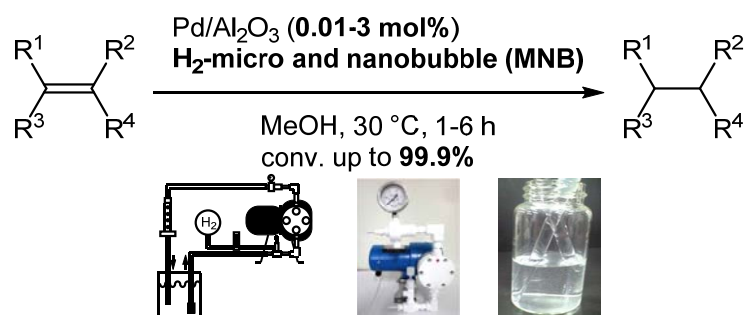
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References

- (1) (a) Vries, J. G. d.; Elsevier, C. J., *The Handbook of Homogeneous Hydrogenation*. ed.; WILEY-VCH Verlag GmbH & Co. KGaA: 2007. (b) Klabunovskii, E.; Smith, G. V.; Zsigmond, A., *Heterogeneous Enantioselective Hydrogenation: Theory and Practice*. ed.; Springer: 2006.
- (2) (a) Yoshida, J.-I. *Chem. Rec.* **2010**, *10*, 332. (b) Irfan, M.; Glasnov, T. N.; Kappe, C. O. *ChemSusChem* **2011**, *4*, 300. (c) Jones, R. V.; Godorhazy, L.; Varga, N.; Szalay, D.; Urge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 110. (d) Kobayashi, J.; Mori, Y.; Okamoto, K.; Akiyama, R.; Ueno, M.; Kitamori, T.; Kobayashi, S. *Science* **2004**, *304*, 1305.
- (3) (a) Mase, N.; Mizumori, T.; Tatemoto, Y. *Chem. Commun.* **2011**, *47*, 2086. (b) Mase, N.; Mizumori, T. *The Piping Engineering* **2011**, *53*, 48. (c) The preliminary results were discussed at the 2010 summer symposium of the Japanese Society for Process Chemistry, 1P-32 on July 15, 2010.
- (4) Wilhelm, E.; Battino, R.; Wilcock, R. J. *Chem. Rev.* **1977**, *77*, 219.
- (5) The typical procedure for hydrogenation of unsaturated carbon-carbon bonds using the H₂-MNB-based strategy: The hydrogenation was carried out in a 100 mL vial equipped with an MNB-generator without additional stirring. Alkene or alkyne **1** (20 mmol) was dissolved in MeOH (80 mL), and then warmed to 30 °C. Using the MNB-generator (MA3-FS), H₂-MNBs were introduced into the reactor in the presence of palladium on alumina spheres (0.5%Pd, 2–4 mm, 0.1 mmol, 0.5 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, MeOH was evaporated *in vacuo* to afford the desired alkane **1** with excellent purity.
We further examined hydrogenation of styrene **1a** in the presence of following heterogeneous catalysts, however increasing back pressure then clogging during operation in flow system was observed. 5% Pd/C, 5% Pd/C E type, 5% Pd/C NX type, 5% Pd/C K type, 2.7 wt% Pd/C spheres
- (6) (a) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331. (b) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.
- (7) The preliminary results were discussed at the 42nd Annual Meeting of Union of Chemistry-Related Societies in Chubu Area, Japan, 1P-08 on November 5, 2011.
- (8) Preliminary experimental determinations of the average size (158 nm) and concentration (0.27×10^8 particles/mL) of H₂-nanobubbles using generator (MA3-FS) were performed by the NanoSight LM10-HS. On the other hand, no formation of H₂-nanobubbles was observed under bubbling or balloon conditions.

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