

Fine-Bubble Slug-Flow Hydrogenation of Multiple Bonds and Phenols

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Fine bubble–slug flow hydrogenation of multiple bonds and phenols

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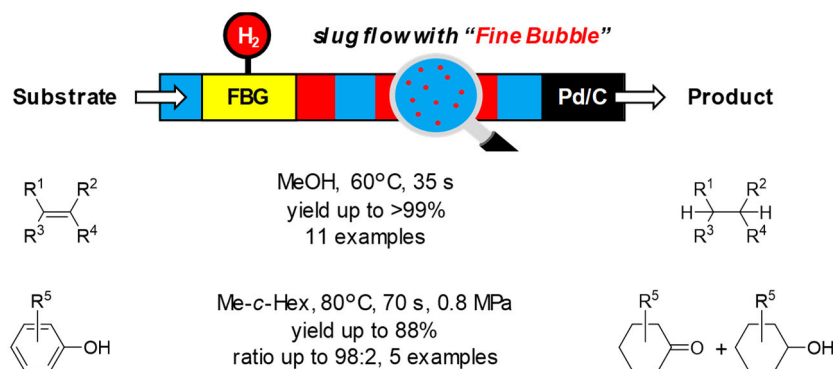
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Abstract We describe a promising method for the continuous hydrogenation of alkenes or alkynes using a newly developed fine bubble generator. The fine-bubble-containing slug flow system was up to 1.4 times more efficient than a conventional slug flow method. When applied for the hydrogenation of phenols to the corresponding cyclohexanones, the fine bubble–slug flow method suppressed over-reduction. As this method does not require the use of excess gas, it is expected to be widely applicable to improving the efficiency of gas-mediated flow reactions.

Keywords Fine Bubbles, Flow Reaction, Gas–liquid Reaction, Hydrogenation

The flow method is an innovative technology that allows for waste minimisation, enhanced safety, easy scale-up, better energy efficiency, and lower costs as compared to traditional batch methods.¹ In particular, the flow method is favourable for clean gas–liquid reactions,^{2–4} as the reaction can be controlled by the introduction and removal of the gas without using a high-pressure autoclave.^{2,k,3} However, a drawback of conventional gas–liquid flow methods, such as slug flow and pipe flow, is that the gas and liquid are separated in the flow channel; thus, excess gas is supplied to improve the reaction efficiency (Figure 1A).⁴ To maximise the performance of gas-mediated reactions, we have developed autoclave-free gas–liquid and gas–liquid–solid multiphase reactions using fine bubbles (FBs) in batch systems.⁵ FBs, which have diameters of 100 μm or less, have large gas–liquid surface areas and a self-pressurising effect, resulting in an excellent gas dissolution ability.⁶ These FB characteristics can enhance the concentration of dissolved reactive gas and the gas consumption efficiency, with increased reaction rates even observed at ambient pressure and temperature.⁵ Therefore, the FB–slug flow approach has the potential to realise highly efficient gas-mediated flow reaction systems without the use of excess gas (Figure 1B).

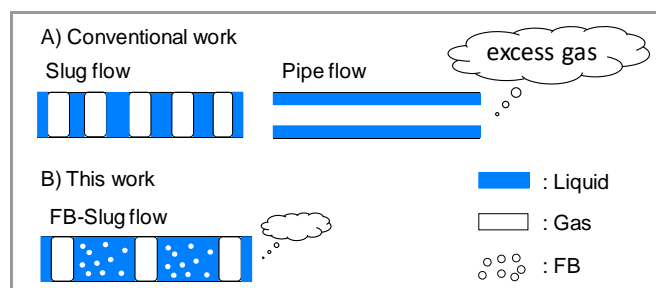


Figure 1 Gas-involved continuous flow methods

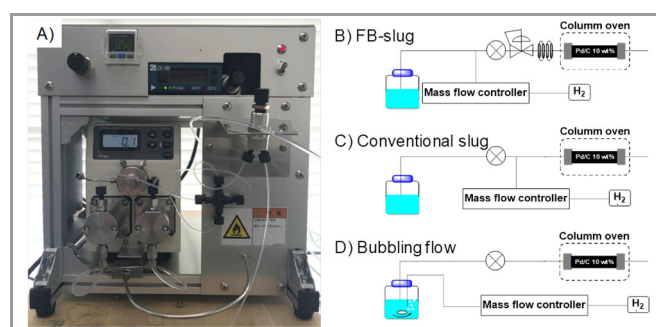


Figure 2 (A) New type of FB generator, (B–D) schematics of various reaction systems

The FB generators used in previous studies had high flow rates of 120–130 mL/min, which limited their use in the laboratory. The productivity was also inadequate because the gas supply rate was 5–10 mL/min and the gas–liquid ratio was only 4–8 vol%.^{5a} We initially developed an FB generator that can generate FBs at a low flow rate and high gas–liquid ratio (Figure 2A) by adopting a hybrid system that combines pressurised dissolution and depressurised generation with shear force as the FB generation mechanism. A small pump with a linear drive mechanism was used to deliver a liquid-containing gas, allowing for low liquid flow rates (0.01–99.99 mL/min) and high gas–liquid ratios (up to

50 vol%). Nanoparticle tracking analysis (NTA)⁷ revealed nanosized ultrafine bubbles (UFBs)⁸ with diameters of approximately 140 nm. Using the newly developed generator, H₂ UFBs can be produced at a concentration of 4.1×10^8 particles/mL by circulating in water for 10 min. Even in a single operation, H₂ UFBs were detected at a concentration of 6.4×10^7 particles/mL (Table S1 in Supporting Information). The newly developed FB generator is now available on the commercial market.⁹

To evaluate the proposed FB–slug flow method, the Pd-catalysed hydrogenation of styrene was investigated as a model reaction using the newly developed high-performance FB generator (Table 1, Figure 2B). A methanol solution of styrene (**1a**) and H₂ gas were continuously supplied to a temperature-controlled Pd/C-packed reactor in a column oven. The maximum amount of catalyst (0.47 mmol) that could be loaded into the reactor was used; employing a radial flow column reactor did not increase the backpressure, even with the use of a powdered Pd catalyst. The hydrogenation reaction at 30°C with 1.0 equiv of H₂ and a residence time of 35 s yielded ethylbenzene (**2a**) in 58% yield (entry 1). A higher temperature (60°C) improved the reactivity, resulting in an 85% yield (entry 2). Moreover, the hydrogen consumption efficiency was 85%, which reduces the requirement for excess gas. A decrease in the catalyst loading led to a decrease in reactivity (entry 3). However, the hydrogenation reaction proceeded quantitatively when the concentration of the substrate was decreased, corresponding to the use of 1.5 equiv of H₂ (entry 4). With the conventional slug flow method (Figure 2C) or the bubbling flow method (Figure 2D), the yields of the hydrogenation reaction were lower than with the FB–slug flow method (entries 2, 5, and 6). The low yield relative to conversion and the absence of by-products in the GC analysis suggests that small amounts of substrates or products were adsorbed onto the catalyst during the slug flow reaction.¹⁰

Table 1 Comparison among flow hydrogenation reaction conditions^a

| Entry | Temperature (°C) | H ₂ (equiv) | Pd/C (mmol) | Conversion ^b (%) | Yield ^b (%) |
|----------------|------------------|------------------------|-------------|-----------------------------|------------------------|
| 1 | 30 | 1 | 0.47 | 59 | 58 |
| 2 | 60 | 1 | 0.47 | 86 | 85 |
| 3 | 60 | 1 | 0.23 | 62 | 62 |
| 4 | 60 | 1.5 | 0.47 | >99 | >99 |
| 5 ^c | 60 | 1 | 0.47 | 85 | 76 |
| 6 ^d | 60 | 1 | 0.47 | 3 | 2 |

^a Reaction conditions: styrene (6.2 or 4.1 mmol), methanol (300 mL), 10 wt% Pd/C (0.23 or 0.47 mmol), H₂ (1.0 mL/min) at 30 or 60°C, 35 s.

^b Determined by GC analysis (for GC conditions, see the Supporting Information).

^c H₂ was supplied by the slug flow method.

^d H₂ was supplied by the bubbling flow method. For details of the slug flow and bubbling flow methods, see the Supporting Information.

The number concentration of H₂ UFBs in water (particles/mL) was measured by the NTA method. The number of UFBs in the FB–slug flow was 7.4 times and 57 times larger than that in the conventional slug and bubbling flow methods, respectively (Table 2). The mean diameters of the UFBs were 80–130 nm, regardless of the UFB generation method. Under the FB–slug flow

conditions, passing through the Pd/C catalyst halved the number of UFBs and slightly increased their mean diameter, indicating that the H₂ UFBs remained, even after passing through the Pd/C catalyst (Figure S5). A GC equipped with a dielectric barrier discharge ionisation detector (BID) was used to analyse the total H₂ molar concentrations (mM) in the dissolved and dispersed states. Compared with the conventional slug and bubbling flow methods, the FB–slug flow method was found to have the highest H₂ molar concentration. Indeed, the dissolution of a much greater amount of H₂ in the FB–slug method led to differences in the sizes of the gas segments for the various flow methods (gas: 1–2 mm, liquid: 5–8 mm for FB–slug flow; gas: 3–6 mm, liquid: 3–4 mm for slug flow, Figure S4). These results suggest that the presence of H₂ UFBs can maintain a high H₂ concentration in the reaction mixture because the self-pressurisation effect of FB⁵ accelerates the dissolution rate of H₂ in the liquid phase after H₂ is consumed during the reaction. Because of these effects, the FB–slug flow method shows high reaction efficiency, even at atmospheric pressure.

Table 2 Number concentration of UFBs and molar concentration of H₂

| Entry | Flow condition | Number of UFBs ^a ($\times 10^7$ particles/mL) | H ₂ concentration (mM) ^b | |
|-------|----------------|--|--|--------------------------------|
| | | | MeOH ^c | Methylcyclohexane ^d |
| 1 | FB–slug flow | 2.00 | 4.1 | 26.5 |
| 2 | Slug flow | 0.27 | 2.4 | 9.8 |
| 3 | Bubbling flow | 0.035 | 2.7 | 8.3 |

^a Conditions: water (2.0 mL/min flow rate), H₂ (1.0 mL/min flow rate) at room temperature and determined by NTA analysis.

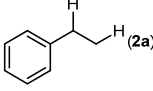
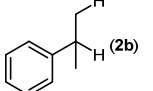
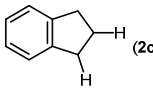
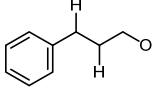
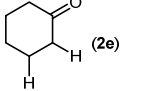
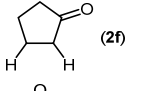
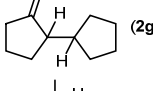
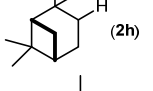
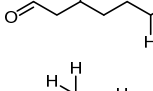
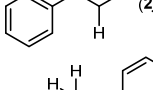
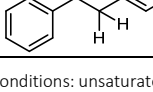
^b Determined by GC-BID analysis.

^c Conditions: MeOH (2.0 mL/min flow rate), H₂ (1.0 mL/min flow rate) at room temperature.

^d Conditions: methylcyclohexane (0.7 mL/min flow rate), H₂ (0.3 mL/min flow rate) at room temperature.

Hydrogenation by the FB–slug flow method was applied to various alkenes and alkynes. For all substrates, the FB–slug flow method resulted in higher yields of hydrogenation products among the tested methods (Table 3). A terminal alkene (**1a**) and disubstituted alkenes (**1b**, **1c**) were hydrogenated smoothly to give almost quantitative yields with 2 equiv of H₂ (entries 1–3). When the hydrogen supply is insufficient, the dehydrogenation of cinnamyl alcohol leads to the formation of cinnamaldehyde, followed by a decarbonylation reaction and subsequent hydrogenation to ethylbenzene.¹¹ For example, the bubbling flow method yielded desired product **2d** in 14% yield, including by-products, with 22% conversion, despite mildly reactive Pd sheets being used instead of reactive powdered Pd/C. In contrast, the FB–slug flow method achieved an 85% yield with 92% conversion (entry 4). Acetalisation was observed when enones (**1e–g**) were used as the substrate. To avoid this reaction, ethyl acetate was used instead of methanol as the solvent. The FB–slug flow method showed the highest reactivity and simultaneously avoided the competing formation of phenols via dehydrogenation at 30°C (entry 5). In these reactions carbonyl hydrogenation was suppressed, allowing olefins to be selectively hydrogenated to the desired products (entries 5–7). Despite the low reactivity, the hydrogenation of tetrasubstituted alkenes (**1g**) and trisubstituted alkenes (**1h**, **1i**) afforded the desired products (**2g–i**) in quantitative or 79% yield using 2 equiv of H₂ (entries 7–9). Terminal or internal alkynes also reacted quantitatively with 4 equiv of H₂ (entries 10 and 11).

Table 3 Scope of FB–slug flow method for hydrogenation of multiple bonds^a

| Entry | Product | Yield (%) ^b | | |
|------------------|---|------------------------|------|----------|
| | | FB–slug ^c | Slug | Bubbling |
| 1 |  | 85 (>99) | 76 | 2 |
| 2 |  | 76 (95) | 73 | 5 |
| 3 |  | 73 (97) | 63 | 2 |
| 4 ^d |  | 85 (95) | 64 | 14 |
| 5 ^{e,f} |  | 87 (95) | 77 | 1 |
| 6 ^e |  | 75 (93) | 71 | 5 |
| 7 ^e |  | 88 (98) | 84 | 2 |
| 8 |  | 70 (>99) | 62 | 2 |
| 9 |  | 32 (79) | 29 | 7 |
| 10 ^g |  | 69 (87) | 51 | 1 |
| 11 ^g |  | 95 (>99) | 74 | 2 |

^a Reaction conditions: unsaturated compounds (8.3 mmol), MeOH (400 mL), 10 wt% Pd/C (0.47 mmol), H₂ (1.0 mL/min) at 60°C, 35 s.

^b Determined by GC analysis (for GC conditions, see the Supporting Information).

^c The yields obtained when the substrate concentration was halved are given in parentheses.

^d 1.5 wt% Pd/sheet (0.7 mmol) was used at 20°C.

^e EtOAc was used as the solvent.

^f The reaction was performed at 30°C.

^g 4.2 mmol of substrate was used.

The applicability of the FB–slug flow method to hydrogenation was extended to control the over-reduction of phenols to cyclohexanones. Although many efforts have been made to achieve partial hydrogenation, over-reduction to cyclohexanols remains an issue.^{12,13} However, the newly developed FB–slug flow method enabled the selective hydrogenation reaction to be achieved by strictly controlling the residence time (Table 4). In the first attempt, Pd/C, methylcyclohexanone, and 4-propylphenol were used as the catalyst, solvent, and substrate, respectively.¹⁴ Although the hydrogenation reaction proceeded using the FB–slug flow method, the results were not satisfactory

at atmospheric pressure, even at 80°C (entry 1). Therefore, a back pressure regulator was installed after the catalyst tube to increase the reaction pressure (Figure S1 and S2).

Under pressurised conditions, the hydrogenation efficiency was improved but the selectivity for ketone formation decreased owing to over-reduction (entries 1–3). Reactions at a lower temperature or with less H₂ to suppress over-reduction resulted in lower conversions but high selectivities (92:8, entries 4 and 5). Further, the reactivity was not significantly affected by doubling the catalyst loading (0.80 mmol, entries 5 and 6). As hydrogen was presumed to flow out of the reaction system before the adsorption/hydrogenation reaction, transparent piping was introduced after the catalyst tube, which allowed observation of the unreacted hydrogen flow. As the residence time was not sufficient for the reaction, it was increased to 70 s, which provided the desired ketone derivative (**4a**) in 88% yield with 90:10 selectivity (entry 7). Notably, the FB–slug flow method was superior to the slug and bubbling flow methods in terms of reactivity and selectivity (entries 7–9).

The scope of this method for the hydrogenation of phenol derivatives was evaluated. With unsubstituted phenol (**3b**), *p*-cresol (**3c**), or *m*-cresol (**3d**), the reaction proceeded in moderate yield and good selectivity (entries 10–15). In the hydrogenation of **3c**, both the FB–slug flow method and the conventional slug flow method gave the corresponding cyclohexanone in the same yield. However, the selectivity was improved with the FB–slug flow system, indicating that the FB-mediated reaction affects not only the reactivity but also the selectivity (entries 12 and 13). The reaction of thymol (**3e**), which has a bulky substituent at the 2-position, gave the desired product in 84% yield under FB–slug flow conditions (entry 16). In contrast, the reaction under conventional slug flow conditions afforded the product in 56% yield (entry 17).

Table 4 Screening of reaction conditions and scope of the FB–slug flow method for the hydrogenation of phenols^a

| Entry | R | Method | Residence time (s) | H ₂ (mL/min) | Yield (4 + 5) (%) ^b | Ratio |
|-----------------|-------------------------------------|----------|--------------------|-------------------------|--|------------|
| | | | | | | 4:5 |
| 1 ^c | 4- <i>n</i> -Pr (3a) | FB–slug | 15 | 1.0 | 22 | 78:22 |
| 2 ^d | 4- <i>n</i> -Pr (3a) | FB–slug | 15 | 1.0 | 89 | 44:56 |
| 3 | 4- <i>n</i> -Pr (3a) | FB–slug | 15 | 1.0 | 92 | 34:66 |
| 4 ^e | 4- <i>n</i> -Pr (3a) | FB–slug | 15 | 1.0 | 22 | 92:8 |
| 5 | 4- <i>n</i> -Pr (3a) | FB–slug | 30 | 0.7 | 59 | 91:9 |
| 6 ^f | 4- <i>n</i> -Pr (3a) | FB–slug | 30 | 0.7 | 69 | 88:12 |
| 7 | 4- <i>n</i> -Pr (3a) | FB–slug | 70 | 0.3 | 88 | 90:10 |
| 8 | 4- <i>n</i> -Pr (3a) | Slug | 70 | 0.3 | 46 | 81:19 |
| 9 | 4- <i>n</i> -Pr (3a) | Bubbling | 70 | 20 | 0.1 | - |
| 10 | H (3b) | FB–slug | 140 | 0.3 | 82 | 93:7 |
| 11 | H (3b) | Slug | 140 | 0.3 | 56 | 89:11 |
| 12 ^g | 4-Me (3c) | FB–slug | 140 | 0.5 | 66 | 90:10 |
| 13 ^g | 4-Me (3c) | Slug | 140 | 0.5 | 67 | 76:24 |
| 14 ^h | 3-Me (3d) | FB–slug | 100 | 0.3 | 75 | 98:2 |
| 15 ^h | 3-Me (3d) | Slug | 100 | 0.3 | 63 | 95:5 |
| 16 ^h | 2- <i>i</i> -Pr, 5-Me (3e) | FB–slug | 70 | 0.3 | 84 | >90:10 |
| 17 ^h | 2- <i>i</i> -Pr, 5-Me (3e) | Slug | 70 | 0.3 | 56 | >90:10 |

^a Conditions: phenol derivative (4.0 mmol), methylcyclohexane (400 mL), 10 wt% Pd/C (0.40 mmol), H₂ (1.0, 0.7, or 0.3 mL/min) at 80°C, 15–100 s, 0.8 MPa.

^b Determined by GC analysis (for GC conditions, see Supporting Information).

^c The back pressure was 0 MPa.

^d The back pressure was 0.5 MPa.
^e The reaction was performed at 30°C.
^f 0.8 mmol of catalyst was used.
^g The back pressure was 1.0 MPa.
^h 5 wt% Pd/C (0.29 mmol) was used.

In methylcyclohexane, the hydrogen concentration under the FB–slug flow conditions was 2.7–3.2 times higher than that under the conditions of the conventional flow methods (Table 2). This higher level of hydrogen in the reaction solution should contribute to the improved reactivity. Moreover, the increased hydrogen concentration might accelerate the desorption rate of partially hydrogenated products from the catalyst, preventing over-reduction.

In conclusion, a novel FB–slug flow method was developed, and its wide applicability was confirmed through the hydrogenation of multiple bonds and the synthesis of ketones by the partial hydrogenation of phenol derivatives. Towards achieving green sustainable chemistry, the FB–slug flow method has potential for replacing conventional gas-involved flow reactions because this environmentally friendly process does not require the use of excess gas.

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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)

References and Notes

- (1) For recent reviews on flow chemistry, see: (a) Rogers, L.; Jensen, K. F. *Green Chem.* **2019**, *21*, 3481. (b) Gérardy, R.; Emmanuel, N.; Toupy, T.; Kassin, V.-E.; Tshibalonza, N. N.; Schmitz, M.; Monbaliu, J.-C. M. *Eur. J. Org. Chem.* **2018**, 2301. (c) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796. (d) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2. (e) Rossetti, I.; Compagnoni, M. *Chem. Eng. J.* **2016**, *296*, 56. (f) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2015**, *54*, 6688.
- (2) There are various recent approaches for flow gas–liquid reactions. For flow microreactors with a falling film, see: (a) Ziegenbalg, D.; Löb, P.; Al-Rawashdeh, M.; Kralisch, D.; Hessel, V.; Schönfeld, F. *Chem. Eng. Sci.* **2010**, *65*, 3557. (b) Zanfir, M.; Gavriilidis, A.; Wille, C.; Hessel, V. *Ind. Eng. Chem. Res.* **2005**, *44*, 1742. (c) Jähnisch, K.; Baerns, M.; Hessel, V.; Ehrfeld, W.; Haverkamp, V.; Löwe, H.; Wille, C.; Guber, A. *J. Fluorine Chem.* **2000**, *105*, 117. For flow microreactors with a cyclone micromixer, see: (d) Hübner, S.; Bentrup, U.; Budde, U.; Lovis, K.; Dietrich, T.; Freitag, A.; Küpper, L.; Jähnisch, K. *Org. Process Res. Dev.* **2009**, *13*, 952. (e) Dietrich, T. R.; Freitag, A.; Scholz, R. *Chem. Eng. Technol.* **2005**, *28*, 477. For flow microreactors with a microfluidic 'pipe', see: (f) Chambers, R. D.; Sandford, G.; Trmcic, J.; Okazoe, T. *Org. Process Res. Dev.* **2008**, *12*, 339. (g) Chambers, R. D.; Fox, M. A.; Sandford, G.; Trmcic, J.; Goeta, A. *J. Fluorine Chem.* **2007**, *128*, 29. (h) Chambers, R. D.; Fox, M. A.; Holling, D.; Nakano, T.; Okazoe, T.; Sandford, G. *Lab Chip* **2005**, *5*, 191. For flow microreactors with a microfluidic 'bollard', see: (i) Wada, Y.; Schmidt, M. A.; Jensen, K. F. *Ind. Eng. Chem. Res.* **2006**, *45*, 8036. For flow reactors with a tube-in-tube, see: (j) O'Brien, M. J. *CO₂ Util.* **2017**, *21*, 580. (k) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349. (l) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250. (m) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596.
- (3) (a) Hone, C. A.; Kappe, C. O. *Top. Curr. Chem.* **2019**, *377*, 2. (b) Mallia, C. J.; Baxendale, I. R. *Org. Process Res. Dev.* **2016**, *20*, 327.
- (4) Sobieszuk, P.; Aubin, J.; Pohorecki, R. *Chem. Eng. Technol.* **2012**, *35*, 1346.
- (5) (a) Mase, N.; Mizumori, T.; Tatemoto, Y. *Chem. Commun.* **2011**, 47, 2086. (b) Mase, N.; Isomura, S.; Toda, M.; Watanabe, N. *Synlett* **2013**, *24*, 2225. (c) Mase, N.; Nishina, Y.; Isomura, S.; Sato, K.; Narumi, T.; Watanabe, N. *Synlett* **2017**, *28*, 2184.
- (6) For recent reviews on fine bubbles, see: (a) Ulatowski, K.; Sobieszuk, P. *Water Environ. J.* **2020**, DOI: 10.1111/wej.12577. (b) Phan, K. K. T.; Truong, T.; Wang, Y.; Bhandari, B. *Trends Food Sci. Technol.* **2020**, *95*, 118. (c) Atkinson, A. J.; Apul, O. G.; Schnieder, O.; Garcia-Segura, S.; Westerhoff, P. *Acc. Chem. Res.* **2019**, *52*, 1196. (d) Temesgen, T.; Bui, T. T.; Han, M.; Kim, T.-I.; Park, H. *Adv. Colloid Interface Sci.* **2017**, *246*, 40. (e) Alheshibri, M.; Qian, J.; Jehannin, M.; Craig, V. S. *J. Langmuir* **2016**, *32*, 11086.
- (7) In the NTA method, many particles are individually and simultaneously analysed, and their hydrodynamic diameters are calculated based on the Stokes–Einstein equation, see: (a) Malloy, A.; Carr, B. *Part. Part. Syst. Charact.* **2006**, *23*, 197. (b) Tian, X.; Nejadnik, M. R.; Baunsgaard, D.; Henriksen, A.; Rischel, C.; Jiskoot, W. *J. Pharm. Sci.* **2016**, *105*, 3366. (c) Filipe, V.; Hawe, A.; Jiskoot, W. *Pharm. Res.* **2010**, *27*, 796.
- (8) Ultrafine bubbles (UFBs) are defined as bubbles with diameters of less than 1000 nm. Although the term nanobubbles (NBs) is also used to describe bubbles that have diameters of less than 1000 nm, we use the term UFBs in this communication based on the International Standards Organization (ISO) standards for fine bubble technology (ISO/TC 281).
- (9) Model: FBG-OS Type 1, liquid flow rate range: 0.01–99.99 mL/min, maximum gas feed rate: 50% of liquid volume, maximum discharge pressure: 5 MPa, distributor: Process Maximize Technologies (PMT) Corporation (2-13-18 Akanedai Aoba-ku, Yokohama 227-0066, Japan; Phone: +81-90-9104-3595; E-mail: odajima@dh.catv.ne.jp).
- (10) Recently, we found that in the hydrogenation of aromatic heterocyclic compounds, the decrease in reactivity owing to catalyst poisoning by the heterocyclic compounds was prevented by H₂ fine bubbles, see: Suzuki, S.; Tadano, G.; Sato, K.; Narumi, T.; Mase, N. presented in part at the 100th Annual Meeting of the Chemical Society of Japan, Chiba, Japan, March, 2020, 2B8-09.
- (11) Keresszegi, C.; Bürgi, T.; Mallat, T.; Baiker, A. *J. Catal.* **2002**, *211*, 244.
- (12) For selected reviews on the selective hydrogenation of phenol, see: (a) Kong, X.; Gong, Y.; Mao, S.; Wang, Y. *ChemNanoMat* **2018**, *4*, 432. (b) Zhong, J.; Chen, J.; Chen, L. *Catal. Sci. Technol.* **2014**, *4*, 3555.
- (13) For recent studies on the selective hydrogenation of phenol, see: (a) Li, X.; Jiang, H.; Hou, M.; Liu, Y.; Xing, W.; Chen, R. *Chem. Eng. J.* **2020**, *386*, 120744. (b) Zhang, J.; Zhang, C.; Jiang, H.; Liu, Y.; Chen, R. *Ind. Eng. Chem. Res.* **2020**, *59*, 10768. (c) Zhang, J.; Jiang, H.; Liu, Y.; Chen, R. *Appl. Surf. Sci.* **2019**, *488*, 555. (d) Valentini, F.; Santillo, N.; Petrucci, C.; Lanari, D.; Petricci, E.; Taddei, M.; Vaccaro, L. *ChemCatChem* **2018**, *10*, 1277. (e) Zhang, H.; Han, A.; Okumura, K.; Zhong, L.; Li, S.; Jaenicke, S.; Chuah, G.-K. *J. Catal.* **2018**, *364*, 354.
- (14) The use of Pd/C and cyclohexane was effective for the selective hydrogenation of phenol to cyclohexanone, see: Higashijima, M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2955.