Syn lett

T. lio et al.

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

Takuya lio <sup>a</sup> Kohei Nagai <sup>a</sup> Tomoki Kozuka <sup>b</sup> Akhtar Mst Sammi <sup>a</sup>	H2     slug flow with "Fine Bubbles"       Substrate     FBG   Pd/C  Pd/C  Product					
Kohei Sato <sup>a,b,c</sup> Tetsuo Narumi <sup>a,b,c,d</sup> Nobuyuki Mase <sup>* a,b,c,d</sup>	$R^1 \xrightarrow{R^2} R^2$	MeOH, 60 °C, 35 s yield up to >99% 11 examples	$\begin{array}{c c} R^1 & R^2 \\ H \xrightarrow{} & H \\ R^3 & R^4 \end{array}$			
<sup>a</sup> Department of Engineering, Graduate School of Integrated Science and Technology, Shizuoka University, 3-5-1 Johoku, Hamamatsu, Shizuoka 432-8561, Japan	<sup>R5</sup> _=_−он	methylcyclohexane, 80 °C, 70 s, 0.8 MPa yield up to 88% ratio up to 98:2. 5 examples				

- 432-8561, Japan
- <sup>b</sup> Department of Applied Chemistry and Biochemical Engineering, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu, Shizuoka 432-8561, Japan
- <sup>c</sup> Graduate School of Science and Technology, Shizuoka University, 3-5-1 Johoku, Hamamatsu, Shizuoka 432-8561, Japan
- <sup>d</sup> Research Institute of Green Science and Technology, Shizuoka University, 3-5-1 Johoku, Hamamatsu, Shizuoka 432-8561, Japan mase.nobuyuki@shizuoka.ac.jp
- Published as part of the Cluster Integrated Synthesis Using Continuous-Flow Technologie

Received: 27.08.2020
Accepted after revision: 16.09.2020
Published online: 21.10.2020
DOI: 10.1055/s-0040-1705948; Art ID: st-2020-u0475-c



Abstract We describe a promising method for the continuous hydrogenation of alkenes or alkynes by 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 in 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 in improving the efficiency of gas-mediated flow reactions.

Key words flow reaction, gas-liquid reaction, hydrogenation, alkynes, alkenes, phenols

The flow method is an innovative technology that permits waste minimization and provides enhanced safety, easy scale-up, better energy efficiency, and lower costs compared with conventional batch methods.<sup>1</sup> In particular, the flow method is favorable for clean gas-liquid reactions,<sup>2-4</sup> as the reaction can be controlled by the introduction and removal of the gas without using a high-pressure autoclave.<sup>2k,3</sup> However, a drawback of conventional gas-liquid flow methods such as slug flow or pipe flow is that the gas and liquid are separated in the flow channel and excess gas must be supplied to improve the reaction efficiency (Figure 1A).<sup>4</sup> To maximize the performance of gas-mediated reactions, we have developed autoclave-free gas-liquid and gas-liquid-solid multiphase reactions that use fine bubbles (FBs) in batch systems.<sup>5</sup> FBs, which have diameters of 100

um or less, have large gas-liquid surface areas and a selfpressurizing effect, resulting in an excellent gas dissolution.<sup>6</sup> These characteristics of FBs can enhance the concentration of dissolved reactive gases and improve gas-consumption efficiency, providing increased reaction rates, even at ambient pressures and temperatures.<sup>5</sup> Therefore, an FB-slug-flow approach has the potential to realize highly efficient gas-mediated flow reactions without the use of excess gas (Figure 1B).



Figure 1 Gas-involved continuous-flow methods

FB generators used in previous studies had high flow rates of 120-130 mL/min, which limited their use in the laboratory. Their productivity was also inadequate because the gas supply rate was 5-10 mL/min and the gas-liquid ratio was only 4–8 vol<sup>8,5</sup> We initially developed an FB generator that can generate FBs at a low flow rate and with a high gas-liquid ratio by adopting a hybrid system that combines pressurized dissolution and depressurized generation with shear force as the FB-generation mechanism (Figure 2A). A

Cluster

### Synlett

T. lio et al.

small pump with a linear drive mechanism was used to deliver a liquid-containing gas, permitting low liquid flow rates (0.01–99.99 mL/min) and high gas–liquid ratios (up to 50 vol%). Nanoparticle tracking analysis (NTA)<sup>7</sup> revealed the presence of nanosized ultrafine bubbles (UFBs)<sup>8</sup> with diameters of approximately 140 nm. By using our newly developed generator, H<sub>2</sub> UFBs can be produced at a concentration of 4.1 × 10<sup>8</sup> particles/mL by circulation in water for 10 minutes. Even in a single operation, H<sub>2</sub> UFBs were detected at a concentration of 6.4 × 10<sup>7</sup> particles/mL [see Supporting Information (SI), Table S1]. The newly developed FB generator is now commercially available.<sup>9</sup>



**Figure 2** (A) The new type of FB generator. (B–D) Schematics of various reaction systems.

To evaluate the proposed FB-slug-flow method, we investigated the Pd-catalyzed hydrogenation of styrene as a model reaction using the newly developed high-performance FB generator (Table 1 and Figure 2B). H<sub>2</sub> gas and a solution of styrene (1a) in methanol 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. The use of a radial-flow column reactor did not increase the backpressure, even when a powdered Pd catalyst was present. The hydrogenation reaction at 30 °C with 1.0 equivalents of H<sub>2</sub> and a residence time of 35 seconds gave ethylbenzene (2a) in 58% yield (Table 1, 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 reduced 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 equivalents of H<sub>2</sub> (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 those from the FB-slug-flow method (entries 2, 5, and 6). The low yield relative to conversion and the absence of byproducts in the GC analysis suggests that small amounts of substrates or products were adsorbed onto the catalyst during the slug-flow reaction.<sup>10</sup>



	1a (2.0 mL/mi	H <sub>2</sub> (FB-slug MeOf	9 flow), Pd/C H, 35 s	H 2a	I
Entry	Temp (°C)	H <sub>2</sub> (equiv)	Pd/C (mmol)	Conv. <sup>b</sup> (%)	Yield <sup>b</sup> (%)
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°	60	1	0.47	85	76
6 <sup>d</sup>	60	1	0.47	3	2

<sup>a</sup> Reaction conditions: styrene (6.2 or 4.1 mmol), MeOH (300 mL), 10 wt% Pd/C (0.23 or 0.47 mmol), H<sub>2</sub> (1.0 mL/min), 35 s. <sup>b</sup> Determined by GC analysis (for GC conditions, see the SI).

<sup>c</sup> H<sub>2</sub> supplied by slug flow.

 $^{\rm d}$  H\_2 supplied by the bubbling-flow method. For details of the slug-flow and bubbling-flow methods, see the SI.

The number concentration of H<sub>2</sub> 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, passage through the Pd/C catalyst halved the number of UFBs and slightly increased their mean diameter, indicating that H<sub>2</sub> UFBs remained after passage through the Pd/C catalyst (Figure S5). A GC equipped with a dielectric barrier discharge ionization detector (BID) was used to analyze the total H<sub>2</sub> molar concentrations (mM) in the dissolved and dispersed states. Compared with conventional slug-flow and bubbling-flow methods, the FB-slug-flow method produced the highest H<sub>2</sub> molar concentration. Indeed, the dissolution of a much greater amount of H<sub>2</sub> in the FB-slug-flow 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; See SI, Figure S4). These results suggest that the presence of H<sub>2</sub> UFBs can maintain a high H<sub>2</sub> concentration in the reaction mixture because the self-pressurization effect of FB<sup>5</sup> accelerates the rate of dissolution of H<sub>2</sub> in the liquid phase after H<sub>2</sub> is consumed during the reaction. Because of these effects, the FB-slug-flow method shows a high reaction efficiency, even at atmospheric pressure.

Hydrogenation by the FB–slug-flow method was applied to various alkenes and alkynes. For all substrates, the FB– slug-flow method resulted in the highest yields of hydrogenation products among the tested methods (Table 3). Terminal alkene **1a** and disubstituted alkenes **1b** and **1c** were hydrogenated smoothly with 2.0 equivalents of  $H_2$  to give

#### T. lio et al.

 Table 2
 Number Concentration of UFBs and Molar Concentration of H<sub>2</sub>

Entry	Flow condition	Number of UFBs <sup>a</sup>	H <sub>2</sub> concentration (mM) <sup>b</sup>	
		(× 10' particles/mL)	MeOH <sup>c</sup>	$MeCy^d$
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

 $^{\rm a}$  Determined by NTA analysis; conditions:  $\rm H_2O$  (2.0 mL/min flow rate),  $\rm H_2$  (1.0 mL/min flow rate), r.t.

<sup>b</sup> Determined by GC-BID analysis.

<sup>c</sup> Conditions: MeOH (2.0 mL/min flow rate),  $H_2$  (1.0 mL/min flow rate), r.t.

<sup>d</sup> Conditions: methylcyclohexane (MeCy) (0.7 mL/min flow rate), H<sub>2</sub> (0.3 mL/min flow rate), r.t.

**2a-c**, respectively, in almost guantitative yields (Table 3, entries 1-3). When the hydrogen supply was inadequate, the dehydrogenation of cinnamyl alcohol gave cinnamaldehvde, which underwent decarbonylation and subsequent hydrogenation to give ethylbenzene.<sup>11</sup> The bubbling-flow method gave the desired product 2d in 14% yield (including byproducts) with 22% conversion, despite mildly reactive Pd sheets being used instead of reactive powdered Pd/C. In contrast, the FB-slug-flow method provided an 85% yield of 2d with 92% conversion (entry 4). Acetalization was observed when enones 1e-g were used as substrates. To avoid this reaction, ethyl acetate was used instead of methanol as the solvent. The FB-slug-flow method then showed the highest reactivity at 30 °C, and also prevented competing formation of phenols through dehydrogenation (entry 5). In these reactions, carbonyl hydrogenation was suppressed, permitting olefins to be hydrogenated selectively to give the desired products **2e-g** (entries 5–7). Despite the low reactivity, the hydrogenation of a tetrasubstituted alkenes 1g and trisubstituted alkenes **1h** and **1i** by using 2.0 equivalents of H<sub>2</sub> afforded the desired products **2g-i** in quantitative or 79% yield (entries 7-9). Terminal or internal alkynes also reacted quantitatively with 4.0 equivalents of H<sub>2</sub> (entries 10 and 11).

 Table 3
 Scope of the FB–Slug-Flow Method for Hydrogenation of Multiple Bonds<sup>a</sup>



Entry	Product	Yield <sup>♭</sup> (%)		
		FB–slug <sup>c</sup>	Slug	Bubbling
2	H (2b)	76 (95)	73	5
3	H (2c)	73 (97)	63	2
4 <sup>d</sup>	H OH (2d)	85 (95)	64	14
5 <sup>e,f</sup>	H (2e)	87 (95)	77	1
6 <sup>e</sup>	0 (2f)	75 (93)	71	5
7ª	(2g)	88 (98)	84	2
8	H (2h)	70 (>99)	62	2
9	0 H (2i)	32 (79)	29	7
10 <sup>g</sup>		69 (87)	51	1
11 <sup>9</sup>	H H (2k)	95 (>99)	74	2

 $^a$  Reaction conditions: 1 (8.3 mmol), MeOH (400 mL), 10 wt% Pd/C (0.47 mmol), H\_2 (1.0 mL/min), 60 °C, 35 s.

<sup>9</sup> Determined by GC analysis (for GC conditions, see the SI).

<sup>c</sup> Yields obtained by halving the substrate concentration are given in parentheses.

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

<sup>e</sup> EtOAc was used as the solvent.

<sup>f</sup> The reaction was performed at 30 °C.

<sup>g</sup> Substrate (4.2 mmol) was used.

The applicability of the FB–slug-flow method to hydrogenation was extended to controlling the over-reduction of phenols to cyclohexanones. Although many efforts have been made to achieve partial hydrogenation of phenols, over-reduction to cyclohexanols remains an issue.<sup>12,13</sup> However, the newly developed FB–slug-flow method permitted a selective hydrogenation reaction to be achieved by strict

© 2020. Thieme. All rights reserved. Synlett 2020, 31, A-F

# Synlett T. lio et al. Cluster

D

control of the residence time (Table 4). In the first attempt, Pd/C, methylcyclohexanone, and 4-propylphenol were used as the catalyst, solvent, and substrate, respectively.<sup>14</sup> Although the hydrogenation reaction proceeded when the FB-slug-flow method was used, the results were unsatisfactory at atmospheric pressure, even at 80 °C (Table 4, entry 1). Therefore, a backpressure regulator was installed after the catalyst tube to increase the reaction pressure (SI; Figures S1 and S2). Under the pressurized conditions, the hydrogenation efficiency was improved, but the selectivity for ketone formation decreased owing to over-reduction (Table 4, entries 1–3). Reactions at a lower temperature or with less H<sub>2</sub> to suppress over-reduction resulted in lower conversions but higher selectivities (92:8; entries 4 and 5). Furthermore, the reactivity was not significantly affected by doubling the catalyst loading to 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 to

permit observation of the flow of unreacted hydrogen. As the residence time was not sufficient for the reaction, it was increased to 70 s, which provided the 4-propylcyclohexanone (**4a**) in 88% yield with 90:10 selectivity (entry 7). Notably, the FB-slug-flow method was superior to both 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 then evaluated. With unsubstituted phenol (**3b**), *p*-cresol (**3c**), or *m*-cresol (**3d**), the reaction proceeded in moderate yield and with good selectivity (entries 10–15). In the hydrogenation of **3c**, both the FB–slugflow method and the conventional slug-flow method gave the corresponding cyclohexanone in the same yield. However, the selectivity was superior 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

Table 4	Screening of Reaction	Conditions and Sco	pe of the FB–Slua-Fl	low Method for the Hy	drogenation of Phenols <sup>a</sup>
---------	-----------------------	--------------------	----------------------	-----------------------	-------------------------------------

$R \xrightarrow{II} \\ 3a-e \\ 3a-e \\ back pressure 0.8 MPa \\ 4a-e \\ 5a-e \\ back pressure 0.8 MPa \\ 4a-e \\ 5a-e \\ 5a-e \\ 5a-e \\ back pressure 0.8 MPa \\ 5a-e \\ 5a-e \\ back pressure 0.8 MPa \\ 5a-e \\ 5a-e \\ back pressure 0.8 MPa \\ 5a-e \\ 5a-e \\ back pressure 0.8 MPa \\ 5a-e \\ back pressure 0.8 MPa \\ back pres$							
Entry	R	Method	Residence time (s)	H <sub>2</sub> (mL/min)	Yield ( <b>4</b> + <b>5</b> ) (%) <sup>b</sup>	Ratio <b>4/5</b>	
1 <sup>c</sup>	4-Pr ( <b>3a</b> )	FB-slug	15	1.0	22	78:22	
2 <sup>d</sup>	4-Pr ( <b>3a</b> )	FB-slug	15	1.0	89	44:56	
3	4-Pr ( <b>3a</b> )	FB-slug	15	1.0	92	34:66	
4 <sup>e</sup>	4-Pr ( <b>3a</b> )	FB-slug	15	1.0	22	92:8	
5	4-Pr ( <b>3a</b> )	FB-slug	30	0.7	59	91:9	
6 <sup>f</sup>	4-Pr ( <b>3a</b> )	FB-slug	30	0.7	69	88:12	
7	4-Pr ( <b>3a</b> )	FB-slug	70	0.3	88	90:10	
8	4-Pr ( <b>3a</b> )	slug	70	0.3	46	81:19	
9	4-Pr ( <b>3a</b> )	bubbling	70	20	0.1	-	
10	H ( <b>3b</b> )	FB-slug	140	0.3	82	93:7	
11	H ( <b>3b</b> )	slug	140	0.3	56	89:11	
12 <sup>g</sup>	4-Me ( <b>3c</b> )	FB-slug	140	0.5	66	90:10	
13 <sup>g</sup>	4-Me ( <b>3c</b> )	slug	140	0.5	67	76:24	
14 <sup>h</sup>	3-Me ( <b>3d</b> )	FB-slug	100	0.3	75	98:2	
15 <sup>h</sup>	3-Me ( <b>3d</b> )	slug	100	0.3	63	95:5	
16 <sup>h</sup>	2- <i>i</i> -Pr,5-Me ( <b>3e</b> )	FB-slug	70	0.3	84	>90:10	
17 <sup>h</sup>	2- <i>i</i> -Pr,5-Me ( <b>3e</b> )	slug	70	0.3	56	>90:10	

<sup>a</sup> Reaction conditions: phenol **3** (4.0 mmol), methylcyclohexane (400 mL), 10 wt% Pd/C (0.40 mmol), H<sub>2</sub> (1.0, 0.7, or 0.3 mL/min), 80 °C, 15–100 s, 0.8 MPa. <sup>b</sup> Determined by GC analysis (for GC conditions, see SI).

<sup>c</sup> Backpressure Ó MPa.

<sup>d</sup> Backpressure 0.5 MPa.

° At 30 °C.

<sup>f</sup> Catalyst (0.8 mmol).

<sup>g</sup> Backpressure 1.0 MPa.

<sup>h</sup> 5 wt<sup>'</sup><sub>8</sub> Pd/C (0.29 mmol).

#### Synlett

T. lio et al.

under FB–slug-flow conditions (entry 16). In contrast, the reaction under conventional slug-flow conditions afforded the product in 56% yield (entry 17).

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 probably contributes 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,<sup>15</sup> and its wide applicability was confirmed through the hydrogenation of multiple bonds and by the synthesis of ketones through 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.

#### **Funding Information**

This work was supported in part by JSPS KAKENHI Grant Numbers JP15H03844 and JP18H02012, and MEXT KAKENHI Grant Number JP18H04397.

#### Acknowledgment

We thank Kawaken Fine Chemicals Co., Ltd. and Nippon Kodoshi Corporation for their generous gifts of 5 wt% Pd/C and Pd/sheet catalysts, respectively. We thank Scitem Co., Ltd. for providing us with a radialflow column reactor. We acknowledge the members of Ushio Chemix Corp. for discussion of the partial reduction of phenol. We would like to thank Editage (www.editage.com) for English language editing.

#### **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1705948.

#### **References and Notes**

- 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. (Amsterdam, Neth.)* **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.

Downloaded by: Macquarie University. Copyrighted material

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. (d) For flow microreactors with a cyclone micromixer, see: (e) Hübner, S.; Bentrup, U.; Budde, U.; Lovis, K.; Dietrich, T.; Freitag, A.; Küpper, L.; Jähnisch, K. Org. Process Res. Dev. 2009, 13, 952. (f) Dietrich, T. R.; Freitag, A.; Scholz, R. Chem. Eng. Technol. 2005, 28, 477. For flow microreactors with a microfluidic 'pipe', see: (g) Chambers, R. D.; Sandford, G.; Trmcic, J.; Okazoe, T. Org. Process Res. Dev. 2008, 12, 339. (h) Chambers, R. D.; Fox, M. A.; Sandford, G.; Trmcic, J.; Goeta, A. J. Fluorine Chem. 2007, 128, 29. (i) 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: (j) Wada, Y.; Schmidt, M. A.; Jensen, K. F. Ind. Eng. Chem. Res. 2006, 45, 8036. For flow reactors with a tube-intube, see: (k) O'Brien, M. J. CO2 Util. 2017, 21, 580. (1) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. Acc. Chem. Res. 2015, 48, 349. (m) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. Chem. Sci. 2011, 2, 1250. (n) 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; corrigendum: Top. Curr. Chem. 2019, 377, 7. (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, in press; 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 analyzed, 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 appropriate standard: ; ISO 20480-1:2017: Fine Bubble Technology: General Principles for Usage and Measurement of Fine Bubbles: Part 1: Terminology; International Standards Organization: Geneva, 2017;
- (9) Model: FBG-OS Type 1: liquid flowrate 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 Aobaku, Yokohama 227-0066, Japan; Phone: +81-90-9104-3595; Email: odajima@dh.catv.ne.jp).
- (10) Suzuki, S.; Tadano, G.; Sato, K.; Narumi, T.; Mase, N.; Fine-Bubble Mediated Hydrogenation Reaction of Heterocyclic Compounds, Presented in part at the 100th Annual Meeting of the Chemical Society of Japan, Chiba, Japan, March 2020; 2B8-09.

F

- (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. (Amsterdam, Neth.)* **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.
- (15) Hydrogenation of Alkenes or Alkynes by the  $\rm H_2\mathchar`-FB\mathchar`-Slug\mathchar`-Slug\mathchar`-FB\mathchar`-Slug\mathchar`-Slug\mathchar`-FB\mathchar`-Slug\mathchar`-Slug\mathchar`-FB\mathchar`-Slug\mat$

A 500 mL Duran bottle was charged with a solution of the appropriate substrate **1** (8.28 mmol) in MeOH (400 mL). The reactor was charged with 10% Pd/C (1.1 g, 0.47 mmol) and placed in a column oven (CTO-10AC; Shimadzu, Japan) at 60 °C. The solution of **1** was delivered at a flow rate of 2.0 mL/min (residence time in the reactor = 35 s), and H<sub>2</sub> gas was delivered at a flow rate of 1.0 mL/min (1 equiv). The pressure in the front of the reactor was set to approximately 4 MPa to generate FBs. After 30 min of operation at 60 °C, the reaction mixture was collected every 10 min and analyzed by GC-FID, without purification.