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# Efficient photosensitized oxygenations in phase contact enhanced microreactors<sup>†</sup>

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A transparent dual-channel microreactor with highly enhanced contact area-to-volume ratio was fabricated for efficient photosensitized oxygenations. The dual-channel microreactor shielded with polyvinylsilazane (PVSZ) consisting of an upper channel for liquid flow and a lower channel for  $O_2$  flow, allows sufficient phase contact along the parallel channels through a gas permeable PDMS membrane for maintaining the  $O_2$  saturated solution. Under full exposure of reactants to light, the reactions in high concentration are completed in minutes rather than hours that it takes to complete in a batch reactor. Moreover, the scale-up process using the microreactor revealed higher productivity than the batch reactor, which would be valuable for the practical applications in a broad range of gas–liquid chemical reactions.

### Introduction

Photosensitized oxygenation conducted only with light and  $O_2$  gas is one of the most promising routes among green chemical processes.<sup>1,2</sup> Besides lab-scale applications in organic synthesis, an activated singlet oxygen ( $^{1}O_{2}$ ) has successfully been utilized in the production of various fragrances, pharmaceuticals, and fine chemicals with high selectivity.<sup>3–7</sup> In a typical batch system, oxygen is bubbled through a liquid reactant under simultaneous irradiation of light. This arrangement requires a prolonged reaction time due to very low surface to volume ratio that results in a poor supply of photons absorbed. Moreover, the short lifetime of  $^{1}O_{2}$  in organic solvents (9.5 µs in CH<sub>3</sub>OH and 77.1 µs in CH<sub>3</sub>CN)<sup>8,9</sup> and long molecular diffusion distance in the system reduce the reaction efficiency significantly.

Microfluidic systems have provided distinct advantages such as very high surface area-to-volume ratio, short molecular diffusion distance, simple feasibility study for scaling up, highly reduced waste, and precise control in reaction parameters.<sup>10–33</sup> Furthermore, the systems can provide high spatial illumination homogeneity, excellent light penetration throughout the micronscale reactor and a very large illuminated surface area per unit volume. With these advantages, the microchemical system could be positioned as a powerful tool for the photoreactions.<sup>34–36</sup>

Pioneering photosensitized oxygenations in microreactors were recently reported by several groups.<sup>37-41</sup> The optical transparency and short light path of the microreactors provided a sufficient amount of light onto reaction species, unlike the batch reactor. However, the insufficient gas transfer between the gas and liquid binary phases in the single channel microreactor lowered the reaction rate in the oxygenation. For this reason, the reactions were often conducted in diluted reactant conditions (less than 0.1 M), or under high pressure of supercritical condition (140 bar). Alternatively, pre-saturation of reactants solution with  $O_2$  was also attempted to ensure better supply of  $O_2$  that is continuously consumed during the reaction. However, it is still unsatisfactory in that the conventional microreactors needed prolonged reaction time with excess solvent wasted to dissolve O<sub>2</sub> into the liquid. These factors have made it difficult to achieve the most important attempt in microchemical society, which is to replace the typical batch system with a microchemical system for the gas-liquid binary phase reactions. Therefore, it still demands a new approach for making the intimate contact between the two phases.

Herein we report a high-throughput microchemical approach for photosensitized oxygenations in condensed solution, with a microreactor specifically designed to ensure efficient supply of  $O_2$  into the liquid and full exposure of the reactants to light. The reactions are completed in minutes rather than hours that it usually takes to complete in a typical batch reactor. Fig. 1 illustrates photosensitized oxygenation in a dual-channel microreactor, which consists of an upper channel for liquid flow and a lower channel for  $O_2$  flow. A gas permeable PDMS membrane ensures separation between gas and liquid flows along

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**Fig. 1** Schematic illustration of photosensitized oxygenation in a dualchannel microreactor shielded with solvent resistant coating.

the parallel channels, and allows supply of  $O_2$  from the lower channel to the upper channel that is sufficient for maintaining the solution saturated with  $O_2$ , even though the reaction consumes the dissolved  $O_2$  continuously.

### **Results and discussion**

### 1. Fabrication of a dual-channel microreactor with PVSZ shielded upper channel

It is well known that PDMS microfluidic channels fabricated by the low-cost soft lithography technique suffer from solvent swelling.<sup>42</sup> Recently, we reported a poly(dimethylsiloxane) (PDMS) based dual-channel microreactor, in which two parallel channels are divided by a gas permeable PDMS membrane and as such, a continuous supply of gas was possible.<sup>43</sup> The intimate contact made possible between the gas and liquid phases led to a significantly enhanced performance in the oxidative Heck reactions with non-swelling solvent. However, the reported PDMS microreactor could be used only for one day operation of the photosensitized reaction due to the swelling problem. Therefore, we needed to come up with a new fabrication technique for the microreactor that can be used for organic syntheses without sacrificing the advantage of easy and cost-saving fabrication that PDMS microfluidic devices offer.44,45 We were motivated by our recent work on a monolithic type of solvent resistant microfluidic device fabricated with polyvinylsilazane (PVSZ, KION VL-20®, Clarient, USA) in that the same approach might lead to an improvement in the chemical stability and solvent compatibility of the plain PDMS channel.<sup>46</sup> We shielded the inner surfaces of the upper channel among the two channels that are in contact with the organic solvent, which involves an inexpensive and simple method. Fig. 2A illustrates the fabrication procedure for the microreactor with PVSZ shielded channel, and Fig. 2B and C, respectively, show a crosssectional view of the dual-channel in the microreactor and the image of the device filled with the reagent, blue photosensitizer, and gaseous O<sub>2</sub> for performing the photosensitized oxygenation. The PVSZ polymer was first spin-coated onto a thick PDMS slab with concave channel structure to obtain a cladding layer. Crosssectional images in Fig. 2B show a variable thickness, depending on locations inside the channel, which ranges from 15 µm at the top to 80 µm at the corner. The coated polymer on the PDMS slab was gently wiped out with a glass slide to remove the excess polymer except for the concave part of the surface. Subsequently,



Fig. 2 (A) Schematic illustration for fabrication of a dual-channel microreactor with PVSZ shielded upper channel. (B) Cross-sectional view of dual microchannel with the PVSZ shielded upper channel. (C) The PVSZ shielded dual-channel microreactor filled with  $O_2$ , methylene blue (photosensitizer), and  $\alpha$ -terpinene (reagent).

the PVSZ cladding layer was solidified through a series of UV and thermal curing steps. The PVSZ shielded, PDMS upper liquid channel was bonded with a thin PDMS membrane and the lower PDMS gas channel through a plasma treatment. Detailed fabrication procedure and stability test against various organic solvents are described in the ESI, Fig. 1S<sup>†</sup>. Eventually, the upper channel surface shielded by the solvent resistant coating definitely promoted the solvent durability of the channel. The bottom part of the upper channel, which is the upper surface of the middle PDMS membrane layer, should not be coated with PVSZ layer to allow gas diffusion. Upon over 60  $\mu$ L min<sup>-1</sup> of continuous O<sub>2</sub> injection flow through the PDMS membrane, the high enough internal pressure could be induced in the PDMS network to prevent solvent diffusion at the upper solution channel, resulting in no deformation under continuous running (see ESI, Fig. 2S<sup>†</sup>). In addition, the PVSZ shielded PDMS channel retained optical transparency as confirmed by UV-Vis absorption spectrum (see ESI, Fig. 3S<sup>†</sup>).

In Fig. 3, we compared the reactor volumes and contact areato-volume ratios in the batch system, single layer channel system (henceforth to be referred to as mono-channel), and the PVSZ shielded dual-channel microreactor (henceforth to be referred to as dual-channel). The measured volume of the upper liquid channel in the dual-channel was 38.9  $\mu$ L, and the calculated contact area between the liquid channel and gas channel was 1.98 cm<sup>2</sup>. The contact area-to-volume ratio was significantly enhanced to 50.9 cm<sup>-1</sup>, that is much larger than 14.9 cm<sup>-1</sup> of the mono-channel and 0.76 cm<sup>-1</sup> of the 50 mL batch system (see ESI, Fig. 4S†). In addition, we prepared an alternative dual-channel microreactor for the feasibility of scale-up (see ESI, Fig. 5S†), which has the upper liquid channel with 285  $\mu$ L volume and the contact area of 12.2 cm<sup>2</sup>, the calculated contact area-to-volume ratio was 42.8 cm<sup>-1</sup>.



Fig. 3 Comparative illustration of contacting modes between the gas and liquid phases in the two types of microreactors and the batch system.

#### 2. Photosensitized oxygenations in various reaction systems

The first choice we made for the photosensitized oxygenation is the reaction of (-)-citronellol which is an important synthetic transformation industrially, and the reaction is used for the bulk production of a fragrance, rose oxide.47 In the experiment we used a 16 W white LED light source (FAWOO-Tech., Korea, LH16-AFE39S-White) instead of classical halogen or filament lamps. The LED lamp is small in size, efficient and "cold" such that it can be kept in close contact with the microreactors without any overheating hazard.48 Summarized in Table 1 are the results obtained from 4 different types of reactors: two dual-channel microreactors with solvent resistant coating,49 a mono-channel microreactor for segmented flow reaction of O<sub>2</sub> and the solution, and a batch system with 20 mL solvent in 50 mL round bottom flask. The reactions in the dual-channel conducted without pretreated  $O_2$  bubbling are completed in 3 min (entry 1) while it took 3 hours for the reactions to complete in the batch systems (entry 3).

**Table 1** Photosensitized oxygenation of (-)-citronellol in 3 different types of microreactors, compared to the batch system<sup>*a*</sup>



<sup>a</sup> Standard reaction conditions: 1 mol% methylene blue, 16 W LED lamp, 5 °C. <sup>b</sup> Yield and ratio were recorded with <sup>1</sup>H NMR analysis using an internal standard after NaBH<sub>4</sub> treatment of crude mixture. <sup>c</sup> Concentration of (–)-citronellol in reactors. <sup>d</sup> Segmented flow reaction of O<sub>2</sub> and reagent solution pretreated with O<sub>2</sub> bubbling for 20 min. <sup>e</sup> 20 mL solution (7 mmol scale) pretreated with O<sub>2</sub> bubbling for 20 min in 50 mL round bottom flask. <sup>f</sup> The dual-channel microreactor for feasible scale-up process with 285 μL reaction volume.

The batch system with the lowest phase contact area-to-volume ratio shows a very slow reaction rate even with the supply of the solution pre-saturated with O2. The mono-channel has an inherent problem of controlling the heterogeneous gas and solution. Increasing the injection rate of O<sub>2</sub> in the mono-channel also caused the acceleration of solution droplets, thereby it resulted in poor conversions with shorter retention times. However, the injection rates and flow rates of the solution and O<sub>2</sub> could be separately controlled in the dual-channel, which forced rapid diffusion of O<sub>2</sub> into the solution through the membrane with the highest phase contact area-to-volume ratio. In the mono-channel and batch system, poor supply of gaseous O<sub>2</sub> into the organic solution lowered the generation rate of <sup>1</sup>O<sub>2</sub> by activated photosensitizer with short lifetime. More importantly, high concentration results clearly show large differences in the throughput (entries 4-6). The dual-channel completed the reaction in exactly the same time as for the low concentration case even though the reactant concentration is increased by a factor of 3.5 (entry 4), while the reaction time required for a similar yield is almost tripled when the reactant concentration is increased by a factor of 3.5 from 0.1 M (entry 3) to 0.35 M when the batch is used (entry 6). A comparison was made between the mono-channel and the dualchannel in terms of the product obtainable in one day for the same reactor volume of 38.9 µL. The dual-channels in entries 1 and 4 could generate 1.81 mmol and 6.34 mmol, respectively, while the mono-channels in entries 2 and 5 only gave 0.35 mmol and 0.59 mmol.<sup>50</sup> The results showed that the dual-channel can generate more than 10 times the amount producible from the monochannel for the case of 0.35 M concentration, while it is more than 5 times in the case of lower reactant concentration of 0.1 M. In this comparison, the volume occupied by O2 was not considered in the calculation for the mono-channel. The volume of O<sub>2</sub> in the 0.35 M solution was such that the reactor volume corresponding to the liquid reactant was less than 20% of the original reactor volume, while the liquid volume in the 0.1 M concentration was a little bit over 40% of the reactor volume.<sup>51</sup> In order to test the feasibility for scale-up, the reaction volume of the dual-channel microreactor was increased to 285 µL (entry 7), which is 7.3 times higher than the volume of the dual-channel microreactor in entries 1 and 4 with 38.9 µL reaction volume. Although the yield in entry 7 was slightly decreased from the original dual-channel, the obtainable product from the 285 µL volume was 45.49 mmol in one day.<sup>52</sup> The productivity was 2.6 times that of the batch system which can generate 17.6 mmol with 50 mL volume flask during the same time (entry 6).53 These results clearly demonstrate the superiority of the dual-channel over the mono-channel and batch system. The highthroughput system in a solvent-saving manner would be a strong incentive for practical applications of the dual-channel for photochemical syntheses in gas-liquid binary phases.

### 3. The effect of reaction parameters in the dual-channel (photosensitized oxygenation of $\alpha$ -terpinene into ascaridole)

To investigate the effect of reaction parameters in the dualchannel (38.9  $\mu$ L reaction volume), photosensitized oxygenation of  $\alpha$ -terpinene to ascaridole was carried out under various reaction conditions: O<sub>2</sub> flow rate, reaction temperature, concentration of photosensitizer (Fig. 4).<sup>38-40,54</sup> The amount of photosensitizer (PS) less than 1 mol% or the temperature higher



	Dual	5 °C	105 $\mu$ L/min.	1 mol%	91% (180 sec)
-	Dual	5 ℃	85 <i>μ</i> L/min.	1 mol%	91% (300 sec)
<del>~~</del>	Dual	5 ℃	60 μL/min.	1 mol%	89% (360 sec)
-*-	Dual	30 ℃	105 μL/min.	1 mol%	91% (210 sec)
-	Dual	5 °C	105 μL/min.	0.7 mol%	91% (360 sec)
-	Batch	5 °C	O <sub>2</sub> Bubbling	1 mol%	82% (180 min)

**Fig. 4** Photosensitized oxygenation of  $\alpha$ -terpinene into ascaridole in the dual-channel (0.35 M substrate, 38.9  $\mu$ L reactor volume) and batch system. The conversion was recorded by GC/MS analysis, yields were measured by <sup>1</sup>H NMR analysis. [a] Photosensitizer (methylene blue). [b] Time required for reaction completion. [c] 7 mol scale in 50 mL round bottom flask.

than 5 °C resulted in unsatisfactory performance, the first due to low efficiency in absorbing photons and the second due to shortened lifetime of the  ${}^{1}O_{2}$  at elevated temperature respectively.<sup>9</sup> The optimized flow rate of  $O_{2}$  was 105 µL min<sup>-1</sup> for 0.35 M concentration with a reaction time of 3 min. N<sub>2</sub> used in place of  $O_{2}$  gave no oxygenation.  $O_{2}$  injection rates of 60 and 85 µL min<sup>-1</sup> were found to slow down the reaction compared with 105 µL min<sup>-1</sup>.  $O_{2}$  injection rate of over 105 µL min<sup>-1</sup> caused bubble formation due to supply in excess of the solubility limit, and the bubbles disturbed the liquid flow in the reaction system. The batch system tested for comparison showed poor reaction yield even after a prolonged reaction time as shown in the results in Table 1. The trial of the condensed reaction with the concentration in excess of 0.35 M was not successful due to the low solubility of methylene blue in the concentration range.

### 4. The photosensitized oxygenation of two allylic alcohols in the dual-channel

The photosensitized oxygenation of two allylic alcohols was taken as an additional model reaction to ascertain the efficiency in the reaction and long term stability of the dual-channel system (Scheme 1).<sup>55</sup> The product is an allyl hydroperoxide alcohol which is used for the synthesis of artemisinin derived antimalarial 1,2,4-trioxanes.<sup>56</sup> Even with continuous running for 4 days, the



Scheme 1 Photosensitized oxygenation of allylic alcohols.

dual-channel successfully retained the consistent reaction efficiency with no degradation and no channel leaking problem. Note that the dual-channel has a high illuminated surface to volume ratio, and efficient  $O_2$  supply as well as highly transparent solvent resistant coating. These factors led to the completion of the reactions in a short retention time of only 122 seconds.

### Conclusion

A phase contact enhanced microreactor most suitable for photosensitized oxygenation is presented that can compete with the conventional batch reactor in practical applications. The dualchannel, in which the surface of the liquid channel is shielded from the ill effects of liquid reactants and solvents by a cured PVSZ, allows efficient supply of  $O_2$  to the liquid and full exposure to light. As a result, the reactions in high concentration are completed in minutes rather than hours that it takes to complete in a batch reactor, the dual-channel with only 285 µL volume can provide 2.6 times productivity from the batch system with 50 mL volume. As such, it would be invaluable not only for the photosensitized oxygenation but also for other gas–liquid organic reactions.

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- 49 An acetonitrile solution (3 mL) of (-)-citronellol (3.5 mmol) was loaded into a gas-tight Hamilton syringe and delivered into the upper channel of the dual-channel. In the same manner, a solution of methylene blue (0.035 mmol) dissolved in acetonitrile (7 mL) and O<sub>2</sub> were delivered into the upper and lower channel of the microreactor respectively. With a variation in flow rates of the two solutions and O<sub>2</sub>, the reaction solutions were collected in a brown glass vial, and immediately analyzed with GC/MS and <sup>1</sup>H NMR instrument.
- 50 Entry 1 = 0.1 mmol/1 mL × 38.9  $\mu$ L × 24 × 60 min/3 min × 0.97 (concentration of (–)-citronellol × reactor volume × running time/ retention time × yield); entry 2 = 0.1 mmol/1 mL × 38.9  $\mu$ L × 24 × 60 min/15 min × 0.95; entry 4 = 0.35 mmol/1 mL × 38.9  $\mu$ L × 24 × 60 min/3 min × 0.97; entry 5 = 0.35 mmol/1 mL × 38.9  $\mu$ L × 24 × 60 min/3 min × 0.94.
- 51 Detailed calculation is described in the ESI, Fig. 6S<sup>+</sup>.
- 52 Entry 7 = 0.35 mmol/1 mL × 285  $\mu$ L × 24 × 60 min/3 min × 0.95 (concentration of (–)-citronellol × reactor volume × running time/ retention time × yield).
- 53 Entry 3 = 0.1 mmol/1 mL × 20 mL × 24 × 60 min/180 min × 0.92; entry 6 = 0.35 mmol/1 mL × 20 mL × 24 × 60 min/510 min × 0.89.
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