Aerobic copper/TEMPO-catalyzed oxidation of primary alcohols to aldehydes using a microbubble strategy to increase gas concentration in liquid phase reactions
An efficient method for the synthesis of aldehydes was achieved by using air-microbubble techniques in aerobic copper/TEMPO-catalyzed oxidation of primary alcohols. Use of air-microbubbles to improve gas absorption into liquid phase is proven to be highly beneficial for gas/liquid phase reactions.

Gas/liquid phase reactions are fundamental reaction types in material syntheses, where a number of gas molecules are employed, for example, O₂, O₃, H₂, NH₃, CO₂, F₂, Cl₂, CH₃=CH₂ and CH≡CH etc. The concentration of gas dissolved in liquid phase largely affects reactive properties, which inherently depends on both pressure and temperature. Although high concentrations of gas dissolved in solvent can be achieved when the reaction is performed under high partial pressure at low temperature, in general these conditions result in decreasing reactivity. If high concentrations of dissolved gas can be achieved at ordinary temperatures and pressures, the utility of gas/liquid phase reactions is significantly improved.

Recently, microbubbles have attracted attention in numerous area of study due to its characteristic features. For example, microbubbles exhibit excellent gas-dissolution abilities because of larger gas/liquid interfacial areas, in addition, a longer stagnation compared to conventional larger bubbles is monitored owing to its small buoyancy. These phenomena cause microbubbles gradually to decrease in size, with eventually disappearance into the liquid phase.

As detailed in this communication, we propose a novel experimental methodology for gas/liquid phase reactions using microbubbles (Figure 1, right), instead of conventional methods (Figure 1, left) involving vigorous stirring and/or high pressure to increase interfacial surface between gas and liquid.

Prior to starting this project, a special microbubble generator, which is resistant to corrosion with acid-, base-, and organic solvent, was required. Furthermore, a small microbubble generator was desired for an academic laboratory setting, though larger generators (pumping rate >10 L/min) have been already commercially available. In cooperation with Asupu Company Limited, stainless steel-components from a small generator were replaced with Teflon® (MA2-FS, pumping rate 120-150 mL/min, Figure 2, upper right).

Performance evaluations measuring dissolved oxygen levels in distilled water showed that the Teflon®-microbubble generator rapidly supersaturated with respect to oxygen at an air-flow rate of 3 mL/min without stirring. The solution of water saturated with oxygen appeared cloudy (Figure 2, lower right). After stopping the air supply for 20 minutes, it remained oversaturated for 40 minutes (Figure 2). On the other hand, air bubbling at an air-flow of rate 3 mL/min using a conventional gas dispersion tube with porous fritted glass tip resulted in low saturation of oxygen in solution after 60 minutes with vigorous stirring. This result is similar to that without air bubbling. These outcomes indicate that a Teflon®-microbubble generator is an efficient instrument to dissolve oxygen into distilled water.

Encouraged by these basic results, we started to investigate novel microbubble strategies for gas/liquid phase reactions. The aerobic copper/2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO)-catalyzed oxidation of primary alcohols (20 mmol) to aldehydes developed by the Sheldon group was chosen as a model reaction Table 1. 2,3,4 First attempts under Sheldon’s condition with microbubbling (air-flow rate: 3 mL/min) afforded the desired benzaldehyde (2a) in 81% conversion without formation of carboxylic acid (3a) (entry 1). Catalytic activity was improved by the addition of 2,2-bipyridine (4b) and MeONa (5b), in which conversion to the aldehyde...
increased to 93% at 30 °C (entries 1-4). Air was replaced by O₂-microbubbles in the oxidation of alcohol 1a, a similar result was observed (entry 4 vs. 5). On the other hand, poor conversion of alcohol 1a to aldehyde 2a (30%) was observed under open conditions after 2 hours of vigorous stirring (entry 6). In addition, air bubbling (air-flow rate: 3 mL/min) using a conventional gas dispersion tube fitted with a porous fritted glass tip resulted in 48% conversion (entry 7). Even when air-flow rate was up to 15 mL/min, conversion was lower than microbubbling procedure (entry 4 vs. 8). Condensers must be attached to the reaction vessel when reactions are performed at high gas-flow rates such as 15 mL/min, whereas microbubbling procedures do not require similar engineering controls.

The microbubble oxidation system displayed a preference for primary versus secondary alcohols (10 mmol each) according to intermolecular competition experiments (Scheme 1). Corresponding benzaldehyde (2a) and acetophenone (7) were obtained in 99% and 3% conversion, respectively, after 30 minutes under optimized air-microbubbling conditions. As expected, poor conversion to the aldehyde 2a was observed using standard air-bubbling and stirring conditions. Therefore, primary alcohols were selectively oxidized in the presence of secondary alcohols in the microbubble oxidation system with excellent conversion.

We next examined microbubble oxidation using aliphatic alcohols as substrates. The aliphatic alcohol geraniol (8) was an excellent substrate giving geranial (9) in 99% conversion with high regioselectivity ([E] : [Z] = 99 : 1) with a short reaction time (1 h). Standard work-up and reduced-pressure distillation afforded geranial (9) in 84% yield and 97% purity as determined by GC analysis. In contrast, oxidation with conventional air-bubbling techniques resulted in only 74% conversion (Scheme 2). The cyclic monoterpene allyl alcohol myrtenol (10) was also oxidized to myrtanal (9) in 99% conversion under the same microbubble conditions (Scheme 2). These exceptional results show the broad potential of our microbubble strategy in aerobic oxidation of primary alcohols.

The scope of this class of microbubble oxidation was examined with a series of benzyl alcohol derivatives 1 under the optimized conditions and the results are summarized in Table 2. Aromatic aldehydes 2 were obtained in good to excellent yields within 4 hours at 30 °C. Overoxidation from aldehyde to carboxylic acid was not observed.

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Aerobic copper/TEMPO-catalyzed oxidation of unmodified aliphatic primary alcohols has great utility in organic synthesis due to their low reactivity, 5 oxidation of 1-octanol carried out by both microbubbling and conventional air-bubbling procedure furnished 1-octanal in almost same conversion (72% and 74%, respectively) after prolonged reaction time (12 h). 6 This is an undesirable result for us, but it suggests that air- and/or O₂-microbubble techniques do not accelerate the rate-determining step but have more effect on the regeneration steps of TEMPO from TEMPOH. The Sheldon group has proposed the mechanism of aerobic copper/TEMPO-oxidations as shown in Scheme 3. 7 Hydrogen abstraction from the α-carbon
atom by TEMPO (C to D in Scheme 3) is the rate-determining step (RDS); therefore, oxidation of an unmodified aliphatic primary alcohol is expected to be much slower than that of benzylic and allylic alcohols. Consequently, the highly oxygenated water present due to air-microbubbling has almost no effect on the rate-determining step. However, it probably accelerates regeneration of TEMPO from TEMPOH during the proposed catalytic cycle in Scheme 3.

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Notes and references

5 Typical procedure for aerobic copper/TEMPO-catalyzed oxidation of primary alcohols 1 to aldehydes 2 using microbubble strategy: The oxidation was carried out in a 50 mL vial equipped with a microbubble generator without additional stirring. The alcohol 1 (20 mmol) was dissolved in CH₂CN/H₂O (2:1, 30 mL), then warmed to 30 °C. To the solution NaOMe (2b, 81 mg, 1.5 mmol) and CuBr₂ (215 mg, 1.5 mmol) were added, resulting in a light blue suspension. After addition of 2,2-bipyridine (4b, 234 mg, 1.5 mmol) to the suspension, colour was changed to blue-green. To the mixture TEMPO (315 mg, 2.0 mmol) was added, leading to a red-brown mixture. Air-microbubble was introduced into the reaction mixture by microbubble generator (MA2-FS) at air-flow rate 3 mL/min. The red-brown mixture gradually turned dark-green. Samples (0.5 mL which were extracted with Et₂O of the reaction mixture were taken out to monitor the reaction by GC analysis. The products 2 were determined by comparison with the commercially available aldehydes.
6 Acetophenone (11) was obtained in 13% conversion after 2 h using microbubble system in oxidation of the secondary alcohol (air-flow rate 3 mL/min).
7 These reactions were carried out using CuBr₂ (10 mol%), ligand 4b (10 mol%), TEMPO (12.5 mol%) and base 5b (10 mol%) in CH₂CN/H₂O (2:1) for 12 h.

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8 Local “hot spot” theory is probably another possibility, however; positive effect was not reported in study of decomposition of perfluorooctanoic acid. M. Takahashi, K. Chiba and P. Li, *J. Phys. Chem. B*, 2007, **111**, 1343.

9 Preliminary results were discussed at the 2010 summer symposium of the Japanese Society for Process Chemistry, 1P-32 on July 15, 2010.