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COMMUNICATION

Aerobic copper/TEMPO-catalyzed oxidation of primary alcohols to aldehydes using a microbubble strategy to increase gas concentration in liquid phase reactions[†]

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An efficient method for the synthesis of aldehydes was achieved by using air-microbubble techniques in aerobic copper/TEMPOcatalyzed 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, O_2 , O_3 , H_2 , NH_3 , CO_2 , F_2 , Cl_2 , CH_2 — CH_2 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 areas of study due to their characteristic features.¹ 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 their small buoyancy. These phenomena cause microbubbles gradually to decrease in size, with eventual disappearance into the liquid phase.

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

Prior to starting this project, a special microbubble generator, which is resistant to corrosion with acids, bases, and organic solvents, was required. Furthermore, a small microbubble generator was desired for an academic laboratory setting, though larger generators (pumping rate > 10 L min⁻¹)



Fig. 1 Gas/liquid phase reactions.

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⁻¹, Fig. 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⁻¹ without stirring. The solution of water saturated with oxygen appeared cloudy (Fig. 2, lower right). After stopping the air supply for 20 minutes, it remained oversaturated for 40 minutes (Fig. 2). On the other hand, air bubbling at an air-flow of rate 3 mL min⁻¹ using a conventional gas dispersion tube with a 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.



Fig. 2 The microbubble generator and degree of oxygenation in distilled water.

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 Table 1
 Aerobic copper/TEMPO-catalyzed oxidation of benzyl alcohol (1a) to benzaldehyde (2a)



Ligand: 1,10-phenanthroline (**4a**), 2,2'-bipyridine (**4b**) Base: *t*-BuOK (**5a**), MeONa (**5b**)

Entry	Ligand	Base	Bubbling (mL min ^{-1})	Conversion ^a (%)
1	4a	5a	Microbubbling (3)	81
2	4a	5b	Microbubbling (3)	87
3	4b	5a	Microbubbling (3)	90
4	4b	5b	Microbubbling (3)	93
5	4b	5b	Microbubbling $(3)^{b}$	94
6	4b	5b	Open $(0)^c$	30
7	4b	5b	Bubbling $(3)^c$	48
8	4b	5b	Bubbling $(15)^c$	84

^{*a*} Determined by GC-analyses (column: GL Sciences TC-17). ^{*b*} O₂-microbubbles were used instead of air-microbubbles. ^{*c*} These reactions were carried out with vigorous stirring.

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 1.²⁻⁴ First attempts under Sheldon's condition with microbubbling (air-flow rate: 3 mL min⁻¹) afforded the desired benzaldehyde (2a) in 81% conversion without formation of carboxylic acid (3a) (entry 1). The 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 O_2 -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⁻¹) using a conventional gas dispersion tube fitted with a porous fritted glass tip resulted in 48% conversion (entry 7). Even when the air-flow rate was up to 15 mL min^{-1} , conversion was lower than that of the microbubbling procedure (entry 4 vs. 8). Condensers must be attached to the reaction vessel when reactions are performed at high gasflow rates such as 15 mL min⁻¹, whereas microbubbling procedures do not require similar engineering controls.

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 $^{\circ}$ C. Overoxidation from aldehyde to carboxylic acid was not observed.

The microbubble oxidation system displayed a preference for primary *versus* secondary alcohols (10 mmol each) according to intermolecular competition experiments (Scheme 1).⁵ 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

НО	CuBr ₂ , 2 TEMPC Air-mic	,2'-bipyridyl D, MeONa O srobubble	\sim	
R 1	CH ₃ CN/H ₂	O (2:1), 30 °C	2 R	
Entry R	Time/h	Conversion ^{<i>a</i>} (%)	Product	
1 H	2	93	2a	
2 <i>i</i> -Pr	2	98	2b	
3 MeO	4	92	2c	
4 HO	4	73	2d	
5 NO ₂	4	85	2e	
5 Cl	4	89	2f	
7 Br	4	91	2g	

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





conversion to the aldehyde **2a** was observed using standard airbubbling 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 allylic 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 73% conversion (Scheme 2). The cyclic monoterpene allyl alcohol myrtenol (10) was also oxidized to myrtenal (11) in 99% conversion under the same microbubble conditions (Scheme 2). These exceptional results show the broad potential



Scheme 2 Aerobic copper/TEMPO-catalyzed oxidation of aliphatic alcohols with the microbubble procedure.



Scheme 3 Sheldon's proposed oxidation mechanism.



Scheme 4 Koskinen's proposed binuclear copper(II) complex.

of our microbubble strategy in aerobic oxidation of primary alcohols.

Aerobic copper/TEMPO-catalyzed oxidation of unmodified aliphatic primary alcohols has great utility in organic synthesis due to their low reactivity,⁴ oxidation of 1-octanol carried out by both microbubbling and conventional air-bubbling procedure furnished 1-octanal in almost the same conversion (72% and 74%, respectively) after a 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 3.² Hydrogen abstraction from the α -carbon atom by TEMPO (C to D in Scheme 3) is the ratedetermining 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.

In addition, the Koskinen group suggested a different reaction species, a binuclear copper(π) complex **G**, which is derived from a monomeric species **F** in the presence of

molecular oxygen (Scheme 4).^{4c} In both Schemes 3 and 4 molecular oxygen (O_2) is the key to oxidation to form reactive species, hence high concentrations of dissolved O_2 should significantly affect the reaction efficiency.

In summary, we have developed a novel experimental methodology by using microbubbles for gas/liquid phase reactions in organic synthesis. The exact role of microbubbles remains unclear,⁷ however, our strategy showed an improved efficiency on the aerobic copper/TEMPO-catalyzed oxidation of primary alcohols to aldehydes. Further studies focusing on the full scope of this unique microbubble system are currently under investigation and will be reported in due course.⁸ In addition, since this new microbubble-system could be potentially used for any gas/liquid phase reactions at least in principle, we believe that this study is an important contribution to all gas/liquid phase reactions including not only the present aerobic oxidation but also hydrogenation, ozonation, reductive amination, halogenation, *etc.* under environmentally-friendly protocols and are currently under investigation.

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