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

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

Nobuyuki Mase,* Tomoya Mizumori and Yuji Tatemoto

An efficient method for the synthesis of aldehydes was achieved by using air-microbubble techniques in aerobic copper/TEMPO-
10 **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,
15 for example, O_2, O_3, H_2, NH_3, CO_2, F_2, Cl_2, $CH_2=CH_2$ and $CH\equiv CH$ *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
20 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.
25 Recently, microbubbles have attracted attention in numerous area of study due to its 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 its
30 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
35 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.
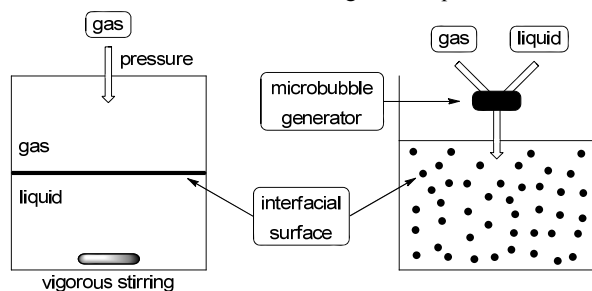

Fig. 1 Gas/liquid phase reactions

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan. Fax: +81-53-478-1196; Tel: +81-53-478-1196; E-mail: tnmase@ipc.shizuoka.ac.jp
† Electronic Supplementary Information (ESI) available: Experimental procedure. See http://dx.doi.org/10.1039/b000000x/

40 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
45 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
50 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
55 (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®-
60 microbubble generator is an efficient instrument to dissolve oxygen into distilled water.
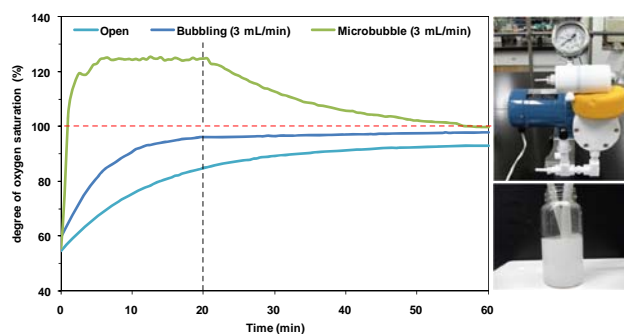

Fig. 2 Microbubble generator and degree of oxygenation in distilled water

65 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
70 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
75 (**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) 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.

Table 1. Aerobic copper/TEMPO-catalyzed oxidation of benzyl alcohol (**1a**) to benzaldehyde (**2a**)[a]
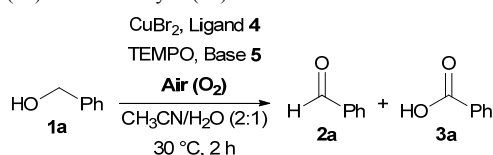
Ligand: 1,10-phenanthroline (**4a**), 2,2'-bipyridine (**4b**)

Base: t-BuOK (**5a**), MeONa (**5b**)

Entry	Ligand	Base	Bubbling (mL/min)	Conversion (%)[b]
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)[c]	94
6	**4b**	**5b**	open (0)[d]	30
7	**4b**	**5b**	bubbling (3)[d]	48
8	**4b**	**5b**	bubbling (15)[d]	84

[a] Conditions: See Notes and references. [b] Determined by GC-analyses (column: GL Sciences TC-17). [c] O_2-microbubble was used instead of air-microbubble. [d] These reactions were carried out with vigorous stirring.

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.[5] 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.

Table 2. Aerobic copper/TEMPO-catalysed oxidation of alcohols **1** to aldehydes **2**[a]
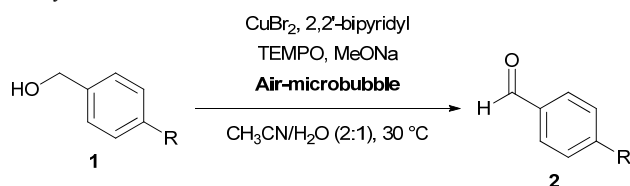
| Entry	R	Time (h)	Conversion (%)[b]	Product
1	H	2	93	**2a**
2	i-Pr	2	98	**2b**
3	MeO	4	92	**2c**
4	HO	4	73	**2d**
5	NO$_2$	4	85	**2e**
6	Cl	4	89	**2f**
7	Br	4	91	**2g**

[a] Conditions: See Notes and references. [b] Determined by GC-analyses (column: GL Sciences TC-17).

The microbubble oxidation system displayed a preference for primary versus secondary alcohols (10 mmol each) according to intermolecular competition experiments (Scheme 1).[6] 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.
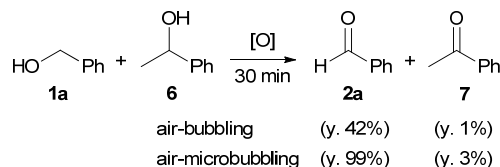

Scheme 1. Competition experiments

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 74% conversion (Scheme 2). The cyclic monoterpene allyl alcohol myrtenol (**10**) was also oxidized to myrtenal (**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.
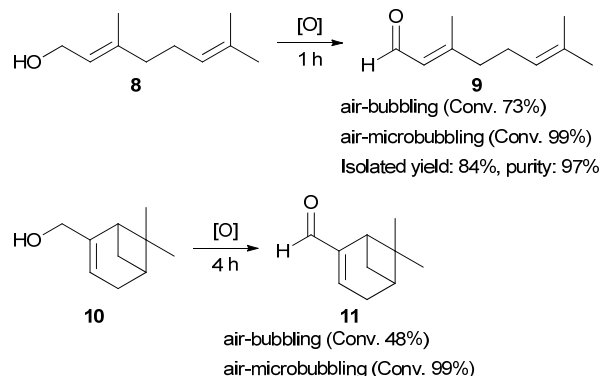
Scheme 2. Aerobic copper/TEMPO-catalyzed oxidation of aliphatic alcohol with microbubble procedure

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 same conversion (72% and 74%, respectively) after prolonged reaction time (12 h).[7] This is an undesirable result for us, but it suggests that air- and/or O_2-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 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.
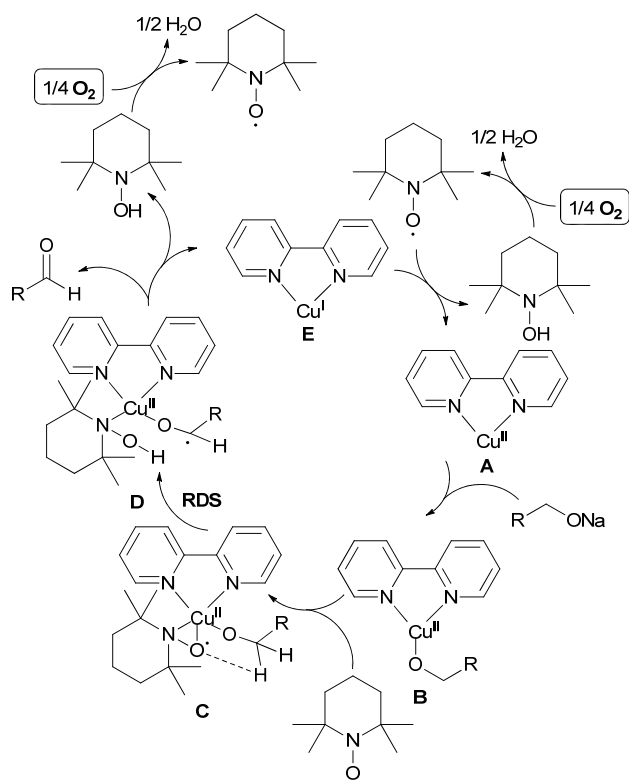
Scheme 3 Sheldon's proposed oxidation mechanism

In addition, the Koskinen group suggested a different reaction species, a binuclear copper(II) 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 a key to oxidizing to form reactive species, hence high concentrations of dissolved O_2 should significantly affect the reaction efficiency.
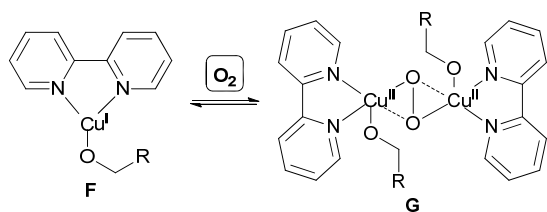
Scheme 4 Koskinen's proposed a binuclear copper (II) complex

In summary, we have developed novel experimental methodology by using microbubbles for gas/liquid phase reactions in organic synthesis. The exact role of microbubbles remains unclear,[8] however; our strategy showed 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.[9] In addition, since this new microbubble-system could potentially use 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 present aerobic oxidation but also hydrogenation, ozonation, reductive amination, halogenation, *etc*. under environmentally-friendly protocols and are currently under investigation.

Acknowledgements

Notes and references

1 (a) E. Stride and M. Edirisinghe, *Soft Matter*, 2008, **4**, 2350-2359. (b) Y.-z. Hu, J.-a. Zhu, Y.-g. Jiang and B. Hu, *Advances in Therapy*, 2009, **26**, 425-434. (c) I. Lentacker, S. S. C. De and N. N. Sanders, *Soft Matter*, 2009, **5**, 2161-2170.

2 P. Gamez, I. W. C. E. Arends, R. A. Sheldon and J. Reedijk, *Adv. Synth. Catal.*, 2004, **346**, 805.

3 Reviews: (a) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal.*, 2004, **346**, 1051. (b) R. Ciriminna and M. Pagliaro, *Org. Process Res. Dev.*, 2009, **14**, 245.

4 Recent aerobic TEMPO-catalyzed oxidation of primary alcohols to aldehydes: (a) W. Yin, C. Chu, Q. Lu, J. Tao, X. Liang and R. Liu, *Adv. Synth. Catal.*, 2010, **352**, 113. (b) C.-X. Miao, L.-N. He, J.-L. Wang and F. Wu, *J. Org. Chem.*, 2010, **75**, 257. (c) E. T. T. Kumpulainen and A. M. P. Koskinen, *Chem. Eur. J.*, 2009, **15**, 10901. (d) P. J. Figiel, A. Sibaouih, J. U. Ahmad, M. Nieger, M. T. Räisänen, M. Leskelä and T. Repo, *Adv. Synth. Catal.*, 2009, **351**, 2625. (e) G. Yang, W. Zhu, P. Zhang, H. Xue, W. Wang, J. Tian and M. Song, *Adv. Synth. Catal.*, 2008, **350**, 542. (f) X. Wang, R. Liu, Y. Jin and X. Liang, *Chem. Eur. J.*, 2008, **14**, 2679-2685. (g) N. Jiang and A. J. Ragauskas, *ChemSusChem*, 2008, **1**, 823. (h) Y. Xie, W. Mo, D. Xu, Z. Shen, N. Sun, B. Hu and X. Hu, *J. Org. Chem.*, 2007, **72**, 4288-4291. (i) S. Mannam, S. K. Alamsetti and G. Sekar, *Adv. Synth. Catal.*, 2007, **349**, 2253-2258. (j) B. Karimi, A. Biglari, J. H. Clark and V. Budarin, *Angew. Chem., Int. Ed.*, 2007, **46**, 7210. (k) C. W. Y. Chung and P. H. Toy, *J. Comb. Chem.*, 2007, **9**, 115-120.

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 CH_3CN/H_2O (2 : 1, 30 mL), then warmed to 30 °C. To the solution NaOMe (**5b**, 81 mg, 1.5 mmol) and $CuBr_2$ (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 (313 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 Et_2O) 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 $CuBr_2$ (10 mol%), ligand **4b** (10 mol%), TEMPO (12.5 mol%) and base **5b** (10 mol%) in CH_3CN/H_2O (2:1) for 12 h.

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.

245

250