

Electronic Supplementary Information

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

Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan

tnmase@ipc.shizuoka.ac.jp

General

Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates (Merck 60 F₂₅₄) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Microbubble generator was used ASPU Co. Ltd. MA2FS (pumping rate 120-150 mL/min). Flash column chromatography was performed using KANTO silica gel 60N (particle size 63-210 μm). ¹H NMR spectra were recorded on JEOL JNM-AL spectrometer at ambient temperature. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants *J* are given in Hz. The spectra were recorded in CDCl₃ as solvent at ambient temperature, TMS served as internal standard ($\delta = 0$ ppm) for ¹H NMR. GC was carried out using SHIMADZU GC-2010 with capillary column GL Sciences TC-17. Oxidation reactions of the primary alcohol were carried out using Microbubble generator (MA2-FS, pumping rate 120-150 mL/min, Figure 2, upper right), which was custom-ordered in cooperation with Asupu Company Limited. All stainless steel-components were replaced with Teflon[®].

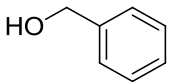
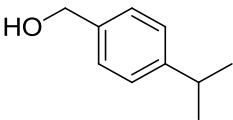
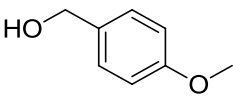
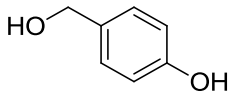
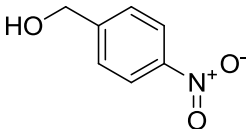
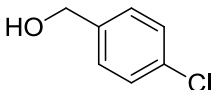
Organic substrates

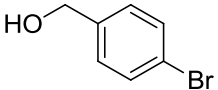
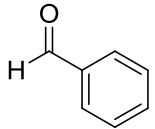
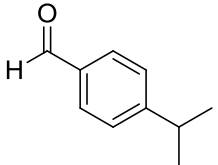
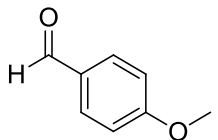
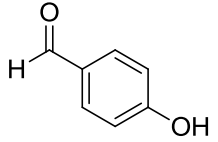
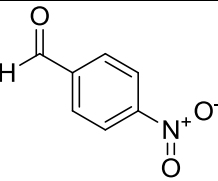
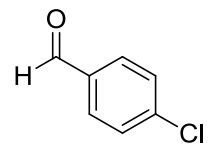
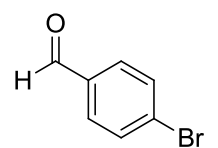
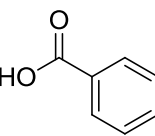
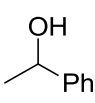
benzyl alcohol (**1a**, 100-51-6), 4-isopropylbenzyl alcohol (**1b**, 536-60-7), 4-methoxybenzyl alcohol (**1c**, 105-13-5), 4-hydroxybenzyl alcohol (**1d**, 623-05-2), 4-nitrobenzyl alcohol (**1e**, 619-73-8), 4-chlorobenzyl alcohol (**1f**, 873-76-7), 4-bromobenzyl alcohol (**1g**, 873-75-6), 1,10-phenanthroline (**4a**, 66-71-7), 2,2'-bipyridine (**4b**, 366-18-7), potassium *tert*-butoxide (**5a**, 865-47-4), sodium methoxide (**5b**, 124-41-4), copper bromide (II) (7789-45-9), 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO, 2564-83-2), acetonitrile (75-05-8), distilled water, 1-phenylethanol (**6**, 98-85-1), geraniol (**8**, 106-24-1), myrtenol (**10**, *rac*-515-00-4, *1R*-19894-97-4, *1S*-6712-78-3) and 1-octanol (111-87-5) were all commercially available and were used without any purification. benzaldehyde (**2a**, 100-52-7), 4-isopropylbenzaldehyde (**2b**, 122-03-2), 4-methoxybenzaldehyde (**2c**, 123-11-5), 4-hydroxybenzaldehyde (**2d**, 123-08-0), 4-nitrobenzaldehyde (**2e**, 555-16-8), 4-chlorobenzaldehyde (**2f**, 104-88-1), 4-bromobenzaldehyde (**2g**, 1122-91-4), benzoic acid (**3a**, 65-85-0), acetophenone (**7**, 98-86-2), citral (**9**, (*E*, *Z*)-5392-40-5, (*E*)-141-27-5 (*Z*)-106-26-3), myrtenal (**11**, *rac*-564-94-3, *1S*-23727-16-4, *1R*-18486-69-6) and octanal (124-13-0) were all commercially available and were used as an authentic sample without any purification.


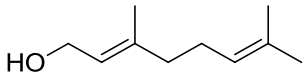
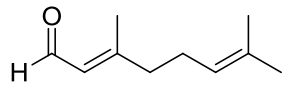
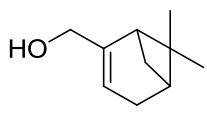
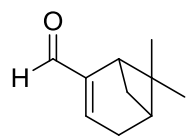
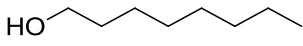
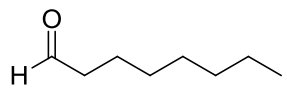
Typical procedure for aerobic copper/TEMPO-catalyzed oxidation of primary alcohols to aldehydes using microbubble strategy

The oxidation was carried out in a 50 mL vial equipped with a microbubble generator. The alcohol (20 mmol) was dissolved in CH₃CN/H₂O (2:1, 30 mL), then warmed to 30 °C. To the solution NaOMe (**5b**, 81.0 mg, 1.5 mmol) and CuBr₂ (215.2 mg, 1.5 mmol) were added, resulting in a light blue suspension. After addition of 2,2-bipyridine (**4b**, 234.4 mg, 1.5 mmol) to the suspension, color was changed to blue-green. To the mixture TEMPO (312.5 mg, 2.0 mmol) was added, leading to a red-brown mixture. Air-Microbubble was introduced into the reaction mixture by microbubble generator at air-flow rate 3 mL/min. The red-brown mixture gradually turned dark-green. Sampling was carried out as follows: 1 mL sample of the reaction mixture was taken out and extracted with Et₂O (4 x 1 mL), washed with brine (1 mL). The combined organic extracts were filtrated through silica gel plug (SiO₂: 1 g, Na₂SO₄: 1 g) to give a sample, which were taken out to monitor the reaction by GC. The products were determined by comparison with the commercially available aldehydes as an external standard.

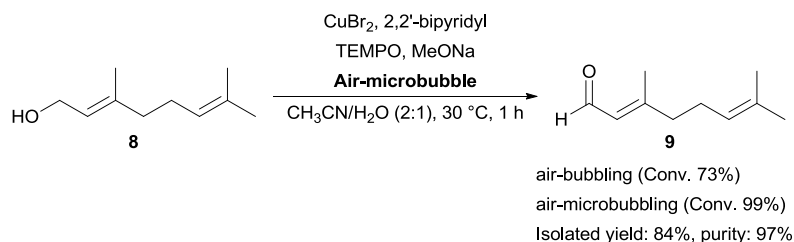
GC (TC-17, He = 0.80 MPa, H₂ = 0.5 MPa, Air = 0.5 MPa)

No.	Structure	T _{inj} (°C)	T _{det} (°C)	T _i (°C, min)	T _f (°C, min)	Rate (°C/min)	GC: t _R (min)
1a		250	250	100, 5	200, 0	10	9.183
1b		250	250	100, 0	250, 0	10	9.150
1c		260	260	100, 0	250, 5	5	14.647
1d		260	260	100, 5	250, 0	5	21.857
1e		250	250	100, 0	250, 10	10	14.120
1f		250	250	100, 0	250, 5	10	9.007

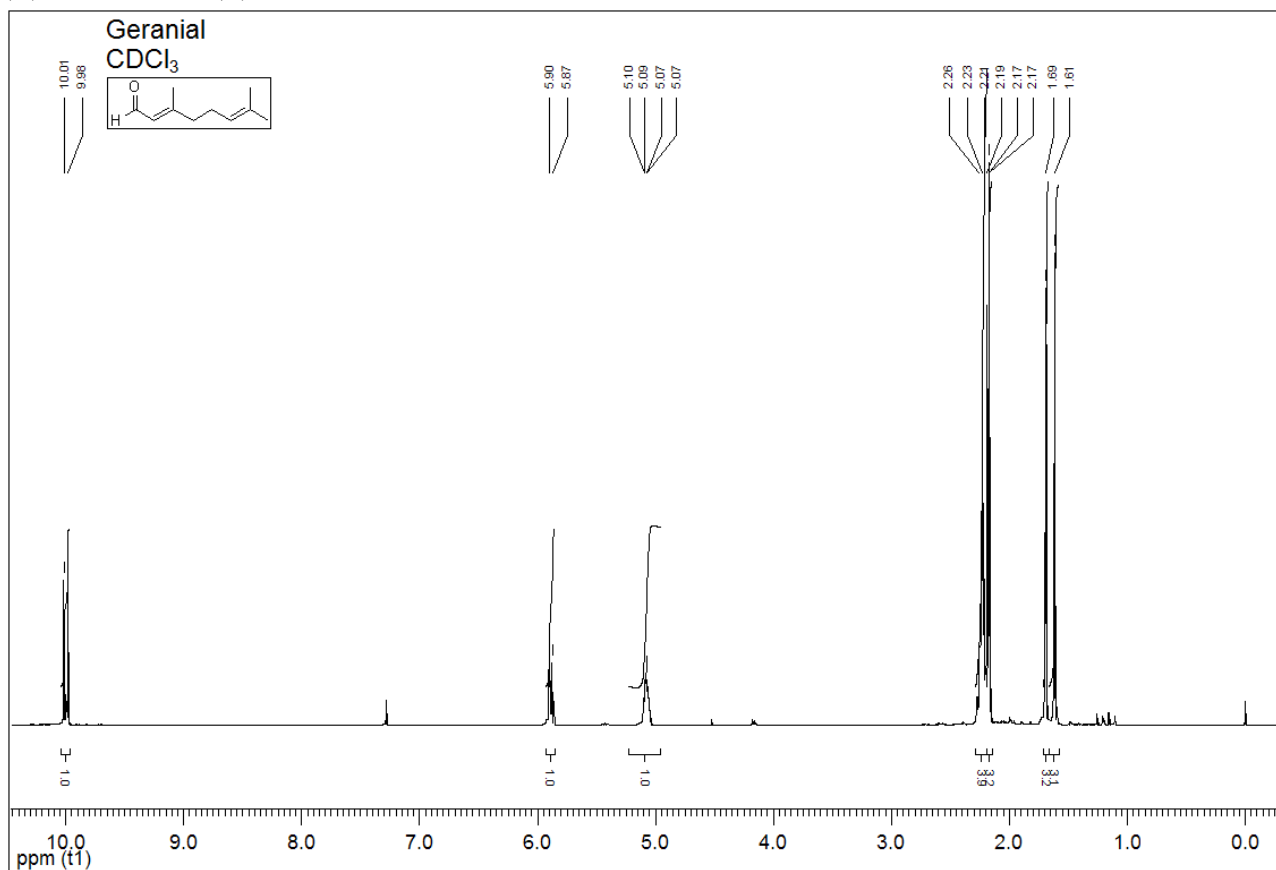
No.	Structure	T _{inj} (°C)	T _{det} (°C)	T _i (°C, min)	T _f (°C, min)	Rate (°C/min)	GC: t _R (min)
1g		250	250	100, 0	250, 5	10	10.663
2a		250	250	100, 5	200, 0	10	7.623
2b		250	250	100, 0	250, 0	10	8.430
2c		260	260	100, 0	250, 5	5	14.130
2d		260	260	100, 5	250, 0	5	22.300
2e		250	250	100, 0	250, 10	10	11.487
2f		250	250	100, 0	250, 5	10	7.390
2g		250	250	100, 0	250, 5	10	9.020
3a		250	250	100, 5	200, 0	10	11.805
6		250	250	100, 10	250, 0	10	12.440

No.	Structure	T _{inj} (°C)	T _{det} (°C)	T _i (°C, min)	T _f (°C, min)	Rate (°C/min)	GC: t _R (min)
7		250	250	100, 10	250, 0	10	13.330
8		250	250	100, 10	200, 0	5	17.530
9		250	250	100, 10	200, 0	5	18.930 (Z) 20.177 (E)
10		250	250	100, 0	250, 0	10	7.300
11		250	250	100, 0	250, 0	10	7.727
		250	250	100, 5	200, 0	10	7.507
		250	250	100, 5	200, 0	10	6.303

Synthesis and isolation of geranial (**9**) using microbubble strategy



Geraniol (**8**, 20 mmol) was dissolved in CH₃CN/H₂O (2:1, 30 mL), then warmed to 30 °C. To the solution, sodium methoxide (**5b**, 81.0 mg, 1.5 mmol) and copper bromide (II) (215.2 mg, 1.5 mmol) were added, resulting in a light blue suspension. After addition of 2,2-bipyridyl (**4b**, 234.4 mg, 1.5 mmol) to the suspension, colour was changed to blue-green. To the mixture TEMPO (312.5 mg, 2.0 mmol) was added, leading to a red-brown mixture. Air-Microbubble was introduced into the reaction mixture by microbubble generator at air-flow rate 3 mL/min. The red-brown mixture gradually turned dark-green. After 1 h, reaction mixture was quenched by the addition of saturated NH₄Cl aq (12 mL). Aqueous layer was extracted with Et₂O (2 x 20 mL) and AcOEt (10 mL). The combined organic layers were washed with brine (1 x 50 mL), filtrated through silica gel plug (SiO₂: 15 g, Na₂SO₄: 20 g) and concentrated *in vacuo*. The resulting liquid product was purified by reduced-pressure distillation (bp. 68-69 °C/1.6 mmHg), giving geranial (**9**) (2544.4 mg, y. 84%, purity >97% (determined by GC), (*E*):(*Z*) = 99 : 1 (determined by GC and ¹H NMR): *R*_f = 0.73 (hexane:AcOEt = 70:30); ¹H NMR (CDCl₃, 300 MHz); δ = 10.0 (d, *J* = 8.0 Hz, 1H, CHO), 5.90-5.87 (m, 1H C=CHCHO), 5.10-5.07 (m, 1H, C=CH), 2.26-2.19 (m, 4H, CH₂), 2.17 (d, *J* = 1.2 Hz, CH₃), 1.69 (s, CH₃) 1.61 (s, CH₃); GC (TC-17, T_{inj} = 250 °C, T_{det} = 250 °C, He = 0.8 MPa, H₂ = 0.5 MPa, Air = 0.5 MPa, T_i = 100 °C (10 min), T_f = 250 °C (5 °C /min, 10 min): *t*_R = 20.177 min (*E*), 18.903 min (*Z*).



¹H NMR

