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Gas–Liquid Segmented Flow Microfluidics for Screening Copper/TEMPO-Catalyzed Aerobic Oxidation of Primary Alcohols

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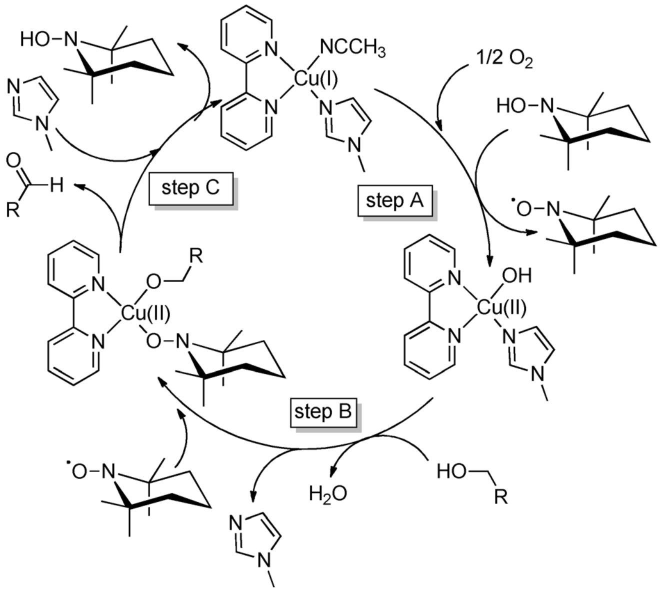
Abstract: Aerobic oxidation using a combination of copper salts and 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) represent useful tools for organic synthesis and several closely related catalyst systems have been reported. To gain further insights, these catalytic systems were evaluated in a gas–liquid segmented flow device. The improvement of oxygen mass transfer has a significant influence on the turnover-limiting step. Hence, an improved catalytic system using copper(II) as copper source was implemented in a microreactor for the safe and efficient oxidation of primary alcohol.

Keywords: aerobic oxidation; alcohols; copper; flow chemistry; 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO)

Green chemistry and green engineering practices have to be integrated into the development of new reaction conditions for fine chemistry. This is particularly true for the oxidation of alcohol where many procedures using stoichiometric metal oxides, activated DMSO, or hypervalent iodine oxidants continue to find widespread use.[1] Over the past decade, major advances have been made in the development of catalytic methods for the oxidation of alcohols[2] and extensive efforts have focused on the development of catalytic methods that use oxygen as the stoichiometric oxidant. Among them, persistent nitroxide[3] and Cu/nitroxide homogenous catalytic systems are some of most versatile catalysts for the aerobic oxidation of alcohol to aldehydes using oxygen.[4] For the latter system, numerous improvements have been reported since the pioneering work of Semmelhack et al. that used Cu(I)/TEMPO in DMF.[5] Sheldon et al. found the accelerating effect of 2,2′-bipyridine (bpy) ligands on the Cu(II) catalytic system,[6] Koskinen et al. optimized the type and amount of base with Cu(II),[7] and Stahl et al. performed scope and limitation studies as well as kinetic and mechanistic investigations demonstrating the importance of Cu(I) salts and *N*-methylimidazole (NMI) as base.[8–11] The applicability of the system has been expanded to prepare nitriles from aldehydes or alcohols using aqueous ammonia[12] or to oxidize amine[13] and amino alcohols[14] into imines and amino carbonyl compounds, respectively.

Increasing reaction efficiency is fundamental to chemistry. It was reported by Stahl et al. that the reaction rate is limited by aerobic oxidation of Cu(I).[11] One way this issue can be addressed is to operate at a higher oxygen pressure and this was recently reported by Stahl et al. in a continuous flow reactor.[15] However, even if near quantitative formation of benzaldehyde from benzyl alcohol was obtained with a residence time of 5 min with 35 bar of diluted oxygen source (9% O_2 in N_2) at 100 °C, these experimental conditions (diluted O_2 and elevated temperature) might not be optimum for the following reasons.

Firstly, for aerobic oxidation, the safety of the process is essential since fuel, oxidant and energy are present at the same time in the reactor. One possibility is to operate outside the flammability limits of the solvent/reactants[15] or to use the safety advantages of flow chemistry already demonstrated for highly reactive chemical processes.[16,17] While the composition and temperature of the gas phase in microreactors are generally far above the flammability limits, the small dimensions of the channels prevent explosion as demonstrated for the H_2/O_2 reaction.[18] The assumption of inherent safety was recently mitigated by investigations showing that an explosion could propagate



Scheme 1. Simplified catalytic cycle for the Cu-catalysed aerobic oxidation of primary alcohols (adapted from refs.[10,11]).

through the microreactor.[19] However, it should be noticed that the small size of the microreactors leads to a small reactor inventory of hazardous chemicals and thus continuous flow methods provide a means to address safety issues associated with aerobic oxidation.

Secondly, small activation energies (Ea) for dioxygen binding (about 4–12 $\mathrm{kJ \cdot mol^{-1}}$) have been found for copper and cobalt complexes.[20] Thus if aerobic oxidation is the turnover-limiting step,[11] the increase in temperature will have a limited effect on the rate of the oxidation. It should also be noticed that a small Ea has also been calculated for the Cu(II)/nitroxyl-mediated oxidation of the alcohol to aldehyde *via* the H abstraction (steps C of the catalytic cycle in Scheme 1).[21,22]

Recently, we have shown that aerobic aldehyde oxidations are frequently limited by oxygen mass transfer resistance.[23] Under lab scale conditions (stirred flask) the chemical performances of aerobic oxidation (chemical rate, selectivity, …) can be falsified by oxygen starvation in the liquid. Microreactors and continuous flow technology in general represent an important opportunity towards greener chemical production.[17] One of the main advantages of continuous flow processing is the enhanced heat and mass transfer characteristics in particular for biphasic reactions. Gas–liquid reactions have been dramatically improved using gas–liquid segmented flows (Taylor flow pattern) owing to an enhanced mass transfer of gaseous reactants into the liquid phase due to of the recirculation within the liquid slugs.[24] As such, the use of microreactors to study aerobic oxidation comprises an important and growing area of research.[25] Using microreactor technology, we have recently shown that aldehydes could be safely and efficiently oxidized into the corresponding carboxylic acid using 5 bar of O_2 at room temperature.[26] This prompted us to re-investigate the continuous-flow aerobic oxidation of primary alcohols with pure O_2 using the Cu/TEMPO catalytic system. The continuous-flow reactor already used for aldehyde oxidation[26] was slightly modified. A sample loop was added (Figure 1) which allowed a rapid scanning of different catalysts, ligands, bases and co-catalyst ratios.

The initial study was carried out using benzyl alcohol in CH_3CN as the model substrate using the experimental conditions previously studied by Stahl et al. [Cu(I)/bpy/NMI/TEMPO].[9,10,27] High conversion (70%) of benzyl alcohol was obtained in 5 min at room temperature using 5 bar of oxygen. The conversion as a function of residence time was then studied (Figure 2).

Residence times can be adjusted by varying the total flow rate of the feed or the PFA tubing length (Figure 2). Within the accuracy of the measurement

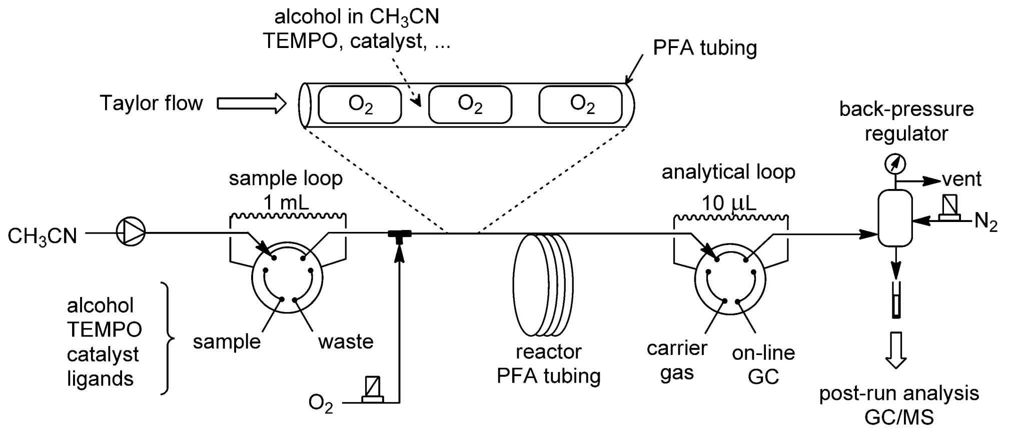


Figure 1. Experimental set-up for the aerobic oxidation of alcohol by the Cu/TEMPO catalytic system.

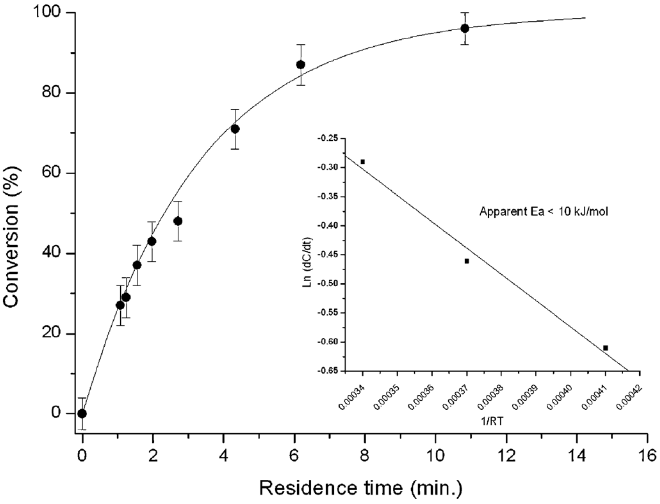


Figure 2. Conversion as the function of residence time for Taylor flow aerobic oxidation of benzyl alcohol with the Cu(I)/bpy/NMI/TEMPO catalyst system. *Reaction conditions:* 6 mM benzyl alcohol in CH_3CN (0.4 M), 5 bar O_2, room temperature, PFA tubing i.d.: 1.6 mm; 0.3 mmol of $Cu(CH_3CN)_4(OTf)$ (5 mol%), 0.3 mmol of bpy (5 mol), 0.6 mmol of NMI (10 mol%), 0.3 mmol of TEMPO (5 mol%). The line in the Figure is only a guide for the eye. *Insert:* Arrhenius plots for Taylor flow aerobic oxidation of benzyl alcohol.

(about 2 and 5% absolute and relative conversion, respectively), both possibilities lead to the same dependency between conversion and residence time. Indeed it has been checked that the total flow rate has no influence on conversion (see the Supporting Information). Benzyl alcohol was totally and selectively converted to benzaldehyde (>98%) at room temperature for residence times above 12 min. The apparent activation energy, Ea, is determined from the Arrhenius plots in the temperature range of 293–353 K (Figure 2, insert). The least-squares analysis yields an Ea value below 10 $kJ \cdot mol^{-1}$ which emphasizes the use of room temperature for Cu/TEMPO oxidation unlike aerobic oxidation using Au or Ru/TEMPO catalytic systems which have higher Ea values (from 20 to 60 $kJ \cdot mol^{-1}$).[21,28] It should be noticed that to the best of our knowledge Ea for benzyl alcohol oxidation was only estimated to be $<60\ kJ \cdot mol^{-1}$.[11]

During the aerobic oxidation of benzyl alcohol using Cu(I)OTf we noticed a progressive colour change at the mid point of the transparent PFA tube (Figure 3 and Supporting Information).

Starting from beige, the colour of the liquid slug changes blue indicating a change in the oxidation degree of the majority of the copper species, i.e., from Cu(I) to Cu(II) (see the Supporting (Information for colour figures). As calculated from the residence time, this colour change was observed for a benzyl alcohol conversion close to 50% under these conditions. From this point, benzyl alcohol oxidation proceeds with copper species present in solution predominantly in the form of Cu(II). With these results in mind, we turned our attention to a previously published catalytic mechanism (Scheme 1). The colour change highlights the benefit of using Taylor flow pattern for aerobic oxidation of alcohol with the Cu(I)/bpy/NMI/TEMPO catalyst system. This behaviour is in accordance with the proposed mechanism where the aerobic oxidation of Cu(I) is rate-controlling (steps A in Scheme 1) in a classical stirred flask.[9,10] The improvement of oxygen mass transfer changes the turnover-limiting step of the catalytic system (Scheme 1) and we can speculate that under Taylor flow conditions, the rate of aerobic oxidation of Cu(I) (steps A) became slightly faster than steps B and C corresponding to the formation of Cu-alkoxide species and oxidation of the alcohol to the aldehyde *via* hydrogen transfer to TEMPO consistent with the reduction of Cu(II) to Cu(I).

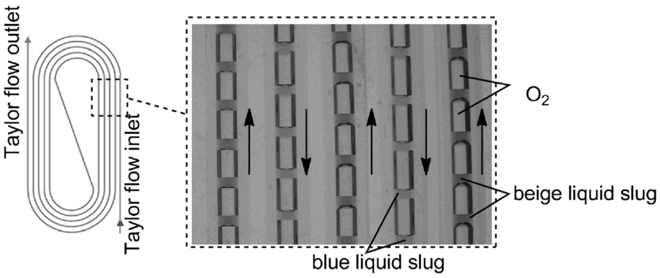
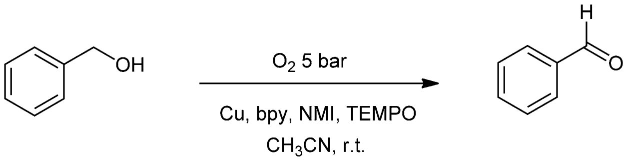


Figure 3. Top view of the PFA tubing layout and visualisation of the colour of the liquid slug during the aerobic oxidation of benzyl alcohol with the Cu(I)/bpy/NMI/TEMPO catalyst system. *Reaction conditions:* 6 mmol benzyl alcohol in CH_3CN (0.4 M), 5 bar O_2, room temperature, PFA tubing i.d.: 1.6 mm; 0.3 mmol of $Cu(CH_3CN)_4(OTf)$ (5 mol%), 0.3 mmol of bpy (5 mol%), 0.6 mmol of NMI (10 mol%), 0.03 mmol of TEMPO (0.5 mol%). Residence time: 10 min (see the Supporting Information for a colour figure).

Scheme 1 highlights the pivotal role of Cu(II) species and in particular Cu(II)OH and Cu(II)-alkoxide. So, the reactivity of the Cu(II) species towards the aerobic oxidation of alcohol was re-evaluated using our microreactor device. The Cu(I) and Cu(II) catalytic systems were compared: the Cu source, ligand, base and cocatalyst ratio were varied while the use of room temperature, 5 bar of oxygen, 0.4 M of benzyl alcohol in CH_3CN and residence time of 5 or 10 min were retained throughout (Table 1).

With a residence time of 5 min or 10 min, benzyl alcohol could be selectively oxidized into benzaldehyde with a conversion of 70% and 98%, respectively (Table 1, entry 1) using Cu(I). As expected from the work of Stahl et al.,[8–10] modification of Cu(I)/bpy/NMI ratio and concentration only decreases conversion. As anticipated by the apparent zero order de-

Table 1. Copper-TEMPO aerobic oxidation of benzyl alcohol to benzaldehyde.[a]



Entry	Cu salt (5 mol%)	Ligand (mol%)	Base (mol%)	Co-catalyst (mol%)	Conversion[b] [%]
1	Cu(I)OTf	bpy (5)	NMI (10)	TEMPO (5)	70[c], >98[d]
2	Cu(I)OTf	bpy (5)	NMI (10)	TEMPO (0.5)	>95[d]
3	Cu(II)(OTf)$_2$	bpy (5)	NMI (10)	TEMPO (5)	<2[c]
4	Cu(II)Br$_2$	bpy (5)	NMI (10)	TEMPO (5)	<2[c]
5	[(bpy)Cu(II)(OH)]$_2$(OTf)$_2$	–	–	TEMPO (5)	<2[c]
6	[(bpy)Cu(II)(OH)]$_2$(OTf)$_2$	–	NMI (10)	TEMPO (5)	<2[c]
7	[(bpy)Cu(II)(OH)]$_2$(OTf)$_2$	bpy (10)	–	TEMPO (5)	55[c]
8	[(bpy)Cu(II)(OH)]$_2$(OTf)$_2$	bpy (5)	NMI (5)	TEMPO (5)	>98[c]
9	[(bpy)Cu(II)(OH)]$_2$(OTf)$_2$	bpy (5)	NMI (5)	TEMPO (0.5)	> 98[c]

[a] *Reaction conditions:* 0.4 M benzyl alcohol in CH_3CN, 5 bar O_2, room temperature, PFA tubing: 2.6 m, i.d.: 1.6 mm.

[b] On-line GC yield. Post-run GC-MS analysis was used to confirm conversion and selectivity.

[c] Residence time 5 min; O_2 flow rate 4 NmL·min^{-1} and liquid flow rate 0.16 mL·min^{-1}.

[d] Residence time 10 min: O_2 flow rate 2 NmL·min^{-1} and liquid flow rate 0.08 mL·min^{-1}. bpy = 2,2′-bipyridine, NMI = *N*-methylimidazole, OTf = trifluoromethanesulfonate, TEMPO = 2,2,6,6-tetramethyl-piperidine *N*-oxyl.

pendency on TEMPO concentration,[9] a conversion >95% could be obtained with a concentration of TEMPO down to 0.5 mol% for a residence time of 10 min (Table 1, entry 2). In our work, Cu(II) salts and particularly CuBr$_2$[8] were found to be an ineffective copper source (Table 1, entries 3 and 4). Experimental data suggests that Cu(II)OH species are key intermediates of the catalytic cycle (Scheme 1).[11] Indeed, [(bpy)Cu(II)(OH)]$_2$(OTf)$_2$ complex could be considered as an interesting Cu(II)OH source. This complex is readily synthesized from Cu(OTf)$_2$[29] but shows no activity (residence time of 5 min) in the presence of 5 mol% of TEMPO (Table 1, entry 5). When 10 mol% of NMI and 5 mol% of TEMPO were added, a Cu/bpy/NMI/TEMPO ratio of 1/1/2/1 comparable with the optimized catalytic system was obtained.[9] However, under our conditions (residence time of 5 min) no conversion could be detected (Table 1, entry 6). It should be noticed that such a catalytic system has been already evaluated by Stahl et al. and was found to have similar rate to that with Cu(I) after an induction period.[9]

A more positive result was obtained by the substitution of NMI by bpy, which gave a 55% conversion (Table 1, entry 7), and the use of 5 mol% of bpy and NMI with the [(bpy)Cu)(II)(OH)]$_2$(OTf)$_2$ complex, leading to a Cu/bpy/NMI/TEMPO ratio of 1/2/1/1, gave a complete conversion (Table 1, entry 8) in 5 min. Thus, we could hypothesise that an excess of bpy can lead to the formation of stabilised Cu(II)OH species from the di-μ-hydroxo-Cu(II) complexes. Under those conditions, the concentration of TEMPO could be decreased to as low as 0.5 mol% while keeping quantitative conversion and high selectivity (Table 1, entry 9). The conversion as the function of residence time for [(bpy)Cu(/II)(OH)]$_2$(OTf)$_2$ complex was then studied (Figure 4).

The presence of an excess of bpy improves the catalytic properties of the new catalytic system using [(bpy)Cu(II)(OH)]$_2$(OTf)$_2$ as the copper source.

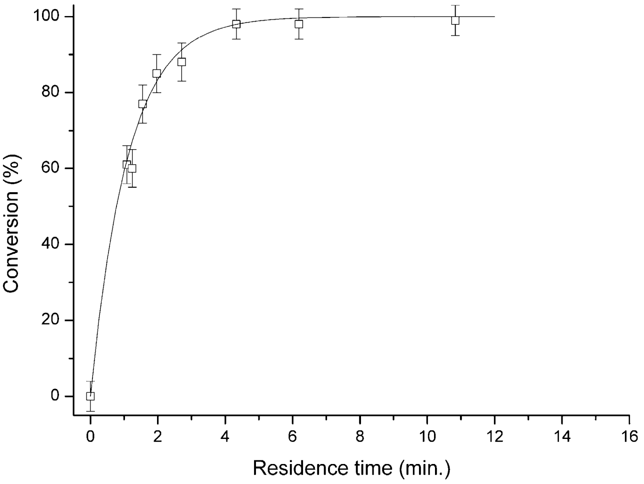


Figure 4. Conversion as the function of residence time for Taylor flow aerobic oxidation of benzyl alcohol with the Cu(II)/bpy/NMI/TEMPO catalyst system. *Reaction conditions:* 6 mmol benzyl alcohol in CH_3CN (0.4 M), 5 bar O_2, room temperature, PFA tubing i.d.: 1.6 mm; 0.15 mmol of [(bpy)Cu(II)(OH)]$_2$(OTf)$_2$ (5 mol%), 0.3 mmol of bpy (10 mol% taking into account of bpy present in the Cu complex), 0.3 mmol of NMI (5 mol%), 0.3 mmol of TEMPO (5 mol%). The line in the Figure is only a guide for the eye.

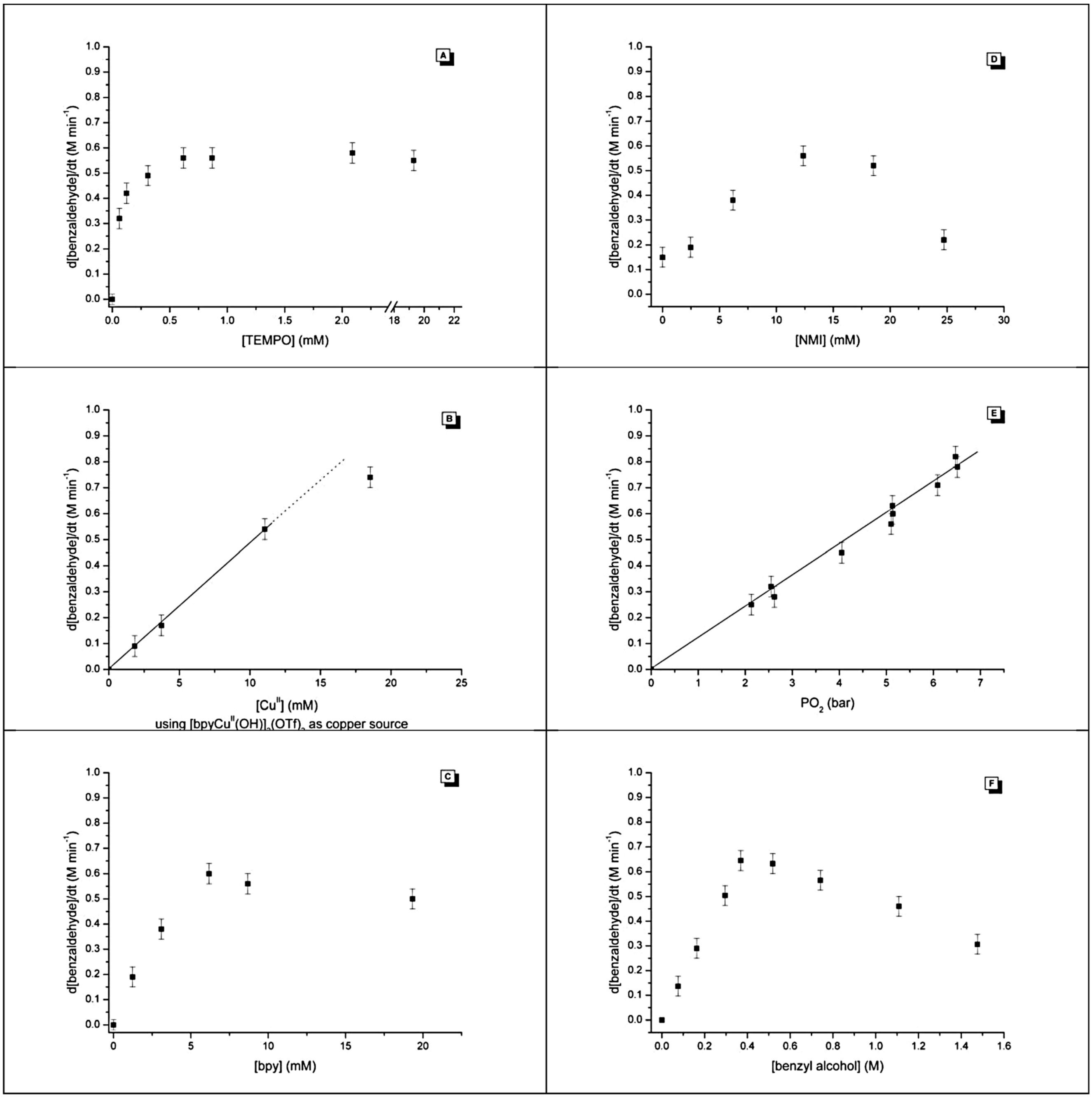


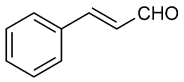
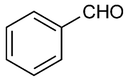
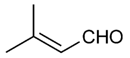
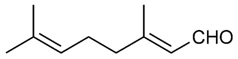
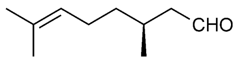
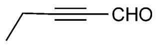
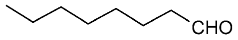
Figure 5. Dependence of [bpyCu(OH)]$_2$(OTf)$_2$/bpy/NMI/TEMPO benzyl alcohol oxidation on (A) initial bpy concentration; (B) initial NMI concentration; (C) initial TEMPO concentration; (D) oxygen pressure; (E) initial benzyl alcohol concentration; (F) initial [(bpy)Cu(OH)]$_2$(OTf)$_2$ concentration. *Standard reaction conditions:* 6 mmol benzyl alcohol in CH_3CN (0.4 M), 5 bar O_2, molar ratio O_2/ROH = 8; residence time = 12 s, room temperature, tube length 0.25 m, id 1.6 mm; 0.15 mmol of [(bpy)Cu(II)(OH)]$_2$(OTf)$_2$ (5 mol%), 0.3 mmol of bpy (10 mol% taking into account of bpy present in the Cu complex), 0.3 mmol of NMI (5 mol%), 0.03 mmol of TEMPO (0.5 mol%).

Under the same conditions, Cu(II) (Figure 4) shows a better reaction rate than Cu(I) (Figure 2). Quantitative conversion of benzyl alcohol is obtained in 5 and 10 min, for Cu(II) and Cu(I) catalytic systems, respectively, at room temperature using 5 bar of oxygen. It should be noticed that, as expected, the Cu(I) catalytic system was found to be sensitive to aging. When a Cu(I) solution (without alcohol and TEMPO) was evaluated after being kept on the shelf for more than 4 h, lower conversions were obtained. On the other hand, when the Cu(II) solution (without alcohol and TEMPO) was evaluated after a night standing on the shelf at room temperature, the same conversions were obtained. These results show that the Cu speciation has a strong impact on the catalytic efficiency. This was noticed previously[7] and the influence of the major components of the $[(bpy)Cu(II)(OH)]_2(OTf)_2$ catalytic system, i.e., TEMPO, bpy, NMI, O_2 pressure and benzyl alcohol concentration, were then investigated independently to understand their role using standard experimental conditions. The kinetic data of the oxidation were easily obtained using our micro-flow reactors (Figure 5).

The dependence on TEMPO concentration was first evaluated using the standard reaction conditions. A saturation dependence on TEMPO concentration was observed under those conditions (Figure 5A), and an optimum ratio of TEMPO/Cu of 1/10 could be found. A concentration of TEMPO of 2 mM (0.5 mol%) was then used throughout the optimisation. A first-order dependence on Cu was obtained, indicating that the reaction is not transfer limited under our conditions (Figure 5B and see also the Supporting Information). However, this increase stalled progressively above 20 mM. This may be explained by the formation of inactive intermediate Cu species due to a non-optimum amount of NMI and bpy. As expected, the chemical speciation of the Cu and accordingly the kinetics of the reaction can be tuned by changing the concentrations of bpy and NMI (Figure 5C and 5D). An optimum ratio between Cu, bpy and NMI of 2/3/2 taking into account the bpy already present in the di-μ-hydroxo-Cu(II) complex can be found. A more detailed investigation on Cu(II) speciation by EPR will be done in due course. At the present time, we can only speculate that excess bpy and NMI could dissociate the initial di-μ-hydroxo-Cu(II) complex and stabilise the Cu(II)OH species (Scheme 1). A first order reaction was observed for O_2 pressure (Figure 5E), clearly demonstrating the usefulness of working with pressurised pure oxygen and accordingly justifying the advantages of using a micro-flow reactor. A first order reaction was also observed for benzyl alcohol up to a concentration of 0.5 M where an inhibition was noticed that could be attributed to a solvent effect (Figure 5F). The fact that both O_2 and the reactant have positive orders implies that both steps A and B (Scheme 1) have comparable rates under those conditions (steps B $\geq$ steps A). This is in accordance with the colour change observed during the course of the experiment using Cu(I) as copper source and lack of colour change using Cu(II) as copper source.

The oxidation of a small series of alcohols was then examined under the optimised conditions for benzyl alcohol oxidation (Table 2). As expected, both benzylic and allylic alcohols were efficiently converted to the corresponding aldehydes at room temperature using pressurised molecular oxygen.

Table 2. Cu(II)/TEMPO-catalysed aerobic oxidation of alcohols to aldehydes.[a]

Entry	Product	Initial rates[b] ($mol \cdot L^{-1} \cdot min^{-1}$)	Conversion at 5 min[c]
1		0.82	>99%
2		0.36	99%
3		0.22	96%
4		0.16	90%
5		0.05	50%
6		0.03	39%
7		0.02	28%

[a] *Reaction conditions:* 6 mmol alcohol in CH_3CN (0.4 M), 5 bar O_2, room temperature, 0.15 mmol of $[(bpy)Cu(II)(OH)]_2(OTf)_2$ (5 mol%), 0.3 mmol of bpy (10 mol% taking into account amount of bpy present in the Cu complex), 0.3 mmol of NMI (5 mol%), 0.03 mmol of TEMPO (0.5 mol%).

[b] Calculated for various residence times for a conversion below 20%.

[c] PFA tubing: 2.6 m, i.d.: 1.6 mm, O_2 flow rate 4 $NmL \cdot min^{-1}$ and liquid flow rate 0.16 $mL \cdot min^{-1}$. On-line GC yield. Post-run GC-MS analysis was used to confirm conversion and selectivity.

The chemical rate was a function of the alcohol structure, allylic and benzylic ones having the higher chemical rates.[8–11] As expected,[7] no by-products could be detected during the oxidation of an unsaturated alcohol (Table 2, entries 4–6). For aliphatic alcohols (Table 2, entries 5 and 7) and propargylic alcohol (Table 2, entry 6), the chemical rates were lower. Conversions below 50% for these alcohols, were obtained with a residence time of 5 min. However, higher conversion could be obtained at higher residence time (i.e., increasing the length of the PFA tubing or decreasing the total flow rate of the feed).

In conclusion, we have demonstrated that the direct aerobic oxidation of primary alcohols to the corresponding aldehydes can be dramatically enhanced by using continuous-flow methodology with a Cu/TEMPO catalytic system and pressurised molecular oxygen at room temperature. We have found that the speciation of the Cu species in solution has a significant effect of the kinetics profile of the Cu/TEMPO catalytic system. Stabilisation of Cu(II)OH using excess of bpy and NMI is essential for the catalytic activity. Cu(II) salts could be used instead of Cu(I) and the reaction times could be significantly reduced from hours to minutes when the oxygen partial pressure is safely increased by using pressurised molecular oxygen and microreactor technology.

Experimental Section

Typical Reaction Conditions with Cu(I)

[Cu(I)(CH_3CN)$_4$]OTf (189 mg, 5 mol%), bpy (47 mg, 5 mol%) and NMI (50 mg, 10 mol%) were dissolved in CH_3CN (15 mL, 11.79 g). Then, TEMPO (47 mg, 5 mol%) and benzyl alcohol (0.65 g, 0.4 M) were added to the solution that should be used promptly.

Typical Reaction Conditions with Cu(II)

[(bpy)Cu/(II)(OH)]$_2$(OTf)$_2$ (9 mg, 5 mol%), bpy (47 mg, 10 mol% taking into account the bpy present in the complex) and NMI (50 mg, 10 mol%) were dissolved in CH_3CN (15 mL, 11.79 g). Then, TEMPO (5 mg, 0.5) and benzyl alcohol (0.65 g, 0.4 M) were added to the solution.

General Flow Procedure for Cu/TEMPO-Catalyzed Aerobic Oxidation of Primary Alcohols

2 mL of freshly prepared solution were injected into the 1 mL sample loop of the device. A PFA tubing of 2.6 m (i.d. of 1.6 mm) was used and for a residence time of 5 min, the flow rate of O_2 was 4 NmL·min^{-1} and the liquid flow rate was 0.16 mL·min^{-1}. A back pressure of 5 bar was applied using a back pressure regulator made in-house and controlled with nitrogen flow (Analyt-MTC massflow controller) and a micro-metering valve. The outlet port of the microreactor was connected to a 6-way gas sampling injection valve (Agilent) for on-line analysis by Agilent 6890 GC equipped with FID detector and Red dot FFAP column (5 m × 0.05 mm × 0.05 μm). Liquid products were retrieved from back-pressure regulator and analysed by a Shimadzu 2010 GC-MS system equipped with a DB-5 column (15 m × 0.1 mm × 0.1 μm.).

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