Continuous-Flow Aerobic Oxidation of Primary Alcohols with a Copper(I)/TEMPO Catalyst

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ABSTRACT: A scalable, continuous-flow process has been developed to implement a homogeneous Cu^I/TEMPO catalyst system for aerobic oxidation of primary alcohols to aldehydes. This catalyst system is compatible with a wide range of alcohols bearing diverse functional groups. A dilute oxygen source (9% O_2 in N_2) is used to avoid flammable oxygen/organic mixtures. Residence times in the heated reaction zone can be as low as 5 min with activated (e.g., benzylic) alcohols. The method has been demonstrated with nine different alcohols, including one up to 100 g scale. This flow-based catalytic method exhibits significant advantages for aerobic oxidation of alcohols, including substantially shorter residence times and broader substrate scope relative to a Pd-catalyzed method that we reported recently.

■ INTRODUCTION

The oxidation of alcohols to aldehydes and ketones is among the most common classes of oxidation reactions encountered in the synthesis of complex organic molecules, such as pharmaceuticals and agrochemicals. A wide range of stoichiometric reagents and catalytic methods is available for these reactions,[1] but there continues to be interest in the development of aerobic oxidation methods that would minimize byproduct formation. Homogeneous and heterogeneous catalysts for aerobic alcohol oxidation have been the focus of extensive fundamental research,[2] but applications of these methods to process-scale pharmaceutical synthesis have been constrained by safety concerns associated with the combination of organic solvent and O_2 and because few aerobic alcohol oxidation methods match the synthetic scope or reliability of existing scalable alcohol oxidation methods (e.g., bleach/TEMPO, pyridine·SO_3).[3]

Homogeneous Pd catalysts are among the most widely studied catalyst systems for aerobic alcohol oxidation.[2c,g] In an effort to test the viability of such methods for process-scale synthesis, we recently developed a continuous-flow process for Pd(OAc)$_2$/pyridine-catalyzed aerobic alcohol oxidation (Chart 1).[4,5] The original laboratory-scale conditions[6] were modified to avoid the use of heterogeneous additives (3 Å molecular sieves) and improve catalyst turnover rate and stability, but the synthetic scope observed for the flow process was very similar to that of the batch method. Oxidation of 1-phenylethanol was demonstrated on a 1 kg scale. Despite these achievements, the homogeneous Pd catalyst system exhibits a number of key limitations: low catalytic turnover rates required the use of long residence times in the flow reactor (2.5−4.5 h) to achieve complete substrate conversion; heterocycles and other functional groups containing nitrogen, sulfur, and related heteroatoms typically poison the Pd^{II} catalyst and significantly limit the substrate scope; and primary aliphatic alcohols are susceptible to overoxidation to carboxylic acids, which inhibit the catalytic turnover. Thus, while this study established a useful benchmark for flow-based aerobic alcohol oxidation, it
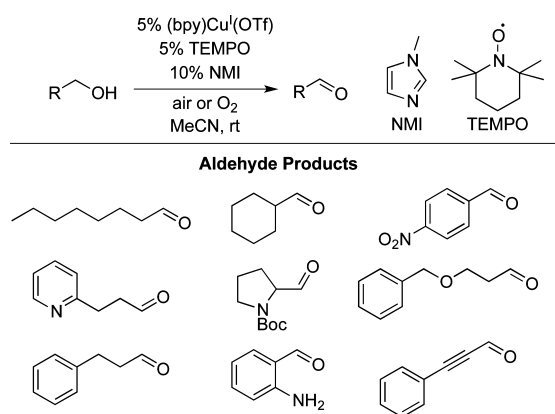
Chart 1. Flow-Based Aerobic Alcohol Oxidation with a Pd(OAc)$_2$/Pyridine Catalyst System
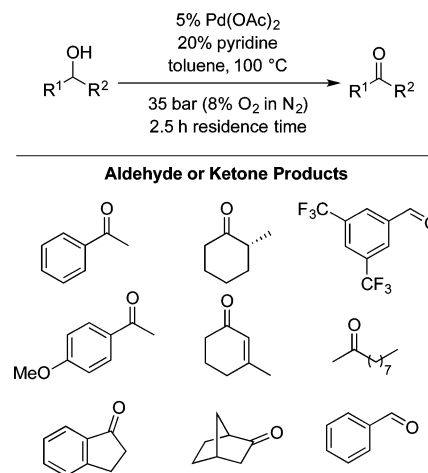
also drew attention to the need for improved catalysts that exhibit higher activity and broader substrate scope.

We recently reported a Cu^I/TEMPO catalyst system, consisting of Cu^I(OTf), bpy, TEMPO, and NMI [bpy = 2,2′-bipyridine, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl, NMI = N-methylimidazole; abbreviated "(bpy)Cu^I/TEMPO"], that overcomes many of the limitations of the Pd-based method (Chart 2).[7,8] This catalyst exhibits much faster catalytic rates; it tolerates a wide range of heteroatom substituents, including pyridines, halogenated arenes, and thioethers, and it is highly selective for the conversion of primary alcohols to aldehydes, including aliphatic substrates. Here, we describe the development of a scalable continuous-flow process for this reaction and compare the results to the previously reported Pd-based method.

Chart 2. (Bpy)Cu^I/TEMPO-Catalyzed Aerobic Alcohol Oxidation

Aldehyde Products

RESULTS AND DISCUSSION

Reactor Description. The reactor used in the present study is a modification of the reactor described previously for continuous-flow aerobic alcohol oxidation with the Pd(OAc)$_2$/pyridine catalyst system (Figure 1).[4] It consists of three principal sections: (1) components for storage and delivery of substrate and catalyst, (2) a heated reaction zone consisting of stainless steel or PTFE tubing, and (3) a liquid/vapor separation unit. The gas is delivered to the reactor as a premixed supply of 9% O$_2$ in N$_2$[9] via a mass flow controller, and it is combined in a series of tees with the liquid solutions. The catalyst and alcohol solutions are delivered via an HPLC pump and a stainless steel syringe pump, respectively. This two-phase mixture flows into the stainless steel (1/8 in. o.d.; 66 mL volume) or PTFE (1/8 in. o.d.; 38 mL volume) tube reactor. A slug flow pattern with alternating segments of gas and liquid is

visibly evident in the PTFE tubing (Figure 2). Upon exiting the heated reaction zone, the liquid is collected through a series of computer-controlled valves into a reservoir. The gas is vented into a fume hood, with the overall pressure adjusted with a back-pressure regulator.
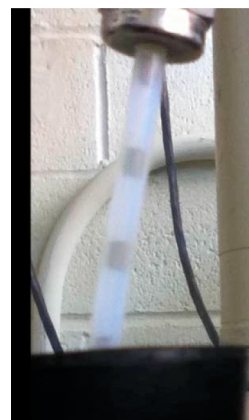

Figure 2. Alternating liquid and gas regions showing slug flow through the PTFE reactor tubing (dark regions are the liquid, and light regions are the gas).

Troubleshooting and Optimization of Flow Process Conditions. The catalytic reaction system includes five different reaction components in acetonitrile solution: Cu-(OTf), bpy, TEMPO, NMI, and the alcohol substrate. Initial studies evaluated combinations of these components that would be stable in solution for an extended period. The stability of the different solutions was evaluated by comparing their performance in small-scale batch reactions. The most consistent yield of aldehyde was obtained when an alcohol solution was
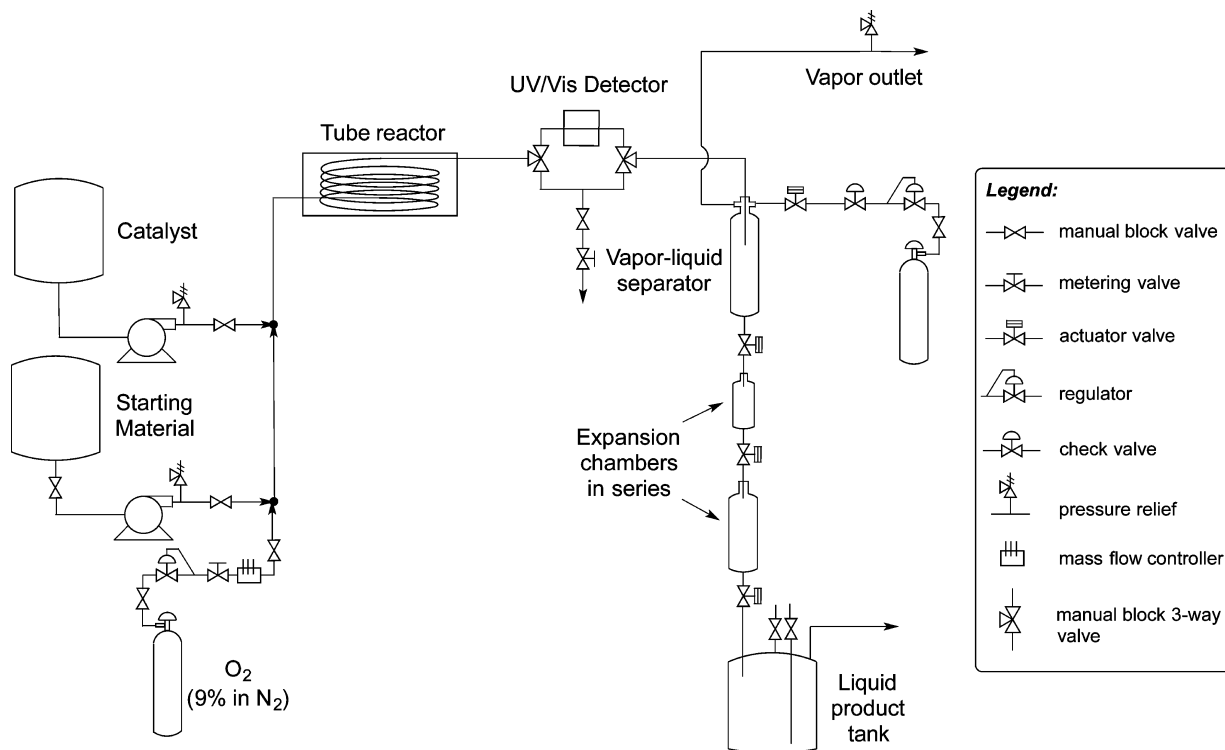

Figure 1. Schematic diagram of the flow reactor used in the present study.

stored separately from a solution containing all of the catalyst components, Cu(OTf), bpy, TEMPO, and NMI. The latter acetonitrile solution was stable for at least a week when stored under nitrogen in a glass vessel. Use of a stainless steel storage vessel resulted in relatively rapid deactivation of the catalyst, with more than 50% loss of catalytic activity observed after 5 h. This deactivation was attributed to reaction of Cu^I with the stainless steel, as has been documented elsewhere.[10] Therefore, one stainless steel syringe pump from the original reactor[4] was replaced with an HPLC pump fed through PTFE supply lines from a glass reservoir under N_2, while the alcohol feed solution retained the stainless steel storage reservoir and syringe pump used previously.

The originally reported reaction conditions were optimized for convenient operation with laboratory-scale applications and focused on operation at room temperature and with ambient air as the source of oxidant. In order to identify conditions with improved performance, we carried out a number of batch experiments in high-pressure reactors to probe the effect of increased temperature and partial pressure of O_2 (Table 1). In

Table 1. Determination of Temperature and Pressure Effects on Aerobic Oxidation of p-Nitrobenzyl Alcohol

entry	Cu salt	T (°C)	pO_2 (bar)	% yield (NMR)
1	Cu(OTf)	22	5	24
2	CuBr	22	5	15
3	Cu(OTf)	60	5	31
4	CuBr	60	5	34
5	Cu(OTf)	60	3	38
6	CuBr	60	3	30
7	**Cu(OTf)**	**100**	**3**	**93**
8	CuBr	100	3	35

addition, CuBr was tested as a less expensive alternative to Cu(OTf) as the Cu^I source. The [Cu] and [TEMPO] were lowered to 1 and 0.1 mol %, respectively, to accentuate the difference among the catalytic reactions. Cu(OTf) and CuBr exhibit comparable results in the oxidation of p-nitrobenzyl alcohol when the reaction was performed at 22 and 60 °C and at 3 and 5 bar pO_2 (Table 1, entries 1−6). The best results, however, were obtained at 100 °C and 3 bar pO_2 (9% O_2 in N_2;[9] total pressure = 35 bar) with Cu(OTf) as the Cu^I source. A 93% yield of the aldehyde was obtained after 1 h under these conditions. The reaction with CuBr formed a Cu-containing precipitate under these conditions. To avoid this potential complication, subsequent studies employed only Cu(OTf).

Batch screening studies similar to those in Table 1 were carried out with cyclohexylmethanol. Aliphatic substrates are more susceptible to overoxidation and/or decomposition at higher temperatures. Oxidation of cyclohexylmethanol at 100 °C resulted in 95% conversion of the substrate after 1 h, but only a 50% yield of aldehyde was obtained, together with several unidentified side products [conditions: 5 M alcohol in CH_3CN, 5 mol % of $(bpy)Cu^I$/TEMPO, 10 mol % of NMI, 3 bar pO_2]. Reducing the catalyst loading lowered the yield and conversion but did not improve the selectivity. Significant improvements were observed, however, by reducing reaction temperature, and excellent conversion to the aldehyde (>95%)

could be achieved at 60 °C. These batch reaction conditions provided the basis for testing the performance of the catalytic reaction in the flow reactor. As shown in Figure 3, oxidation of cyclohexylmethanol to the aldehyde could be achieved in 95% yield with a residence time of 45 min.
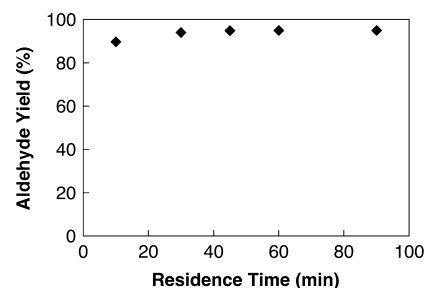

Figure 3. Flow reaction data for the aerobic oxidation of cyclohexylmethanol with the $(bpy)Cu^I$/TEMPO catalyst system. Yields determined by GC with mesitylene as an internal standard. Reaction conditions: 0.2 M cyclohexylmethanol in CH_3CN, 5 mol % of Cu(OTf), 5 mol % of bpy, 10 mol % of NMI, 5 mol % of TEMPO, 35 bar 9% O_2 in N_2, 60 °C, 11 mol % of mesitylene as internal standard.

Aerobic Oxidation of Diverse Primary Alcohols in Flow. The catalytic conditions employed in the flow reaction illustrated in Figure 3 were applied to a number of different substrates (Table 2). Reactions with aliphatic alcohols were carried out at 60 °C, while activated alcohols were performed at 100 °C. Aliphatic alcohols underwent oxidation to the corresponding aldehyde in high yield within 30−45 min (entries 1−5). Activated alcohols, including several benzylic and a propargylic substrate, reached nearly quantitative conversion to the aldehydes with a 5 min residence time (entries 6−9).

Larger Scale Application with Lower Catalyst Loading. Further process optimization is possible for large-scale applications of specific substrates. This prospect was demonstrated in the 100 g scale oxidation of benzyl alcohol to benzaldehyde. A series of reactions were carried out in batch format to assess the reaction performance at lower catalyst loading. In particular, recent kinetic studies of this reaction have shown that the rate is independent of [TEMPO],[7c] thereby allowing significant reduction in the TEMPO loading. The screening experiments led to catalytic conditions consisting of 4 M alcohol in CH_3CN, 2.5 mol % of Cu(OTf)/bpy, 5 mol % of NMI, and 0.25 mol % of TEMPO. Use of these conditions in the flow reactor resulted in near-quantitative formation of benzaldehyde (>99%) with a residence time of 5 min. The performance was sustained over 24 h (Figure 4). Large-scale product purification protocols were not investigated thoroughly in this study, but purification methods such as aqueous extraction of the Cu salts and filtration through silica[11] have been described previously.[7b] Various other adsorbent methods and ion exchange resins could be considered for Cu removal.[12] Ideally, the aldehyde products of these reactions can be carried forward into subsequent synthetic operations without purification.

Overall, these results highlight several significant benefits of the Cu/TEMPO catalyst system relative to the recently reported homogeneous Pd catalyst system in flow-based aerobic alcohol oxidation. The Cu/TEMPO catalyst system exhibits much broader substrate scope, including tolerance of diverse functional groups and utility in the oxidation of primary

Table 2. Scope of (Bpy)Cu^I/TEMPO-Catalyzed Aerobic Oxidization in Flow[a]

R$\diagdown$OH 0.2M → (5% Cu^I(OTf), 5% bpy / 5% TEMPO, 10% NMI / 35 bar (9% O$_2$ in N$_2$), MeCN) → R$\diagdown$O

Entry	Alcohol	Residence Time	Yield
1	(n-octanol chain)–OH	45 min	95%
2	(cyclohexylmethanol)–OH	45 min	95%
3	(3-phenyl-1-propanol)	30 min	99%
4	(3-benzyloxy-1-propanol)	30 min	98%
5	(2-pyridinepropanol)	30 min	99%
6	(benzyl alcohol)	5 min	>99%
7[b]	(2-aminobenzyl alcohol)	5 min	>99%
8	(4-nitrobenzyl alcohol)	5 min	>99%
9	(3-phenyl-2-propyn-1-ol)	5 min	>99%

[a] Entries 1−5 performed at 60 °C. Entries 6−8 performed at 100 °C. Residence times determined by a slug flow reactor model. Yield determined by GC with mesitylene as an internal standard. [b] Yield determined by ^{1}H NMR with 1,3,5-*tert*-butyl benzene as internal standard.
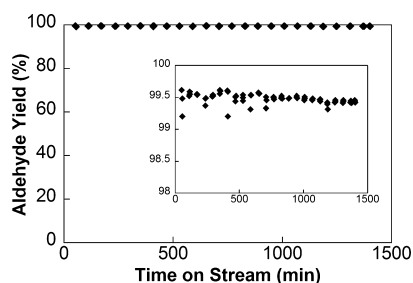

Figure 4. Steady-state profile of (bpy)Cu^I/NMI/TEMPO-catalyzed aerobic oxidation of 100 g of benzyl alcohol. Reaction conditions: 4 M benzyl alcohol in CH$_3$CN, 2.5 mol % of Cu(OTf), 2.5 mol % of bpy, 5 mol % of NMI, 0.25 mol % of TEMPO, 35 bar 9% O$_2$ in N$_2$, 100 °C, 5 min residence time, 5.5 mol % of mesitylene as internal standard.

aliphatic alcohols, with little formation of carboxylic acid byproducts. The faster rates of the Cu/TEMPO system enable significantly shorter residence times than the Pd-based flow conditions (2.5−4.5 h), and the Cu/TEMPO catalyst system is less susceptible to decomposition relative to Pd catalyst systems. The latter feature makes it more amenable to process intensification through the use of higher reaction concentrations and temperatures. Homogeneous Pd catalysts tend to decompose via aggregation into inactive Pd black, and this

deactivation pathway is more problematic at elevated temperatures and increased concentration.[13] These advantages of the Cu/TEMPO system provide the basis for a greener and more efficient method for the production of pharmaceutical intermediates.

CONCLUSION

In this study, we have shown that a homogeneous (bpy)Cu^I/TEMPO catalyst system is well suited for application to flow-based aerobic oxidation of primary alcohols to aldehydes. Reactions of benzylic and other activated alcohols are especially effective, undergoing near-quantitative conversion to the corresponding aldehyde with ≤5 min residence times. Aliphatic alcohols also undergo efficient aerobic oxidations in flow with residence times of 30−45 min. The high activity and stability of this catalyst offers several significant advantages over Pd-based catalysts, and the results provide an important foundation for implementation of large-scale, flow-based aerobic oxidation reactions in pharmaceutical process chemistry.

EXPERIMENTAL SECTION

General Considerations. GC analyses were performed using a DB-Wax column (30 m) installed in a Shimadzu GC-17A equipped with flame-ionization detector. A 22.5 min GC method was used consisting of 1 min at 70 °C, ramp at 20 °C/min to 200 °C (6.5 min), and 15 min at 200 °C. The injector and detector were held at 225 °C, and the column flow was 1.5 mL/min of He with a split ratio of 20. Retention times were as follows: mesitylene (3.7 min), benzyl alcohol (7.7 min)/benzaldehyde (5.7 min), cyclohexylmethanol (5.8 min)/cyclohexanecarbaldehyde (3.9 min), octanol (5.7 min)/octanal (4.0 min), 3-phenyl-1-propanol (8.9 min)/3-phenyl propanal (7.2 min), 3-benzyloxy-1-propanol (11.4 min)/3-benzyloxy-propionaldehyde (9.3 min), 2-pyridinepropanol (9.8 min)/2-pyridine-propionaldehyde (8.0 min), 2-aminobenzyl alcohol (15.5 min)/2-aminobenzaldehyde (10.1 min), 3-phenyl-2-propyn-1-ol (12.3 min)/3-phenyl-2-propynal (8.1 min). Commercially available reagents were obtained from Aldrich and used as received. Acetonitrile was obtained from solvent purification columns, in which the solvent was passed through a column of activated molecular sieves. The catalyst solution was kept under a blanket of flowing nitrogen during the reaction.

Representative Procedure for the Oxidation of Alcohols in Batch Format. A solution of alcohol (0.4 mmol, 0.2 M) and mesitylene as an internal standard (0.08 mmol, 0.04 M) in acetonitrile (1 mL) was added to a 45 mL stainless steel Parr pressure vessel containing a solution of [Cu(CH$_3$CN)$_4$]OTf (7.5 mg, 0.02 mmol, 5 mol %), bpy (3.1 mg, 0.02 mmol, 5 mol %), TEMPO (3.1 mg, 0.02 mmol, 5 mol %), and NMI (3.2 μL, 0.04 mmol, 10 mol %) in acetonitrile (1 mL). The Parr vessel was sealed and pressurized to 35 bar of premixed gas consisting of 9% of O$_2$ in N$_2$. The reaction mixture was stirred with a 3/4 in. octagonal stir bar, heated to the designated reaction temperature and reacted for 1 h. Upon completion, the reaction mixture was filtered through silica and analyzed by GC to determine the product and reactant concentrations.

Representative Procedure for Alcohol Oxidation in Flow. The substrate (8.4 mmol) was prepared as a stock solution in acetonitrile (20 mL) containing mesitylene (0.23 mL, 1.7 mmol, 0.08 M) as an internal standard. This solution was added to a 260 mL syringe pump (Teledyne ISCO 260D).

The catalyst solution of $[Cu(CH_3CN)_4]OTf$ (158 mg, 0.42 mmol, 5 mol %), bpy (66 mg, 0.42 mmol, 5 mol %), TEMPO (66 mg, 0.42 mmol, 5 mol %), and NMI (67 μL, 0.84 mmol, 10 mol %) was dissolved in acetonitrile (23 mL) and was loaded into an HPLC pump (Hitachi L6000). A 1 gallon stainless steel gas reservoir was filled with O_2 (8.7 bar) followed by N_2 (79.5 bar), resulting in a 88.2 bar 9% O_2 in N_2 gas mixture. The gas was regulated to an outlet pressure of 42.4 bar and delivered through a mass flow controller to achieve an O_2/substrate molar ratio of 2:1. The gas and liquid feeds were mixed in a 1/16 in. tee prior to entering the 1/8 in. tube reactor. The reactor was submerged in a Paratherm HE heat transfer fluid maintained at the designated temperature (60 or 100 °C). The residence time was controlled by adjusting the gas and liquid flow rates. Small aliquots (100−500 μL) of the product solution were periodically removed through a small tee for GC analysis, and the remaining liquid and gas were separated using a large tee with the liquids collected at the bottom of the reactor using two valves in series and the gases vented out the top through a pressure relief valve. The pressure relief valve controls the reaction pressure and is maintained at 500 psig.

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Notes

The authors declare no competing financial interest.

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