

# Aerobic Alcohol Oxidation Using a Copper(I)/TEMPO Catalyst System: A Green, Catalytic Oxidation Reaction for the Undergraduate Organic Chemistry Laboratory

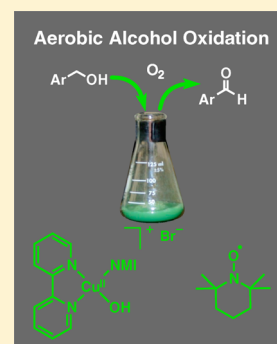
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## S Supporting Information

**ABSTRACT:** Modern undergraduate organic chemistry textbooks provide detailed discussion of stoichiometric Cr- and Mn-based reagents for the oxidation of alcohols, yet the use of such oxidants in instructional and research laboratories, as well as industrial chemistry, is increasingly avoided. This work describes a laboratory exercise that uses ambient air as the source of oxidant and a readily available Cu<sup>I</sup>/TEMPO catalyst system to convert benzyl alcohols to the corresponding aldehydes in standard glassware at room temperature. The procedure is well suited for a high-enrollment undergraduate course, and the complete exercise fits easily within a 3-h lab period. The structures of the organic starting materials and products are determined by NMR spectroscopy and EI-MS. The protocol is adapted from the contemporary research literature and provides students with practical experience of a modern, “green” oxidation method. In addition to the practical aspects, the experiment encourages student discussion and exploration of transition-metal-catalyzed reactions, a topic that is underrepresented in the contemporary undergraduate organic chemistry curriculum.

**KEYWORDS:** Second-Year Undergraduate, Laboratory Instruction, Organic Chemistry, Inorganic Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Alcohols, Catalysis, Green Chemistry, Oxidation/Reduction



Conversions of alcohols to aldehydes and ketones are among the most important and widely used oxidation reactions in organic chemistry.<sup>1</sup> Modern undergraduate organic chemistry textbooks typically present a number of methods to effect these reactions, and among the most commonly featured oxidants are chromium and manganese oxides, such as pyridinium chlorochromate, pyridinium dichromate, CrO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub> (Jones reagent), KMnO<sub>4</sub>, and MnO<sub>2</sub>.<sup>2</sup> These reagents have found widespread utility in organic chemistry, but they are toxic, difficult to dispose of, and used in stoichiometric quantities. The latter considerations explain why such oxidants are rarely used in large-scale industrial synthesis of organic chemicals and are often avoided even in laboratory-scale organic synthesis. Furthermore, use of such oxidizing agents in undergraduate instructional laboratories is increasingly discouraged.<sup>3</sup> In concert with the declining use of heavy-metal oxidants, there have been efforts to develop laboratory exercises that feature more environmentally benign methods for alcohol oxidation. Examples include methods that utilize bleach (NaOCl)/acetic acid,<sup>4,5</sup> bleach/TEMPO [TEMPO = (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl],<sup>6</sup> Oxone (2KHSO<sub>5</sub>·KHSO<sub>4</sub>·K<sub>2</sub>SO<sub>4</sub>),<sup>7</sup> Na<sub>2</sub>WO<sub>4</sub>·2H<sub>2</sub>O/H<sub>2</sub>O<sub>2</sub>,<sup>8</sup> and hypervalent iodine reagents<sup>9</sup> as the oxidant have been reported. These procedures are now commonly used in the undergraduate laboratory.

Over the past decade, extensive efforts have been directed toward the development of catalytic methods for alcohol oxidation that are capable of using atmospheric oxygen as the stoichiometric oxidant.<sup>10</sup> Such methods are potentially attractive from practical, environmental, and pedagogical viewpoints; however,

catalysts composed of expensive noble metals and/or that use ligands obtained from multistep syntheses, together with the common use of halogenated solvents and pure O<sub>2</sub> as the oxidant have hindered the implementation of aerobic oxidation methods into the instructional laboratory.

Homogeneous Cu/TEMPO catalyst systems<sup>11</sup> avoid most of these limitations, and a recent (bpy)Cu<sup>I</sup>/TEMPO catalyst (bpy = 2,2′-bipyridine) is particularly versatile and effective.<sup>11a,12</sup> This report describes an operationally simple implementation of this catalyst system for aerobic alcohol oxidation that is well suited for a high-enrollment undergraduate organic laboratory course. For example, the procedure has been successfully completed by >1000 students during the fall 2011 and spring and summer 2012 terms in an introductory organic chemistry lab course. This laboratory exercise meets the goals of providing students with practical experience of a “green” and catalytic oxidation method, highlighting principles of transition-metal-catalyzed reactions in organic chemistry, and guiding students through a simple metal-based catalytic mechanism.

## LABORATORY OVERVIEW

The (bpy)Cu<sup>I</sup>/TEMPO catalyst that provides the basis for the laboratory exercise described herein employed acetonitrile as the solvent and [Cu(MeCN)<sub>4</sub>][X] (X = OTf<sup>−</sup>, BF<sub>4</sub><sup>−</sup>, PF<sub>6</sub><sup>−</sup>) salts as the copper(I) source.<sup>11a,12</sup> This catalyst system is highly effective for the oxidation of a wide range of primary alcohols, including

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aliphatic, allylic, and benzylic substrates. Benzylic alcohols are particularly appropriate for a teaching laboratory because they undergo complete conversion to aldehydes within 30–60 min. The enhanced reactivity of benzylic alcohols also enabled the development of reaction conditions that were better suited for a teaching laboratory environment, including the use of CuBr as the Cu<sup>I</sup> source and technical-grade acetone as solvent, which are substantially less expensive than [Cu(MeCN)<sub>4</sub>][X] and acetonitrile. In the laboratory protocol described herein, diverse para-substituted benzyl alcohols are oxidized to the corresponding aldehydes. The reactions proceed in standard glassware at room temperature with ambient air as the stoichiometric oxidant, and the entire procedure is readily completed within a 3-h laboratory period.

A typical experiment was carried out in the following manner. The starting para-substituted benzyl alcohol, 4-R-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>OH (R = Me, <sup>i</sup>Pr, OMe, Cl, Br) was dissolved in acetone in an Erlenmeyer flask, followed by addition of solid CuBr, bpy, and TEMPO (10 mol % each) while the solution was stirred. Color changes were observed upon addition of these solids. For example, the colorless acetone solution of the alcohol became green upon addition of solid CuBr and changed to deep red-brown upon the addition of bpy and TEMPO. The latter color was due to a bpy-coordinated copper(I) complex. Several drops of *N*-methyl imidazole (NMI; 4 drops is ~10 mol %) were then added, and the reaction mixture stirred rapidly while open to the air. The reaction typically reached completion within 30–60 min, the end point correlating with a change in color of the red-brown solution to a turbid green mixture.<sup>13</sup> Addition of water to the reaction mixture, followed by extraction with pentane, afforded a pale pink organic phase (the color corresponding to residual TEMPO) and a blue aqueous phase (the color due to an aqueous Cu<sup>II</sup> species). After the pentane extracts were dried over anhydrous MgSO<sub>4</sub>, they were filtered and evaporated to afford the corresponding aldehydes as solids (R = Cl, Br) or oils (R = Me, OMe, <sup>i</sup>Pr). Overoxidation of the aldehyde to the corresponding benzoic acid was not observed in these reactions, even upon prolonged stirring of the reaction mixture. The observed reaction times and product yields obtained by the students are provided in Table 1. A detailed experimental procedure is provided in the Supporting Information.

**Table 1. Summary of Reaction Times and Product Yields Based on Student Laboratory Results**

Benzyl Alcohol Derivative	Time/min	Yield (%)
	Avg. (Max, Min) <sup>a</sup>	Avg. (Max, Min) <sup>b</sup>
4-Cl	36 (54, 20)	59 (95, 19)
4-Br	47 (90, 15)	68 (95, 40)
4-Me	30 (45, 18)	70 (97, 36)
4-MeO	29 (45, 16)	59 (88, 24)
4 <sup>i</sup> Pr	34 (60, 19)	69 (95, 34)

<sup>a</sup>Average time for reaction mixture to turn green; longest and shortest times observed by the students are noted in parentheses. <sup>b</sup>Average percent yield of product; highest and lowest percent yields recorded by the students are noted in parentheses.

The students were supplied with an unknown para-substituted benzyl alcohol derivative, and they were asked to determine the

identity of the starting material based upon <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic, EI-MS, and elemental composition data provided by the instructor. The oxidation product was then characterized by <sup>1</sup>H NMR spectroscopy and EI-MS. The range of para-substituted benzyl alcohols noted in Table 1 was selected based on commercial availability, ease of handling, and diagnostic <sup>1</sup>H NMR spectral data (see the Supporting Information).

## HAZARDS

The substituted benzyl alcohols and benzaldehydes used in this experiment are irritants and harmful if ingested. Copper(I) bromide, TEMPO, and NMI are corrosive. 2,2'-Bipyridine is toxic if ingested. Acetone and pentane are flammable. Appropriate personal protective equipment such as protective gloves, lab coat, and goggles should be worn at all times, in a laboratory equipped with appropriate ventilation (e.g., a fume hood). Solid and liquid waste should be disposed into appropriately labeled containers. The aerobic oxidation reactions presented herein employ organic solvents in the presence of air; therefore, precautions appropriate for the handling of flammable solvents (acetone, pentane) should be employed.<sup>14</sup>

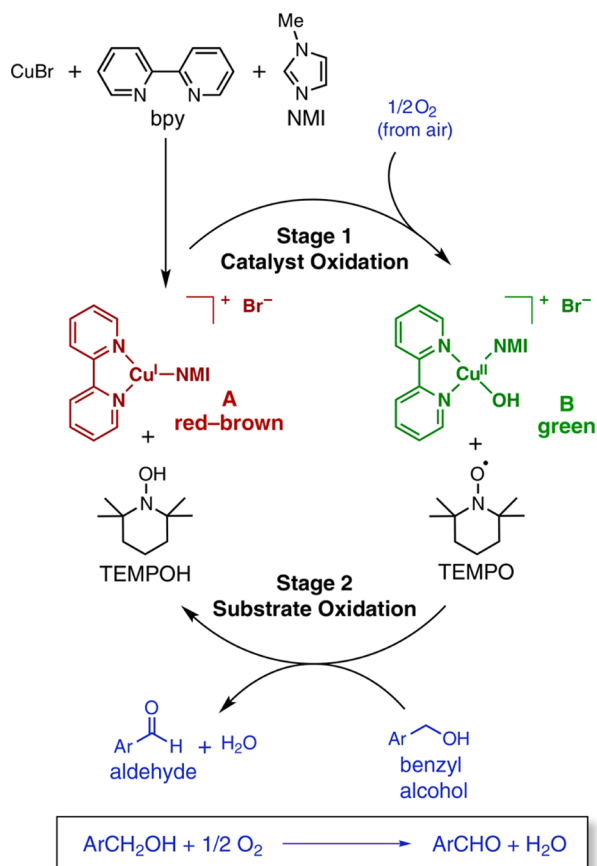
## MECHANISTIC DISCUSSION

Transition-metal-catalyzed reactions are widely used in academic and industrial chemical synthesis, but they are not discussed extensively in undergraduate organic chemistry textbooks or lecture courses.<sup>15</sup> In the absence of textbook or lecture coverage, students may find it difficult to comprehend the concept of metal-catalyzed organic reactions when they are presented in a laboratory course. Complications often arise from student confusion about where to begin the catalytic cycle, the perceived lack of electron-pushing mechanistic steps involving the metal, and presentation of the reaction in a closed cycle rather than a linear series of reaction steps. Although a detailed discussion of the catalytic cycle for the aerobic oxidation reaction described here is beyond the scope of an introductory organic course, a simplified catalytic cycle that emphasizes the important steps in the process can be presented (Scheme 1). The objectives in showing this simplified cycle are (1) to illustrate that the copper and TEMPO cocatalysts are involved in the key steps of the process, (2) to clarify how the aldehyde is produced and how the copper and TEMPO intermediates are regenerated in the cycle, and (3) to link the colors observed during the experimental procedure to the corresponding Cu<sup>I</sup> and Cu<sup>II</sup> species that form in solution.

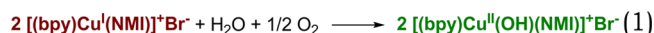
The overall reaction can be divided into two key stages: a catalyst oxidation stage (stage 1) and a substrate oxidation stage (stage 2). CuBr enters the catalytic cycle upon coordination of bpy and NMI, producing the red-brown Cu<sup>I</sup> complex [Cu(bpy)(NMI)]Br (**A**). In stage 1 of the catalytic cycle, Cu<sup>I</sup> complex **A** is oxidized to the green Cu<sup>II</sup>-hydroxide species [Cu(bpy)(OH)(NMI)]Br (**B**) by O<sub>2</sub> in ambient air, together with the oxidation of TEMPOH to TEMPO. In stage 2 of the cycle, the benzyl alcohol is oxidized to the aldehyde by the Cu<sup>II</sup>-hydroxide species **B** and TEMPO. More details of the steps involved in stage 2 are provided below. The Cu<sup>I</sup> species and TEMPOH formed in stage 2 can continue the catalytic cycle until the benzyl alcohol substrate is fully consumed. The copper species remaining after complete conversion of the substrate is likely a copper(II) hydroxide complex analogous to **B**.

A subtle mechanistic point may need to be clarified with the students. The stable form of TEMPO is the oxidized species, and therefore, TEMPOH is not present when the reaction is

**Scheme 1. Simplified Catalytic Cycle for the Aerobic Oxidation of Benzyl Alcohols Using a Cu/TEMPO Catalyst System**



initiated. The Cu<sup>II</sup>-hydroxide species B can also be generated by direct oxidation of A by O<sub>2</sub>, according to eq 1. This reaction is slower than oxidation of A in the presence of TEMPOH, but it explains how the reaction is initiated.

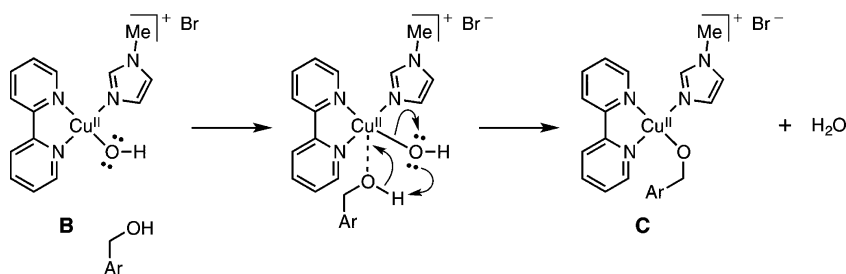


Mechanistic details of the oxidation of Cu<sup>I</sup> and TEMPOH by O<sub>2</sub> are not fully understood and are beyond the scope of an introductory course; however, the alcohol oxidation steps in stage 2 are more straightforward. Presentation of the fundamental steps and electron-pushing mechanisms associated with these steps should enhance student engagement and learning.

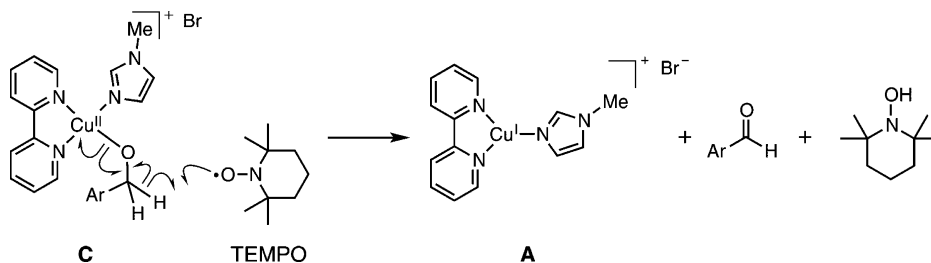
The substrate oxidation sequence (stage 2, Scheme 1) can be presented as a pair of simplified electron-pushing mechanisms (Schemes 2 and 3). The alcohol substrate can react with the Cu<sup>II</sup>-hydroxide complex B to form the Cu<sup>II</sup>-alkoxide intermediate C with concomitant release of water (Scheme 2). This reaction, which may involve initial coordination of the alcohol to the Cu<sup>II</sup> center (see intermediate in Scheme 2), corresponds to an acid–base-mediated, ligand-substitution reaction. The Cu<sup>II</sup>-bound alkoxide of complex C can then react with the TEMPO radical in a homolytic mechanism to afford the aldehyde product (Scheme 3). The Cu<sup>II</sup> center is reduced to Cu<sup>I</sup> in this step, resulting in the formation of complex A together with TEMPOH. Overall, the conversion of an alcohol to an aldehyde is a net two-electron oxidation reaction. The Cu<sup>II</sup> center and TEMPO serve as complementary one-electron oxidants capable of mediating this transformation.

In summary, an operationally simple and pedagogically rich undergraduate laboratory experiment consisting of Cu/TEMPO-catalyzed aerobic oxidation of benzylic alcohols has been described. The protocol reported herein is well suited for incorporation into a high-enrollment introductory organic laboratory course.

**Scheme 2. Electron-Pushing Mechanism for Formation of the Cu<sup>II</sup>-Alkoxide Intermediate C**



**Scheme 3. Electron-Pushing Mechanism for Formation of the Aldehyde Product from the Reaction of Cu<sup>II</sup>-Alkoxide Complex C and TEMPO**



## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Student laboratory manual chapter, instructor notes,  $^1\text{H}$  NMR and GC–MS spectroscopic data, CAS registry numbers. This material is available via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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(13) The reaction progress can also be monitored by TLC (hexanes/ethyl acetate) and visualized with a UV lamp or  $\text{KMnO}_4$  stain, if desired. See reference 11a for TLC conditions of similar substrates.

(14) Control experiments show that hydrogen peroxide does not accumulate under the reaction conditions, based on analysis of the reaction mixture with KI-starch test strips.

(15) See reference 2 in Ballard, C. E. *J. Chem. Educ.* **2011**, *88*, 1148–1151 for a list of introductory organic chemistry textbooks in which metal-catalyzed organic reactions are mentioned.