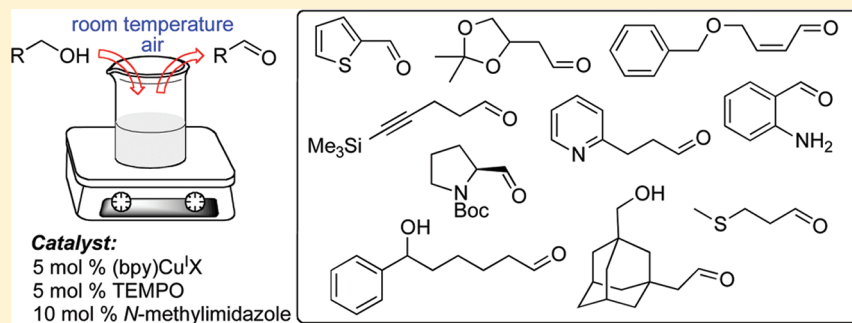# Highly Practical Copper(I)/TEMPO Catalyst System for Chemoselective Aerobic Oxidation of Primary Alcohols

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S *Supporting Information*

ABSTRACT:

Aerobic oxidation reactions have been the focus of considerable attention, but their use in mainstream organic chemistry has been constrained by limitations in their synthetic scope and by practical factors, such as the use of pure O_2 as the oxidant or complex catalyst synthesis. Here, we report a new (bpy)Cu^I/TEMPO catalyst system that enables efficient and selective aerobic oxidation of a broad range of primary alcohols, including allylic, benzylic, and aliphatic derivatives, to the corresponding aldehydes using readily available reagents, at room temperature with ambient air as the oxidant. The catalyst system is compatible with a wide range of functional groups and the high selectivity for 1° alcohols enables selective oxidation of diols that lack protecting groups.
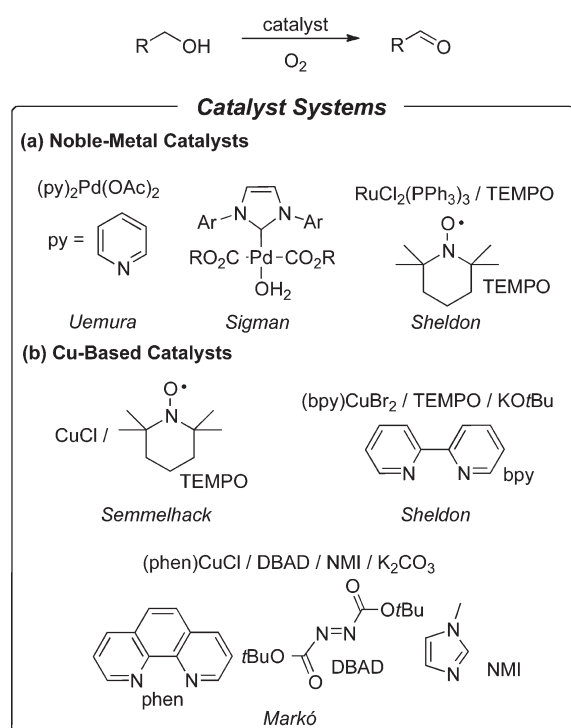
■ INTRODUCTION

The oxidation of alcohols to aldehydes, ketones, and carboxylic acids is among the most important and widely used class of oxidation reactions in organic chemical synthesis. Numerous classical reagents and methods are available for these reactions,[1] including chromium[2] and manganese[3] oxides, "activated DMSO" methods,[4] and hypervalent iodine reagents,[5] which are well-suited for small-scale applications; and pyridine·SO_3[6] and NaOCl/TEMPO (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl),[7] which are frequently employed in large-scale applications. In recent years, there has been growing demand for new environmentally benign methods suitable for large-scale applications, particularly within the pharmaceutical industry.[8] Molecular oxygen is an ideal oxidant, and significant progress has been made in the development of catalytic methods for aerobic alcohol oxidation.[9] Nevertheless, key challenges must be addressed in order for such reactions to find widespread use in the synthesis of complex molecules. Large-scale applications of aerobic alcohol oxidation are constrained by safety concerns associated with the combination of O_2 and organic solvents and reagents,[8a,b] as well as the frequent use of halogenated solvents.[8b] On laboratory scale, existing aerobic alcohol oxidation reactions often have more-limited scope and offer few, if any, synthetic advantages over traditional reagents and methods. Practical considerations also limit the use of aerobic reactions on small scale. For example,

few synthetic laboratories routinely stock O_2 gas cylinders needed for reactions that require pure O_2 as the oxidant; oxidation methods optimized with nonstandard solvents, such as fluorinated arenes or ionic liquids, are less likely to be evaluated in routine synthetic applications; and some of the catalysts with the best reported activity are not commercially available, they must be independently synthesized, and/or they have limited shelf life.[10,11] Limitations such as these hinder widespread adoption of aerobic oxidation reactions in synthetic chemistry.

Many of the recently developed catalyst systems for aerobic alcohol oxidation are based on coordination complexes of noble metals, such as Pd[12,13] and Ru[14] (Scheme 1a). These catalysts are effective with a variety of alcohols, including 1° and 2° allylic, benzylic and aliphatic substrates; however, they are often inhibited by heterocycles and other nitrogen-, oxygen-, and sulfur-containing functional groups and can promote competing oxidation of other functional groups (e.g., Pd catalysts oxidize alkenes[15]). In addition, they typically use pure O_2 (1 atm) as the oxidant. In recent years, we have performed mechanistic studies of Pd-based catalysts[16] and explored their potential use in large-scale applications,[17] but the limitations on the synthetic scope of these

Scheme 1. Representative Catalyst Systems for Aerobic Oxidation of Primary Alcohols

fluorobenzene as the optimal solvent has limited their use in traditional synthetic chemistry applications.

The oxidation of primary aliphatic alcohols to aldehydes is among the most synthetically important classes of alcohol oxidation reactions, but it is also among the most challenging. As already noted, aliphatic alcohols are less reactive than allylic and benzylic substrates, and the aliphatic aldehyde products are also more susceptible to overoxidation to the carboxylic acids. Here, we report a new, highly active (bpy)Cu^I/TEMPO catalyst system that effects selective aerobic oxidation of a broad range of primary alcohols, including allylic, benzylic, and aliphatic derivatives, to the corresponding aldehydes. The reactions proceed in high yield, exhibit broad functional-group compatibility, and achieve chemoselective formation of aldehydes with negligible overoxidation to the carboxylic acids. Furthermore, the reactions exhibit exquisite selectivity for 1° over 2° alcohols, enabling selective oxidation of diols, without requiring the use of protecting groups. The use of a traditional organic solvent (acetonitrile), and the ability to carry out most of the reactions at room temperature with ambient air as the oxidant greatly enhances the practicality of these methods. Overall, the utility of these methods rivals or surpasses that of traditional laboratory-scale alcohol oxidation reactions. The development, scope, and limitations of these methods are elaborated below.

■ RESULTS AND DISCUSSION

**Optimization of a New (bpy)Cu^I/TEMPO Catalyst System.** In the course of studying Pd-catalyzed aerobic oxidation reactions, we attempted to prepare the aldehyde derived from the primary alcohol *trans*-4-hexen-1-ol via aerobic oxidation with a $(py)_2Pd(OAc)_2$[13a] catalyst system. Only a low yield (5%) of the desired aldehyde was obtained, however, and little improvement (14% yield) was achieved by using the RuCl$_2$(PPh$_3$)$_3$/TEMPO[10b] catalyst system (cf. Scheme 1a). Anticipating that first-row transition-metal catalysts of this type should be less susceptible to inhibition by the alkene in this substrate, we focused our attention on previously reported Cu-based catalyst systems described above. In addition, we targeted reactions performed at room temperature with ambient air as the source of oxidant.

To identify an efficient catalyst system that meets the criteria outlined above, we evaluated conditions related to those published previously by Semmelhack (CuCl/TEMPO),[18a] Sheldon ((bpy)CuBr$_2$/TEMPO/KOtBu),[24] and Markó (CuCl/phen/DBAD)[19] (Table 1; see Supporting Information, SI, for full screening data). The Cu source, cocatalyst (TEMPO or DBAD), base, and solvent were varied, while the use of ambient temperature and air as the oxidant was retained throughout. Testing of the three previous catalysts, and modification of the Markó catalyst system using nonhalogenated solvents, led to low product yields under the ambient conditions (0−36%; entries 1−5). Significant improvements were observed upon modifying the Sheldon catalyst system, specifically by replacing KOtBu with *N*-methylimidazole (NMI) and using acetonitrile as the solvent, without including water as a cosolvent. CuBr$_2$ and CuBr were effective copper sources for small-scale reactions, such as those in Table 1, but they were not always reliable in larger scale reactions. For example, the reactions would occasionally form insoluble precipitates and fail to reach completion within 24 h. The use of Cu^I salts with noncoordinating anions (e.g., Cu^I(OTf)) as the catalyst afforded the desired aldehyde in quantitative yield, based on

systems prompted us to consider other options in our pursuit of practical aerobic alcohol oxidation methods.

First-row transition metals tend to undergo more-facile ligand exchange, and empirical data suggest aerobic alcohol oxidation catalysts derived from these metals exhibit broader functional-group compatibility (e.g., Cu,[18,19] Co,[20] Fe,[21] and V[22]). Copper-based catalyst systems, particularly those employing TEMPO[18] or a dialkylazodicarboxylate[19] as redox-active cocatalysts (Scheme 1b), have emerged as some of the most effective catalysts.[23] One of the earliest examples is a CuCl/TEMPO catalyst system reported by Semmelhack and co-workers in 1984,[18a] which was shown to be effective for the oxidation of 1° benzylic and allylic alcohols. Oxidation of aliphatic alcohols required the use of stoichiometric CuCl$_2$ (2.2 equiv). Sheldon and co-workers developed a related catalyst system capable of using ambient air as the oxidant, which consisted of a Cu^{II} salt with 2,2′-bipyridine (bpy) as a ligand and KOtBu as a base.[24] The reduced reactivity of aliphatic alcohols was again noted, and 1-octanol was the only successful example reported, employing a higher temperature and catalyst loading to achieve full conversion.[25] Some progress in the oxidation of aliphatic alcohols was reported recently by Koskinen et al. albeit still using pure O$_2$ as the oxidant.[25c] Another Cu/TEMPO catalyst system, introduced by Knochel and co-workers, uses fluorous biphasic conditions in combination with a fluoroalkyl-substituted bpy ligand.[18b] Independently, Markó and co-workers have developed a series of catalyst systems for aerobic alcohol oxidation employing (phen)CuCl (phen =1,10-phenanthroline) as the catalyst, in combination with dialkylazodicarboxylates as redox-active cocatalysts.[9e,19] These reactions exhibit the broadest scope of aerobic alcohol oxidation reported to date, successfully oxidizing a wide range of diversely functionalized 1° and 2° allylic, benzylic, and aliphatic alcohols. Despite the advantages of these reactions, the use of pure O$_2$ as the oxidant and

Table 1. Optimization of Cu/TEMPO Catalyst System for the Oxidation of *trans*-4-Hexen-1-ol

| entry	Cu salt (5 mol %)	ligand (5 mol %)	cocatalyst (5 mol %)	base	mol %	solvent	yield[a]
1	CuCl[b]	none	TEMPO[b]	none		DMF	29%
2	CuBr$_2$	bpy	TEMPO	KO*t*Bu	5	MeCN/H$_2$O	33%
3	CuCl	phen	DBAD	KO*t*Bu	5	PhCF$_3$	36%
				NMI	7		
4	CuCl	phen	DBAD	KO*t*Bu	5	toluene	26%
				NMI	7		
5	CuCl	phen	DBAD	KO*t*Bu	5	MeCN/H$_2$O	ND[c]
				NMI	7		
6	CuCl	phen	TEMPO	KO*t*Bu	5	MeCN/H$_2$O	12%
				NMI	7		
7	CuCl	bpy	TEMPO	KO*t*Bu	5	MeCN/H$_2$O	85%
				NMI	7		
8	CuCl	bpy	TEMPO	KO*t*Bu	5	MeCN/H$_2$O	11%
9	CuCl$_2$	bpy	TEMPO	KO*t*Bu	5	MeCN/H$_2$O	14%
10	CuBr$_2$	bpy	TEMPO	NMI	7	MeCN	95%
11	CuBr	bpy	TEMPO	NMI	7	MeCN	98%
12	**Cu(OTf)**	**bpy**	**TEMPO**	**NMI**	**10**	**MeCN**	**100%**
13	Cu(OTf)$_2$	bpy	TEMPO	NMI	10	MeCN	ND[c]
14	Cu(OTf)	bpy	TEMPO	none		MeCN	92%
15	Cu(OTf)	none	TEMPO	NMI	10	MeCN	68%
16	Cu(OTf)	bpy	none	NMI	10	MeCN	ND[c]

[a] Yields were determined by GC analysis and are based on the ratio of product/(product + starting material). [b] 10 mol %. [c] No product detected.
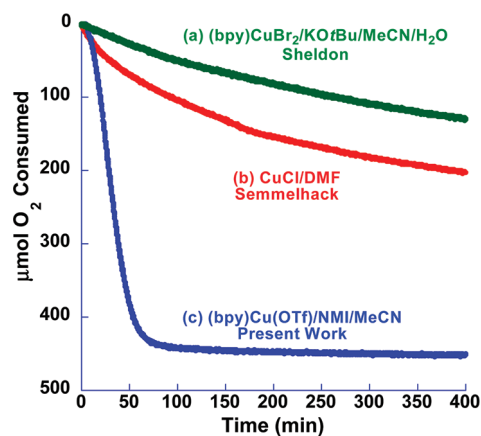
Figure 1. Comparison of three different Cu/TEMPO catalyst systems in the aerobic oxidation of 1-octanol (1.0 mmol) at 27 °C. Catalyst systems include the following: (a) "Sheldon conditions"[24] (similar to Table 1, entry 2): CuBr$_2$ (5 mol %), bpy (5 mol %), TEMPO (5 mol %), and KO*t*Bu (5 mol %) in 2:1 MeCN:H$_2$O (0.67 M) (green); (b) "Semmelhack conditions"[18a] (similar to Table 1, entry 1): CuCl (10 mol %) and TEMPO (10 mol %) in DMF (0.4 M) (red); and (c) Cu(OTf) (5 mol %), bpy (5 mol %), TEMPO (5 mol %), and NMI (10 mol %) in MeCN (0.2 M) (blue). See the SI for additional details.

GC analysis (Table 1, entry 12). Reactions employing Cu(OTf) remained homogeneous throughout, and the results were highly reproducible on larger scales (see below).

The dramatic improvement in catalytic activity with this (bpy)Cu[I](OTf)/TEMPO system over related catalyst systems
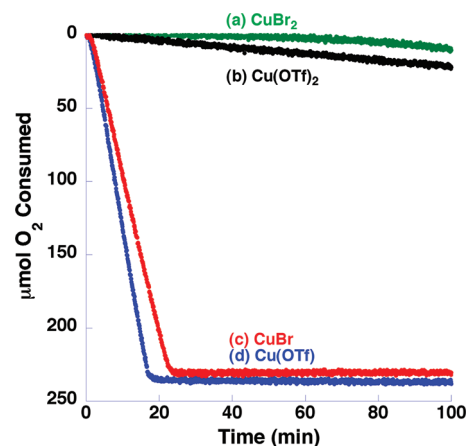
Figure 2. Effect of Cu source on the rate of aerobic oxidation of benzyl alcohol (0.5 mmol) at 27 °C. The Cu source (5 mol %) was combined with TEMPO (5 mol %), NMI (10 mol %), and bpy (5 mol %) with [Cu] = (a) CuBr$_2$ (green), (b) Cu(OTf)$_2$ (black), and (c) CuBr (red), and (d) Cu(OTf) (blue). Reactions employing CuBr$_2$ consistently exhibit a long induction period. See the SI for additional details.

is apparent from a comparison of their gas-uptake kinetic profiles for the oxidation of 1-octanol (Figure 1; 1 atm of O$_2$ was used in these experiments). As shown in the time course plot, the new catalyst system enables complete conversion of this aliphatic alcohol within approximately 1 h at room temperature. A 10−15 min induction period is observed at the start of the reaction, the

mechanistic origin of which is currently under investigation. Sheldon and Koskinen have noted the beneficial effect of non-coordinating anions with Cu^{II}-based catalyst systems;[24b,25c] however, we observe that the initial oxidation state of the copper catalyst has the most significant impact on the reaction efficiency (Figure 2). Cu^{I} salts exhibit much higher reactivity than Cu^{II} salts. It is reasonable to expect that Cu cycles between +1 and +2 oxidation states during the catalytic mechanism, so the origin of the dramatic difference in rates using Cu^{I} vs Cu^{II} precursors is not clear. Ongoing mechanistic studies are focused on elucidating the origin of this unusual effect.
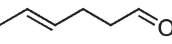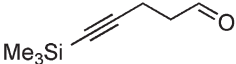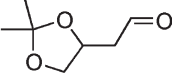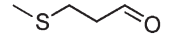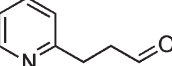
Scope and Functional Group Tolerance of (bpy)Cu^{I}/TEMPO-Catalyzed Alcohol Oxidation. In a preliminary effort to assess the potential scope and utility of this catalyst system, the oxidation of a small series of aliphatic alcohols with various functional groups was examined (Table 2). A broader context for the results was provided by investigating the same substrates with two of the most effective noble-metal catalyst systems that have been reported in the literature, Pd(OAc)$_2$/pyridine,[13a] and RuCl$_2$(PPh$_3$)$_3$/TEMPO,[10b] as well as the (bpy)CuBr$_2$/TEMPO/KOtBu catalyst system.[24a] Reactions performed with catalysts from the literature used the conditions reported with the broadest substrate scope (see Table 2 for details). The data highlight the efficiency and broad functional-group compatibility of the new (bpy)Cu^{I}/TEMPO catalyst. Good-to-excellent product yields were obtained with substrates containing a number of coordinating functional groups, including alkynes, heterocycles, ethers and thioethers. These data amplify the higher activity of the (bpy)Cu^{I}/TEMPO/NMI catalyst system relative to the previous (bpy)CuBr$_2$/TEMPO/KOtBu in the oxidation of aliphatic alcohols. The improved functional-group tolerance of the (bpy)Cu^{I}/TEMPO/NMI catalyst system relative to the noble-metal catalyst systems is clearly evident from the data in entries 2−6.

These preliminary data provided the basis for more-thorough analysis of the substrate scope, and a number of different benzylic, aliphatic, allylic, and propargylic alcohols undergo efficient reaction with this (bpy)Cu^{I}/TEMPO catalyst system (Table 3). No oxidation of the alkene or alkyne is observed, even if the product remains in the reaction mixture after completion of the reaction. The method is compatible with an Me$_3$Si-terminated alkyne (entry 12). Purification of this aldehyde results in a reduced yield; however, the product was obtained in 86% yield with 95% purity following workup of the crude reaction mixture.
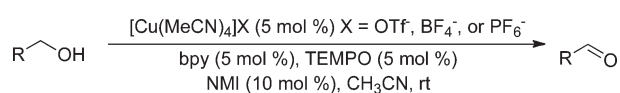
Functionalized alcohols also undergo facile oxidation to the corresponding aldehydes (Table 4). Alcohols containing esters, ethers and thioethers (entries 1, 3, 4, 5 and 10), oxygen-, nitrogen-, and sulfur-containing heterocycles (entries 2, 6, 7, and 11), as well as alcohols with an unprotected aniline (entry 8) and a Boc-protected secondary amine (entry 9) undergo efficient oxidation in excellent yields. Aryl halides, including those with *ortho* iodo substituents, are also compatible with the reaction conditions (entries 12−15). Some alcohols (e.g., Table 4, entries 5, 6, and 9) did not reach completion within 24 h at ambient temperature; however, full conversion was achieved in this time period by performing the reaction at 50 °C.[26]
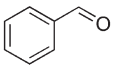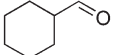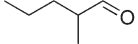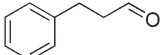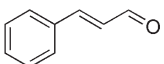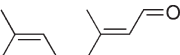
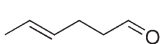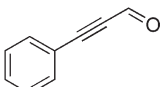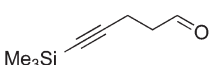The mildness of the reaction conditions is evident by the lack of epimerization of the α-stereocenter of the prolinal product (Table 4, entry 9) and the two formylcyclohexane derivatives (Table 3, entry 6 and Table 4, entry 5). Moreover, we observe near-complete retention of *cis*-alkene stereochemistry in the oxidation of *cis*-allylic alcohols (Table 3, entry 9 and Table 4, entry 4). Aldehyde products derived from the latter reactions are highly susceptible to isomerization, even under mildly basic conditions.[27]

Table 2. Comparison of Known Catalyst Systems for the Aerobic Oxidation of Alcohols Bearing Functional Groups[a]

entry	aldehyde	Pd(OAc)$_2$ pyridine	RuCl$_2$(PPh$_3$)$_3$ TEMPO	CuBr$_2$ KO^{t}Bu TEMPO	Cu(I) NMI TEMPO
1		93%	71%	56%	**>98%**
2		<5%	43%	47% 52%[b]	**>98%**
3		23%	24%	33%	**97%**
4		26%	53%	29%	**85%[c]**
5		<5%	14%	<5%	**76%**
6		12%	7%	28%	**>98%**

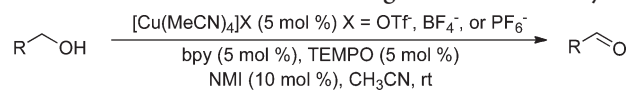[a] Reaction conditions: *Pd(OAc)$_2$/pyridine*:[13a] alcohol (0.20 mmol, 0.1 M in toluene), Pd(OAc)$_2$ (5 mol %), py (20 mol %), 3 Å MS (100 mg), O$_2$ balloon, 80 °C, 2 h; *RuCl$_2$(PPh$_3$)$_3$/TEMPO*:[10b] alcohol (0.50 mmol, 0.5 M in toluene), RuCl$_2$(PPh$_3$)$_3$ (2 mol %), TEMPO (12 mol %), O$_2$ balloon, 100 °C, 7 h; *CuBr$_2$/TEMPO/KOtBu*:[24a] alcohol (0.25 mmol, 0.17 M in 2:1 MeCN:H$_2$O), CuBr$_2$ (5 mol %), bpy (5 mol %) TEMPO (5 mol %), KOtBu (5 mol %); *Cu^{I}/TEMPO/NMI*: alcohol (0.25 mmol, 0.2 M in MeCN), Cu(OTf), bpy (5 mol %), TEMPO (5 mol %), NMI (10 mol %), rt. Yields were determined by GC analysis and are based on the ratio of product/(product + starting material). Low yields primarily reflect incomplete conversion of starting material. [b] 40 °C with 7.5 mol % TEMPO [c] 1 atm O$_2$ in place of air.
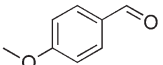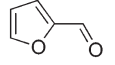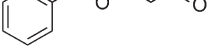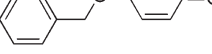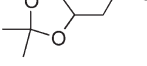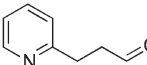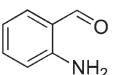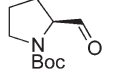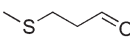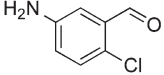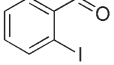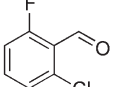
Table 3. Scope of (bpy)Cu^{I}/TEMPO-Catalyzed Aerobic Oxidation of Hydrocarbon-Containing Alcohols to Aldehydes

$$R\diagup OH \xrightarrow[\substack{\text{bpy (5 mol \%), TEMPO (5 mol \%)}\\ \text{NMI (10 mol \%), CH}_3\text{CN, rt}}]{\text{[Cu(MeCN)}_4]X \text{ (5 mol \%) X = OTf}^-, \text{BF}_4^-, \text{ or PF}_6^-} R\diagup O$$

entry	aldehyde	time	comments	yield[a]
1		3 h		95%
2		22 h 23 h	X = OTf⁻ BF₄⁻	>98% 98%
3		24 h 11 h	air bal. O₂ bal.	92% 88%
4		24 h 11 h	air bal. O₂ bal.	83% 98%
5		6 h 4 h	1 mmol 10 mmol	>98% 97%
6		24 h	>20:1 dr	>98%

Alkenes and Alkynes

entry	aldehyde	time	comments	yield[a]
7		2 h		92%
8		3 h 4 h	X = OTf⁻ BF₄⁻ PF₆⁻	>98% >99% 97%
9		2 h	20:1 Z:E	>98%
10		24 h 24 h 5 h	air air bal. O₂ bal.	72% 88% 92%
11		2 h		>98%
12	Me₃Si	24 h		(86%)[b] 65%

[a] Yields given are for isolated material. All reactions were with 1 mmol alcohol unless otherwise noted. [b] Yield of crude reaction product, 95% purity by ^{1}H NMR spectroscopy.

This new (bpy)Cu^{I}/TEMPO catalyst system has many appealing practical characteristics. Most of the reactions were carried out in open reaction vessels employing ambient air as the source of oxidant. In some cases, low-boiling aldehydes can be lost to evaporation over the course of the reaction, in which case a balloon of house air (or O$_2$) enables the aldehydes to be obtained in high yields (Table 3, entries 3, 4, and 10). In addition, separation and isolation of the aldehyde is very straightforward, in most cases requiring only filtration of the reaction mixture through a silica plug or an aqueous extraction to remove the Cu salts to provide aldehyde product that is pure, based on ^{1}H NMR spectroscopic analysis.

Table 4. Scope of (bpy)Cu^{I}/TEMPO-Catalyzed Aerobic Oxidation of Heteroatom-Containing Alcohols to Aldehydes

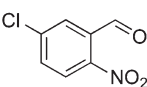$$R\diagup OH \xrightarrow[\substack{\text{bpy (5 mol \%), TEMPO (5 mol \%)}\\ \text{NMI (10 mol \%), CH}_3\text{CN, rt}}]{\text{[Cu(MeCN)}_4]X \text{ (5 mol \%) X = OTf}^-, \text{BF}_4^-, \text{ or PF}_6^-} R\diagup O$$

entry	aldehyde	time	comments	yield[a]
Oxygen				
1		2.5 h 1.5 h	1 mmol 50 mmol	>98% 96%
2		3 h		83%
3		5 h		>98%
4		1.5 h	19:1 Z:E	>98%
5		24 h	50 °C >98 : 2 dr	>98%
6		24 h	50 °C O₂ bal.	(79%)[b] 47%
Nitrogen				
7		3 h		95%
8		3 h 4 h	X = OTf⁻ BF₄⁻	>98% >98%
9		21 h[c]	50 °C >20:1 er[c]	>98%
Sulfur				
10		24 h		(78%)[d] 25%
11		3 h		83%
Aryl Halides				
12		5 h		94%
13		1 h		96%
14		1.5 h		96%
15		3 h		>98%

[a] Isolated yields. [b] Yield determined by ^{1}H NMR spectrocopy and is based on the ratio of product/(product + starting material). [c] Enantiomeric ratio based on ^{1}H NMR determination of the diastereomeric ratio of derivatized product, full details given in SI. [d] Yield of crude reaction product, 94% purity by ^{1}H NMR spectroscopy.

(A) Overoxidation

37% GC yield

mixture of products

(B) Inhibited Oxidation

>98% SM   64% SM   >98% SM

>98% SM   75% SM   53% SM
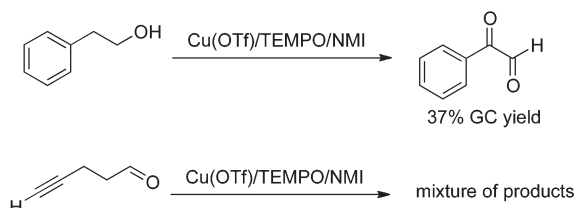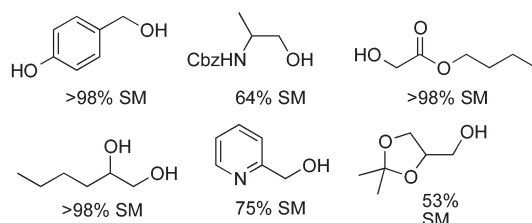
Figure 3. Limitations of (bpy)Cu^I/TEMPO oxidation system due to (A) overoxidation and (B) inhibited oxidation.

Reproducibly high yields of aldehyde following these procedures were obtained on scales up to 50 mmol (Table 3, entry 5 and Table 4, entry 1). Finally, the Cu^I catalyst is commercially available with several noncoordinating anions (OTf$^-$, BF$_4^-$, and PF$_6^-$), each of which proved effective in the reactions (Table 3, entry 8).

Some limitations were identified in the course of these studies. For example, a homobenzylic alcohol underwent oxygenation at the benzylic position to afford the corresponding α-ketoaldehyde in low yield, and a terminal alkyne reacted to form a complex mixture of products (Figure 3A). Vicinal diols and other 1° alcohols bearing vicinal chelating groups (e.g., ethers, amines, and esters), and substrates with phenol substituents proved to be less reactive and led to incomplete conversion of the starting material (SM) (Figure 3B). The latter limitations probably arise from chelation of the adjacent functional group or preferential formation of an unreactive Cu-phenolate species. That similar limitations are not evident with other TEMPO and related nitroxyl-based alcohol oxidation reactions (e.g., TEMPO/NaOCl)[7a,11] suggest that these observations are associated with the Cu-based catalyst system.

Chemoselective Oxidation of Unprotected Diols by (bpy)Cu^I/TEMPO. The studies outlined above reveal that most primary alcohols undergo very efficient oxidation with this catalyst system. These results, together with the very poor reactivity of secondary alcohols (data not shown), suggested that it might be possible to achieve chemoselective oxidation of unprotected diols containing 1° and 2° alcohols with the (bpy)Cu^I/TEMPO catalyst. Such reactivity has very limited precedent, even with traditional oxidants for alcohol oxidation, and selective oxidation of diols often requires the use of protecting groups. In cases where selectivity has been observed (e.g., with halogen, hypervalent iodine and peroxide-based reagents), 2° alcohols typically react more readily.[28,29] Few methods exist for the selective oxidation of a 1° alcohol within a diol. The best examples employ stoichiometric OsO$_4$,[30] stoichiometric RuCl$_2$(PPh$_3$)$_3$,[31] or Br$_2$ with a Ni-(O$_2$CPh)$_2$ catalyst.[32] Sheldon et al. reported selective oxidation of benzyl alcohol in an intermolecular competition

experiment with 2-octanol or 2-phenyl ethanol using their (bpy)CuBr$_2$/TEMPO/KOtBu catalyst system.[24b] Intramolecular competition studies with substrates containing both 1° and 2° alcohols were not investigated. Our efforts to explore the chemoselective oxidation of diols were based on a series of substrates (**1–10**) that exhibit specific selectivity challenges, including the oxidation of 1° versus 2° alcohols, aliphatic versus benzylic alcohols, and sterically differentiated 1° alcohols (Chart 1).

Initial studies focused on substrates **1**, **3**, **8**, and **10**, and we tested their reactivity with the (bpy)Cu^I/TEMPO catalyst system and the three previously reported catalyst systems tested above: Pd(OAc)$_2$/pyridine, RuCl$_2$(PPh$_3$)$_3$/TEMPO, and CuBr$_2$/TEMPO/KOtBu (Table 5). The Pd(OAc)$_2$/pyridine catalyst shows essentially no selectivity for any of these substrates. The Ru catalyst system is moderately selective for oxidation of the less-hindered 1° alcohol in substrates **1**, **3** and **10**; however, competing oxidation of the 2° benzylic alcohol is observed with substrate **8**. As noted in the Introduction, the (bpy)CuBr$_2$/TEMPO/KOtBu catalyst system also shows a preference for oxidation of less-hindered 1° alcohols; however, it is substantially less reactive than the new (bpy)Cu^I/TEMPO catalyst system. The latter catalyst affords very good product yields, in all cases leading to products that reflect oxidation of the least hindered alcohol. Building upon these results, we investigated the full scope of substrates **1–10** in order to assess the preparative utility of these reactions.

Diols **1–10** all underwent selective oxidation with nearly exclusive oxidation of 1° over 2° alcohols (Table 6). In some cases, however, the Cu(OTf)-based catalyst system is too active to achieve optimal selectivity, and improved results could be obtained with an alternate Cu source. For example, to obtain selective oxidation between the 1° and 2° benzylic positions of substrates **1** and **2**, more selective oxidation was observed with a catalyst in which Cu(OTf) was replaced with the less active CuBr$_2$. With substrate **1**, undesired oxidation of the 2° position was further attenuated by using 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in place of NMI, and the aldehyde product **11** could be obtained in very high selectivity and yield. With other substrates, no modification of the parent catalyst system was required. For example, oxidation of 1,5-hexanediol (**4**) with Cu(OTf)/TEMPO/NMI afforded selective oxidation at the primary position, followed by cyclization and further oxidation to yield the corresponding lactone **14**. Lactonization with the Cu(OTf)/TEMPO/NMI system can also occur to form 7-membered lactones; however, the use of CuBr reduces lactonization and yields the linear aldehydes preferentially (**13** and **17**).

In a competition between a 1° benzylic and a 1° aliphatic alcohol, selective oxidation at the more activated benzylic position is observed (**5** and **6** to yield **15** and **16**, repectively). More challenging selectivities arise when an activated 2° benzylic alcohol and an unactivated 1° aliphatic alcohol are present within the same molecule (diols **7** and **8**); however, selective oxidation of the 1° position of diol **8** can be achieved to yield lactone **18.** In the absence of cyclization, (**7** → **17**), the (bpy)Cu^I(OTf)/TEMPO/NMI system is sufficiently active to oxidize both alcohols with little selectivity. Using a CuBr salt, however, provides a more selective catalyst that leads to preferential oxidation of the 1° alcohol. A similar benefit was observed in the competition between aliphatic 1° and 2° alcohols in the conversion of **3** to **13**. Steric differentiation between two 1°

Chart 1. Unprotected Diol Substrates Examined for Selective Oxidation
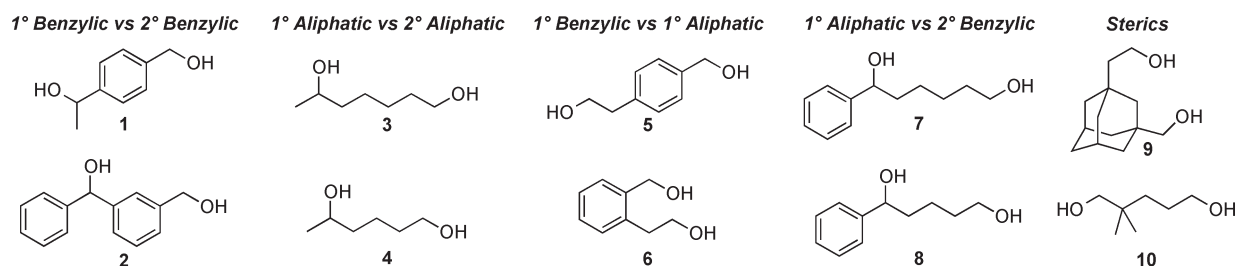
Table 5. Comparison of Different Catalyst Systems in the Aerobic Oxidation of Unprotected Diols [a]


diol		aldehyde product	ketone product	overoxidation
Pd(OAc)$_2$/py (13 min, 80 °C)	41%	32%	12%	15%
RuCl$_2$(PPh$_3$)$_3$/TEMPO (7 h, 100 °C)	<1%	75%	<1%	19%
CuBr$_2$/TEMPO/KOtBu (24 h, rt)	<1%	86%	<1%	14%
CuBr/TEMPO/NMI (6 h, rt)	*<1%*	*64%*	*<1%*	*36%*
CuBr$_2$/TEMPO/NMI (1 h, rt)	*<1%*	*94%*	*<1%*	*6%*
Pd(OAc)$_2$/py (13 min, 80 °C)	7%	33%[b]	14%	46%
RuCl$_2$(PPh$_3$)$_3$/TEMPO (7 h, 100 °C)	44%	39%[b]	<1%	3%
CuBr$_2$/TEMPO/KOtBu (24 h, rt)	38%	62%[b]	<1%	<1%
Cu(OTf)/TEMPO/NMI (24 h, rt)	*<1%*	*97%[b]*	*<1%*	*2%*
Pd(OAc)$_2$/py (2 h, 80 °C)	40%	17%	27%	5%
RuCl$_2$(PPh$_3$)$_3$/TEMPO (7 h, 100 °C)	7%	36%	13%	11%
CuBr$_2$/TEMPO/KOtBu (24 h, rt)	34%	34%	<1%	18%
Cu(OTf)/TEMPO/NMI (24 h, 50 °C)	*4%*	*6%*	*86%*	*7%*
Pd(OAc)$_2$/py (2 h, 80 °C)	<1%	<1%	61%	39%
RuCl$_2$(PPh$_3$)$_3$/TEMPO (7 h, 100 °C)	7%	26%	67%	<1%
CuBr$_2$/TEMPO/KOtBu (24 h, rt)	32%	62%	6%	<1%
Cu(OTf)/TEMPO/NMI (3 h, 50 °C)	*<1%*	*4%*	*96%*	*<1%*

[a] For reactions conditions, see Table 2 and refs 13b, 10b, and 24a. Yields determined by GC analysis. [b] Linear aldehyde and lactone are indistinguishable by GC analysis.

aliphatic alcohols is also possible, as reflected by the selective oxidation of subrates **9** and **10** into **19** and **20**, respectively. With both of these substrates, the presence of an adjacent quaternary center enables selective oxidation of the less hindered alcohol.

These observations demonstrate that the activity of the (bpy)Cu/TEMPO catalyst system can be tuned to achieve highly selective oxidation of unprotected diols. The parent (bpy)Cu^I(OTf)/NMI catalyst appears to be the most active, giving high yields of aliphatic aldehydes and showing high steric

selectivity. Replacement of OTf$^-$ with other noncoordinating counterions (BF$_4^-$ or PF$_6^-$) has no impact on the catalyst activity. This catalyst, however, can effect oxidative lactonization and oxidation of 2° benzylic alcohols. The Cu^{I}Br/NMI pair is less active and more selective, affording aldehydes in high yields while minimizing the sequential oxidation of the substrate to form lactones (e.g., **7** → **17**).[33] The CuBr$_2$ salt, in combination with NMI or DBU, is the least active and most selective, enabling control over the selectivity between 1° and 2° benzylic alcohols.

Table 6. Selective Oxidation of Unprotected Diols using Cu/TEMPO/NMI.[a]
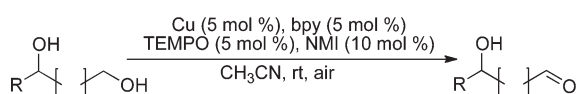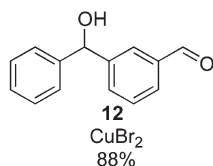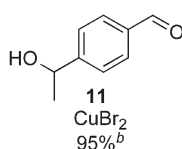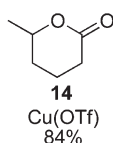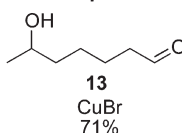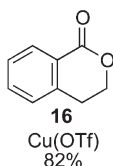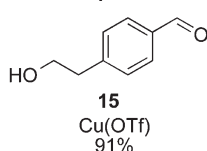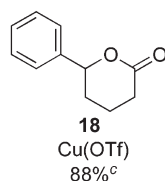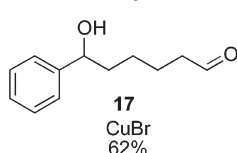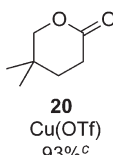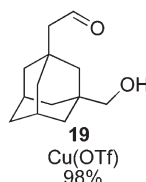
a Isolated yields. *b* With DBU instead of NMI. *c* 50 °C.

CONCLUSIONS

The present report highlights the development of a highly practical (bpy)Cu[I]/TEMPO catalyst system for the selective oxidation of 1° alcohols to aldehydes. Several features of the catalyst system suggest that it is ideally suited for widespread use in synthetic chemistry. It is the first aerobic alcohol oxidation catalyst that exhibits high selectivity for primary alcohols and mediates efficient oxidation of aliphatic substrates. The methods are compatible with substrates bearing a variety of important functional groups, including heterocycles and other heteroatom-containing groups, as well as unprotected 2° alcohols. Also, the methods exhibit a number of highly favorable practical characteristics: (1) ambient air can be used as the oxidant, (2) acetonitrile, a standard organic solvent, is the reaction medium, and (3) all of the catalyst components (CuX salt, bpy, TEMPO, and NMI) are inexpensive, stable, and commercially available reagents.

EXPERIMENTAL SECTION

General Considerations. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance 300 MHz or Varian Mercury 300 MHz spectrometer. Chemical shifts (δ) are given in parts per million and referenced to the residual solvent signal;[34] and all coupling constants are reported in Hz. High resolution mass spectra were obtained by the mass spectrometry facility at the University of Wisconsin. GC analyses were performed using a DB-Wax column installed in a Shimadzu GC-17A equipped with flame-ionization detector. Melting points were taken on a Mel-Temp II melting point apparatus. Column chromatography was performed on an Isco Combiflash system using Silicycle 60 silica gel.

The catalyst components and other commercially available reagents were obtained from Aldrich and used as received, unless otherwise noted. Most alcohols were obtained from commercial sources and used as received; however, diols were typically synthesized by reduction of the corresponding carboxylic acids with LiAlH$_4$ in THF and purified by silica column chromatography (gradient elution of EtOAc in Hexanes). CH$_3$CN was obtained from a solvent drying column present in the laboratory packed with activated molecular sieves; however, identical results were obtained with solvent used directly from commercial sources (e.g., Aldrich, HPLC grade). No precautions were taken to exclude air or water from the solvent or reaction mixtures. Reaction mixtures were monitored by TLC using KMnO$_4$ as a staining agent.

Representative Procedure for the Oxidation of Primary Alcohols. To a solution of alcohol (1 mmol) in dry CH$_3$CN (1 mL) in a 20 mm culture tube were added the following solutions: (1) [Cu(MeCN)$_4$]X (X = OTf$^-$, BF$_4^-$, or PF$_6^-$, 0.05 mmol in 1 mL CH$_3$CN) (2) bpy (0.05 mmol in 1 mL CH$_3$CN) (3) TEMPO (0.05 mmol in 1 mL CH$_3$CN) (4) *N*-methyl imidazole (0.1 mmol in 1 mL CH$_3$CN). The dark red/brown reaction mixture was stirred rapidly open to air and monitored by TLC until no starting material remained (often accompanied by a change in reaction color to green/blue). Preliminary studies indicate that the reactions described here are not subject to mass-transfer effects, and the rate of mixing and stir bar shape do not have a significant impact on the outcome of the reaction.

Larger scale reactions were run in oversized round-bottom flasks: (i) 10 mmol scale reactions were carried out with 50 mL of CH$_3$CN in a 250 mL flask; (ii) 50 mmol scale reactions were carried out with 250 mL of CH$_3$CN in a 1 L flask. Reactions to form volatile aldehydes were carried out in a round-bottom flask fitted with a reflux condenser, a septum, and a balloon of house air (or O$_2$).

Representative Procedure for the Selective Oxidation of Unprotected Diols. To a solution of alcohol (1 mmol) in dry CH$_3$CN (1 mL) in a 20 mm culture tube were added the following solutions: (1) Cu salt (0.05 mmol in 1 mL CH$_3$CN) (2) bpy (0.05 mmol in 1 mL CH$_3$CN) (3) TEMPO (0.05 mmol in 1 mL CH$_3$CN) (4) base (0.1 mmol in 1 mL CH$_3$CN). The reaction mixture was stirred rapidly open to air and monitored by TLC (see Table S3 of the SI) until no starting material remained. The product was then worked up according to one of the following two methods (see SI for details):

Workup Method A. The reaction mixture was then neutralized with 1 N HCl and diluted with water ($\sim$10 mL) and extracted with dichloromethane (3 × 20 mL). The combined organics were washed with brine, dried over Na$_2$SO$_4$, and concentrated. The crude product was purified by silica column chromatography (gradient elution of EtOAc in Hex).

Workup Method B. The crude reaction mixture was concentrated and purified by silica column chromatography (gradient elution of EtOAC in Hex).

ASSOCIATED CONTENT

S **Supporting Information.** Additional catalyst screening data, experimental details, and characterization data for all new

compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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have been developed that are functional mimics of galactose oxidase, a Cu-containing enzyme that mediates primary alcohol oxidation. These catalysts are important from a mechanistic perspective, specifically their use of Cu in combination with a ligand-based radical to effect two-electron alcohol oxidation, but they typically exhibit rather narrow synthetic scope. For leading references, see: (a) Wang, Y.; DuBois, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P. *Science* **1998**, *279*, 537–540. (b) Chaudhuri, P.; Hess, M.; Flörke, U.; Wieghardt, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2217–2220. (c) Chaudhuri, P.; Hess, M.; Müller, J.; Hildenbrand, K.; Bill, E.; Weyhermüller, T.; Wieghardt, K. *J. Am. Chem. Soc.* **1999**, *121*, 9599–9610.

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