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Copper(I)/TEMPO Catalyzed Aerobic Oxidation of Primary Alcohols to Aldehydes with Ambient Air

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Abstract

This protocol describes a practical laboratory-scale method for aerobic oxidation of primary alcohols to aldehydes, using a chemoselective Cu^I/TEMPO catalyst system. The catalyst is prepared in situ from commercially available reagents, and the reactions are performed in a common organic solvent (acetonitrile) with ambient air as the oxidant. Three different reaction conditions and three procedures for the isolation and purification of the aldehyde product are presented. The oxidations of eight different alcohols, described here, include representative examples of each reaction condition and purification method. Reaction times vary from 20 min to 24 h, depending on the alcohol, while the purification methods each take about 2 h. The total time necessary for the complete protocol ranges from 3 – 26 h.

Keywords

oxidation; alcohol; aldehyde; alcohol oxidation; TEMPO; Cu; copper; aerobic

INTRODUCTION

The selective oxidation of primary alcohols to aldehydes is an important reaction in the synthesis of organic molecules. Many common methods are available for this transformation, including those that use of chromium^{i–iii} or manganese^{iv,v} oxides, activated-DMSO reagents,^{vi–viii} or hypervalent iodine^{ix,x} oxidants. These procedures continue to find widespread use, but they also have drawbacks and limitations. Undesirable features include the use and requisite separation and disposal of expensive or toxic stoichiometric reagents, careful control of low-temperature reaction conditions (e.g., Swern oxidations), or the cautious handling of sensitive materials (e.g., 2-iodoxybenzoic acid [IBX]). Catalytic methods can potentially alleviate these problems. For example, the tetrapropylammonium perruthenate (TPAP) is a versatile catalyst for alcohol oxidation, when used in combination with stoichiometric *N*-methylmorpholine-*N*-oxide.^{xi} Catalysts capable of using molecular oxygen as the stoichiometric oxidant would be especially appealing, but laboratory applications of aerobic oxidation are quite rare.

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AUTHOR CONTRIBUTIONS

J.M.H. developed the catalyst system described here and performed the experimental work described here. J.E.S. confirmed the reproducibility of experimental procedures and performed the oxidation reaction and product characterization for Table 1, entry 3. S.S.S. conceived and supervised the project. Manuscript assembly was completed by J.M.H., with assistance by J.E.S. and S.S.S.

COMPETING FINANCIAL INTERESTS

The authors declare that they have no competing financial interests.

Over the past decade, significant advances have been made in the development of catalytic methods for the aerobic oxidation of alcohols, and these have been summarized in a number of recent reviews.^{xii–xviii} In order for such methods to be adopted in the laboratory, they must compete favorably with traditional oxidation methods with respect to operational simplicity, reaction efficiency and yield, predictable reactivity and chemoselectivity, and reagent cost. Few existing aerobic oxidation reactions fulfill these criteria. For example, reactions that require pure O₂ as the oxidant are less likely to be used because few organic chemistry laboratories routinely stock O₂ gas cylinders, and the potential benefits of an aerobic oxidation do not offset the inconvenience and cost of acquiring and using O₂ from a cylinder. Catalytic methods capable of using ambient air as the oxidant eliminate this problem. Ideal catalysts also should exhibit long-term shelf-stability or be readily prepared *in situ* from commercially available reagents. Catalysts that require independent synthesis and purification prior to use are less likely to be adopted.

Many recent catalyst systems employ noble metals, such as Pd and Ru.^{xii,xv,xvii,xviii} Their cost is not prohibitive because they are used in small quantities, and they mediate efficient oxidation of a variety of alcohols, including 1° and 2° benzylic, allylic, and aliphatic alcohols. The most significant limitations of these catalysts include their inhibition by many heterocycles and other N-, O-, and S-containing functional groups, which restricts the substrate scope and synthetic utility, and the common requirement for pure O₂ as the oxidant to ensure catalyst stability. Copper-based catalyst systems appear to exhibit the broadest functional group tolerance and substrate scope,^{xvi,xix,xx–xxii} and one of the most versatile is the system reported by Markó et al., consisting of CuCl in combination with phenanthroline and a dialkylazodicarboxylate redox-active cocatalyst.^{xvi,xxiii} This catalyst system mediates the oxidation of a broad range of 1° and 2° alcohols, including substrates containing heterocycles and other heteroatom substituents; however, the practical limitations include the use of pure O₂ as the oxidant and a non-traditional solvent (fluorobenzene) in the optimized conditions.

We recently reported a highly practical Cu^I/TEMPO-based catalyst system (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy) that exhibits broad substrate scope and is capable of using ambient air as the oxidant (Fig. 1).^{xxiv} Cu/TEMPO-based catalysts for aerobic alcohol oxidation have been reported previously,^{xix,xxi,xxii} but the present catalyst system exhibits significantly higher catalytic activity, enabling efficient oxidation of aliphatic alcohols with ambient air and allowing many reactions to be performed at room temperature. The reactions are carried out in acetonitrile, a common organic solvent, and the catalyst is prepared *in situ* from shelf-stable, commercially available reagents. Primary benzylic, allylic, and aliphatic alcohols bearing a variety of heterocycles or N-, O- and S-containing functional groups undergo efficient and selective oxidation to the aldehyde, without over oxidation to the carboxylic acid. This catalyst exhibits higher selectivity and functional-group tolerance than Pd- and Ru-based catalyst systems, and it represents a compelling and practical alternative to traditional reagents and methods for the oxidation of primary alcohols (e.g., Swern, Dess-Martin periodinane, pyridinium chlorochromate, etc). In this contribution, we describe the detailed protocol for the aerobic oxidation of primary alcohols to aldehydes using this new Cu^I/TEMPO catalyst system.

Experimental design

The reactions detailed below describe the synthesis of aldehydes on 1 mmol (~100–200 mg) scale. These procedures can be scaled up to 10 g with the appropriate scaling of glassware, and a detailed procedure for larger scale reactions is provided in the Supplementary Information. The protocol reported here employs dry acetonitrile (MeCN) solvent, readily available from solvent purification columns in our laboratory; however, we have found that

essentially identical results may be obtained from reactions that use MeCN from commercial sources, without purification.

Benzylic, allylic, and most aliphatic alcohols undergo complete oxidation at room temperature. Benzylic and allylic alcohols typically reach completion within several hours, whereas the oxidation of aliphatic alcohols often requires 20 – 24 h reaction times. The oxidation of sterically hindered aliphatic alcohols, such as those with vicinal substituents (Table 1, entries 5 and 6), can be even less reactive; in such cases, elevated reaction temperatures (50–70 °C) or the use of an O₂ balloon enable complete reaction within 24 h. In reactions that produce volatile aldehydes, the use of reaction vessels open to the air can lead to evaporation of the product and lower yield. These issues provide the basis for the three reaction protocols presented below, which include (1) the standard reaction conditions (Conditions A), (2) conditions employing elevated reaction temperatures (Conditions B), and (3) conditions suitable for the synthesis of volatile aldehydes (Conditions C). In addition, three reaction workup procedures are described: (1) an aqueous extraction (Workup Method A), (2) filtration through a silica plug (Workup Method B), and (3) purification by silica column chromatography (Workup Method C). All workup methods afford aldehyde that is pure by NMR spectroscopy; however, workup methods A and B afford product with trace quantities of TEMPO, evident by a faint pink color. The residual TEMPO may be removed with workup method C.

This Cu^I/TEMPO catalyst system shows high selectivity for the oxidation of 1° alcohols in the presence of 2° alcohols, allowing for the selective oxidation of unprotected diols. In most diol oxidations, the optimized [Cu^I(MeCN)₄](OTf) catalyst system achieves high chemoselectivity (i.e., oxidation of 1° vs. 2° alcohol). With some diol substrates, however, better selectivity is observed with the use of less active Cu^IBr or Cu^{II}Br₂ catalyst precursors, rather than [Cu^I(MeCN)₄](OTf). Table 2 provides guidelines for the selection of the appropriate Cu salt in the chemoselective oxidation of unprotected diols.

Limitations

The Cu^I/TEMPO catalyst system tolerates a variety of functional groups including alkenes and alkynes, and heterocycles such as pyridines, furans, thiophenes. Alcohols containing free anilines, ethers, esters, thioethers, acetals, and aryl halides also undergo facile oxidation to the corresponding aldehyde. Moreover, the reaction conditions are sufficiently mild that (*Z*)-allylic alcohols and alcohols with adjacent stereocenters proceed efficiently without isomerization of alkene or stereocenter. For example, *N*-Bocprolinol (Boc = *tert*-butyloxycarbonyl) is oxidized to *N*-Boc-prolinal with complete retention of stereochemistry (Table 1, entry 6).

Despite the broad scope, several substrates were found to be problematic with this catalyst system in the course of our investigations: (1) primary alcohols bearing unprotected phenols are not oxidized under these conditions, perhaps because the acidic O–H group prevents formation of a reactive Cu–alkoxide species, (2) 4-pentyn-1-ol, which has a terminal alkyne, decomposed to unidentified products, (3) the homobenzylic alcohol 2-phenylethanol underwent oxygenation at the benzylic position to afford the aketoaldehyde derivative, (4) in some cases, alcohols containing a vicinal heteroatom, such as an ether or free amine, underwent slow or incomplete oxidation, and (5) *N*-Boc valinol was oxidized in good yield (92%), but substantial epimerization of the stereocenter was evident in the product, *N*-Boc valinal.

MATERIALS

REAGENTS

- alcohol substrate
- copper(I) tetrakis(acetonitrile) trifluoromethanesulfonate ($[\text{Cu}^{\text{I}}(\text{MeCN})_4](\text{OTf})$, Aldrich 685038)
- 2,2'-bipyridine (bpy, Aldrich D216305)
- 2,2,4,4-tetramethylpiperidine 1-oxyl (TEMPO, Aldrich 214000)
- *N*-methylimidazole (NMI, Aldrich M50834)
- anhydrous acetonitrile (MeCN, anhydrous solvent was employed, but has been shown to not be necessary)
- ethyl acetate (EtOAc, Aldrich 319902), hexanes (Hex, Aldrich 178918), pentane (Aldrich 148941), diethyl ether (Aldrich 673811). These solvents are used for reaction workup and need not be anhydrous.
- sodium sulfate (Na_2SO_4 , Aldrich 23913)

EQUIPMENT

- weighing balance (Mettler Toledo)
- 13 × 100 mm test tubes (VWR 47729-572)
- spatula (VWR 82027-490)
- magnetic stirplate (Corning)
- Teflon coated stir bar, 1/2" × 1/8" (VWR 58948-091)
- 20 × 150 mm test tube (VWR 47729-584)
- 10 mL graduated cylinder
- TLC plates (EMD 5715-7)
- TLC spotters (Chemglass 1182-01)
- polypropylene funnel (Fisher 10-347G)
- 500 mL round bottom flask (Chemglass 1506-20)
- rotary evaporator (Heidolph WB eco)
- ice

For Conditions B:

- silicon oil (Aldrich 378380)
- crystallizing dish (VWR)

For Conditions C:

- rubber septum (SubaSeal 17 mm Aldrich Z124621)
- latex balloon (Aldrich Z154989)
- 3 mL plastic syringe (Becton Dickinson-309604)
- disposable needle (Becton Dickinson 20 g 1½ VWR BD-305175)

- electrical tape

For Purification Method A:

- separatory funnel with Teflon stopcock, 250 mL (Chemglass 1742-04)
- polypropylene funnel (Fisher 10-347G)
- 3 × 250 mL Erlenmeyer flasks (Chemglass 8496-250)
- filter paper, 18.5 cm diameter (Whatman)

For Purification Method B:

- 30 mL M porosity fritted Büchner funnel (Chemglass 8590-30M)
- 125 mL filter flask (Chemglass 8522-125)
- vacuum filtration adapter (VWR 24035)

For Purification Method C:

- glass flash chromatography column with a 250 mL reservoir, 2 in id × 12 in EL with a Teflon stopcock
- silica gel (Silicycle Ultrapure)
- test tubes for collecting column fractions (16 × 150 mm VWR 47729-580)

PROCEDURE

1. Weigh the alcohol (1 mmol) into a 20 mm culture tube and add a stir bar and 2 mL of MeCN (We typically use MeCN obtained from a drying column, however untreated MeCN was shown to give similar yields and reactions times. More details concerning the effect of added water can be found in the Supporting Information).
2. Weigh $[\text{Cu}(\text{MeCN})_4](\text{OTf})$ (19 mg, 0.05 equiv, 0.05 mmol), bpy (8 mg, 0.05 equiv, 0.05 mmol) and TEMPO (8 mg, 0.05 equiv, 0.05 mmol) into separate small test tubes. For the selective oxidation of a diol, replace $[\text{Cu}(\text{MeCN})_4](\text{OTf})$ with the appropriate copper salt (see Table 2).
3. Add sequentially the $[\text{Cu}(\text{MeCN})_4](\text{OTf})$, bpy, and TEMPO as solids to the reaction vessel, following each addition with a 1 mL rinse of the test tubes with MeCN (for a total of 5 mL solvent volume).
4. Add NMI (8 μL , 0.1 equiv, 0.1 mmol). The reaction mixture is typically dark red/brown at this point (Figure 2a).
5. Depending on the desired reaction conditions (see Table 1, and refer to the Introduction for more detail), set up the remaining apparatus as described in the intext table below and Figure 2.

A	Standard Procedure	Stir open to air at room temperature in the 20 mm culture tube (Figure 2a)
B	Substrates requiring higher temperatures	Submerge the bottom portion of the reaction vessel in a preheated 50 °C oil bath (Figure 2b).

C	Synthesis of volatile aldehydes	Fit the culture tube with a septum and balloon of house air or O ₂ attached to a needle inserted through the septum in order to maintain a closed system and prevent evaporation of the product (Figure 2c).
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6. Stir the reaction rapidly and monitor by TLC until no starting material remains. TLC conditions using 2:1 Hex/EtOAc and a KMnO₄ stain works for most alcohols. Completion of the reaction often occurs with a color change from dark red/brown to green/blue (Figure 2c).
7. Purify the aldehyde by either aqueous extraction (Option A), silica plug (Option B), or silica column chromatography (Option C).

Options A and B are both reliable methods to obtain product that is pure by the analytical techniques described in step 8. They do, however, leave trace residual TEMPO which can be removed by silica column chromatography (Option C).

TROUBLESHOOTING

(A) Purification by Aqueous Extraction

- i. Transfer the reaction mixture to a 250 mL separatory funnel with water (50 mL) and pentanes (50 mL).
- ii. Extract the aldehyde into the organic solvent with vigorous shaking. The aqueous layer should be blue at this point (Figure 3a).
- iii. Remove the aqueous layer and extract it with pentanes (2 × 25 mL).
- iv. Combine the organic layers and wash with saturated NaCl solution (~25 mL).
- v. Dry the combined organic layers over NaSO₄ (~50 g) for about 20 min.
- vi. Remove the NaSO₄ by filtration through filter paper into a weighed round bottom flask.
- vii. Remove the solvent by rotary evaporation.

CRITICAL STEP. For volatile aldehydes solvent removal should be done with the flask in an ice bath at ~0°C (Figure 3c). For most other aldehydes, solvent removal proceeds smoothly at 20–30 °C without loss of product.

(B) Purification by Silica Plug

- i. Prepare the setup for vacuum filtration by placing a 30 mL medium porosity fritted funnel containing ~10g of silica gel in a filter flask attached to a vacuum source.
- ii. Dilute the reaction mixture with 1:1 pentanes/ether (20 mL).
- iii. Filter the diluted reaction mixture through the silica plug and rinse with 1:1 pentanes/ether (3 × 10 mL). The top of the silica should turn blue from Cu, leaving a slightly pink colored filtrate (Figure 3b).
- iv. Transfer the filtrate to a weighed round bottom flask and remove the solvent by rotary evaporation.

CRITICAL STEP. For volatile aldehydes solvent removal should be done with the flask in an ice bath at ~0°C (Figure 3c). For most other aldehydes, solvent removal proceeds smoothly at 20–30 °C without loss of product.

(C) Purification by Silica Column Chromatography

- i. Transfer the crude reaction mixture to a round bottom flask and concentrate by rotary evaporation.

PAUSE POINT. The concentrated crude reaction mixture can be stored overnight at -10°C .

- ii. Purify the crude product by flash chromatography on silica gel using a mixture of hexanes and ethyl acetate.
- iii. Collect the fractions that contain the pure product (determined by TLC) into a round bottom flask and remove the solvent using a rotary evaporator.

CRITICAL STEP. For volatile aldehydes solvent removal should be done with the flask in an ice bath at $\sim 0^{\circ}\text{C}$ (Figure 3c). For most other aldehydes, solvent removal proceeds smoothly at $20\text{--}30^{\circ}\text{C}$ without loss of product.

8. Confirm the structure and purity of the product using ^1H and ^{13}C NMR spectroscopy.

TROUBLESHOOTING**TROUBLESHOOTING**

See Table 3 for Troubleshooting guidance.

TIMING

Steps 1–5, Reaction setup: 15 min

Step 6, Oxidation of alcohol: 30 min – 24 h

Step 7, Product purification: 1 – 2 h

ANTICIPATED RESULTS**Typical Yields**

Yields are usually very good for these reactions (most aldehyde products, entries 1–3, 5–8, 90% yield, see Table 1). The yields of volatile aldehydes may vary because of losses during product purification.

Analytical Data

4-nitrobenzaldehyde—Using reaction conditions A and purification method B: 146 mg (0.97 mmol, 97 % y) of a colorless solid. TLC: $R_f(\text{aldehyde}) = 0.72$, $R_f(\text{alcohol}) = 0.28$, in 2:1 Hex:EtOAc. ^1H NMR (300 MHz, CDCl_3): 10.15 (s, 1H, CHO), 8.40 (dd, $J = 6.9, 1.8$, 2H, Ar), 8.05 (dd, $J = 8.7, 1.8$, 2H, Ar). ^{13}C NMR (CDCl_3): δ 190.36 (CHO), 140.19 (Ar), 130.62 (Ar), 124.46 (Ar), 100.53 (Ar). The spectral properties are consistent with literature values.^{xxv}

trans-2-hexenal—Using reaction conditions C and purification method A: 96 mg recovered material which is a 17.5:1 mixture of the title compound:pentane providing aldehyde in 93% yield (0.93 mmol) as a pale orange oil. TLC: $R_f(\text{aldehyde}) = 0.79$, $R_f(\text{alcohol}) = 0.55$ in 2:1 Hex:EtOAc. ^1H NMR (300 MHz, CDCl_3): δ 9.51 (d, $J = 7.9$ Hz, 1H, CHO), 6.86 (dt, $J = 15.7, 6.5$ Hz, 1H, CH=), 6.13 (ddt, $J = 15.7, 7.9, 1.2$ Hz, 1H, CH=), 2.33 (qd, $J = 6.9, 1.3$ Hz, 2H, CH_2), 1.56 (dp, $J = 7.5, 7.4$ Hz, 2H, CH_2), 0.97 (t, $J = 7.4$ Hz,

3H, CH_3). ^{13}C NMR (CDCl_3): δ 193.4 (CO), 158.0 ($\text{CH}=\text{}$), 132.5 ($\text{CH}=\text{}$), 34.0 (CH_2), 20.5 (CH_2), 13.0 (CH_3). The spectral properties are consistent with literature values.^{xxvi}

(±)-2-ethylhexanal—Using reaction conditions B and purification method A: 134.1 mg (1.05 mmol, 91 % y) of a lightly colored oil. TLC: R_f (aldehyde) = 0.97, R_f (alcohol) = 0.68, in 2:1 Hex:EtOAc. ^1H NMR (300 MHz, CDCl_3): 9.581 (d, J = 3.6, CHO), 2.18 (m, 1H, CH), 1.3–1.7 (m, 8H, 4 CH_2), 0.93 (m, 6 H, 2 CH_3). ^{13}C NMR (CDCl_3): 205.58 (CHO), 53.33 (CH), 29.14 (CH_2), 28.07 (CH_2), 22.68 (CH_2), 21.77 (CH_2), 13.80 (CH_3), 11.37 (CH_3). The spectral properties are consistent with literature values.^{xxvii}

(±)-5-phenyl-dihydro-furan-2-one—Using reaction conditions A and purification method C: 143 mg (0.88 mmol, 90 % y) of a white solid. TLC: R_f (lactone) = 0.50, R_f (alcohol) = 0.1 in 2:1 Hex:EtOAc. ^1H NMR (300 MHz, CDCl_3): 7.36 (m, 5 H, Ar), 5.50 (dd, J = 7.5, 6.6, 1 H, CH), 2.64 (m, 3 H, 2 CH_2), 2.19 (m, 1 H, CH_2). ^{13}C NMR (CDCl_3): δ 176.99 (CO), 139.49 (Ar), 128.86 (Ar), 128.54 (Ar), 125.38 (Ar), 81.32 (CH), 31.05 (CH_2), 29.05 (CH_2). The spectral properties are consistent with literature values.^{xxviii}

Analytical data for other aldehydes reported in Table 1 can be found in reference xxiv.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

General reaction scheme of the (bpy)Cu^I/TEMPO-catalyzed aerobic oxidation of primary alcohols to aldehydes.

Figure 2. Reaction conditions **(a)** standard reaction conditions (Conditions A). **(b)** higher temperature reaction conditions (Conditions B) **(c)** reaction conditions for the synthesis of volatile aldehydes (Conditions C).

Figure 3. Purification conditions **(a)** aqueous extraction (purification method A) **(b)** filtration through a silica plug (purification method B) **(c)** rotary evaporation in an ice bath for the isolation of volatile aldehydes.

Table 1

Representative aldehydes synthesized using the described protocol.

$$\text{R-CH}_2\text{OH} + 1/2 \text{O}_2 \xrightarrow[\text{NMI (10 mol \%), CH}_3\text{CN}]{[\text{Cu}(\text{MeCN})_4](\text{OTf}) (5 \text{ mol \%})} \text{R-CHO} + \text{H}_2\text{O}$$

bpy (5 mol %), TEMPO (5 mol %)

entry	aldehyde	reaction conditions ^a	purification method ^b	Yield
1		A	B	97%
2		A	C	97%
3		C	A	93%
4		C	A	83%
5		B	A	91%
6		B	B	>98%
7		A	C	95%
8		A	C	90%

^a Conditions A: reaction at room temperature open to ambient air, Conditions B: 50°C open to ambient air, Conditions C: reaction at room temperature employing a closed system and a balloon of house air.

^b Purification method A: aqueous extraction, Purification method B: filtration through a silica plug, Purification method C: silica column chromatography.

Table 2

Guidelines for the selection of Cu salt for the selective oxidation of unprotected diols.

Copper salt	Selectivity required	Example product
$[\text{Cu}^{\text{I}}(\text{MeCN})_4](\text{OTf})$	<ol style="list-style-type: none"> selective oxidation of 1° benzylic over 1° aliphatic alcohols selective oxidation of 1° benzylic over 2° aliphatic alcohols selective oxidation of 1° aliphatic over 2° benzylic alcohols selective oxidation of sterically accessible alcohol over sterically hindered 1° alcohols
$\text{Cu}^{\text{II}}\text{Br}_2$	selective oxidation of 1° benzylic over 2° benzylic
$\text{Cu}^{\text{I}}\text{Br}$	when four (4) carbons exist between the two alcohols of the diol, and the linear aldehyde is the desired product

Table 3

Troubleshooting table.

Step	Problem	Possible reason	Solution
7	low yield	1 aldehyde was lost during...	
		A. aqueous extraction	A. try extracting with larger volumes of organic solvent or extract with a more polar solvent (such as EtOAc)
		B. rotary evaporation	B. remove solvent at 0 °C
		2 substrate is incompatible with this method	
	Cu present in aldehyde	inefficient removal of Cu during purification	If the purification method was...
			1 aqueous extraction: use a larger volume of water
			2 silica plug: dilute with a larger volume of solvent prior to filtration
8	low conversion	1 the reaction was stopped before reaching completion	1 run the reaction for longer
		2 the substrate requires more forcing conditions	2 try the reaction again with either a higher temperature (50–70 °C) or an O ₂ balloon in place of air