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Chemoselective Oxidation of Benzyl, Amino, and Propargyl Alcohols to Aldehydes and Ketones under Mild Reaction Conditions

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This article is dedicated to the fond memory of the late Professor A. Sri Krishna from the Indian Institute of Science, Bangalore.

Catalytic oxidation reactions often suffer from drawbacks such as low yields and poor selectivity. Particularly, selective oxidation of alcohols becomes more difficult when a compound contains more than one oxidizable functional group. In order to deliver a methodology that addresses these issues, herein we report an efficient, aerobic, chemoselective and simplified approach to oxidize a broad range of benzyl and propargyl alcohols containing diverse functional groups to their corresponding aldehydes and ketones in excellent yields under mild reaction conditions. Optimal yields were obtained at room temperature using 1 mmol substrate, 10 mol% copper(I) iodide, 10 mol% 4-dimethylaminopyridine (DMAP), and 1 mol% 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) in acetonitrile, under an oxygen balloon. The catalytic system can be applied even when sensitive and oxidizable groups such as alkynes, amines, and phenols are present; starting materials and products containing such groups were found to be stable under the developed conditions.

Developing chemoselective and sustainable catalytic oxidation methods is important due to their significance in both academe and industry (e.g., to make chemical intermediates for the pharmaceutical, perfume, dye, and agrochemical industries).[1] In order to achieve this, various stoichiometric and catalytic methods were developed using chromium, manganese, ruthenium, osmium, palladium, platinum, iron, cobalt, nickel, copper, activated DMSO,[2] hypervalent iodine reagents,[3] metal-free systems,[4] and other reagents.[5] Among these reagents, copper is an essential metal that can easily associate with different functional groups via Lewis acid interactions or π-coordination.[6d] Significant efforts towards the chemoselective oxidation of alcohols using various copper-catalyzed and copper—2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)-catalyzed systems have been made.[1a,6,7] Recently, chemoselective aerobic oxidation of amino alcohols to carbonyl compounds using 2-azaadamantane-*N*-oxyl (AZADO)/copper complex was reported.[8] While the reported methods are synthetically useful, they do possess some limitations like commercial nonavailability of reagents and high operating costs caused by the reaction conditions required, which make them inconvenient and undesirable.[9] Synthesizing amino carbonyl derivatives from their respective amino alcohols remains a big challenge to the synthetic chemist because protection and deprotection steps have to be used when other oxidizable groups are present within the same molecule.[10] The fact might be that interactions between the electron-rich amino groups and the oxidant lead to formation of the desired product in poor yield.

α,β-Acetylenic carbonyl compounds are highly important precursors for the construction of various bioactive heterocyclic compounds and DNA-cleavage agents, and have a wide range of applications in medicinal chemistry.[11] Various methods in literature exist for the oxidation of propargyl alcohols to carbonyl compounds. These include stoichiometric oxidation systems, such as 2-iodoxybenzoic acid and sodium periodate,[12] transition-metal-catalyzed oxidation reactions, such as with copper(II), ruthenium(II), iron(III) nitrate nonahydrate, vanadyl acetylacetonate,[13] copper(II) acetylacetonate–*N*-hydroxyphthalimide (NHPI),[14] and copper nanoparticles,[15] and TEMPO/calcium hypochlorite.[16a] Although the developed methods are useful, they do have some limitations such as the instability of the produced carbonyl compounds in the reaction system, catalyst deactivation by the formation of metallic polymers, formation of stable complexes between metal salts and some electron donors on the starting alcohols,[16b] and use of stoichiometric oxidants.[16a,17a–b] Therefore, it is highly important to develop a more desirable reagent for chemoselective oxidation that works under simple and mild reaction conditions and does not affect other oxidizable functional groups (e.g., amino, alkyne, hydroxy, etc.).

Our research interest is on oxidation catalysis, where we develop mild and widely applicable selective oxidation methods.[17] Our recent and ongoing efforts towards the synthesis of azo compounds and hydrazines use a copper(I) bromide/azobisisobutyronitrile (AIBN)/4-dimethylaminopyridine (DMAP) catalytic system via dehyrogenative coupling of aromatic amines under mild reaction conditions.[17c] During our studies on the selective oxidation of 2-aminobenzyl alcohol, surprisingly, we could notice only 2-amino benzaldehyde in 42% yield

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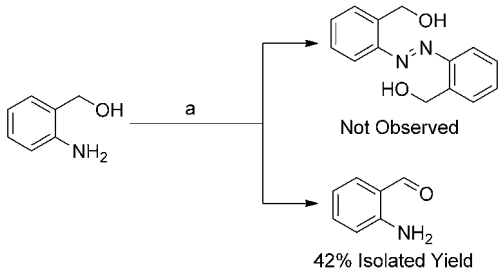
instead of the azo compound [(*E*)-(diazene-1,2-diylbis(2,1-phenylene) dimethanol] under the reported reaction conditions (Scheme 1).

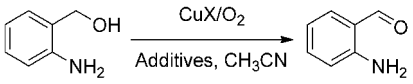


Scheme 1. Copper(I)-catalyzed oxidation of (2-aminophenyl)methanol. *Reagents and conditions*: a) CuBr, AIBN, O_2, DMAP, CH_3CN, rt, 12 h, 42% (aldehyde).

This observation prompted us to further investigate the chemoselective oxidation of amino, propargyl, and a wide range of diversely functionalized benzyl alcohols. We herein report an oxidation reaction that can be performed under very mild conditions (room temperature) in the presence of commercially available DMAP as the ligand with a copper(I) iodide/TEMPO catalyst system, without use of an external base, where molecular oxygen acts as a stoichiometric oxidant, and where water is the only byproduct.

Preliminary experiments were carried out using 2-aminobenzyl alcohol as model substrate. The first set of experiments was examined using copper(I) bromide as standard catalyst while changing the amount of AIBN and TEMPO. In the copper(I) bromide/DMAP/AIBN system, the maximum yield obtained was 42% (Table 1, entries 1 and 2). By increasing the reaction temperatures to 60 and 80 °C, the reaction was not selective, and unidentified products were formed in the reaction mixture along with the desired product. Next, AIBN was replaced with TEMPO, and varying the amounts of TEMPO and DMAP resulted

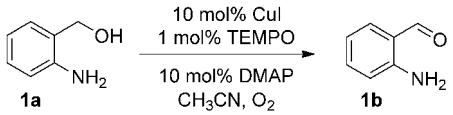
Table 1. Optimizing conditions for Aerobic oxidation of *o*-aminobenzyl alcohol.[a]

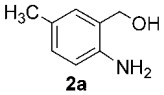
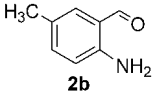
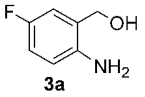
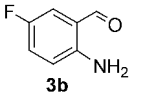
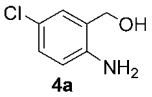
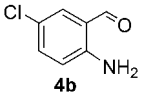
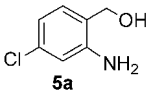
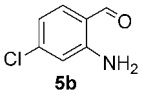
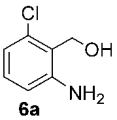
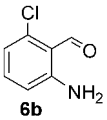
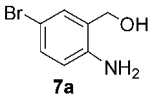
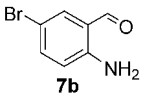
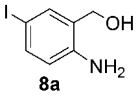
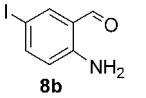
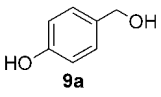
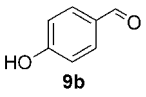
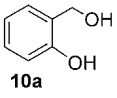
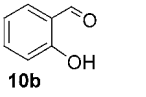
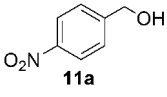
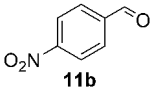
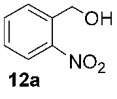
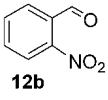
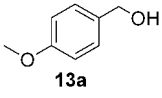
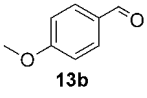


Entry	CuX	DMAP [mol%]	AIBN [mol%]	TEMPO [mol%]	Temp	Time [h]	Yield [%]
1	CuBr	120	30	–	rt	12	42
2	CuBr	120	100	–	rt	12	42
3	CuBr	120	–	10	rt	12	78
4	CuBr	120	–	5	rt	12	78
5	CuBr	20	–	5	rt	12	85
6	CuCl	20	–	5	rt	12	76
7	CuI	20	–	5	rt	3	87
8	CuI	20	–	1	rt	3	88
9	CuI	10	–	1	60–65 °C	3	88
10	CuI	–	–	1	rt	12	-
11	CuI	10	–	1	rt	3	88

a] *Reagents and conditions*: substrate (1 mmol), Cu catalyst (10 mol%), CH_3CN (3 mL) under O_2 balloon.

Table 2. Selective oxidation of benzyl and aminobenzyl alcohols.[a]



Entry	Substrate	Time [h]	Product	Yield[b] [%]
1	 **2a**	6	 **2b**	86
2	 **3a**	6	 **3b**	85
3	 **4a**	14	 **4b**	84
4	 **5a**	6	 **5b**	84
5	 **6a**	12	 **6b**	65
6	 **7a**	6	 **7b**	81
7	 **8a**	16	 **8b**	80
8	 **9a**	3	 **9b**	92
9	 **10a**	6	 **10b**	90
10	 **11a**	1.5	 **11b**	92
11	 **12a**	1.5	 **12b**	92
12	 **13a**	3	 **13b**	91

[a] *Reagents and conditions*: substrate (1 mmol), CuI (10 mol%), DMAP (10 mol%), and TEMPO (1 mol%) in CH_3CN (5 mL) under O_2 balloon at rt; reaction time as mentioned in the table. [b] Isolated yield after column chromatography.

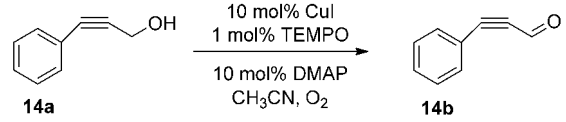
ed in an increase in yield to 85% in 12 h (Table 1, entry 5). The second set of experiments was performed under similar conditions using copper(I) chloride, which resulted in a 76% yield of desired product (Table 1, entry 6). The third set of experiments was examined by using copper(I) iodide in place of copper(I) bromide and copper(I) chloride and varying the amount of DMAP and TEMPO (Table 1, entries 7–11).

Among the copper(I) halides, copper(I) iodide was the most effective (Table 1). The maximum isolated yield of 88% was observed in the reaction lasting 3 h with copper(I) iodide (10 mol%,), DMAP (10 mol%), and TEMPO (1 mol%) (Table 1, Entry 11). Interestingly, in the presence of copper(I) iodide and TEMPO without using DMAP, no reaction takes place under optimized conditions (Table 1, entry 10).

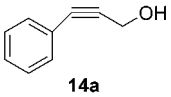
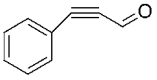
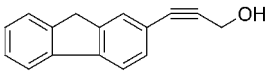
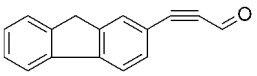
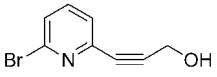
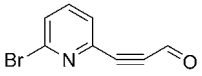
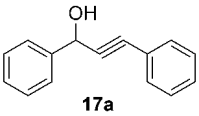
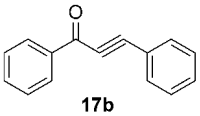
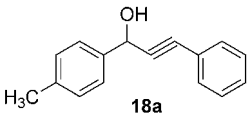
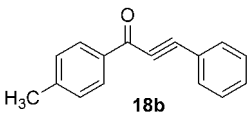
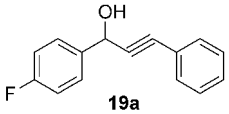
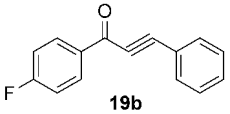
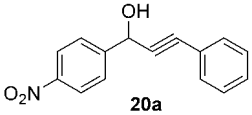
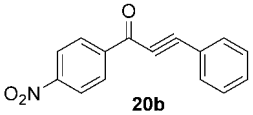
Next, the scope of this oxidation system was extended to various substituted 2-aminobenzyl alcohols to produce a series of amino aldehydes under the developed reaction conditions (Table 2). Next experiments were carried out with electron rich (2-amino-5-methylphenyl)methanol (**2a**, Table 2). The reaction progressed smoothly and gave the corresponding aldehyde **2b** in excellent yield (Table 2). Furthermore, aminobenzyl alcohols bearing a halogen substitution (**3a–8a**, Table 2) were converted into their respective carbonyl derivatives (**3b–8b**, Table 2) in good to excellent yields. When the chloro group was in *ortho*-position to the benzyl alcohol, the resultant aldehyde was obtained in 65% yield due to the *ortho* effect of chlorine. Notably, no overoxidized products, like carboxylic acids or other N-oxidized byproducts, were observed. In addition to the selective oxidation of aminobenzyl alcohols to aldehydes, the developed protocol was extended to various hydroxy-, nitro-, and methoxy-substituted benzyl alcohols (**9a–13a**, Table 2). As anticipated, substrates containing *ortho*-hydroxy and *para*-hydroxy groups, that is, 4-(hydroxymethyl)phenol (**9a**) and 2-(hydroxymethyl)phenol (**10a**), were selectively converted into their respective aldehydes in excellent yields (**9b** and **10b**, Table 2). Notably, benzyl alcohols with deactivating *ortho*- and *para*-nitro groups or an activating *para*-methoxy group were converted to their respective aldehydes in excellent yields (**11b, 12b**, and **13b**, Table 2).

Finally, the scope of this oxidation system was extended to propargyl alcohols to produce their respective aldehydes and ketones. Our initial experiments were carried out without any substituent on the phenyl moiety, that is, 3-phenylprop-2-yn-1-ol (**14a**, Table 3), which was successfully converted to the desired aldehyde **14b** with excellent yield. Here starting materials of fluorine and pyridine-containing propargyl alcohols were synthesized according to reported methods.[18] The synthesized propargyl alcohols were efficiently converted to their respective aldehydes in excellent yields. In addition, the developed protocol was extended to the oxidation of secondary propargyl alcohols (**17a–20a**, Table 3). Significantly, secondary alcohols with both electron-donating (hydrogen and methyl) and electron-withdrawing (nitro, fluoro, and bromo) groups were successfully converted to their corresponding ketones at room

Table 3. Selective oxidation of propargyl alcohols.[a]



14a **14b**

Entry	Substrate	Time [h]	Product	Yield[b] [%]
1	 **14a**	6	 **14b**	81
2	 **15a**	6	 **15b**	86
3	 **16a**	8	 **16b**	84
4	 **17a**	3	 **17b**	95
5	 **18a**	3	 **18b**	88
6	 **19a**	3	 **19b**	86
7	 **20a**	3	 **20b**	89

[a] *Reagents and conditions*: substrate (1 mmol), CuI (10 mol%), DMAP (10 mol%), and TEMPO (1 mol%) in CH_3CN (5 mL) under O_2 balloon at rt; reaction time as mentioned in the table. [b] Isolated yield after column chromatography.

temperature in excellent yields after 3 h of reaction time (**17b–20b**, Table 3).

In conclusion, the developed chemoselective oxidation method is simple, clean and requires mild reaction conditions to produce a wide variety of functional-group-containing amino aldehydes, hydroxy aldehydes, and α,β-acetylenic carbonyl compounds. A highlight of the proposed method is the use of commercially available and cheap reagents. Remarkably, sensitive groups like alkynes and oxidizable groups such as activated benzylic carbons, hydroxy groups of phenols, amino groups, and heteroatoms (as in pyridine) did not undergo oxidation; rather, these reactions selectively gave the respective aldehydes and ketones in excellent yields. Furthermore, the target molecules were obtained without formation of any by-products in the reaction mixture.

Experimental Section

Materials: The materials were purchased from Sigma–Aldrich and Merck, and were used without any additional purification. All reactions were monitored by thin-layer chromatography (TLC). Melting points were recorded in open capillaries on an Elchem digital melting point apparatus and are uncorrected. NMR spectra were obtained on a Bruker Avance-400 MHz instrument at room temperature. Samples for ^{1}H and ^{13}C NMR were ~0.03 M solutions in $CDCl_3$ using tetramethylsilane as internal reference. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were obtained using electrospray ionization mass spectrometry (ESI-MS) and gas-chromatography mass spectrometry (GC-MS) on a PerkinElmer Clarus 680.

General procedure for oxidation of alcohols: A mixture of 2-aminobenzyl alcohol (123 mg, 1 mmol), CuI (19.2 mg, 0.1 mmol), and CH_3CN (5 mL) in a 25 mL round-bottom flask was stirred for 5–10 min. DMAP (12.1 mg, 0.1 mmol) and TEMPO (1.56 mg, 1 mol%,) were added, and the resulting mixture was stirred under an O_2 balloon at rt until the reaction reached completion as determined by TLC. The resulting reaction mixture was filtered and washed with CH_3CN (2×5 mL), and the solvent was removed in vacuo. The obtained residue was purified by column chromatography using 100—200 mesh silica gel (*n*-hexane/EtOAc, 98:2) to provide the desired product.

Supporting Information is available for detailed experimental procedures, characterization data, and spectral data of the synthesized compounds.

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Keywords: aldehydes · benzyl alcohols · copper(I) catalyst · ketones · oxidation · propargyl alcohols

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