

Copper(II)-Catalyzed Aerobic Oxidation of Primary Alcohols to Aldehydes in Ionic Liquid [bmpy]PF₆

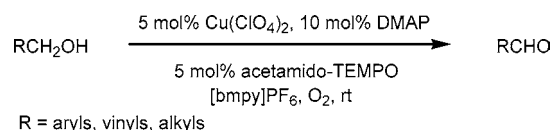
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ABSTRACT



A room-temperature aerobic oxidation of primary alcohols to aldehydes catalyzed by the three-component system acetamido-TEMPO/Cu(ClO₄)₂/DMAP in the ionic liquid [bmpy]PF₆ has been developed, and the catalysts can be recycled and reused for five runs without any significant loss of catalytic activity.

With ever-increasing environmental concerns, much attention has been directed toward the reduction or replacement of volatile organic compounds (VOCs) from the reaction media in the Green Chemistry focus area,¹ and a variety of environmentally benign media such as water, ionic liquids, immobilized solvents, fluorinated solvents, and supercritical fluids have been promoted as replacements to VOCs.² Ionic liquids, composed entirely of ions with a melting point below 100 °C,³ have been emerging as promising and attractive alternatives due to their unique properties, including low volatility, high polarity, good thermal stability, capacity to dissolve various organic, inorganic, and organometallic compounds, and a fine-tuning of their miscibility with water and organic solvents by a proper choice of cation and anion. So far, ionic liquids have been used as solvents in a wide range of organic reactions.⁴ However, only recently has the potential of transition-metal-catalyzed oxidation in ionic liquids been recognized.⁵

Selective alcohol oxidation is widely recognized as one of the most fundamental transformations in organic synthe-

sis.⁶ Numerous oxidizing reagents (i.e., KMnO₄, MnO₂, CrO₃, SeO₂, Br₂, etc.) in stoichiometric amount have been traditionally employed to accomplish this transformation⁷ with considerable drawbacks such as high cost and a large amount of waste byproducts. From an economic and environmental perspective, catalytic aerobic alcohol oxidation represents a promising protocol. The use of molecular oxygen as the primary oxidant has several benefits, including low cost, improved safety, abundance, and water as the sole byproduct. Accordingly, many transition metals such as cobalt,⁸ copper,⁹

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molybdenum,¹⁰ nickel,¹¹ osmium,¹² palladium,¹³ ruthenium,¹⁴ and vanadium¹⁵ have been used as catalysts for alcohol oxidation with molecular oxygen as the terminal oxidant. As an alternative, the nitroxyl radical TEMPO (2,2,6,6-tetramethyl-piperidyl-1-oxy) has emerged to be the catalyst of choice for the mild and selective alcohol oxidation.^{16,17} TEMPO-catalyzed aerobic alcohol oxidation in the absence of transition metal has also been recently reported.¹⁸ Of the particular interest are the catalytic systems consisting of TEMPO and an inexpensive transition-metal compound.

However, TEMPO is a rather expensive chemical agent, and efficient recycling of TEMPO is a very desirable goal. Several groups have addressed this problem by involving

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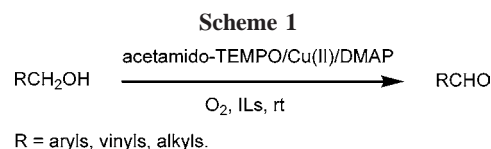
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heterogeneous variants of TEMPO.¹⁹ Recently, we reported a commercially available acetamido-TEMPO that can be recycled and reused in an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆), for selective oxidation of benzylic alcohols to aldehydes with hydrogen peroxide as the terminal oxidant.²⁰ In continuation of our interest in exploring green oxidation of alcohols in ionic liquids, we herein report a mild and effective procedure for the selective aerobic oxidation of primary alcohols to aldehydes using a three-component catalytic system consisting of acetamido-TEMPO, copper(II) salt, and DMAP with an ionic liquid as the solvent (Scheme 1). Furthermore, we demonstrate that the catalytic system can be recycled and reused for five runs without any significant loss of catalytic activity.



The initial study was carried out using 4-methoxybenzyl alcohol as the substrate to optimize the reaction conditions, and the results are summarized in Table 1. At first, three

Table 1. Optimization of the Reaction Conditions for Oxidizing 4-Methoxybenzyl Alcohol to 4-Methoxybenzaldehyde^{a,b}

entry	copper salt	ionic liquid	conversion (%) ^c	yield (%) ^d
1	CuCl ₂	[bmim]PF ₆	52	43
2	CuCl ₂	[bmim]BF ₄	47	45
3	CuCl ₂	[mmim]OSO ₃ Me	44	32
4	CuCl ₂	[bmpy]PF ₆	87	81
5	Cu(OAc) ₂	[bmpy]PF ₆	66	59
6	CuBr ₂	[bmpy]PF ₆	91	88
7	Cu(CIO ₄) ₂	[bmpy]PF ₆	99	91
8 ^e	Cu(CIO ₄) ₂	[bmpy]PF ₆	4	—
9 ^f	Cu(CIO ₄) ₂	[bmpy]PF ₆	0	—
10 ^g	—	[bmpy]PF ₆	0	—

^a 2 mmol 4-methoxybenzyl alcohol, 5 mol% acetamido-TEMPO, 5 mol% copper(II) salt, 10 mol% DMAP, 1 atm O₂, 0.50 g ionic liquid, room temperature for 5 h. ^b Selectivity is over 99% determined by ¹H NMR of the crude product mixture. ^c Conversion by ¹H NMR of the crude product mixture. ^d Isolated yield by flash chromatography. ^e No DMAP was added. ^f No acetamido-TEMPO was added. ^g No copper salt was added.

imidazolium-type ionic liquids, [bmim]PF₆, [bmim]BF₄, and [mmim]OSO₃Me (1,3-dimethylimidazolium methyl sulfate),

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and one pyridinium-type ionic liquid, [bm_{py}]⁺PF₆⁻ (1-butyl-4-methylpyridinium hexafluorophosphate), were tested with CuCl₂ as the catalyst precursor. The imidazolium-type ionic liquids gave only mild conversions (Table 1, entries 1–3), and [bm_{py}]⁺PF₆⁻ proved to be optimal, providing an 87% conversion and 81% isolated yield (Table 1, entry 4). Next, various types of copper(II) salts were tested as catalyst precursors in [bm_{py}]⁺PF₆⁻. All the copper salts gave good to excellent conversions (Table 1, entries 4–7), and Cu(ClO₄)₂ was found to be the best catalyst precursor with 99% conversion and 91% isolated yield (Table 1, entry 7). Furthermore, all three components (copper salt, acetamido-TEMPO, and DMAP) are crucial for this aerobic oxidation, and the lack of any component leads to very low conversion or no reaction (Table 1, entries 8–10). Most importantly, no over-oxidized product (4-methoxybenzoic acid) was detected by ¹H NMR analysis of the crude reaction mixtures in all the cases.

Having optimized the reaction conditions, we examined the recyclability of the three-component catalytic system acetamido-TEMPO/Cu(ClO₄)₂/DMAP for the aerobic oxidation of 4-methoxybenzyl alcohol in [bm_{py}]⁺PF₆⁻ (Table 2).

Table 2. Recycling of the Catalytic System for the Oxidation of 4-Methoxybenzyl Alcohol to Aldehyde^{a,b}

run	time (h)	conversion (%) ^c	yield (%) ^d
1	5	99	91
2	5	96	91
3	5	94	92
4	8	93	85
5	8	87	81

^a 2 mmol 4-methoxybenzyl alcohol, 5 mol% acetamido-TEMPO, 5 mol% Cu(ClO₄)₂·6H₂O, 10 mol% DMAP, 1 atm O₂, 0.50 g [bm_{py}]⁺PF₆⁻, room temperature. ^b Selectivity is over 99% determined by ¹H NMR of the crude product mixture. ^c Conversion by ¹H NMR of the crude product mixture. ^d Isolated yield by flash chromatography.

Due to the good solubility of acetamido-TEMPO and DMAP in the ionic liquid [bm_{py}]⁺PF₆⁻, the reuse of the catalysts was performed without any significant loss of catalytic activity after full extraction of the product five times with 5 mL *n*-pentane per extraction.²¹ It is important to stress that this system was shown to be readily recyclable for four additional runs with only a slight drop in activity.

Subsequently, the three-component catalytic system was then applied to various benzylic, allylic, and aliphatic alcohols as summarized in Table 3.²² It is clear that all primary alcohols have been selectively oxidized to aldehydes. Surprisingly, no oxidation was observed with secondary alcohols such as 1-phenylethanol and cyclohexanol (Table

(21) It has to be noted that both acetamido-TEMPO and DMAP are insoluble in *n*-pentane and that [bm_{py}]⁺PF₆⁻ is immiscible with *n*-pentane.

Table 3. Aerobic Oxidation of Alcohols in [bm_{py}]⁺PF₆⁻^a

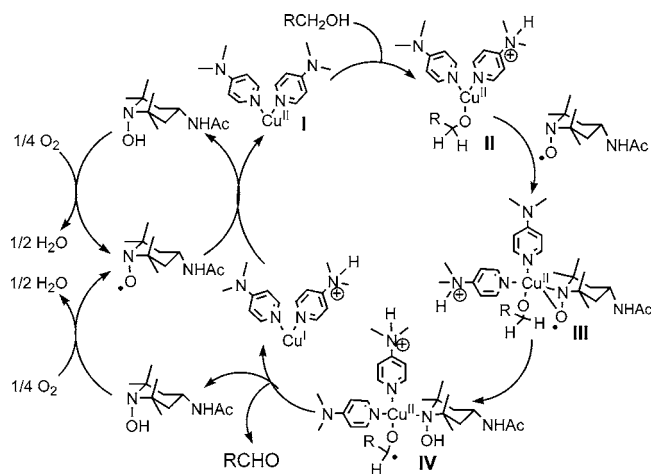
entry	alcohols	time (h)	product	convn ^b /yield ^c (%)
1		5		99/92
2		5		98/90
3		5		100/90
4		5		99/91
5		5		99/84
6		5		98/92
7		5		100/81
8		5		96/89
9		5		100/89
10		5		100/77
11		24 24 ^d		48/26 94/61
12		24 ^d		100/54
13		24		-
14		24		-
15		4		97/75
				12/-

^a Alcohol (2 mmol), 5 mol% acetamido-TEMPO, 5 mol% Cu(ClO₄)₂·6H₂O and 10 mol% DMAP were stirred at room temperature under 1 atm oxygen for the appropriate time. ^b Conversion by ¹H NMR. ^c Isolated yield. ^d The reaction was carried out at 40 °C.

3, entries 13 and 14). In addition, the conversion of benzylic and allylic alcohols to aldehydes is faster and more efficient with over 96% conversions in 5 h (Table 3, entries 1–10), which are excellent results for a copper-catalyzed room-temperature aerobic alcohol oxidation performed in an ionic liquid. However, aliphatic primary alcohols were less reactive, and longer reaction time and elevated temperature were needed to reach good conversions (Table 3, entries 11 and

(22) **Representative Experimental Procedure.** A mixture of 4-methoxybenzyl alcohol (276 mg, 2 mmol), 4-(dimethylamino)pyridine (DMAP, 24.4 mg, 0.2 mmol), and Cu(ClO₄)₂·6H₂O (37.1 mg, 0.1 mmol) was heated at 40 °C under magnetic stirring for 5 min, and [bm_{py}]⁺PF₆⁻ (0.50 g) was added to the mixture. After 5 min of stirring, acetamido-TEMPO (21.3 mg, 0.1 mmol) was added, and the dark green color of the reaction mixture turned into pale yellow. The reaction mixture was stirred at room temperature under O₂ (1 atm) for 5 h and then extracted with *n*-pentane (5 × 5 mL). The combined *n*-pentane phase was concentrated in vacuo. The residue was subjected to ¹H NMR analysis and then purified by flash chromatography (*n*-pentane/diethyl ether = 10:1) to afford 4-methoxybenzaldehyde (colorless oil, 247 mg, yield 91%).

Scheme 2



12). Furthermore, a mixture of 4-methoxybenzyl alcohol and 3-phenyl-1-propanol was reacted with molecular oxygen in the present catalytic system for 4 h. The result shows the good selectivity of the catalytic system toward benzylic alcohol oxidation. Thus, 97% of the 4-methoxybenzyl alcohol was converted to aldehyde, whereas only 12% of the 3-phenyl-1-propanol was oxidized (Table 3, entry 15). This may be of great interest in synthetic organic chemistry when different alcoholic functions (primary benzylic/allylic, primary and secondary aliphatic) are present in the same molecule.

A possible mechanism for the primary alcohol oxidation (Scheme 2) could involve DMAP coordinating copper(II)

species, similar to the $\text{CuBr}_2(2,2'\text{-bipyridine})\text{-TEMPO}$ system reported by Sheldon and co-workers.²³ The inactivity of the secondary alcohol might be attributed to steric effects of the complex **II**, which hinder TEMPO's coordination to form the complex **III**. At this point, it has to be mentioned that DMAP, in the catalytic system, might have dual roles: the base to deprotonate the primary alcohol and the N-donor ligand to copper(II) salt. This could be partially confirmed by very low conversions (less than 10%) of 4-methoxybenzyl alcohol oxidation when DMAP is replaced by pyridine or *N,N*-dimethylaniline under the identical conditions.

In conclusion, an efficient and selective aerobic oxidation of primary alcohols to aldehydes using an acetamido-TEMPO/Cu(ClO₄)₂/DMAP system has been developed in the ionic liquid [bmpy]PF₆. Most importantly, the catalysts are very easy to handle and can be recycled and reused for five runs without any significant loss of catalytic activity. The scope, mechanism, and synthetic applications of the oxidation are currently under investigation.

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Supporting Information Available: Representative experimental procedure and the full characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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