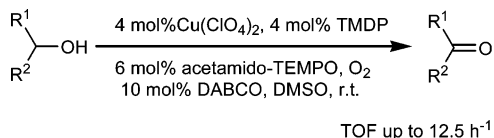# Cu(II)-Catalyzed Selective Aerobic Oxidation of Alcohols under Mild Conditions

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TOF up to 12.5 h^{-1}

Aerobic Alcohol Oxidation. An efficient four-component system consisting of acetamido-TEMPO/Cu(ClO$_4$)$_2$/TMDP/DABCO in DMSO has been developed for room-temperature aerobic alcohol oxidation. Under the optimal conditions, various alcohols could be converted into their corresponding aldehydes or ketones in good to excellent yields. The newly developed catalytic system could also be recycled and reused for three runs without any significant loss of catalytic activity.

The design of efficient catalytic systems that provide facile recovery of catalysts and isolation of a catalyst-free product are highly attractive due to practical economic and environmental manufacturing considerations.[1] To address this challenge, different strategies are being developed including the use of ionic liquids,[2] fluorous biphasic systems,[3] soluble polymer-based ligands,[4] and aqueous biphasic systems.[5] However, the use of the polar aprotic solvent dimethyl sulfoxide (DMSO) to recycle and reuse homogeneous transitional metal catalysts is less developed.[6] Nonetheless, considering its capacity to dissolve various organic, inorganic, and organometallic compounds and its immiscibility with many nonpolar organic solvents, it was anticipated that these properties would facilitate catalyst−product separation by simple extraction. Thus, the use of DMSO as the reaction media should provide opportunities for facilitating the recovery and recycling of catalysts.

Selective alcohol oxidation is a fundamental transformation for the production of a variety of important intermediates and fine chemicals.[7] Although numerous inorganic oxidants (i.e., CrO$_3$, KMnO$_4$, MnO$_2$, SeO$_2$, etc.) in a stoichiometric amount have been traditionally used to accomplish this transformation,[8] there are considerable drawbacks such as their high cost and the production of environmental hazardous/toxic byproducts. Clearly, the most promising protocol to address these issues is the development of catalytic aerobic alcohol oxidation methodologies. The use of molecular oxygen as the primary oxidant has remarkable advantages, including abundance, low cost, improved safety, and benign byproducts (H$_2$O and/or H$_2$O$_2$). Accordingly, many transitional metals (mainly copper,[9] palladium,[10] and ruthenium[11]) alone or in combination with the nitroxy radical 2,2,6,6-tetramethyl-piperidyl-1-oxy (TEMPO)[12,13] have been intensively studied for the aerobic catalytic oxidation of alcohols. Of particular interest are the catalytic systems consisting of an inexpensive transition-metal compound and TEMPO for mild and selective aerobic alcohol oxidations. However, TEMPO is a rather expensive chemical agent and efficient recycling of TEMPO is highly desirable, especially when the reactions are run on a large scale. Several groups have

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SCHEME 1

addressed this problem by involving silica-supported,[14] polymer-supported,[15] fluorous-tagged,[16] or cation-tagged[17] variants of TEMPO. Recently, we reported the three-component system acetamido-TEMPO/Cu(ClO4)2/DMAP (DMAP, 4-(dimethylamino)-pyridine) for room-temperature aerobic alcohol oxidation in the ionic liquid [bmpy]PF6,[18] where a wide range of primary alcohols can be highly selectively converted into aldehydes and the catalysts, including acetamido-TEMPO, can also be recycled and reused without significant loss of catalytic activity. As acetamido-TEMPO is insoluble in *n*-pentane, hexanes, or ether, we envision that the use of DMSO as the reaction media for aerobic alcohol oxidation can achieve the product−catalysts separation by simple extraction of the product (aldehydes or ketones) with *n*-pentane, which is immiscible with DMSO, leaving the catalysts immobilized in the DMSO phase. Herein, we report a four-component system acetamido-TEMPO/Cu(ClO4)2/TMDP/DABCO for mild and selective aerobic alcohol oxidation in DMSO (Scheme 1). Furthermore, the catalytic system can be recycled and reused for selective oxidation of various benzylic and allylic alcohols into aldehydes.

Our previous study[18] demonstrated that Cu(ClO4)2 is a good copper catalyst precursor and that a pyridine-type ligand is needed to perform room-temperature aerobic alcohol oxidation. The optimization of this catalytic system was accomplished employing 4-methoxybenzyl alcohol as the substrate, and the results are summarized in Table 1. At first, DMAP, 2,2′-bipyridine

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TABLE 1. Optimization of Aerobic Oxidation of 4-Methoxybenzyl Alcohol[a,b]

entry	ligand	additive (mol %)	conversion (%)[c]	yield (%)[d]
1	DMAP	none	56	41
2	Bipy	none	53	45
3	Phen	none	45	30
4	TMDP	none	76	66
5	TMDP	KOH (10)	21	
6	TMDP	K2CO3 (10)	85	70
7	TMDP	pyridine (10)	90	84
8	TMDP	Et3N (10)	96	90
9	TMDP	DABCO (10)	100	96
10[e]	TMDP	DABCO (10)	100	92
11	TMDP	Et3N (20)	99	91
12[e,f]	TMDP	DABCO (10)	100	94
13[e,g]	TMDP	DABCO (10)	0	
14[e,h]		DABCO (10)	0	

[a] Reaction conditions: 2 mmol of 4-methoxybenzyl alcohol, 6 mol % of acetamido-TEMPO, 4 mol % of Cu(ClO4)2·6H2O, 4 mol % of ligand (8 mol % of DMAP), 1 atm O2, 0.3 mL of DMSO, room temperature for 4 h. [b] Selectivity is over 99% determined by ^{1}H NMR of the crude product mixture. [c] Conversion by ^{1}H NMR of the crude product mixture. [d] Isolated yield by flash chromatography. [e] Reaction was run for 2 h. [f] Water (0.1 mL) was added. [g] No acetamido-TEMPO was added. [h] No TMDP was added.

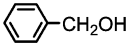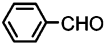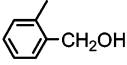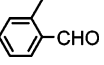TABLE 2. Recycling of the Catalytic System for Aerobic Oxidation of Benzylic and Allylic Alcohols[a,b]
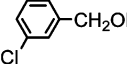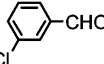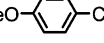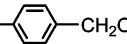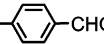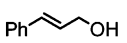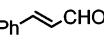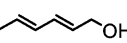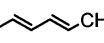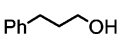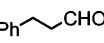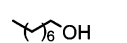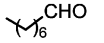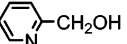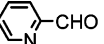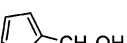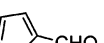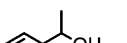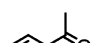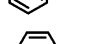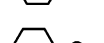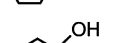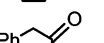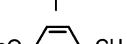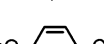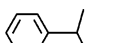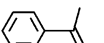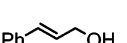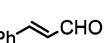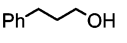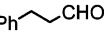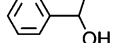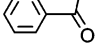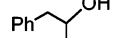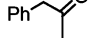
entry	R	cycle no. (time, h) conversion[c]/yield[d] (%)		
1	4-MeOPh	1 (2) 100/90	2 (2) 94/89	3 (3) 88/82
2	Ph	1 (2) 100/85	2 (2) 93/92	3 (3) 90/89
3	3-ClPh	1 (2) 99/93	2 (2) 95/85	3 (3) 92/90
4	4-MePh	1 (2) 100/92	2 (2) 96/91	3 (3) 89/83
5	*trans*-PhCH=CH	1 (2) 99/93	2 (2) 93/84	3 (3) 90/87
6[e]	Ph	1 (4) 98/88	2 (4) 90/85	3 (6) 81/78

[a] Reaction conditions: 2 mol of alcohol, 6 mol % of acetamido-TEMPO, 4 mol % of Cu(ClO4)2·6H2O, 4 mol % of TMDP, 10 mol % of DABCO, 1 atm O2, 0.3 mL of DMSO, room temperature for a specific time. [b] Selectivity is over 99% determined by ^{1}H NMR of the crude product mixture. [c] Conversion by ^{1}H NMR of the crude product mixture. [d] Isolated yield by flash chromatography. [e] 20 mol % of Et3N was used to replace DABCO.

(Bipy), 1,10-phenanthroline (Phen), and 4,4′-trimethylenedipyridine (TMDP) were tested as the pyridine-type ligands for this catalysis. All the ligands were shown to be effective to afford good conversions, with TMDP providing an optimal 76% conversion and 66% isolated yield (Table 1, entries 1−4). Next, selected additives KOH, K2CO3, pyridine, Et3N, and DABCO (1,4-diazabicyclo[2.2.2]octane) were screened to improve this transformation with TMDP as the ligand. Although KOH was found to decrease the reaction significantly, the others afforded better conversions and isolated yields (Table 1, entries 5−9). DABCO proved to be the best, and the use of 10 mol % of DABCO provided 100% conversion and 96% isolated yield. Furthermore, reducing the reaction time from 4 to 2 h with DABCO as the additive also afforded the complete conversion

TABLE 3. Aerobic Oxidation of Alcohols in DMSO[a,b]

entry	alcohols	product	time (h)	conversion[c] (%)	yield[d] (%)
1	Ph–CH$_2$OH	Ph–CHO	2	100	98
2	2-methylphenyl–CH$_2$OH	2-methylphenyl–CHO	2	98	90
3	3-chlorophenyl–CH$_2$OH	3-chlorophenyl–CHO	2	99	93
4	MeO–C$_6$H$_4$–CH$_2$OH	MeO–C$_6$H$_4$–CHO	2	100	92
5	4-alkylphenyl–CH$_2$OH	4-alkylphenyl–CHO	2	100	92
6	Ph–CH=CH–CH$_2$OH	Ph–CH=CH–CHO	2	99	93
7	CH$_3$CH=CH–CH=CH–CH$_2$OH	CH$_3$CH=CH–CH=CH–CHO	2	100	85
8	Ph–CH$_2$CH$_2$CH$_2$–OH	Ph–CH$_2$CH$_2$–CHO	24 / 24[e]	19 / 71	11 / 40
9	(CH$_3$)$_2$CH(CH$_2$)$_6$–OH	(CH$_3$)$_2$CH(CH$_2$)$_5$–CHO	24[e]	58	33
10	pyridin-2-yl–CH$_2$OH	pyridin-2-yl–CHO	2	98	71
11	thiophen-2-yl–CH$_2$OH	thiophen-2-yl–CHO	2	99	92
12	Ph–CH(OH)CH$_3$	Ph–C(=O)CH$_3$	24 / 24[e]	35 / 98	27 / 90
13	cyclohex-2-enol	cyclohex-2-enone	24[e]	87	74
14	cyclohexanol	cyclohexanone	24[e]	–	–
15	Ph–CH$_2$CH(OH)CH$_3$	Ph–CH$_2$C(=O)CH$_3$	24[e]	–	–
16	MeO–C$_6$H$_4$–CH$_2$OH	MeO–C$_6$H$_4$–CHO	1.5	97	75
	Ph–CH(OH)CH$_3$	Ph–C(=O)CH$_3$		7	–
17	Ph–CH=CH–CH$_2$OH	Ph–CH=CH–CHO	1.5	98	85
	Ph–CH$_2$CH$_2$CH$_2$–OH	Ph–CH$_2$CH$_2$–CHO		4	–
18	Ph–CH(OH)CH$_3$	Ph–C(=O)CH$_3$	24[e]	95	84
	Ph–CH$_2$CH(OH)CH$_3$	Ph–CH$_2$C(=O)CH$_3$		–	–

[a] Alcohol (2 mmol), 6 mol % of acetamido-TEMPO, 4 mol % of Cu(ClO$_4$)$_2$·6H$_2$O, 4 mol % of TMDP, 10 mol % of DABCO, and 0.3 mL of DMSO were stirred at room temperature under 1 atm oxygen for the specific time. [b] Selectivity is over 99% for aerobic oxidation of primary alcohols. [c] Conversion by ^{1}H NMR. [d] Isolated yield by flash chromatography. [e] The reaction was carried out at 40 °C.

(Table 1, entry 10). On the other hand, 20 mol % of Et$_3$N can provide 99% conversion after 4 h (Table 1, entry 11). It is interesting to note that many catalytic aerobic alcohol oxidation systems have a very low tolerance toward water despite the fact that water forms as the stoichiometric byproduct of aerobic alcohol oxidation. Thus, water was purportedly added to the reaction system to examine its effect on this transformation, and a quantitative conversion was obtained (Table 1, entry 12).

However, a system without TMDP or acetamido-TEMPO failed to oxidize the alcohol (Table 1, entries 13 and 14). Moreover, no overoxidized product (4-methoxybenzoic acid) was detected by ^{1}H NMR analysis of the crude reaction mixtures in all the cases.[19]

Having optimized the reaction conditions, we next examined the recyclability of the catalytic system for aerobic oxidation of various benzylic and allylic alcohols in DMSO (Table 2).

Because of the good solubility of acetamido-TEMPO, TMDP, DABCO, and $Cu(ClO_4)_2$ (coordinated with TMDP) in DMSO, the recovery and reuse of the catalytic system was accomplished after full extraction of the aldehydes with *n*-pentane.[20] It is important to stress that this system was shown to be readily recyclable for two additional runs with only a slight drop in activity. Furthermore, the electronic property of the substituents on the benzene rings does not affect the reaction times (Table 2, entries 1−4). For the comparison, the use of Et_3N as the additive was also tested for the recycling and reuse of the catalytic system. Besides longer reaction times, 20 mol % of Et_3N needed to be added to the catalytic system every run after full extraction of benzaldehyde (Table 2, entry 6).

Subsequently, the catalytic system[21] was then applied to various benzylic, allylic, and aliphatic alcohols as summarized in Table 3. It is clear that all primary alcohols have been selectively oxidized to aldehydes. In addition, the conversion of benzylic and allylic alcohols to aldehydes is faster and more efficient with over 98% conversions in 2 h (Table 3, entries 1−7), which are excellent results for a copper-catalyzed room-temperature aerobic alcohol oxidation (TOF of 12.5 h^{-1}). Aliphatic primary alcohols are less reactive, and thus longer reaction times and elevated temperature were needed to reach good conversions (Table 1, entries 8 and 9). Although these latter reactions were incomplete, there were no overoxidized byproducts (i.e., acids) detected by ^1H NMR analysis of the crude product mixtures. Hence, the reduced conversion was attributed to the instability of TEMPO under the reaction conditions used.[13a] It has to be noted that the heteroatom-containing (N,S) substrates, 2-pyridine methanol and 2-thiophene methanol, can be smoothly converted into their corresponding aldehydes in excellent conversions and yields (Table 3, entries 10 and 11). Surprisingly, the reactive secondary alcohols, such as 1-phenylethanol and 2-cyclohexen-1-ol, could be oxidized into the corresponding ketones in excellent conversions and isolated yields (Table 3, entries 12 and 13). It has to be pointed out that no aerobic oxidation of 1-phenylethanol in our previous $Cu(ClO_4)_2$−TEMPO−DMAP system[18] or in Sheldon's $CuBr_2$-(2,2′-bipyridine)−TEMPO−^tBuOK system[13g] was observed. Thus DABCO, in the present catalytic system, might have dual roles: the base to promote the deprotonation of 1-phenylethanol and a weak N-donor ligand to Cu(II) salt, which could be partially confirmed by very low conversion of 1-phenylethanol oxidation (less than 5%) when 10 mol % of DABCO was replaced by 10 mol % of Et_3N under the identical conditions (40 °C and 24 h). However, no oxidation was observed with cyclohexanol or 1-phenyl-2-propanol (Table 3, entries 14 and 15). Furthermore, a mixture of 4-methoxybenzyl alcohol and 1-phenylethanol was reacted with molecular oxygen in the present catalytic system for 3 h. The result demonstrates the good selectivity of the catalytic system toward primary alcohol, with 98% conversion of 4-methoxybenzyl and only 7% conversion of 1-phenylethanol. At the same time, a mixture of *trans*-cinnamyl alcohol and 3-phenyl-1-propanol was also tested, showing excellent selectivity toward oxidation of allylic alcohol (98% conversion of *trans*-cinnamyl alcohol and 4% conversion of 3-phenyl-1-propanol). Similarly, the competing reaction between 1-phenylethanol and 1-phenyl-2-propanol led to 95% conversion of 1-phenylethanol, leaving 1-phenyl-2-propanol intact. These experiments demonstrate the excellent selectivity of the present catalytic system providing considerable advantages in synthetic organic chemistry, considering that different alcohol functions in the same molecule could be selectively oxidized.

In conclusion, we have developed an efficient four-component system consisting of acetamido-TEMPO/$Cu(ClO_4)_2$/TMDP/DABCO for aerobic alcohol oxidation. At room temperature, the catalytic system shows excellent selectivity toward oxidation of benzylic or allylic alcohols and is notably not deactivated by heteroatom-containing (S,N) compounds. Moreover, the use of DMSO as the reaction media allows the catalysts to be recycled and reused for three runs with no significant loss of catalytic activity.

Experimental Section

General Procedure for Catalytic Aerobic Alcohol Oxidation in DMSO. A mixture of alcohol (2 mmol), 4,4′-trimethylenedipyridine (TMDP, 15.8 mg, 0.08 mmol), $Cu(ClO_4)_2$·$6H_2O$ (29.7 mg, 0.08 mmol), and 0.3 mL of DMSO was stirred at room temperature for 5 min, and then acetamido-TEMPO (25.6 mg, 0.12 mmol) was added to the mixture. After 5 min of stirring, DABCO (22.4 mg, 0.2 mmol) was added, and the reaction mixture was vigorously stirred at room temperature under O_2 (1 atm) for 2 h. With 1 mL of water added to the reaction mixture, the product was extracted with *n*-pentane (3 × 5 mL). The combined organic phase was washed by 3 mL of water and dried by anhydrous $MgSO_4$. After concentration in vacuo, the residue was subjected to ^1H NMR analysis and then purified by flash chromatography to afford aldehyde (ketone).

General Procedure for Recycling of the Catalytic System for Aerobic Oxidation of Benzylic and Allylic Alcohols. A mixture of alcohol (2 mmol), 4,4′-trimethylenedipyridine (TMDP, 15.8 mg, 0.08 mmol), $Cu(ClO_4)_2$·$6H_2O$ (29.7 mg, 0.08 mmol), and 0.3 mL of DMSO was stirred at room temperature for 5 min, and then acetamido-TEMPO (25.6 mg, 0.12 mmol) was added to the mixture. After 5 min of stirring, DABCO (22.4 mg, 0.2 mmol) was added. The reaction mixture was vigorously stirred at room temperature under O_2 (1 atm) for 2 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 to afford aldehyde. The next run was performed by adding fresh alcohol (2 mmol) to the catalytic system under the same experimental conditions for the specific reaction time (see Table 2 in paper for the reaction time).

Supporting Information Available: ^1H and ^{13}C NMR spectra for all isolated products. This material is available free of charge via Internet at http://pubs.acs.org.

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(19) It has to be noted that in the present catalytic system DMSO was not oxidized into methyl sulfone, which was confirmed by ^1H NMR analysis of the reaction mixture.

(20) It is observed that approximately 50−70 mg of DMSO (around 17−23%) was extracted into the *n*-pentane phase after full extraction of the aldehyde from the reaction system, which can be confirmed by ^1H NMR of the crude reaction mixture, and no additional DMSO needed to be added into the reaction system for the next run. At the same time, it has to be pointed out that there is 4% copper leaching into the crude product mixture during the extraction, analyzed by inductively coupled plasma emission spectroscopy.

(21) It has to be mentioned that the catalytic aerobic oxidation of 2 mmol of alcohol requires only 0.3 mL of DMSO (not optimized) as the solvent, which is water miscible and enables product separation by adding water and extraction.