Biomimetic Oxidation of Alcohols Catalyzed by TEMPO-Functionalized Polyethylene Glycol and Copper(I) Chloride in Compressed Carbon Dioxide

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Abstract: Recyclable TEMPO-functionalized polyethylene glycol [PEG_{6000}-$(TEMPO)_2$] in combination with cuprous chloride were developed for biomimetic oxidation of a series of benzylic, allylic, heterocyclic alcohols, and 2-phenylethanol into the corresponding aldehydes or ketones in high selectivity and in moderate to high conversion in compressed CO_2, which enhanced the catalytic activity as well as improved the selectivity.

Key words: alcohol oxidation, TEMPO, carbon dioxide, polymer, copper(I) chloride

The selective oxidation of primary and secondary alcohols into the corresponding aldehydes or ketones is undoubtedly one of the most important and challenging transformations in organic chemistry.[1] One particular interest in this field is use of stable nitroxyl radical 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) in conjunction with certain terminal oxidants.[2] However, many explored systems based on TEMPO using stoichiometric amounts of terminal oxidants such as bleach, sodium chlorite, *m*-chloroperoxybenzoic acid (MCPBA), hypervalent iodine(III) compounds generally suffer from the production from large amounts of waste.[3] From economic and environmental perspectives, using molecular oxygen or hydrogen peroxide as a terminal oxidant has received great attention nowadays since only water is formed as a byproduct. Unfortunately, the relatively expensive TEMPO species is unable to be regenerated directly by molecular oxygen alone, so a cocatalyst is required for activation of molecular oxygen. In 1984, Semmelhack et al.[4] ingeniously described the aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones catalyzed by CuCl/TEMPO. The reaction was regarded to go through a copper-centered oxidation, which bears a superficial resemblance to the mononuclear copper enzyme galactose oxidase.[5] Consequently, many efforts have been devoted to developing effective ligands or additives for the Cu(I)/TEMPO system.[6] Unfortunately, separation of products required tedious workup procedures. In this context, recycling TEMPO has been realized by immobilizing it onto inorganic or organic supports.[7] In particular, supporting TEMPO species onto soluble homogeneous polymers would be promising.[8] Increased solvent compatibility with accelerated reaction rate is attained in the case of soluble homogeneous supports in comparison with heterogeneous analogues.

Polyethylene glycol (PEG) is an inexpensive, nonvolatile, and environmentally benign solvent, which represents an interesting reaction medium in place of conventional solvents.[9] On the other hand, commercial availability of PEG derivatives with either two or one CH_2OH end group make it easy to prepare a variety of PEG-supported ligands and/or catalysts, for instance, PEG_{6000}-$(TEMPO)_2$.[8c–g] In addition, the PEG-supported catalyst could precipitate quantitatively after reaction upon adjusting certain parameters, such as temperature, solvent, polarity, and pH value of the solution. At present, PEG-supported catalysts have been widely used in many reactions for recycling homogeneous catalyst.[7d,10] Various strategies have been developed for chemical functionalization of PEG with TEMPO,[8c–g] such as via 5-hydroxyisophthalic acid[8d] or directly to generate PEG-supported TEMPO derivatives, for example, PEG_{6000}-$(TEMPO)_2$[8d] being used as active, recoverable catalysts in the aerobic oxidation of alcohols, both in the presence of Cu(I)[7a] and of other metal salts.[8g] However, a stoichiometric amount of terminal oxidant such as NaOCl, 1,3,5-trichloro-2,4-triazinetrione (TCCA), or [bis(acetoxy)iodo]benzene (BAIB), whereby easily resulting in a large amount of waste, is often required. On the other hand, metal salts such as CuCl[7a] or $Mn(NO_3)_2$ and $Co(NO_3)_2$[8g] in combination with the PEG-supported TEMPO were used for the aerobic oxidation of alcohols in toxic organic solvents or corrosive acids. So an efficient and greener method for oxidizing of alcohols to carbonyl compounds catalyzed by TEMPO-based catalyst still remains challenging.

Compressed CO_2 has attracted much attention as a replacement for organic solvents, because CO_2 is considered nontoxic, relatively cheap, and nonflammable.[11] In particular, CO_2 appears to be an ideal medium for oxidations. Unlike almost any organic solvent, CO_2 will not be oxidized further, and hence the use of CO_2 as a reaction medium eliminates byproducts originating from the solvent. In addition, high miscibility of O_2 in compressed CO_2 could eliminate interphase transport limitations.[12]

On the basis of our previous work on PEG-supported catalysts, such as PEG-supported quaternary ammonium salts, quaternary phosphonium salts, or guanidinium bromide for the cycloaddition reaction of aziridines or epoxides with CO_2,[13] we would like to perform biomimetic oxidation of alcohols catalyzed by the TEMPO-function-

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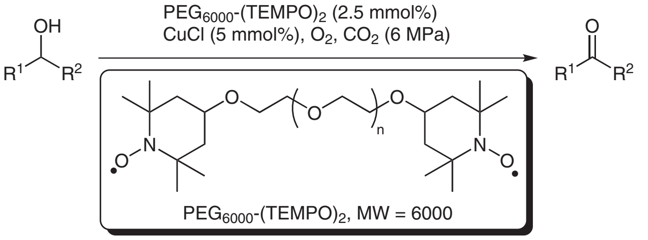


Scheme 1 The aerobic oxidation of alcohol catalyzed by PEG_{6000}-$(TEMPO)_2$/CuCl in compressed carbon dioxide

alized PEG/CuCl in compressed CO_2 (Scheme 1) through a so-called 'mono-phase reaction, two-phase separation' process to recover the catalyst, thus leading to conducting a homogeneous catalysis in a continuous mode. In particular, compressed CO_2 in this study could not only provide a safe environment for the oxidation reaction by using molecular oxygen as an oxidant under solvent-free conditions, but also enhance the catalytic activity as well as improve the selectivity.

In an exploratory study, the oxidation of benzyl alcohol into benzyl aldehyde was chosen as a model reaction (Table 1).[14] As shown in Table 1, CuCl, PEG_{6000}-$(TEMPO)_2$, and oxygen were essential for this oxidation (Table 1, entries 1–3). To our delight, the presence of CO_2 improved the reaction (entry 4 vs. 5), and the reaction was further facilitated by altering CO_2 pressure to 8 MPa (entries 6, 9, and 10). As a consequence, an appropriate pressure of CO_2 could accelerate the reaction. This would be presumably ascribed to high miscibility of O_2 in compressed CO_2, thus eliminating interphase transport limitation. Additionally, the 'expandable effect' of PEG in compressed CO_2 would also be beneficial to the reaction. Indeed, as judged by visual inspection through a window-equipped high-pressure reactor, it was found that PEG_{6000}-$(TEMPO)_2$ can be expandable with CO_2, which possibly improves the solubility of O_2 and CO_2 in PEG-supported catalyst as reported in the literature.[13,15] However, the yield decreased when CO_2 pressure was further increased to 11 MPa (entry 11), probably due to the dilution effect of CO_2.

The reaction temperature also had a great influence on the reaction. Screening the reaction temperature revealed that 60 °C was the appropriate temperature in terms of energy consumption and reaction efficiency (entries 6, 13, and 14). Interestingly, CuCl was more active in comparison to $CuCl_2$ (entries 6 and 12), being consistent with the reported results.[4] In addition, a series of catalytic cycles were examined to test the catalyst recycling. In each cycle, the catalyst [PEG_{6000}-$(TEMPO)_2$/CuCl] was solidified by cooling the resultants, followed by addition of diethyl ether, and thus recovered by the simple filtration [about 95% of PEG_{6000}-$(TEMPO)_2$ could be recycled every run].[16] It was found that the catalytic system retained excellent catalytic performance after 3 runs (entries 7 and 8).

According to the accepted mechanism of the biomimetic oxidation process, the reaction was completed through a copper-mediated oxidation rather than an oxoammonium-based mechanism.[5] The presence of base should be crucial for the oxidation of alcohols, which could deprotonate the alcohol and coordinate to Cu.[6a,17] So the base effect was also evaluated, and the results were summarized in Table 2. In Wei's system,[6a] sodium hydroxide and triethylamine with low coordinating ability still showed accelerative effect with moderate activity compared to the blank experiment. In contrast, pyridine and 1-methylimidazole played an accelerative role in our study (entries 3 and 4). Both inorganic bases and organic bases such as DMAP and DBU with bulky steric hindrance showed a detrimental effect upon the reaction (entries 1, 2, and 5–8). In addition, the optimal amount of 1-methyl-imidazole was found to be one equivalent of CuCl in the experiment conditions (entry 4 and 9–12).

To evaluate the utility of the present methodology, the reaction was carried out with alcohol (1.93 mmol), 2.5 mmol% of PEG_{6000}-$(TEMPO)_2$, 5 mmol% of CuCl, 5 mmol% 1-methylimidazole, 1 MPa of oxygen, and 6 MPa of CO_2. It was found that benzylic, allylic, heterocyclic, and aliphatic alcohols were selectively converted into

Table 1 The Aerobic Oxidation of Benzyl Alcohol Catalyzed by PEG_{6000}-$(TEMPO)_2$ and CuCl[a]

Entry	Temp (°C)	P_{O2} (MPa)	$P_{O2} + P_{CO2}$ (MPa)	Conversion (%)[b]	Yield (%)[b]	
					Aldehyde	Acid
1[c]	60	1	7	1	1	0
2[d]	60	1	7	trace	trace	0
3	60	0	0	trace	trace	0
4	60	1	1	30	29	0
5	60	1	4	43	42	0.5
6	60	1	7	60	60	0
7[e]	60	1	7	61	61	0
8[f]	60	1	7	59	59	0
9	60	1	8	60	60	0
10	60	1	9	62	62	0
11	60	1	12	27	27	0
12[g]	60	1	7	22	22	0
13	30	1	7	11	10	0
14	100	1	7	70	69	0

[a] Reaction conditions: benzyl alcohol (0.2 mL, 1.93 mmol), PEG_{6000}-$(TEMPO)_2$ (0.3045 g, 2.5 mmol%), CuCl (9.6 mg), 2 h.

[b] Determined by GC using biphenyl as an internal standard.

[c] Without CuCl.

[d] Without PEG_{6000}-$(TEMPO)_2$.

[e] The second run of PEG_{6000}-$(TEMPO)_2$ recovered by the procedure **B** after the run in entry 6.

[f] The third run of PEG_{6000}-$(TEMPO)_2$ recovered after the run in entry 7

[g] $CuCl_2$ (13 mg) was used instead of CuCl.

Table 2 The Effect of the Base[a]

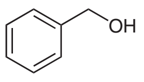
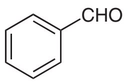
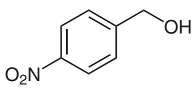
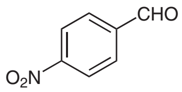
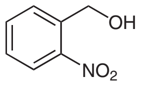
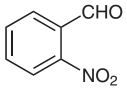
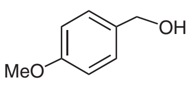
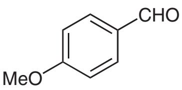
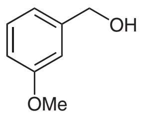
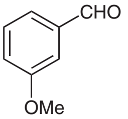
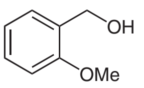
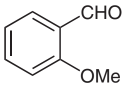
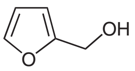
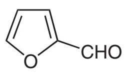
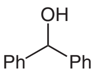
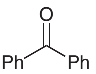
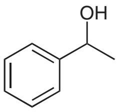
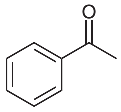
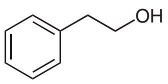
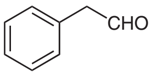
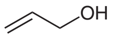
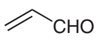
Entry	Base	Conversion (%)[b]	Yield (%)[b]
1	DMAP[c]	39	39
2	DBU[d]	38	38
3	pyridine	74	74
4	1-methylimidazole	86	86
5	Et_3N	20	20
6	$NaHCO_3$	10	10
7	Na_2CO_3	18	18
8	NaOH	16	16
9[e]	1-methylimidazole	43	42
10[f]	1-methylimidazole	69	69
11[g]	1-methylimidazole	58	58
12[h]	1-methylimidazole	19	19

[a] Reaction conditions: benzyl alcohol (0.2 mL, 1.93 mmol), PEG_{6000}-$(TEMPO)_2$ (0.3045 g, 2.5 mmol%), base (0.098 mmol), CuCl (9.6 mg), 60 °C, 2 h.
[b] Determined by GC using biphenyl as an internal standard.
[c] 4-Dimethylaminopyridine.
[d] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[e] Based (0.025 mmol), nCuCl/nbase = 4:1.
[f] Based (0.049 mmol), nCuCl/nbase = 2:1.
[g] Based (0.194 mmol), nCuCl/nbase = 1:2.
[h] Based (0.388 mmol), nCuCl/nbase = 1:4.

their corresponding aldehydes or ketones, as summarized in Table 3. And the overoxidized products were rarely detected. The reaction rate was not significantly affected by electronic properties of the substituents on the benzene ring in the cases of primary benzylic alcohols (entries 1–7), which was similar to the reported results.[6a,b] However, *ortho*-substituted primary benzyl alcohols were less active compared to other primary benzylic alcohols, presumably owing to steric hindrance. In addition, other activated primary alcohols, such as allylic alcohol, could be effectively and selectively oxidized to the corresponding aldehyde (entry 13). Fortunately, a type of heterocyclic alcohol (such as 2-furfurylmethanol), which was less active in many systems, could also be converted to the desired compounds (entries 8 and 9). Furthermore, even secondary alcohols such as diphenylmethanol and 1-phenylethanol with bulky groups and aliphatic alcohols (2-phenyl ethanol) were, respectively, oxidized to ketones and aldehyde in high selectivity by prolonging the reaction time (entries 10–12).

In summary, recyclable TEMPO-functionalized PEG combined with copper(I) chloride, that is, PEG_{6000}-$(TEMPO)_2$/CuCl, was developed to efficiently catalyze the aerobic oxidation reaction of benzylic, allylic, heterocyclic alcohols, and 2-phenylethanol in compressed CO_2 producing the corresponding aldehydes or ketones with high selectivity and moderate to high yields. The 'expandable effect' of TEMPO-functionalized PEG and miscibility with oxygen in compressed CO_2 could improve the reaction rate and enhance the selectivity. This process looks promising as a strategy for homogeneous catalyst recycling.

Table 3 Catalytic Aerobic Oxidation of Alcohol[a]

Entry	Substrate	Product	Temp (°C)	Time (h)	Conv. (%)[b]	Yield (%)[b]
1[c]			60	2	86	86
2			100	2	99	94
3			100	3	85	82
4			60	3	78	76
5			100	3	99	92
6			60	3	83	82
7			60	3	63	62
8[c]			60	3	19	16
9[c]			60	10	95	91
10			100	24	30	26
11			100	24	42	38
12			60	24	30	26
13[c]			60	3	98	95

[a] Reaction conditions: alcohol (1.93 mmol), PEG_{6000}-$(TEMPO)_2$ (0.3045 g), 2.5 mmol% catalyst loading with respect to the initial amount of benzyl alcohol), CuCl (9.6 mg), 1-methylimidazole (7.7 μL), P_{o2} = 1 MPa, P_{total} = 7 MPa.
[b] Isolated yield.
[c] Determined by GC.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Representative Procedure for the Aerobic Oxidation of Alcohols**

A mixture of substrate (1.93 mmol), PEG_{6000}-$(TEMPO)_2$ (0.3045 g, 2.5 mmol%), and CuCl (9.6 mg, 5 mmol%) was placed in a 25 mL autoclave equipped with an inner glass tube. 2 MPa CO_2 and 1 MPa O_2 were introduced into the autoclave, and the reactor was heated to the reaction temperature. Then final pressure was adjusted to the desired pressure at the reaction temperature by introducing amount of CO_2. The mixture was stirred continuously for the designed reaction time. After cooling, products were then extracted by Et_2O and analyzed by gas chromatography with a Shimadzu GC-2014 equipped with a capillary column (RTX-5, 30 m × 0.25 μm) using a flame-ionization detector. The residue was purified by column chromatography on silica gel (200–300 mesh, eluting with 20:1 PE–EtOAc) to afford the desired product. The structure and purity of products were further identified using NMR (Bruker 300 or 400 MHz), GC-MS (HP G1800A), HPLC-MS (LCQ Advantage), GC, and HPLC by comparing retention times and fragmentation patterns with those of authentic samples. Safety warning: Experiments using large amounts of compressed gases, especially molecular oxygen and supercritical fluids, are potentially hazardous and must only be carried out by using the appropriate equipment and under rigorous safety precautions. In particular, CO_2 is introduced into the substrate-loaded reactor before oxygen is added.

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(16) **The Typical Procedure for the Recycling of TEMPO-Functionalized PEG**

(A) The reaction mixture was extracted with compressed CO_2 (202.7 bar, 50 °C) to afford the corresponding carbonyl compound. The TEMPO-functionalized PEG phase containing CuCl was reused without further purification or activation.

(B) Extract procedure with Et_2O: after addition of Et_2O (3 × 10 mL) to the resulting mixture upon completion of reaction, the PEG phase was solidified when cooled to –10 °C to –20 °C, and followed by simple decantation of the ether phase containing oxidized products. Subsequently, the PEG phase was dried under vacuum for next run. We conducted further oxidation by addition of successive portions of the alcohol and run the reaction under identical reaction conditions.

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