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Green and reusable homogeneous oxidative system with ceric ammonium nitrate/[Imim-PEG$_{1000}$-TEMPO] for efficient aerobic oxidation of alcohols and one-pot synthesis of benzimidazoles from alcohols under ambient conditions

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An efficient and reusable catalytic system for aerobic oxidation of alcohols and one-pot synthesis of benzimidazoles from alcohols with ceric ammonium nitrate and PEG$_{1000}$–ionic liquid-immobilized 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) is described. This system shows excellent activity and selectivity, affording the target products with good yields. Moreover, the catalytic system can be recycled and reused without significant loss of catalytic activity after seven runs. Copyright © 2014 John Wiley & Sons, Ltd.

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Keywords: aerobic oxidation of alcohols; ceric ammonium nitrate; [Imim-PEG$_{1000}$-TEMPO]; homogeneous oxidative system; ambient conditions

Introduction

Benzimidazoles are very useful compounds in the development of the pharmaceutical industry, which exhibit significant biological activity against several viruses,[1] such as HIV,[1] herpes simplex virus-1,[2] influenza[3] and human cytomegalovirus.[1] Many methods have been reported for the synthesis of benzimidazoles, and compounds such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[4] $FeCl_3$,[5] MnO_2,[6] H_2O_2,[7] $Pb(OAc)_4$,[8] Oxone,[9] $PhI(OAc)_2$,[10] $Na_2S_2O_5$,[11] benzofuroxan[12] and $K_4[Fe(CN)_6]$[13] have been employed in the reaction. Although these methods are effective, they usually require stoichiometric amounts of chemical oxidants, and large amounts of waste are formed. From an economic and environmental viewpoint, catalytic oxidations are particularly promising due to their being inexpensive, non-toxic, inexhaustible and benign, and many efforts have been devoted over the last few years to the development of efficient procedures for the synthesis of benzimidazoles employing O_2 (or air) as the ultimate oxidant.[14,15]

2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO), as a stable nitroxyl free radical, has proved to be very effective for the aerobic oxidation of alcohols.[16–23] Recently, immobilized TEMPO has drawn much interest in the synthesis field. Room temperature ionic liquids (ILs) have been the subject of increasing studies over the last few decades due to several advantages like negligible volatility, thermal stability, remarkable solubility and a variety of available structures.[24–31] In 2010, Falla *et al.*[32] described an efficient synthesis of an IL-supported TEMPO ([Imim-TEMPO][BF_4^-]) which was used for the oxidation of alcohols to aldehydes and ketones. The predictable solubility of ILs allows easy separation of the oxidation products. Furthermore, IL-supported TEMPO can be recycled and used several times without loss of efficiency. Wu *et al.*[33] also described a novel TEMPO radical bearing an IL-type appendage and its catalytic activity for the selective oxidation of alcohols to the corresponding carbonyl compounds in IL–aqueous biphasic conditions. The IL-supported TEMPO radical shows catalyst properties similar to those of its non-supported counterpart in terms of activity and selectivity, and can be easily recycled and reused without loss of activity and selectivity.

Ceric ammonium nitrate (CAN) is a very inexpensive and easily available oxidizing agent.[34] In recent times, CAN has attracted special attention and is extensively employed as a useful catalyst for C–C, C–N, C–S and C–Se bond-forming reactions in synthetic organic chemistry[34–37] as it is economically viable, water soluble with profound reactivity with reduction potential. Also, Zhi *et al.*[38] recently developed a new poly(ethylene glycol) (PEG)-supported IL, which exhibits good compatibility of the tandem catalyst/substrate, excellent catalytic effect in promoting reaction and easy recovery from the reaction system. In continuation of our interest in exploring systems for environmentally benign protocols, a novel catalytic system based on Ce(IV)/Ce(III) redox with CAN and PEG$_{1000}$ IL-immobilized

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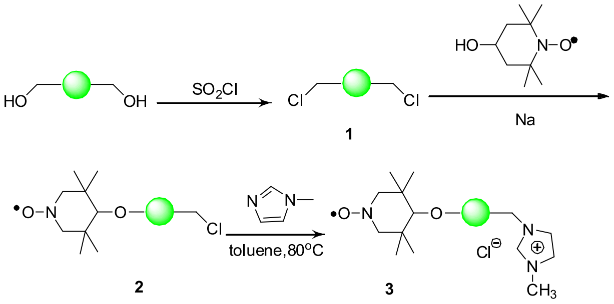
TEMPO (Imim-PEG_{1000}-TEMPO) was designed in our work, and which has proved to be an effective catalyst for selective aerobic oxidation of primary and secondary alcohols into the corresponding aldehydes or ketones. It was also found that the catalytic system afforded excellent yields for one-pot synthesis of benzimidzoles from alcohols. Moreover, better compatibility and easier separation could be achieved due to the presence of PEG. The protocol presented here provides an efficacious strategy from the viewpoint of green chemistry.

Results and Discussion

The synthesis steps of Imim-PEG_{1000}-TEMPO are as shown in Scheme 1. Imim-PEG_{1000}-TEMPO is readily prepared in a three-step procedure. PEG_{1000} was treated with thionyl chloride in dry toluene at 0°C under an inert gas for 24 h to afford intermediate **1**. This intermediate was then treated with sodium salt of 4-hydroxy-TEMPO for 12 h at room temperature to afford intermediate **2**. This was subsequently added to *N*-methylimidazole in toluene at 80°C for 20 h to generate the corresponding ionic liquid immobilized TEMPO.

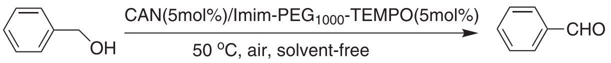


Scheme 1. Synthesis of PEG_{1000}–IL-immobilized TEMPO.

Initially, benzyl alcohol was selected as model substrate to optimize the reaction conditions for $(NH_4)_2Ce(NO_3)_6$/[Imim-PEG_{1000}-TEMPO] catalyzing the aerobic oxidation of alcohols. The results are summarized in Table 1. When benzyl alcohol is treated with $(NH_4)_2Ce(NO_3)_6$ (5 mol%)/Imim-PEG_{1000}-TEMPO (5 mol%) at 50°C for 6 h, the desired product is obtained in 95% yield. It is found that $(NH_4)_2Ce(NO_3)_6$ and TEMPO are essential for the aerobic oxidation of benzyl alcohol (Table 1, entries 1–3). In the absence of either of them, the reaction does not proceed automatically. Also, the [Imim-PEG_{1000}-TEMPO] IL shows catalytic properties similar to those of its non-supported counterpart in terms of activity and selectivity affording the target products with good yield (Table 1, entry 4). Catalyst screening shows that $(NH_4)_2Ce(NO_3)_6$ is superior to other catalysts under the defined conditions and gives a higher yield (Table 1, entries 5–7). The oxidation gave the best performance at 50°C, and also could be carried out even at room temperature (Table 1, entries 8–10). Control experiments were carried out in the commercial solvents CH_3CN, DMSO, dioxane and benzene (Table 1, entries 11–14). The solubility of the catalyst would likely be more important for this reaction. As expected, DMSO and CH_3CN give moderate yields, while dioxane and benzene do not well dissolve the catalyst and demonstrate a poor performance under identical conditions, whereas Imim-PEG_{1000}-TEMPO is capable of forming a homogeneous system to enhance the reaction.

Encouraged by these results, some other alcohols were further examined to extent the substrate scope for this methodology. The results are shown in Table 2. The catalytic system is effective and highly selective for the oxidation of alcohols to the respective carbonyl compounds under ambient conditions. The activities of primary benzylic alcohols are best, and the activities of those primary benzylic alcohols are not significantly affected by the electronic properties and steric hindrance of the substituents on the benzene ring (Table 2, entries 1–7). Secondary benzylic alcohols such as benzhydrol also give good conversion with a prolonged reaction time (Table 2, entry 8). Interestingly, the designed oxidation system proved to be chemoselective. In the case of a double bond-

Table 1. Reaction conditions for CAN/IL-TEMPO-catalyzed oxidation of benzyl alcohol under solvent-free conditions[a]



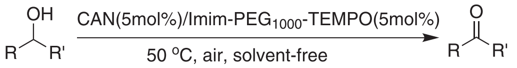
Entry	Catalyst (mol%)	Co-catalyst	Solvent	*T* (°C)	Conv.[b] (%)	Yield[c] (%)
1	CAN (5)	Imim-PEG_{1000}-TEMPO (5)	—	50	100	95
2	None	Imim-PEG_{1000}-TEMPO (5)	—	50	—	—
3	CAN (5)	None	—	50	—	—
4	CAN (5)	TEMPO (5)	—	50	>99	94
5	$FeCl_3$ (5)	Imim-PEG_{1000}-TEMPO (5)	—	50	—	—
6	$CuCl_2$ (5)	Imim-PEG_{1000}-TEMPO (5)	—	50	61	60
7	CuCl (5)	Imim-PEG_{1000}-TEMPO (5)	—	50	89	85
8	CAN (5)	Imim-PEG_{1000}-TEMPO (5)	—	rt	45	41
9	CAN (5)	Imim-PEG_{1000}-TEMPO (5)	—	75	100	83
10	CAN (5)	Imim-PEG_{1000}-TEMPO (5)	—	100	100	72
11	CAN (5)	TEMPO (5)	CH_3CN	50	74	70
12	CAN (5)	TEMPO (5)	DMSO	50	68	65
13	CAN (5)	TEMPO (5)	Dioxane	50	35	31
14	CAN (5)	TEMPO (5)	Benzene	50	25	24

[a] Reaction conditions: benzyl alcohol (10 mmol), $(NH_4)_2Ce(NO_3)_6$ (0.5 mmol), Imim-PEG_{1000}-TEMPO (0.5 mmol), 50°C.

[b] Determined by HPLC.

[c] Isolated yield.

Table 2. CAN/IL-TEMPO-catalyzed oxidation of various alcohols[a]



Entry	R	R′	Time (h)	Conv. (%)	Yield (%)
1	Ph	H	6	100	95
2	*p*-Me$_2$N-Ph	H	5	100	96
3	*p*-OH-Ph	H	5	99	96
4	*p*-Cl-Ph	H	8	93	91
5	*o*-Cl-Ph	H	8	94	90
6	*p*-Br-Ph	H	7	95	90
7	*m*-NO$_2$-Ph	H	10	94	85
8	Ph	CH$_3$	12	96	93
9	PhCH=C–	H	8	97	89
10	C$_{12}$H$_{25}$–	H	12	61	54

Reaction conditions:[a] alcohols (10 mmol), $(NH_4)_2Ce(NO_3)_6$(0.5 mmol), Imim-PEG$_{1000}$-TEMPO(0.5 mmol), 50°C.

containing substrate, the double bond is not influenced by this method (Table 2, entry 9). An aliphatic alcohol, dodecyl alcohol, gives lower yields when added to the system (Table 2, entry 10).

Having successfully achieved the oxidation of alcohols, the catalytic system was expanded to catalyze the aerobic oxidative synthesis of benzimidazoles from *o*-phenylenediamine and aromatic alcohols. The results are shown in Table 3. A series of aromatic alcohols were reacted with *o*-phenylenediamine under the optimized reaction conditions. In most cases, *o*-phenylenediamine reacts with various benzyl alcohols smoothly to give the corresponding products in good to excellent yields. It is also found that substituent groups on the aromatic ring and the steric hindrance of the substituted benzyl alcohols do not influence the reaction (Table 3).

The recyclability of the catalytic system was also investigated. After completion of the oxidation reaction, the mixture was allowed to cool to room temperature and extracted with ether. The upper layer containing the product was removed by decantation. The remaining lower layer was dried in vacuum to remove the small amount of water and fresh substrates were then recharged to react once again. With *o*-phenylenediamine and benzyl alcohol as model substrates, the catalytic system proves to be efficient after utilization for seven times in view of both yield and selectivity (Fig. 1).

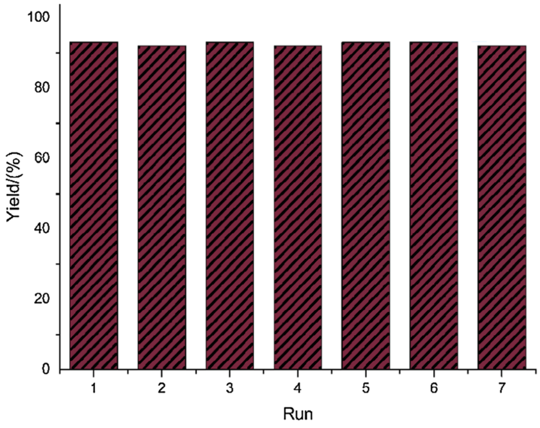
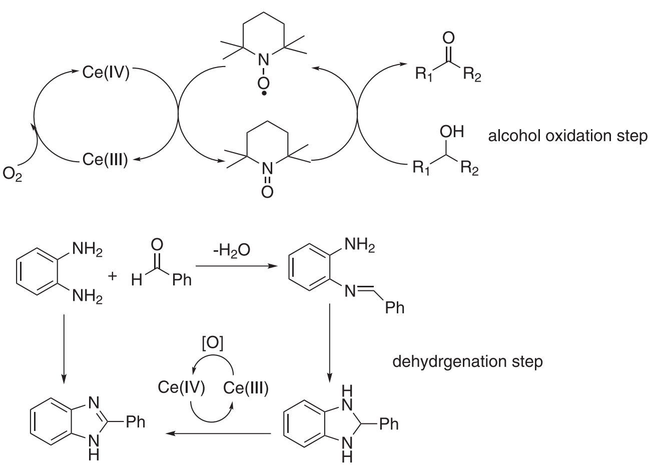


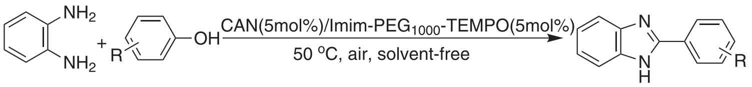
Figure 1. Recycling tests.

According to the literature and the observations from our reactions, a possible mechanism is proposed (Scheme 2). In this reaction, TEMPO is first oxidized to *N*-oxopiperidinium that initiates a series of electron and proton transfer steps with the help of Ce(IV). Then alcohol is dehydrogenated by *N*-oxopiperidinium



Scheme 2. The mechanism of aerobic oxidative synthesis of benzimidazole from alcohols

Table 3. Synthesis of benzimidazoles from aromatic alcohols and diamines[a]



Entry	R	Time (h)	Yield[b] (%)
1	H	8	93
2	4-OH	6	90
3	4-Me$_2$N	6	91
4	2-Cl	10	96
5	4-Cl	9	94
6	4-Br	9	95
7	3-NO$_2$	12	96

[a] Reaction conditions: *o*-phenylenediamine (10 mmol) and aldehyde (10 mmol), $(NH_4)_2Ce(NO_3)_6$ (0.5 mmol), Imim-PEG$_{1000}$-TEMPO (0.5 mmol), 50°C.

[b] Products were purified by column chromatography and confirmed by HPLC, ^{1}H NMR, elemental analysis and melting point.

to obtain the corresponding aldehyde. Then the aldehyde reacts with *o*-phenylendiamine and dehydrates to form a Schiff base. During the next steps, ring closure leads to a five-membered ring followed by dehydrogenation with Ce(IV) and Ce(III) redox to form benzimidazole.

Conclusions

We have developed an efficient and environmentally friendly method for the aerobic oxidation of alcohols and one-pot synthesis of benzimidzoles from alcohols catalyzed by CAN/[Imim-PEG$_{1000}$-TEMPO] with excellent yields. Owing to the high efficiency and good compatibility, the catalytic system had a good catalytic performance to effectively promote the reaction. Moreover, it could be recycled and reused without significant loss of catalytic activity for seven runs. This environmentally friendly catalytic system could find wider applications in various reactions, which is an ongoing project.

Experimental

General Information

All starting materials were purchased from commercial sources and used without further treatment. Analytical thin-layer chromatography (TLC) was performed on precoated silica plates. Yields of the products refer to purification by silica gel column chromatography. ^{1}H NMR spectra were recorded using a Bruker Advance III (500 MHz) spectrometer with tetramethylsilane as an internal standard. High-performance liquid chromatography experiments were performed with a liquid chromatograph (Shimadzu LC-20AT, Japan).

General Procedure for Oxidation of Alcohols

To a 10 ml round-bottom flask, $(NH_4)_2Ce(NO_3)_6$ (0.5 mmol), Imim-PEG$_{1000}$-TEMPO (0.5 mmol) and benzyl alcohol (10 mmol) were successively added under constant vigorous stirring. The reaction was carried out at a temperature of 50°C and monitored using TLC. Upon completion, the reaction mixture was cooled to room temperature and extracted three times by adding ether. The organic phase was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give benzaldehyde (95% yield) with spectral data consistent with the assigned structures for the products. The next run was performed under identical reaction conditions.

Typical Procedure for Synthesis of Benzimidazoles

o-Phenylenediamine (1.08 g, 10 mmol), benzyl alcohol (1.08 g, 10 mmol), $(NH_4)_2Ce(NO_3)_6$ (0.5 mmol) and Imim-PEG$_{1000}$-TEMPO (0.5 mmol) were thoroughly mixed in a 10 ml three-necked flask equipped with a water-cooled condenser and a gas inlet with vigorous stirring at room temperature. Then, the temperature was raised to 50°C and the reaction monitored usong TLC. Upon completion, the mixture was extracted with ether three times, and the organic layer was dried with anhydrous $MgSO_4$ and rotary evaporated under reduced pressure. The residue was purified by column chromatography on a silica gel using petroleum ether–ethyl acetate (7:1) as eluent to afford the pure product in 93% yield (m.p. 292–294°C). The next run was performed under identical reaction conditions.

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References

[1] A. R. Porcari, R. V. Devivar, L. S. Kucera, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1998**, *41*, 1252.
[2] M. T. Migawa, J. L. Girardet, J. A. Walker, G. W. Koszalka, S. D. Chamberlain, J. C. Drach, L. B. Townsend, *J. Med. Chem.* **1998**, *41*, 1242.
[3] I. Tamm, *Science* **1957**, *126*, 1235.
[4] K. J. Lee, K. D. Janda, *Can. J. Chem.* **2001**, *79*, 1556.
[5] M. P. Singh, S. Sasmal, W. Lu, M. N. Chatterjee, *Synthesis* **2000**, 1380.
[6] I. Bhatnagar, M. V. George, *Tetrahedron* **1968**, *24*, 1293.
[7] K. Bahrami, M. M. Khodaei, F. Naali, *J. Org. Chem.* **2008**, *73*, 68358.
[8] F. F. Bower, D. Janda, *J. Chem. Soc.* **1949**, 2971.
[9] P. L. Beaulieu, B. Haché, E. von Moos, *Synthesis* **2003**, 1683.
[10] L. H. Du, Y. G. Wang, *Synthesis* **2007**, 675.
[11] R. L. Lombardy, F. A. Tanious, K. Ramachandran, R. R. Tidwell, W. D. Wilson, *J. Med. Chem.* **1996**, *39*, 1452.
[12] F. Patzold, F. T. Zeuner, H. Heyer, H. J. Niclas, *Synth. Commun.* **1992**, *22*, 281.
[13] K. A. Shaikh, V. A. Patil, *Org. Commun.* **2012**, *5*, 12.
[14] Y. Kawashita, N. Nakamichi, H. Kawabata, M. Hayashi, *Org. Lett.* **2003**, *20*, 3713.
[15] S. N. Lin, L. H. Yang, *Tetrahedron Lett.* **2005**, *46*, 4315.
[16] T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2000**, *65*, 6502.
[17] R. Lenz, S. V. Ley, *J. Chem. Soc. Perkin Trans.* **1997**, 3291.
[18] I. E. Marko, P. R. Giles, M. Tsukazaki, I. Chelle-Regnaut, C. J. Urch, S. M. Brown, *J. Am. Chem. Soc.* **1997**, *119*, 12661.
[19] M. J. Schultz, C. C. Park, M. S. Sigman, *Chem. Commun.* **2002**, 3034.
[20] B. Z. Zhan, M. A. White, T. K. Sham, J. A. Pincock, R. J. Doucet, K. V. R. Rao, K. N. Robertson, T. S. Cameron, *J. Am. Chem. Soc.* **2003**, *125*, 2195.
[21] H. B. Ji, T. Mizugaki, K. Ebitani, K. Kaneda, *Tetrahedron Lett.* **2002**, *43*, 7179.
[22] M. F. Semmelhack, C. R. Schmid, D. A. Cortés, C. S. Chou, *J. Am. Chem. Soc.* **1984**, *106*, 3374.
[23] M. F. Semmelhack, C. R. Schmid, D. A. Cortés, *Tetrahedron Lett.* **1986**, *27*, 1119.
[24] R. Sheldon, *Chem. Commun.* **2001**, 2399.
[25] T. Welton, *Coord. Chem. Rev.* **2004**, *248*, 2459.
[26] J. S. Wilkes, *J. Mol. Catal. A* **2004**, *214*, 11.
[27] R. D. Rogers, K. R. Seddon, *Science* **2003**, *302*, 792.
[28] Y. L. Wang, J. Luo, Z. L. Liu, *Appl. Organometal. Chem.* **2013**, *27*, 601.
[29] W. Gil, A. M. Trzeciak, J. J. Ziółkowski, *Appl. Organometal. Chem.* **2006**, *20*, 766.
[30] J. S. Yadav, B. V. S. Reddy, K. Premalatha, *Adv. Synth. Catal.* **1998**, *345*, 948.
[31] C. A. Ohlin, Z. Béni, G. Laurenczy, N. Ruiz, A. M. Masdeu-Bultó, *Appl. Organometal. Chem.* **2007**, *21*, 156.
[32] A. Falla, M. Senea, M. Gayeb, G. Gómeza, Y. Fall, *Tetrahedron Lett.* **2010**, *51*, 4501.
[33] X. E. Wu, L. Ma, M. X. Ding, L. X. Gao, *Synlett* **2005**, *4*, 607.
[34] V. Nair, A. Deepthi, *Chem. Rev.* **2007**, *107*, 1862.
[35] A. Dhakshinamoorthy, K. Pitchumani, *Catal. Commun.* **2009**, *10*, 872.
[36] L. Wang, H. Jing, X. Bu, T. Chang, L. Jin, Y. Liang, *Catal. Commun.* **2007**, *8*, 80.
[37] P. Haldar, J. K. Ray, *Tetrahedron Lett.* **2008**, *49*, 3659.
[38] H. Z. Zhi, C. X. Lü, Q. Zhang, J. Luo, *Chem. Commun.* **2009**, 2878.

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