

Transition-Metal-Free: A Highly Efficient Catalytic Aerobic Alcohol Oxidation Process

Renhua Liu, Xinmiao Liang,* Chunyan Dong, and Xinquan Hu*

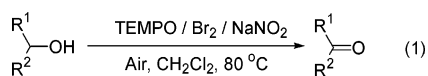
Dalian Institute of Chemical Physics, the Chinese Academy of Sciences, Dalian 116023, P. R. China

Received December 17, 2003; E-mail: xinquan@ms.dicp.ac.cn; liangxm@mail.dlptt.ln.cn

The oxidation of alcohols into the corresponding aldehydes or ketones is one of the most important functional group transformations in organic synthesis.¹ Recently, the use of molecular oxygen as terminal oxidant has received great attention for both economic and environmental benefits, and many highly efficient systems have been developed for catalytic aerobic alcohol oxidation using copper,² palladium,³ or ruthenium catalysts.⁴ Of particular interest are the catalysis systems involving both transition metals and nitroxyl radicals (e.g., 2,2,6,6-tetramethyl-piperidyl-1-oxy TEMPO).^{5,6} However, only a few catalyst systems, for example, small amounts of cheap metal salts, together with TEMPO, provided an efficient catalyst for aerobic oxidation of alcohols under mild conditions.^{6c,h} Therefore, attempting to obtain more efficient processes, chemists have paid much attention to screening various transition metals and designing new ligands while largely ignoring the advantages inherent in a nonmetal catalytic system. We are particularly interested in exploring the potential of such a transition-metal-free catalyst system for aerobic alcohol oxidations.

Our research was inspired by the results of the TEMPO-Cl₂ oxidation system by Bjørsvik et al.^{7a} and the TEMPO-Br₂/I₂ system by Miller et al.^{7b} In their procedures, NaHCO₃ or Na₂CO₃ was used to neutralize the coproduct HX (X = Cl, Br, I). We reasoned that if HX can be oxidized to regenerate X₂ in situ by molecular oxygen rather than being scavenged by inorganic base, a TEMPO-catalyzed process with a catalytic amount of X₂ could be established. In this communication, we report a highly efficient catalytic system without transition metal for the aerobic oxidation of a variety of alcohols.

Initial investigation of TEMPO-catalyzed (1 mol %) aerobic oxidation was carried out using benzyl alcohol as substrate with 4 mol % of Br₂ and 0.5 MPa of oxygen under 100 °C for 1 h. The preliminary result (8.36% of conversion) clearly indicated the role of Br₂ as an active catalyst. Prolonging the reaction time to 5 h increased the conversion to 20.4%.⁸ Recognizing that the first incorporation of molecular oxygen into the reaction system has been the keystone for successful aerobic oxidations, we sought to find a cocatalyst to bridge the gap between O₂ activation and HBr reoxidation. The ready availability and unique redox property of NaNO₂ as a source of NO under acidic conditions attracted our attention.⁹ Although NaNO₂ alone showed almost no activity in TEMPO-catalyzed aerobic oxidation, when 4 mol % of Br₂ and 8 mol % of NaNO₂ were both employed in TEMPO-catalyzed aerobic oxidation, a highly efficient catalyst system emerged (eq 1).⁸ The



quantitative oxidation of benzyl alcohol can be achieved without acid either under 0.5 MPa of oxygen at 100 °C or under 0.2 MPa of oxygen at 60 °C.⁸ Indeed, the transition-metal-free catalyst system for aerobic alcohol oxidations exhibited extremely high selectivities and are remarkably easy to control. After systematic optimization

of reaction temperature, composition of catalyst, and pressure of oxygen, we successfully developed a highly efficient and generally applicable catalytic system for the oxidation of alcohols with oxygen. When air was used to replace pure oxygen, we observed a slightly lower conversion rate, which can be easily compensated by a modest air pressure increase.⁸

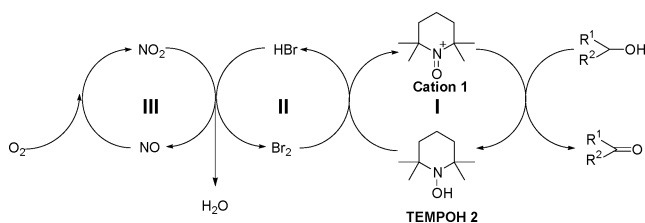
Under the following conditions: 10 mmol of alcohol, 1 mol % of TEMPO, 4 mol % of Br₂, 4 mol % of NaNO₂, 0.4 MPa of air, 10 mL of CH₂Cl₂, 80 °C, all benzylic alcohols were converted into their corresponding aldehydes in high isolated yields within 2 h (Table 1). α -Methyl benzyl alcohol was also oxidized to acetophenone in near quantitative isolated yield. Compared to benzylic alcohols, aliphatic alcohols showed relatively low activities in the oxidation. To address this, we increased the amount of the least expensive component (NaNO₂, 8 mol %) in the catalyst system and raised the air pressure (0.9 MPa) to improve the reaction rate. Under these modified conditions, the oxidation of 1-octanol can be completed within 3 h, accompanied by some ester as byproduct, which could be formed according to a free radical mechanism (entry 9).¹⁰ 2-Octanol, 3-octanol, and cyclohexanol can be completely converted into the corresponding ketones in high selectivities. When 2-thiophene methanol was used, the oxidation can be completed in 5 h. Usually, the thiophene ring was incompatible with Br₂. We did observe some 5-bromo-2-thiophene-aldehyde, which was probably produced by bromination of 2-thiophene-aldehyde rather than that of 2-thiophene methanol. At least, the oxidation dominated bromination when the substrate was not completely consumed. As for 3-pyridine methanol, the slow oxidation was observed even for 12 h with method B (entry 14). We assumed that the HBr was partially neutralized by the basic pyridine. Increasing the amount of catalyst and raising the reaction temperature to 100 °C led to a 94.4% conversion and 100% selectivity in 5 h (entry 15). Generally, allylic alcohols are found as active substrates in the aerobic oxidations, with the exception of 3-methyl-2-buten-1-ol as Br₂ adds quickly to double bond. However, the oxidation can be performed in moderate conversion using pyridine hydrobromide perbromide, which was inert to the carbon-carbon double bond,¹¹ as a surrogate of Br₂.

A possible overall mechanism of this new and transition-metal-free catalytic oxidation can be described as a sequential tricycle in Scheme 1. Thus, transformation of alcohols into carbonyl compounds is fulfilled by the coupling of multiple redox reactions. Oxoammonium cation (**1**), which is initially oxidized from TEMPO, is an active oxidant of alcohols in this system.⁵ The running of Cycle I continuously provides the cation **1** by oxidizing TEMPOH **2**, the reduced form of TEMPO, with Br₂, and the latter is reduced into HBr. One proof of the existence of HBr is the formation of a trace amount of benzyl bromide, which we observed during the optimization process and is obviously a byproduct derived from benzyl alcohol and HBr.⁸ In addition, the slow reaction with 3-pyridine methanol, which can form salt with HBr, indicated the

Table 1. Catalytic Aerobic Alcohol Oxidation^a

Entry	Substrate	Product	Method	Time (h)	Conv (%)	Select (%)	Yield (%)
1			A	1	100	100	95
2			A	1.5	100	99	95
3			A	1.5	100	100	93
4			A	1.5	100	99.5	94
5			A	2	100	100	96
6			A	2	100	99.3	96
7			A	2	100	100	96
8			A	1.5	100	99	98
9	1-C ₈ H ₁₇ OH	1-C ₇ H ₁₅ CHO	B	3	100	86 ^b	-
10	2-C ₈ H ₁₇ OH	2-Octanone	B	4	99.4	100	98
11	3-C ₈ H ₁₇ OH	3-Octanone	B	4	99.1	99.3	88
12			B	4	100	99.4	89
13			B	5	100	94.7 ^c	99 ^e
14			B	12	50.7	100	-
15			B _d	5	94.4	100	98
16			B ^e	3	70.2	95.1	-

^a Reaction conditions: alcohol (10 mmol), TEMPO (0.1 mmol), Br₂ (0.4 mmol), CH₂Cl₂ (10 mL), 80 °C (oil bath temperature). Method A: NaNO₂ (0.4 mmol), 0.4 MPa air pressure; method B: NaNO₂ (0.8 mmol), 0.9 MPa air pressure. Conversions and selectivities are based on the GC with area normalization. All yields are for pure, isolated products. ^b Ester (14%) was formed. ^c 5-Bromo-thiophene-2-aldehyde was formed as major byproduct in 5.3%. ^d Conditions: 4 mol % of TEMPO, 8 mol % Br₂, and 8 mol % NaNO₂ at 100 °C. ^e PyHBr₃ (4 mol %) was used in place of Br₂.

Scheme 1. Overall Catalytic Mechanism

essential role of HBr played in the catalytic cycle. The reoxidation of HBr to Br₂ by NO₂ is illustrated as Cycle II,¹² which is the key for a catalytic amount of Br₂ in the oxidation system. NO₂ is reduced to NO when it completes the oxidation of HBr.^{9b} The oxidation of NO into NO₂ is a process easily accomplished with molecular oxygen^{9a} (Cycle III), and the coupling of the three cycles furnishes a novel, coherent, and efficient aerobic oxidation system (Scheme 1).

In conclusion, we have successfully developed a highly efficient, transition-metal-free catalytic process for the aerobic oxidation of alcohols. The oxidation is carried out under air and promoted by a mixture of TEMPO/Br₂/NaNO₂ in catalytic amounts. Under optimal reaction conditions, a wide range of alcohols can be converted into corresponding aldehydes or ketones in high selectivity. Moreover, the newly developed catalyst system can be readily adjusted to suit various substrates. Mechanistically, the novel use of NO to activate molecular oxygen plays a crucial role in the TEMPO/Br₂/NaNO₂ catalytic oxidation cycle. Further studies will focus on the improvement of the process for industrial applications of aerobic alcohol oxidation.

Acknowledgment. This work was supported by the Young Faculty Research Fund of DICP.

Supporting Information Available: Detailed experimental procedures and GC diagrams for all substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990.
- (2) (a) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044. (b) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433.
- (3) (a) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (b) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (c) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozev, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188. (d) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355. (e) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (f) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179. (g) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034. (h) Uozumi, Y.; Nakao, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194. (i) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810.
- (4) (a) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Urch, C. J.; Brown, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 12661. (b) Csjerniyik, G.; Ell, A. H.; Fadini, L.; Pugin, B.; Backvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657. (c) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4538. (d) Musawir, M.; Davey, P. N.; Kelly, G.; Kozhevnikov, I. V. *Chem. Commun.* **2003**, 1414. (e) Zhan, B.-Z.; White, M. A.; Sham, T.-K.; Pincock, J. A.; Doucet, R. J.; Ramana Rao K. V.; Robertson, K. N.; Cameron, T. S. *J. Am. Chem. Soc.* **2003**, *125*, 2195.
- (5) For reviews of TEMPO-catalyzed alcohol oxidation, see: (a) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (b) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499. (c) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijkman, A. *Acc. Chem. Res.* **2002**, *35*, 774.
- (6) For transition-metal-assisted TEMPO-catalyzed aerobic alcohol oxidations, see: (a) Semmelhack, M. F.; Schmid, C. R.; Cortes, D. A.; Chou, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 3374. (b) Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343. (c) Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651. (d) Dijkman, A.; Marino-Gonzalez, A.; Mairata i Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826. (e) Ben-Daniel, R.; Alsters, P.; Neumann, R. *J. Org. Chem.* **2001**, *66*, 8650. (f) Ansari, I. A.; Gree, R. *Org. Lett.* **2002**, *4*, 1507. (g) Gamez, P.; Arends, I. W. C. E.; Reedijk, J.; Sheldon, R. A. *Chem. Commun.* **2003**, 2414. (h) Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini, M. *J. Mol. Catal. A: Chem.* **2003**, *204–205*, 63. (i) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem.* **2004**, 109.
- (7) (a) Björsvik, H.-R.; Liguori, L.; Costantino, F.; Minisci, F. *Org. Process Res. Dev.* **2002**, *6*, 197. (b) Miller, R. A.; Hoerner, R. S. *Org. Lett.* **2003**, *5*, 285.
- (8) See Supporting Information for experimental details and the optimization procedure of aerobic oxidation.
- (9) (a) Stamier, J. S.; Singel, D. J.; Loscalzo, J. *Science* **1992**, *258*, 1898. (b) Wang, P. G.; Xian, M.; Tang, X.; Wu, X.; Wen, Z.; Cai, T.; Janczuk, A. *J. Chem. Rev.* **2002**, *102*, 1091.
- (10) For a reasonable free radical mechanism of the formation of esters in aerobic alcohol oxidation, see: Amati, A.; Dosualdo, G.; Zhao, L.; Bravo, A.; Fontana, F.; Minisci, F.; Björsvik, H.-R. *Org. Process Res. Dev.* **1998**, *2*, 261.
- (11) Matsumoto, S.; Fukushima, M.; Torii, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 796.
- (12) Ratcliffe, C. T.; Shreeve, J. M. In *Inorganic Synthesis*; Jolly, W. L., Ed.; Prentice Hall, Inc.: Englewood Cliffs, NJ, 1968; Vol. 11, p 194.

JA031765K