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Efficient NO Equivalent for Activation of Molecular Oxygen and Its Applications in Transition-Metal-Free Catalytic Aerobic Alcohol Oxidation

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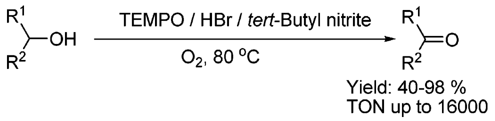
Received March 23, 2007



tert-Butyl nitrite (TBN) was identified as an efficient NO equivalent for the activation of molecular oxygen. The unique property of TBN enabled TEMPO-catalyzed aerobic alcohol oxidation to be performed in high-volume efficiency. Up to a 16 000 turnover number was achieved in this transition-metal-free aerobic catalytic system. Under the optimal reaction conditions, various alcohols were converted into their corresponding carbonyl compounds with TEMPO/HBr/TBN as catalyst. The newly developed method was suitable for the oxidation of solid substrate alcohols with high melting point and/or low solubility under the help of minimum solvent to form a slurry.

Conversion from alcohols to the corresponding aldehydes or ketones is one of the most fundamental transformations in organic chemistry.[1] For obvious reasons, many research efforts have been directed at using molecular oxygen as the terminal oxidant in recent years.[2] In the past decade, chemists have developed many efficient catalytic oxidation systems using molecular oxygen as the terminal oxidant. Among the transition-metal catalysts, copper,[3] palladium,[4] and ruthenium catalysts[5] played the major roles in the aerobic alcohol oxidations, while gold was also found to be the effective catalyst for aerobic alcohol oxidation.[6] Recently, the combinations of transition metals and nitroxy free radicals (e.g., 2,2,6,6-tetramethylpiperidyl-1-oxy, TEMPO) have shown to be very efficient in this transformation.[7] Most of the research is seeking an effective bridge, where transition metals play important roles between molecular oxygen and alcohol substrates. However, our interests are the molecular nitric oxide (NO) for its ability to activate molecular oxygen, although it widely attracted attention because of its unique biological activity and once was named "the molecule of the year" in 1992 by the editors of the journal

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(1) (a) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington D.C., 1990. (b) Larock, R. C. *Comprehensive Organic Transformation*, 2nd ed.; Wiley-VCH: New York, 1999; p 1197. (c) Sheldon, R. A.; Arends, I. W. C. E. In *Modern Oxidation Methods*; Backvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004; p 83. (d) Tojo, G.; Fernandez, M. In *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*; Tojo, G., Ed.; Springer: New York, 2006.

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(3) For copper-catalyzed aerobic alcohol oxidation, see: (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. (c) Marko, I. E.; Gautier, A.; Dumeunier, R.; Doda, K.; Philippart, F.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1588.

(4) For palladium-catalyzed aerobic oxidation, see: (a) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185. (b) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (c) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636. (d) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188. (e) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355. (f) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766. (g) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179. (h) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034. (i) Uozumi, Y.; Nakao, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 194. (j) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810. (k) Iwasawa, T.; Tokunaga, M.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2004**, *126*, 6554. (l) Mori, K.; Hara, T.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 10657. (m) Buffin, B. P.; Clarkson, J. P.; Belitz, N. L.; Kundu, A. *J. Mol. Catal. A: Chem.* **2005**, *225*, 111. (n) Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park, J. *Org. Lett.* **2005**, *7*, 1077. (o) Hou, Z.; Theyssen, N.; Brinkmann, A.; Leitner, W. *Angew. Chem., Int. Ed.* **2005**, *44*, 1346. (p) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343. (q) Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861.

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10.1021/jo0705824 CCC: $37.00

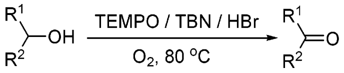
TABLE 1. Catalytic Aerobic Oxidation of Benzyl Alcohol[a]

entry	TEMPO (mol %)	HBr (mol %)	TBN (IAMN) (mol %)	time (h)	conv (%)	select (%)	TON[b]
1	1 (1)	4 (5)	4 (5)	1 (1)	100 (100)	99.7 (100)	100
2	0.5 (0.5)	4 (5)	4 (5)	1 (1)	100 (100)	99.9 (100)	200
3	0.1 (0.1)	4 (5)	4 (5)	1 (1)	100 (100)	99.7 (100)	1000
4	0.01 (0.02)	4 (5)	4 (5)	2.5 (7)	100 (99.5)	100 (100)	10 000
5	0.001	4	4	24	16.1	100	16 100
6	0.1 (0.1)	1 (1)	1 (1)	1 (1)	99.9 (100)	100 (100)	1000
7	0.1 (0.1)	0.4 (0.5)	0.4 (0.5)	4 (1.5)	100 (100)	100 (98)	1000
8	0.1 (0.1)	0.1 (0.1)	0.4 (0.5)	4 (2)	100 (100)	100 (99)	1000
9	0.1 (0.1)	0.4 (0.5)	0.1 (0.1)	10 (6)	15.0 (21)	99.8 (100)	150
10	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	10 (6)	55.6 (96)	100 (100)	550

[a] Aerobic oxidation conditions were as follows: benzyl alcohol (10.8 g, 100 mmol), 1 mL of water, initial 0.6 MPa oxygen pressure, 80 °C (oil bath temperature). End point of the reaction with complete conversion was judged by the barometer. Conversions and selectivity were based on the gas chromatography with area normalization. Data in parentheses were obtained with IAMN as NO equivalent. [b] TON = turnover number.

Science.[8] We have previously reported a triple-component catalytic oxidation system to enable the efficient use of O_2 as the terminal oxidant, with $NaNO_2$ as an NO equivalent under acidic condition playing the pivotal role of activating molecular oxygen. This novel oxidation pathway has been applied to various alcohol substrates,[9] and extended to the application of total degradation of environmental pollutants such as 2,4,6-trichlorophenol (TCP).[10] Very recently, the utility of the NO-mediated oxidation mechanism has been applied to other fields including methane oxidation.[11] However, efficiency gaps still exist between these catalytic aerobic oxidation systems and the leading catalytic oxidation processes, such as Anelli oxidation,[1d,2f] from the economic and throughput point of view.

Further examination of our catalytic system led us to identify that the weakest link within the three catalytic cycles is the oxidation of Br^- by an NO source, which resulted in a narrow tunable ranges of the catalyst molar ratios. Though the catalytic cycle can be revived by addition of catalytic amount of Br_2, a more robust system is clearly desirable. One to overcome this inherent limitation is to develop a more efficient NO source. Toward this end, we considered organic nitrites, typically, *tert*-butyl nitrite (TBN) and *iso*-amyl nitrite (IAMN), which have been frequently used as the reagents for nonaqueous nitrozation and diazotization, as an alternative NO source for their property of thermal instability.[8] In this paper, we report a new and more robust triple-component catalyst system, TEMPO/HBr/TBN, which provides a robust and economic catalytic oxidation of various alcohols to their corresponding aldehydes and ketones with a high turnover number (TON; eq 1).



(1)

Our previous studies demonstrated that each catalytic cycle in the transition-metal-free oxidation system can be adjusted to match the activity of substrates with the different solvents.[9] The question is the lower volume efficiency if the developed methodology is to be applied in the practical scale, because solvent or water significantly dilutes the effective volume. Only if the volume efficiency was greatly improved could the developed aerobic oxidation of alcohols be considered to compete with the convenient catalytic oxidation using cheap catalyst and stoichiometric oxidants. After careful studies of the transition-metal-free catalytic cycles, two aspects could be adjusted. One is cutting down the dosage of the catalyst system for economic reasons and the other is to minimize the solvent to increase the volume efficiency. Many experiments data showed that a new modified catalyst system, TEMPO/HBr/IAMN could meet the above requirement. Our initial efforts focused on the application of IAMN because of its widespread use. We chose neat benzyl alcohol (0.1 mol scale) as the substrate to pursue the best combination of the catalyst system for the new aerobic oxidations. It did work well in the aerobic oxidation, where partial results were listed in the parentheses of Table 1, and showed very good results. Unfortunately, *iso*-amyl alcohol resulted from the decomposition of IAMN, which probably participated in the oxidation in some cases and complicated the purification. On the contrary, the decomposed byproduct of TBN is *tert*-butyl alcohol, which cannot be oxidized in most cases and does not affect most potential applications of carbonyl compounds. Thus, we turned our attention to the use of TBN as the new NO source. As seen from Table 1, the results showed that the newly modified triple-component catalyst system, TEMPO/HBr/TBN, greatly improves the catalytic efficiency and can tolerate a high degree of variations on catalyst loading. For example, with TEMPO ranging from 1 to 0.1 mol %, together with both 4 mol % of HBr and TBN, the model substrate, benzyl alcohol, could be totally oxidized into benzaldehyde within 1 h.

By further decreasing the amount of TEMPO to 0.01 mol %, the reaction was complete within 2.5 h with a TON up to 10 000 (entry 5). To the best of our knowledge, this is the highest TON for the homogeneous catalytic aerobic alcohol oxidation to date. Trying to reduce the amount of TEMPO to 10 ppm resulted in 16% conversion after 24 h (entry 6). The loading effects of the other two cocatalysts were also investigated in the presence of 0.1 mol % of TEMPO as catalyst. For example, a full conversion was obtained with 0.4 mol % of TBN, while the dosage of HBr was flexible (entries 7 and 8). However, the oxidation with 0.4 mol % of HBr, together with 0.1 mol % of TBN showed extremely low conversion (entry 9), even with prolonged reaction time. Interestingly, when both

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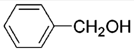
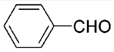
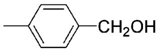
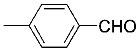
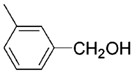
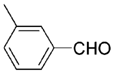
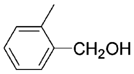
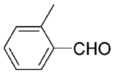
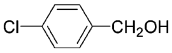
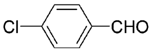
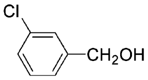
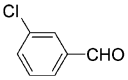
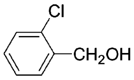
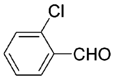
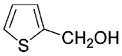
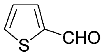
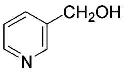
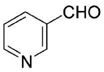
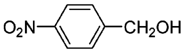
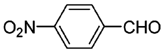
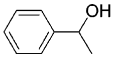
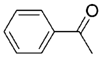
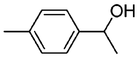
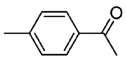
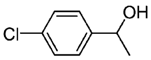
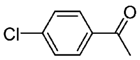
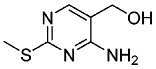
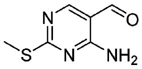
(8) Wang, P. G.; Cai, T. B.; Taniguchi, N. *Nitric Oxide Donors: for Pharmaceutical and Biological Application*; Wang, P. G., Cai, T. B., Taniguchi, N., Eds.; Wiley-VCH: Weinheim, 2005.

(9) (a) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112. (b) Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. *J. Org. Chem.* **2005**, *70*, 729.

(10) Liang, X.; Fu, D.; Liu, R.; Zhang, Q.; Zhang, T. Y.; Hu, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 5520.

(11) (a) Mu, R. Z.; Liu, Z. Q.; Yang, Z. J.; Liu, Z. G.; Wu, L. M.; Liu, Z. L. *Adv. Synth. Catal.* **2005**, *347*, 1333. (b) Wang, N.; Liu, R.; Chen, J.; Liang, X. *Chem. Commun.* **2005**, 5322. (c) Herrerias, C. I.; Zhang, T. Y.; Li, C.-J. *Tetrahedron Lett.* **2006**, *47*, 13. (d) Zhang, G.; Liu, R.; Xu, Q.; Ma, L.; Liang, X. *Adv. Synth. Catal.* **2006**, *348*, 862. (f) An, Z. J.; Pan, X. L.; Liu, X. M.; Han, X. W.; Bao, X. H. *J. Am. Chem. Soc.* **2006**, *128*, 16028.

TABLE 2. Catalytic Aerobic Oxidation to Various Alcohols[a]

Entry	Substrate	Product	Cat.[b] (mol%)	t (h)	Yield (%)
1			0.1 : 0.4 : 0.4	4	96.7
2			0.1 : 0.4 : 0.4	4	97.0
3			0.1 : 0.4 : 0.4	4	95.9
4			0.1 : 0.4 : 0.4	4	97.5
5			0.1 : 0.4 : 0.4	3.5	96.5
6			0.1 : 0.4 : 0.4	4	97.5
7			0.1 : 0.4 : 0.4	4	96.8
8[d]			1 : 1 : 4	2	95.5
9[c]			1 : 4 : 4	6	92.0
10[d]			0.5 : 2 : 2	6	97.0
11			0.1 : 4 : 4	3	96.3
12			0.1 : 4 : 4	5	96.2
13			0.1 : 4 : 4	2	98.1
14[e]	2-$C_8H_{17}OH$	2-Octanone	2 : 4 : 4	4	95.2
15[e]	1-$C_8H_{17}OH$	1-$C_7H_{15}CHO$	2 : 4 : 4	2	40.2[f]
16[g]			2 : 8 : 8	6	81.8

[a] Aerobic oxidations were carried out with 0.1 mol of alcohol substrate at 80 °C (oil bath temperature) under initial oxygen (0.6 MPa). Conversions for all substrates were over 99.5%. All yields are for pure, isolated products. [b] Cat. = TEMPO/HBr/TBN. [c] 6.0 mL of acetic acid was added. [d] With 20 mL of acetonitrile. [e] With 10 mL of 1,2-dichloroethane. [f] The GC area ratio of 1-octanal/1-octyl 1-octanoate is 54/45; distillation yield of pure 1-octanal. [g] With 40 mL of acetonitrile and 6 mL of acetic acid.

HBr and TBN were decreased to 0.1 mol %, a moderate conversion level was maintained (entry 10). Based on our previous proposed cascade mechanism,[9] we reckoned that the high ratio of HBr to NO did not favor for the equilibrium in the oxidation HBr to Br_2, and the excess HBr could accelerate the decomposition of TEMP-OH, thus inhibiting the reaction.

A wide range of primary and secondary alcohols have been tested under the optimized conditions (0.1 mol of alcohol substrate, 0.1 mol % of TEMPO, 0.4 mol % HBr, 0.4 mol % of TBN, 0.6 MPa of initial oxygen, 1.0 mL of water, 80 °C) and the results are summarized in Table 2. All benzylic alcohols, with either electron-donating or electron-withdrawing substituents, can be oxidized into their corresponding aldehydes in high isolated yields within 4 h (entries 2−7 in Table 2). The hetero-aromatic analogs showed low activity under this condition, but with a higher catalyst loading, the complete oxidation could also be achieved. In the presence of acetonitrile and with a higher ratio of TBN/HBr, 2-thiophene methanol was oxidized into 2-thiophene carboxaldehyde in a 95.5% yield (entry 8). Less HBr can significantly reduce the bromination impurity at the 5-position of the thiophene ring. As usual, the oxidation of 3-pyridine methanol was driven to completion with the help of equal mole amount of acetic acid to keep the system under weak acidic conditions (entry 9). Interestingly, with the strong ability to activate molecular oxygen, the new aerobic catalytic system with TBN could efficiently oxidize those substrates with high melting points and/or low solubility. Under the assistance of 20 mL of acetonitrile to form a slurry, *p*-nitro benzylic alcohol was totally oxidized with 0.5 mol % of TEMPO, 2 mol % of HBr, and 2 mol % of TBN. Pure *p*-nitro benzaldehyde was isolated by a simple filtration in high yield (entry 10). The neat α-methyl benzyl alcohols were converted to their corresponding acetophenones in high yields in the presence of 0.1 mol % of TEMPO and 4 mol % of both cocatalysts (entries 11−13). In the presence of 1,2-dichloroethane, secondary aliphatic alcohol, 2-octanol for an example, could also be oxidized into 2-octanone in high yield (entry 14). For primary aliphatic alcohol substrate, 1-octanol for an example, high conversion with a moderate selectivity can be achieved. Pure 1-octanal can be separated via distillation in 40% yield (entry 15). As an example for the potential application of this newly developed method of aerobic oxidation of alcohol to aldehyde, it was successfully applied in the oxidation of the highly functionalized 4-amino-2-methylthio-pyrimidine-5-methanol to its corresponding aldehyde in a 0.1 mol scale (entry 16). The obtained aldehyde is a useful pharmaceutical intermediate.[12] For the large-scale preparation of this compound, this method is superior to all the reported ones.[12b,13]

In conclusion, we have identified *tert*-butyl nitrite as an efficient NO equivalent for the activation of molecular oxygen and have applied this to a highly volume efficient and economically competitive, transition-metal-free catalytic aerobic alcohol oxidation process. Under the optimal reaction conditions, various alcohols can be converted to their corresponding aldehydes and ketones in high yields. The newly developed process also exhibited a high potential for the oxidations, as solid alcohols were demonstrated to be oxidizable with the help of minimum amount of solvent.

Experimental Section

Procedure of Oxidation of 4-Nitrobenzyl Alcohol (Entry 10 in Table 2): To a teflon-line 316L stainless steel autoclave (300 mL) was added 15.31 g (100 mmol) of 4-nitro benzyl alcohol, 78.0 mg (0.5 mmol, 0.5 mol %) of TEMPO, 350 mg (2.0 mmol, 2 mol %) of 48% HBr, 210 mg (2.0 mmol, 2 mol %) of TBN, and 20 mL of acetonitrile (the minimum volume to form a slurry at room temperature). Then the autoclave was closed and charged with oxygen to 0.6 MPa. The autoclave was put into an oil bath that was preheated to 80 °C. Six h later, the barometer dropped to 0.2 MPa, which indicated that the reaction was finished. The autoclave was taken out of the heating bath, cooled to room temperature, and carefully depressurized. A sampling was taken from the slurry, the sample was diluted with CH_2Cl_2, and conversion and selectivity was detected by GC without any purification. GC results showed the reaction was complete. The slurry was diluted with 20 mL of water, filtered, washed with water (10 mL × 2), and dried to yield 14.65 g (97.0%) as a pale yellow solid: mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (m, 2H), 8.42 (m, 2H), 10.18 (s, 1H); GC purity (area) >99%.

Procedure of Oxidation of 4-Amino-2-methylthio-pyrimidine-5-methanol (Entry 16 in Table 2): A similar operating procedure was used for aerobic oxidation of 4-nitrobenzyl alcohol. A total of 16.40 g (96 mmol) of 4-amino-2-methylthio-pyrimidine-5-methanol, 0.30 g (1.92 mmol, 2 mol %) of TEMPO, 1.34 g (7.68 mmol, 8 mol %) of 48% HBr, 0.79 g (7.68 mmol, 8 mol %) of TBN, 6 mL of acetic acid, 40 mL of acetonitrile (the minimum volume to form a slurry at room temperature), and 0.6 MPa of oxygen were heated to 80 °C for 6 h. After carefully depressurizing the autoclave, the slurry was diluted with 40 mL of water and then filtered. The solid was washed with aqueous acetonitrile (1:1, v/v, 20 mL × 2) and dried to yield 13.30 g (81.8%) as a yellow solid: mp 178−180 °C; ^{1}H NMR (DMSO-d_6) δ 2.50 (s, 3H), 8.02 (b, 1H), 8.22 (b, 1H), 8.56 (s, 1H), 9.77 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 13.6, 109.2, 160.1, 163.6, 175.8, 191.8; HPLC purity (area) >99%.

Acknowledgment. This work was supported by the start-up grant of Zhejiang University of Technology and the Natural Science Foundation of Zhejiang Province (Y406419). The authors thank Dr. Tony Y. Zhang at Eli Lilly and Company for his helpful discussion.

Supporting Information Available: Complete ref 12a, detailed experimental procedures, GC diagrams for all substrates and products, and NMR spectra for selected products. This material is available free of charge via the Internet at http://pubs.acs.org.

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