Organic LETTERS
Letter
pubs.acs.org/OrgLett

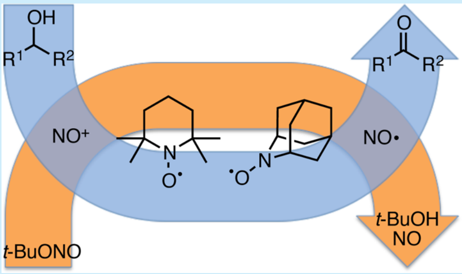
Anaerobic Nitroxide-Catalyzed Oxidation of Alcohols Using the NO^+/NO· Redox Pair

Martin Holan and Ullrich Jahn*

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo náměstí 2, 166 10 Prague 6, Czech Republic

Supporting Information

ABSTRACT: A new method for alcohol oxidation using TEMPO or AZADO in conjunction with $BF_3 \cdot OEt_2$ or $LiBF_4$ as precatalysts and *tert*-butyl nitrite as a stoichiometric oxidant has been developed. The system is based on a NO^+/NO· pair for nitroxide reoxidation under anaerobic conditions. This allows the simple, high-yielding conversion of various achiral and chiral alcohols to carbonyl compounds without epimerization and no formation of nonvolatile byproducts.



The oxidation of alcohols catalyzed by nitroxides is a widely used methodology in organic synthesis.[1] Usually 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) **1** is used as the catalyst with stoichiometric oxidants such as bleach, *tert*-butyl hypochlorite, elemental halogens, bis(acetoxy)iodobenzene (BAIB), or trichloroisocyanuric acid. Catalysis based on azaadamantane- (AZADO) **2** and azabicyclo[3.3.1]nonane- (ABNO) **3** type nitroxyl radicals has been more recently developed (Figure 1).[2] A common disadvantage of many of these catalytic systems is the formation of nonvolatile reduced species, resulting from the consumption of the stoichiometric oxidant, such as iodobenzene, isocyanuric acid, or inorganic salts. Oxygen has been used as the stoichiometric oxidant in TEMPO catalyzed alcohol oxidations based on the catalytic use of transition metal compounds.[3]

The first transition-metal-free aerobic oxidation process using TEMPO/Br_2/$NaNO_2$ was reported in 2004.[4] Other TEMPO/nitrite-based systems followed shortly after,[5] and versions with supported catalysts were also developed.[6] Besides metal nitrites, NH_2OH and HNO_3 were also applied.[7] A common feature of these catalytic systems is the operation of the NO·/NO_2· pair as mediator between O_2 and the TEMPOH/TEMPO/$TEMPO^+$ manifold. Even though these conditions are environmentally friendly, the use of O_2 often requires work in autoclaves, which makes them impractical and potentially hazardous. Moreover NO_2 that is formed in situ may interfere with some functional groups, such as alkenes.[8]

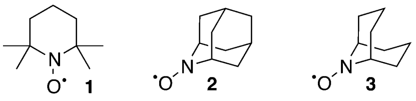


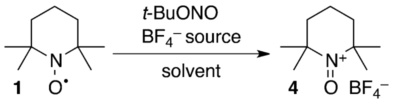
Figure 1. Types of nitroxyl radicals used in alcohol oxidations.

Alkyl nitrites are a source of the nitrosonium ion, a strong oxidizing agent with a redox potential of 1.0 V vs ferrocene.[9] Some time ago, we used the NO^+/NO· pair as stoichiometric SET oxidants.[10] This triggered our interest to apply it for TEMPO reoxidation.[11]

We report here that *tert*-butyl nitrite (TBN) as a convenient and cheap NO^+ precursor efficiently mediates alcohol oxidations catalyzed by **1** or **2** in the presence of $BF_3 \cdot OEt_2$ or $LiBF_4$ providing aldehydes and ketones in high yield without compromising resident stereocenters.

The investigation began with finding conditions for the stoichiometric oxidation of **1** to *N*-oxopiperidinium salt **4** (Table 1). When **1** was added to an ethereal solution of TBN and $BF_3 \cdot OEt_2$, salt **4** precipitated in 67% yield (entry 1).

Table 1. Screening of the Oxidation Conditions for TEMPO 1[a]



entry	solvent	BF_4^- source	yield (%)
1	Et_2O	$BF_3 \cdot OEt_2$	67
2[b]	Et_2O	$BF_3 \cdot OEt_2$	79
3[b,c]	CH_2Cl_2	$BF_3 \cdot OEt_2$	70
4[d]	Et_2O	HBF_4	79
5[c]	Et_2O	$LiBF_4$	65

[a]Conditions: **1** (1 mmol) added to a solution (4 mL) of BF_4^- source (1 mmol) and TBN (1 mmol). [b]$BF_3 \cdot OEt_2$ (1.35 mmol) used. [c]TBN (1.5 mmol) used. [d]TBN (1 mmol) added to **1** (1 mmol) and HBF_4 (1 mmol).

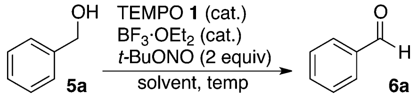
Received: October 21, 2013

© XXXX American Chemical Society

Increasing the amount of $BF_3\cdot OEt_2$ to 1.35 equiv improved the yield of **4** to 79% (entry 2). *n*-Butyl nitrite was similarly effective. The oxidation in CH_2Cl_2 also proceeded in 70% yield (entry 3). HBF_4 and $LiBF_4$ provided **4** in good yields, although the reaction with $LiBF_4$ was considerably slower (entries 4, 5).

Benzyl alcohol **5a** served to optimize the catalytic oxidations (Table 2). Using diethyl ether as the solvent gave **6a** only in 30% yield, probably due to precipitation of the active oxidant. Switching to CH_2Cl_2 at a 10 mol % loading of **1** at room temperature provided **6a** in a very good 94% yield after 4 h (entry 2). Heating the reaction mixture to reflux and reduction of the catalyst loading to 5 mol % led to similar yields (entries 3, 4). However, when the amount of catalyst **1** was further decreased to 1 mol %, a drop in the yield to 82% was observed (entry 5). A reaction in the absence of TEMPO under otherwise identical conditions also gave **6a**, however in a lower yield after a considerably longer reaction time (entry 6; see the Supporting Information for further details).[12]

Table 2. Oxidation of Benzyl Alcohol 5a Catalyzed by 1[a]

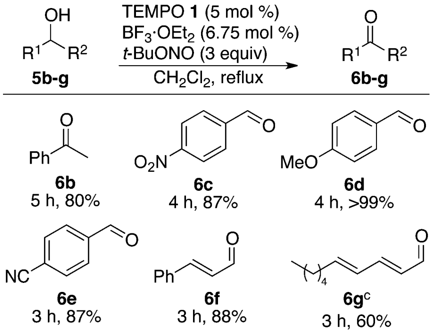


entry	solvent	temp	time (h)	**1** (mol %)	yield (%)
1	Et_2O	rt	5	10	30[b]
2	CH_2Cl_2	rt	4	10	94
3	CH_2Cl_2	reflux	0.75	10	95
4	CH_2Cl_2	reflux	1.5	5	97
5	CH_2Cl_2	reflux	5	1	82
6	CH_2Cl_2	reflux	5.5	–[c]	73

[a] Conditions: **5a** (2 mmol), solvent (10 mL), $BF_3\cdot OEt_2$ (1.35 times the amount of **1**), TBN (4 mmol), **1**, added and stirred at the indicated temperature. [b] Determined by ^1H NMR. [c] $BF_3\cdot OEt_2$ (6.75 mol %) used.

With optimal conditions in hand, the scope of the oxidation of aromatic and allylic alcohols was studied (Scheme 1). Electronically diverse benzylic alcohols **5b–e** were converted to the corresponding carbonyl compounds **6b–e** in good yields. Cinnamic aldehyde **6f** was similarly obtained in high yield. 2,4-Decadienol **5g** gave dienal **6g** in 60% yield using $LiBF_4$ instead of $BF_3\cdot OEt_2$, provided it was added as the last component to the reaction mixture.

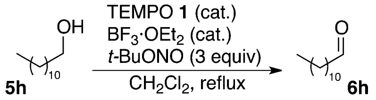
Scheme 1. Oxidation of Benzylic and Allylic Alcohols 5b–g[a,b]



[a] Conditions: **5b–f** (2 mmol), CH_2Cl_2 (10 mL), $BF_3\cdot OEt_2$ (6.75 mol %), TBN (6 mmol), **1** (5 mol %), reflux. [b] Isolated yields. [c] Conditions: CH_2Cl_2 (5 mL), $LiBF_4$ (5 mol %), TBN (3 mmol), **1** (5 mol %), **5g** (1 mmol), reflux.

Attempts to apply identical conditions to aliphatic aldehydes gave only moderate results. Dodecanol **5h** converted only to a 50% yield after 3 h, and the catalytic process stopped after some time (Table 3, entry 1). Addition of a new batch of **1** induced complete conversion after 5.5 h (entry 2). Addition of further $BF_3\cdot OEt_2$ led to a deterioration of the reaction mixture as indicated by GC analysis, whereas a decrease in the $BF_3\cdot OEt_2$ amount was beneficial (entry 3). A high conversion was observed with only 5 mol % of $BF_3\cdot OEt_2$, even if the second batch of **1** was not added (entry 4). Thus, it was important to use a maximum of 1 equiv of $BF_3\cdot OEt_2$ and **1** or even a slight excess of **1** over $BF_3\cdot OEt_2$ for the oxidation of aliphatic aldehydes. $LiBF_4$ could also be used as the anion source (entry 5).

Table 3. Oxidation of Dodecan-1-ol 5h[a]

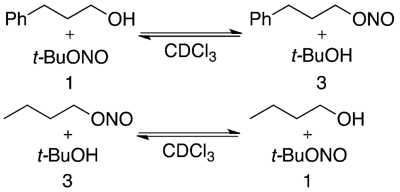


entry	BF_4^- source (mol %)	time (h)	**1** (mol %)	conv. (%)[b]
1	$BF_3\cdot OEt_2$ (6.75)	3	5	50
2	$BF_3\cdot OEt_2$ (6.75)	5.5	5 + 5	98
3	$BF_3\cdot OEt_2$ (5)	5	5 + 5	92
4	$BF_3\cdot OEt_2$ (5)	5	5	88
5	$LiBF_4$ (5)	5	5	92

[a] Conditions: **5h** (1 mmol), CH_2Cl_2 (5 mL), $BF_3\cdot OEt_2$, TBN (3 mmol), **1**, stirring under reflux. [b] Determined by GC.

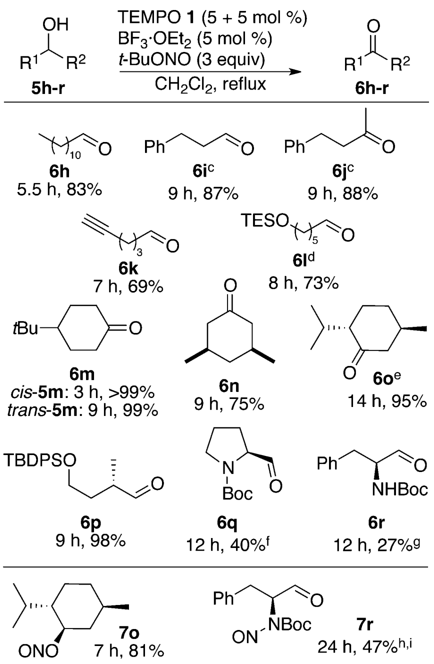
The reason for the lower reactivity of aliphatic alcohols was traced to a competing nitroso group transfer forming aliphatic nitrites and *tert*-butanol (Scheme 2). Indeed, when TBN was mixed with an equimolar amount of 3-phenylpropanol in $CDCl_3$ the equilibrium established quickly to a 3:1 ratio of 3-phenylpropyl nitrite and 3-phenylpropanol ($K = 9$), with no further change. Similarly, when equimolar amounts of *n*-BuONO and *t*-BuOH were mixed, a 3:1 ratio of *n*-BuONO and *n*-BuOH was established ($K = 0.11$). Therefore only relatively small amounts of free **5** are present under the reaction conditions thus reducing the rate of oxidation.

Scheme 2. NMR Study of Alcohol/Nitrite Equilibria



Based on these results, the scope for oxidation of aliphatic alcohols was determined using 5 mol % of **1** and $BF_3\cdot OEt_2$ in the presence of 3 equiv of TBN. It proved to be useful to add 5 mol % of catalyst **1** after 1 h at reflux (Scheme 3). Aldehydes or ketones **6h–6j** were oxidized in high yields. 5-Hexynal **6k** was obtained in a slightly lower yield, probably due to its volatility. For one of the most Lewis acid sensitive substrates, 6-triethylsilyloxy-1-hexanol **5l**, $LiBF_4$ proved to be the better anion source providing aldehyde **6l** in 73% yield. The rate of oxidation of cyclic alcohols depended on their configuration. *cis*-4-*tert*-Butylcyclohexanol with an axial hydroxy group was oxidized in essentially quantitative yield in 3 h, whereas

Scheme 3. Oxidation of Aliphatic Alcohols[a,b]



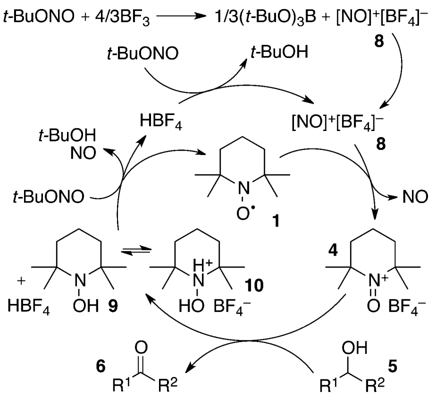
[a]Conditions: **5h–k,m–r** (2 mmol), CH_2Cl_2 (10 mL), $BF_3{\cdot}OEt_2$ (5 mol %), TBN (6 mmol), **1** (5 + 5 mol %), reflux. [b]Isolated yields. [c]TBN (8 mmol) used. [d]Conditions: CH_2Cl_2 (5 mL), $LiBF_4$ (5 mol %), TBN (3 mmol), **1** (5 + 5 mol %), **5l** (1 mmol), reflux. [e]AZADO **2** (5 + 5 mol %) used instead of **1**. [f]**5q** (25%) recovered. [g]**5r** (10%) recovered, **7r** (14%) isolated. [h]Also **6r** (14%) isolated. [i]CAUTION: *N*-Nitrosamines are potentially carcinogenic; proper care should be taken when working with them.

diequatorial *trans*-4-*tert*-butylcyclohexanol required a much longer reaction time for completion. Commercial **5n** having a *cis*-configuration at the methyl groups but existing as a 66:34 mixture of *cis*/*trans*-isomers at the hydroxy group gave ketone **6n** in 75% yield under standard conditions. However when the conditions for the oxidation of benzylic alcohols were applied, the *cis,trans*-isomer was oxidized in 46% yield, whereas 30% of the all-*cis* isomer of **5n** was recovered. Thus, the former conditions can be applied for separating mixtures or oxidizing cyclic alcohols with a defined configuration selectively. L-Menthol **5o**, a recognized difficult substrate for TEMPO-catalyzed oxidations, did not react under the standard conditions, but provided nitrite **7o** in 81% yield. However, replacing **1** with AZADO **2**[2] under otherwise identical conditions afforded L-menthone **6o** in high yield.

Enantiomerically pure alcohols **5p–r** with potentially labile stereocenters at the α-position were applicable under the reaction conditions without compromising the optical purity of the products **6p–r**. The integrity of the stereocenters in the products was proven by reducing aldehydes **6p–r** back to the starting alcohol and analysis of the corresponding Mosher esters of **5p** and **5r**[13,14] or the benzoate of **5q**[15] (see the Supporting Information). However, amino alcohols, such as *N*-Boc-prolinol **5q** or phenylalaninol **5r**, reacted slowly and the conversion stopped after some time, even though they were oxidized previously by **1**.[1d] *N*-Boc-Prolinal **6q** was obtained in 40% yield; the remainder of the mass balance was recovered **5q**. For amino alcohols bearing acidic NH functions, the method is not suitable, since *N*-nitrosation competed. An attempt to promote concomitant oxidation and *N*-nitrosation using 10 equiv of TBN gave **7r** as the main product in 47% yield.

The mechanism of this oxidation can be proposed as follows (Scheme 4). First TBN reacts with the catalytic amount of $BF_3{\cdot}OEt_2$ to generate nitrosonium tetrafluoroborate **8** and the borate ester.[16] The nitrosonium salt **8** oxidizes **1** to the *N*-oxopiperidinium salt **4** as shown in the stoichiometric experiments. The alcohols **5** are subsequently oxidized by salt **4** to the corresponding aldehydes or ketones **6** resulting in hydroxylamine **9** and tetrafluoroboric acid, which is in equilibrium with its salt **10**. Another equivalent of TBN subsequently reoxidizes **9** to **1** thus closing the catalytic cycle.

Scheme 4. Proposed Mechanism of Alcohol Oxidation with TBN



In conclusion, we reported a convenient nitroxide-catalyzed alcohol oxidation, using TEMPO or AZADO and $BF_3{\cdot}OEt_2$ or $LiBF_4$ as precatalysts and TBN as the stoichiometric oxidant. The catalytic system based on the $NO^+/NO{\cdot}$ pair differs significantly from the aerobic $NO{\cdot}/NO_2{\cdot}$ pair for catalyst reoxidation. The mild oxidation conditions allow oxidation of enantiomerically pure substrates without racemization. A limitation is the competing nitrosation of acidic N–H-containing amides or carbamates. The use of TBN, a low molecular weight organic oxidant, enables simple and fast purification by chromatography, since all side products are volatile. However, the crude aldehydes may also be used directly in further reaction steps.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jahn@uochb.cas.cz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by the grant agency of the Czech Republic (13-40188S), the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic (RVO: 61388963), and the Gilead Sciences & IOCB research center is gratefully acknowledged.

REFERENCES

(1) Recent reviews: (a) Tebben, L.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 5034. (b) Brückner, C. In *Stable Radicals: Fundamentals and Applied Aspects of Odd-Electron Compounds*; Hicks, R. G., Ed.; Wiley: 2010; p 433. (c) Bobbitt, J. M. *TCIMeru* **2010**, *146*, 2. (d) Bobbitt, J. M.; Brückner, C.; Merbouh, N. *Org. React.* **2009**, *74*, 103.

(2) (a) Shibuya, M.; Pichierri, F.; Tomizawa, M.; Nagasawa, S.; Suzuki, I.; Iwabuchi, Y. *Tetrahedron Lett.* **2012**, *53*, 2070. (b) Hayashi, M.; Shibuya, M.; Iwabuchi, Y. *J. Org. Chem.* **2012**, *77*, 3005. (c) Dohi, T.; Kamitanaka, T.; Mochizuki, E.; Ito, M.; Kita, Y. *Chem. Pharm. Bull.* **2012**, *60*, 1442 and references cited therein.

(3) For reviews, see: (a) Parmeggiani, C.; Cardona, F. *Green Chem.* **2012**, *14*, 547. (b) Sheldon, R. A.; Arends, I. W. C. E. *J. Mol. Catal. A: Chem.* **2006**, *251*, 200. (c) Minisci, F.; Punta, C.; Recupero, F. *J. Mol. Catal. A: Chem.* **2006**, *251*, 129.

(4) Liu, R.; Liang, X.; Dong, C.; Hu, X. *J. Am. Chem. Soc.* **2004**, *126*, 4112.

(5) (a) Zhang, J.; Jiang, Z.; Zhao, D.; He, G.; Zhou, S.; Han, S. *Chin. J. Chem.* **2013**, *31*, 794. (b) Qiu, C.; Jin, L.; Huang, Z.; Tang, Z.; Lei, A.; Shen, Z.; Sun, N.; Mo, W.; Hu, B.; Hu, X. *ChemCatChem* **2012**, *4*, 76. (c) He, X.; Shen, Z.; Mo, W.; Sun, N.; Hu, B.; Hu, X. *Adv. Synth. Catal.* **2009**, *351*, 89. (d) Wang, X.; Liu, R.; Jin, Y.; Liang, X. *Chem.—Eur. J.* **2008**, *14*, 2679. (e) Xie, Y.; Mo, W.; Xu, D.; Shen, Z.; Sun, N.; Hu, B.; Hu, X. *J. Org. Chem.* **2007**, *72*, 4288. (f) Herrerías, C. I.; Zhang, T. Y.; Li, C.-J. *Tetrahedron Lett.* **2006**, *47*, 13. (g) Liu, R.; Dong, C.; Liang, X.; Wang, X.; Hu, X. *J. Org. Chem.* **2005**, *70*, 729.

(6) (a) Zhu, J.; Wang, P.-c.; Ming, L. *Synth. Commun.* **2013**, *43*, 1871. (b) Karimi, B.; Badreh, E. *Org. Biomol. Chem.* **2011**, *9*, 4194. (c) Miao, C.-X.; He, L.-N.; Wang, J.-Q.; Wang, J.-L. *Adv. Synth. Catal.* **2009**, *351*, 2209. (d) Karimi, B.; Biglari, A.; Clark, J. H.; Budarin, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7210.

(7) (a) Rahimi, A.; Azarpira, A.; Kim, H.; Ralph, J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 6415. (b) Aellig, C.; Scholz, D.; Conrad, S.; Hermans, I. *Green Chem.* **2013**, *15*, 1975 and references cited therein.

(8) (a) Naveen, T.; Maity, S.; Sharma, U.; Maiti, D. *J. Org. Chem.* **2013**, *78*, 5949. (b) Maity, S.; Naveen, T.; Sharma, U.; Maiti, D. *Org. Lett.* **2013**, *15*, 3384. (c) Astolfi, P.; Charles, L.; Gigmes, D.; Greci, L.; Rizzoli, C.; Sorana, F.; Stipa, P. *Org. Biomol. Chem.* **2013**, *11*, 1399 and references cited therein.

(9) Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, *96*, 877.

(10) Jahn, U.; Aussieker, S. *Org. Lett.* **1999**, *1*, 849.

(11) Borodkin, G. I.; Elanov, I. R.; Shakirov, M. M.; Shubin, V. G. *Russ. J. Org. Chem.* **2003**, *39*, 1144.

(12) (a) Olah, G. A.; Ho, T.-L. *Synthesis* **1976**, 609. (b) Hamasaki, A.; Kuwada, H.; Tokunaga, M. *Tetrahedron Lett.* **2012**, *53*, 811.

(13) Cooksey, J. P.; Kocienski, P. J.; Li, Y.-f.; Schunk, S.; Snaddon, T. N. *Org. Biomol. Chem.* **2006**, *4*, 3325.

(14) Kokotos, G.; Noula, C. *J. Org. Chem.* **1996**, *61*, 6994.

(15) Kurokawa, M.; Shindo, T.; Suzuki, M.; Nakajima, N.; Ishihara, K.; Sugai, T. *Tetrahedron: Asymmetry* **2003**, *14*, 1323.

(16) Precedence: Lee, S.; Fuchs, P. L. *Can. J. Chem.* **2006**, *84*, 1442.