Synthetic Methods

DOI: 10.1002/ange.201307144

3-Methyl-4-oxa-5-azahomoadamantane: Alkoxyamine-Type Organocatalyst for Alcohol Oxidation**

*Yusuke Sasano, Keiichi Murakami, Tomohiro Nishiyama, Eunsang Kwon, and Yoshiharu Iwabuchi**

The unique behavior and eminent reactivity of organic/inorganic nitrogen oxides have continuously attracted the attention of chemists not only because of their profound chemistry, but also because of their use in various fields of material and life sciences.[1] Herein, we report the discovery of a novel alkoxyamine-type organocatalyst, 3-methyl-4-oxa-5-azahomoadamantane (**1**), which enables highly efficient oxidation of primary and secondary alcohols into their corresponding carbonyl compounds using NaOCl as the terminal oxidant. The present work first shows a useful pathway from an alkoxyamine/alkoxyaminyl radical to a nitroxyl radical/oxoammonium ion under oxidative conditions (Figure 1).[2,3]

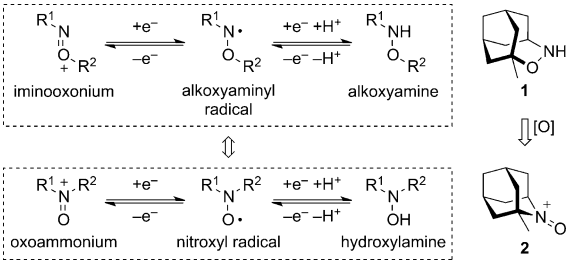
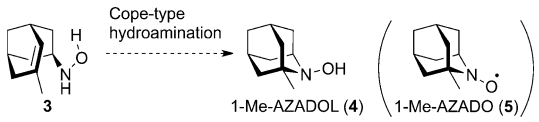


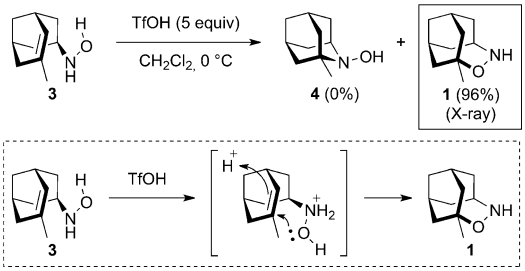
Figure 1. Redox properties of nitroxyl radicals and alkoxyaminyl radicals.

The synthesis of a homoadamantane-embedded alkoxyamine and its use as a catalyst for alcohol oxidation were unexpectedly discovered during our attempts to develop 1-methyl-2-azaadamantan-2-ol (1-Me-AZADOL; **4**), which is a functional equivalent of the nitroxyl radical 1-Me-AZADO (**5**), a highly active catalyst for alcohol oxidation.[4] Thus, we envisaged that 1-Me-AZADOL (**4**) could be obtained from hydroxylamine (**3**) by an intramolecular Cope-type hydroamination (Scheme 1).[5–7]



Scheme 1. Synthetic plan of 1-Me-AZADOL (**4**).

Although the intended cyclization reaction of **3** did not proceed even in boiling xylene, the treatment of **3** with 5 equivalents of TfOH in CH_2Cl_2 at 0 °C induced a rapid and clean reaction to give the polar product **1**, for which spectral data were not consistent with those of **4** (Scheme 2).[8,9] After detailed spectral analysis and single-crystal X-ray crystallography, we concluded that the structure of **1** is that of 3-methyl-4-oxa-5-azahomoadamantane (Figure 2). It was concluded that, upon treatment with TfOH, **3** did not undergo the intended Cope-type hydroamination, but instead reacted



Scheme 2. Discovery of the alkoxyamine **1**. Tf = trifluoromethanesulfonyl.

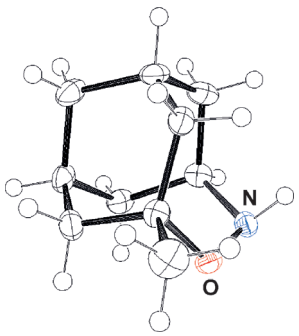


Figure 2. ORTEP drawing of **1** with probability ellipsoids drawn at the 50% level.

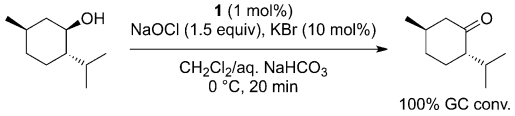
[*] Y. Sasano, K. Murakami, T. Nishiyama, Prof. Dr. Y. Iwabuchi
Department of Organic Chemistry
Graduate School of Pharmaceutical Sciences, Tohoku University
6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578 (Japan)
E-mail: y-iwabuchi@m.tohoku.ac.jp
Dr. E. Kwon
Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578 (Japan)

[**] This work was partly supported by a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysis" from the Ministry of Education, Culture, Sports, Science and Technology (Japan), by a Grant-in-Aid for Scientific Research (B) (No. 24390001), and by a Grant-in-Aid for Young Scientists (B) (No. 25860001) from the Japan Society for the Promotion of Science (JSPS).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307144.

through hydroetherification to form a less stable seven-membered ring.[10]

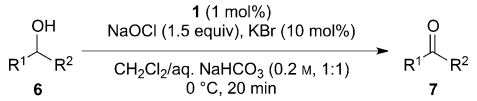
Our curiosity urged us to examine the catalytic activity of **1** in connection with **4**. We surprisingly found that **1** exhibited exceptionally high catalytic efficiency in the presence of NaOCl to oxidize menthol in quantitative conversion (Scheme 3).[11]

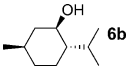
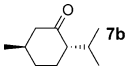
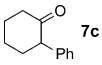
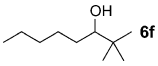
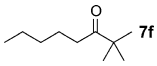
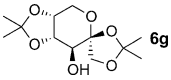
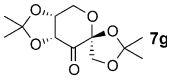
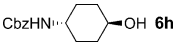
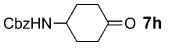
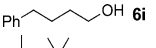
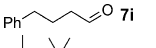
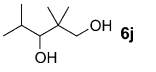
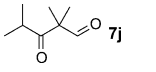


Scheme 3. Catalytic activity of **1** for alcohol oxidation.

Encouraged by the excellent catalytic activity of **1**, we evaluated the scope of the alcohol oxidation catalyzed by **1** using NaOCl as the bulk oxidant (Table 1). Various alcohols,

Table 1: Scope of the **1**-catalyzed oxidation.

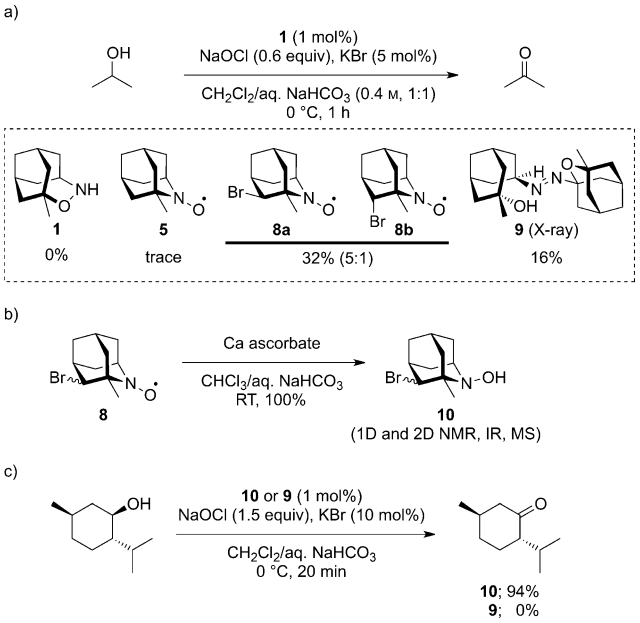


Entry	Substrate	Product	Yield [%][a]
1	 **6a**	 **7a**	90
2	 **6b**	 **7b**	93
3	 **6c**	 **7c**	99
4	 **6d**	 **7d**	92
5	 **6e**	 **7e**	98
6	 **6f**	 **7f**	90
7	 **6g**	 **7g**	100
8	 **6h**	 **7h**	99
9[b]	 **6i**	 **7i**	87
10[c]	 **6j**	 **7j**	84

[a] Yield is that of the isolated product. [b] Used 1.2 equiv of NaOCl. [c] Used 2.5 equiv of NaOCl. Cbz = benzyloxycarbonyl.

including the sugar derivative **6g** and the *N*-protected amino alcohol **6h**, were efficiently oxidized to the corresponding carbonyl compounds with 1 mol% catalyst in high yield.

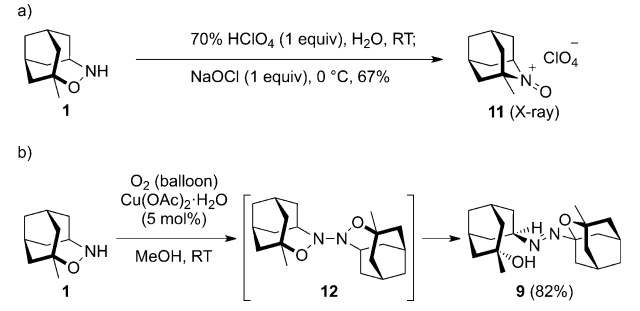
To gain mechanistic insight into the **1**-catalyzed oxidation, we attempted to identify active species generated in situ. We conducted a large-scale oxidation of isopropyl alcohol (20 mmol) with 0.6 equivalent of NaOCl and obtained the



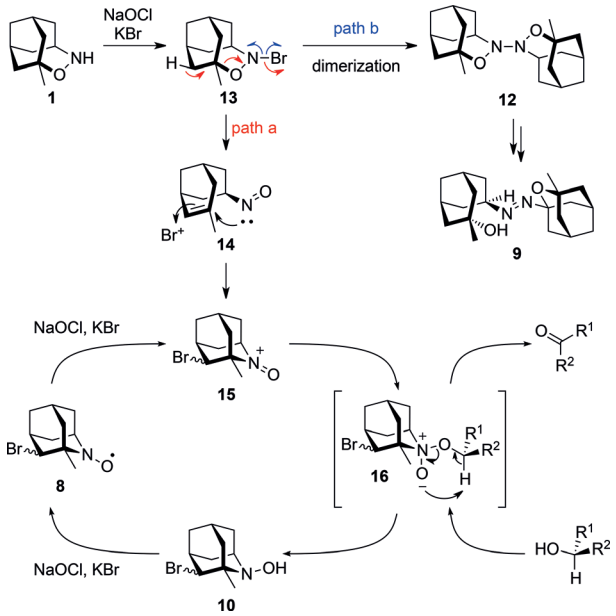
Scheme 4. Experiments for determination of active species. a) Isolation of products derived from **1**. b) Structure elucidation of 8-Br-1-Me-AZADO (**8**). c) Catalytic activities of isolated compounds.

residue after extraction and evaporation. Chromatographic purification of the residue gave products derived from **1** (Scheme 4a). The 8-Br-1-Me-AZADO (**8**) and dimeric diazo compound **9** were isolated as the major products. Notably, **1** and related homoadamantane skeletal compounds were not isolated. The structure of **8** was determined by the spectral analysis of the corresponding hydroxylamine **10**, and that of the diazo compound **9** was determined by single-crystal X-ray crystallography (Scheme 4b). The isolated **9** and **10** were employed in the catalytic oxidation of menthol (Scheme 4c). Although **9** did not oxidize menthol, **10** smoothly oxidized the alcohol to afford menthone in 94% yield. Notably, a similar oxidative transformation of **1** into the oxoammonium salt **11** proceeded in 67% yield using NaOCl in the presence of $HClO_4$ (Scheme 5a).[12] In contrast, the oxidative dimerization and spontaneous isomerization proceeded under one-electron oxidation conditions to give the diazo compound **9** in high yield (Scheme 5b).

Considering the above results, we propose a possible reaction mechanism (Scheme 6). First, **1** is brominated by



Scheme 5. Oxidative transformation of the alkoxyamine **1**. a) Isolation of the oxoammonium salt **11**. b) One-electron oxidation of catalyst **1**.



Scheme 6. Possible reaction mechanism of the **1**-catalyzed oxidation.

NaOCl and KBr to give the bromoamine **13**. Unstable **13** is degraded by either heterolytic (path a) or homolytic (path b) cleavage. The heterolytic cleavage of **13** gives the nitrosoalkene **14** as a transient intermediate,[13] which immediately undergoes bromoamination to give the oxoammonium species **15**.[14] The oxoammonium species plays the same role as this species in TEMPO/AZADO oxidation.[4] It oxidizes an alcohol to give the corresponding carbonyl compound and **10**, which is then converted into **15** by NaOCl and KBr to establish the catalytic cycle. In contrast, an alkoxyaminyl radical generated by the homolytic cleavage of **13** immediately dimerizes,[15] then isomerization proceeds to afford the diazo compound **9**, which does not function as a catalyst.[16]

In summary, we have discovered an alkoxyamine-type organocatalyst (**1**) for alcohol oxidation. The alkoxyamine is readily accessed and efficiently oxidizes various primary and secondary alcohols to give their corresponding carbonyl compounds in high yield. The novel oxidative pathway involving transformation of an alkoxyamine into an oxoammonium ion plays a key role. The novel oxidative pathway disclosed in this study should inspire new avenues for the design of redox catalysts as well as of organic paramagnetic compounds.

Experimental Section

General procedure for alcohol oxidation: A 20 mL round-bottomed flask equipped with a magnetic stirring bar was charged with a solution of the alcohol **6** (1.00 mmol), the alkoxyamine **1** (1.67 mg, 10 μmol), and KBr (11.9 mg, 0.100 mmol) in CH_2Cl_2 (2.7 mL) and sat. $NaHCO_3$ (1 mL). To this cooled (0 °C, ice water bath) and well-stirred (800 rpm) mixture was added dropwise a premixed solution of aqueous NaOCl (1.0 mL, 1.5 mmol: 1.45 M, purchased from Junsei Chemical Co., Ltd. and titrated) and sat. $NaHCO_3$ (1.7 mL) over 5 min. The reaction mixture was stirred for 20 min at 0 °C, then quenched with 20 % aqueous $Na_2S_2O_3$ (3 mL). The aqueous layer was separated and extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O/*n*-hexane) to give the corresponding carbonyl compound **7** in 84–100 % yield.

Received: August 14, 2013
Published online: October 11, 2013

Keywords: alcohols · *N*-oxides · organocatalysis · oxidation · synthetic methods

[1] a) *Stable Radicals* (Ed.: R. G. Hicks), Wiley, Chichester, **2010**; b) G. I. Likhtenshtein, J. Yamauchi, S. Nakatsuji, A. I. Smirnov, R. Tamura, *Nitroxides*, Wiley-VCH, Weinheim, **2008**.
[2] For reviews of nitroxyl-radical-mediated oxidation, see: a) L. Tebben, A. Studer, *Angew. Chem.* **2011**, *123*, 5138 – 5174; *Angew. Chem. Int. Ed.* **2011**, *50*, 5034 – 5068; b) R. Ciriminna, M. Pagliaro, *Org. Process Res. Dev.* **2010**, *14*, 245 – 251; c) T. Vogler, A. Studer, *Synthesis* **2008**, 1979 – 1993; d) R. A. Sheldon, I. W. C. E. Arends, *J. Mol. Catal. A* **2006**, *251*, 200 – 214; e) R. A. Sheldon, I. W. C. E. Arends, *Adv. Synth. Catal.* **2004**, *346*, 1051 – 1071; f) W. Adam, C. R. Saha-Moller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499 – 3548; g) A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, 1153 – 1174; h) J. M. Bobbitt, M. C. L. Flores, *Heterocycles* **1988**, *27*, 509 – 533.
[3] The redox properties of alkoxyamines and related alkoxyaminyl radicals have been explored from the aspect of physical chemistry. However, to the best of our knowledge, the application of alkoxyamines or alkoxyaminyl radicals as catalysts for oxidation reactions has not yet been reported. For representative reports on alkoxyamines/alkoxyaminyl radicals, see: a) Y. Miura, T. Tomimura, *Chem. Commun.* **2001**, 627 – 628; b) W. C. Danen, C. T. West, *J. Am. Chem. Soc.* **1971**, *93*, 5582 – 5584.
[4] M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412 – 8413.
[5] For a review of Cope-type hydroamination, see: N. J. Cooper, D. W. Knight, *Tetrahedron* **2004**, *60*, 243 – 269.
[6] For recent examples of the Cope-type hydroamination of alkenes with hydroxylamines, see: a) M. J. MacDonald, C. R. Hesp, D. J. Schipper, M. Pesant, A. M. Beauchemin, *Chem. Eur. J.* **2013**, *19*, 2597 – 2601; b) A. R. Brown, C. Uyeda, C. A. Brotherton, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 6747 – 6749; c) S. B. Zhao, E. Bilodeau, V. Lemieux, A. M. Beauchemin, *Org. Lett.* **2012**, *14*, 5082 – 5085; d) E. H. Krenske, E. C. Davison, I. T. Forbes, J. A. Warner, A. L. Smith, A. B. Holmes, K. N. Houk, *J. Am. Chem. Soc.* **2012**, *134*, 2434 – 2441; e) N. Guimond, M. J. MacDonald, V. Lemieux, A. M. Beauchemin, *J. Am. Chem. Soc.* **2012**, *134*, 16571 – 16577; f) M. J. MacDonald, D. J. Schipper, P. J. Ng, J. Moran, A. M. Beauchemin, *J. Am. Chem. Soc.* **2011**, *133*, 20100 – 20103; g) J. Moran, S. I. Gorelsky, E. Dimitrijevic, M. E. Lebrun, A. C. Bedard, C. Seguin, A. M. Beauchemin, *J. Am. Chem. Soc.* **2008**, *130*, 17893 – 17906; h) A. M. Beauchemin, J. Moran, M. E. Lebrun, C. Seguin, E. Dimitrijevic, L. Zhang, S. I. Gorelsky, *Angew. Chem.* **2008**, *120*, 1432 – 1435; *Angew. Chem. Int. Ed.* **2008**, *47*, 1410 – 1413.
[7] For examples of intramolecular Cope-type hydroamination to form *N*-hydroxypiperidine: a) M. E. Lebrun, J. Y. Pfeiffer, A. M. Beauchemin, *Synlett* **2009**, 1087 – 1090; b) M. P. Coogan, D. W. Knight, *Tetrahedron Lett.* **1996**, *37*, 6417 – 6420.
[8] We have constructed the azaadamantane skeleton by intramolecular hydroamination promoted by TfOH. See: M. Shibuya, Y. Sasano, M. Tomizawa, T. Hamada, M. Kozawa, N. Nagahama, Y. Iwabuchi, *Synthesis* **2011**, 3418 – 3425.
[9] 1-Me-AZADOL (**4**) was prepared by the reduction of 1-Me-AZADO (**5**); see the Supporting Information.
[10] R. N. Farr, *Tetrahedron Lett.* **1998**, *39*, 195 – 196.

[11] a) P. L. Anelli, S. Banfi, F. Montanari, S. Quici, *J. Org. Chem.* **1989**, *54*, 2970 – 2972; b) P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559 – 2562.
[12] M. Shibuya, T. Sato, M. Tomizawa, Y. Iwabuchi, *Chem. Commun.* **2009**, 1739 – 1741.
[13] G. V. Shustov, N. B. Tavakalyan, L. L. Shustova, A. P. Pleshkova, R. G. Kostyanovskii, *Bull. Acad. Sci. Ussr Ch+* **1982**, *31*, 330 – 339.
[14] The density functional theory (DFT) calculations at the B3LYP/6-311 + G(2d,p) level show that the hydroxylamine **4** is thermodynamically more stable than the alkoxyamine **1** by ca. 12 kcal mol^{-1} in the gas phase. See the Supporting Information.
[15] R. G. Kostyanovsky, V. F. Rudchenko, V. G. Shtamburg, I. I. Chervin, S. S. Nasibov, *Tetrahedron* **1981**, *37*, 4245 – 4254.
[16] The DFT calculations at the B3LYP/6-311 ++ G(d,p) level show that **9** is thermodynamically more stable than **12** by ca. 62 kcal mol^{-1} in the gas phase. See the Supporting Information.

