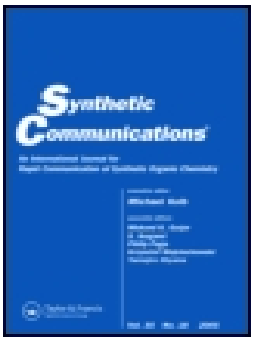


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

Efficient selective oxidation of alcohols to aldehydes catalyzed by a morpholinone nitroxide

Zhenhua Dong, Pengwei Gao & Yongmei Xiao

To cite this article: Zhenhua Dong, Pengwei Gao & Yongmei Xiao (2019): Efficient selective oxidation of alcohols to aldehydes catalyzed by a morpholinone nitroxide, Synthetic Communications, DOI: 10.1080/00397911.2019.1666284

To link to this article: https://doi.org/10.1080/00397911.2019.1666284

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1666284

Taylor & Francis
Taylor & Francis Group

Efficient selective oxidation of alcohols to aldehydes catalyzed by a morpholinone nitroxide

Zhenhua Dong, Pengwei Gao, and Yongmei Xiao

College of Chemistry and Chemical Engineering, Academician Workstation for Natural Medicinal Chemistry of Henan Province, Henan University of Technology, Zhengzhou, PR China

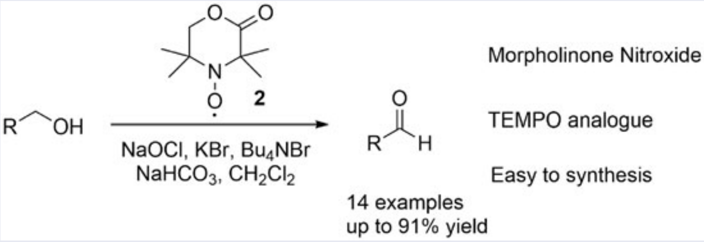
ABSTRACT

Efficient chemoselective oxidation of primary alcohols to the corresponding aldehydes is described. The transformation is promoted by a catalytic morpholinone nitroxide radical catalyst which can be easily synthesized. A broad range of substrates including aromatic and aliphatic primary alcohols are converted with excellent yields under mild conditions. The control experiments reveal that the morpholinone nitroxide can be used as a selective oxidant for primary alcohols in the presence of secondary alcohols.

ARTICLE HISTORY
Received 2 August 2019

KEYWORDS
Aaldehyde; nitroxide; oxidation; primary alcohol; TEMPO analog

GRAPHICAL ABSTRACT



Introduction

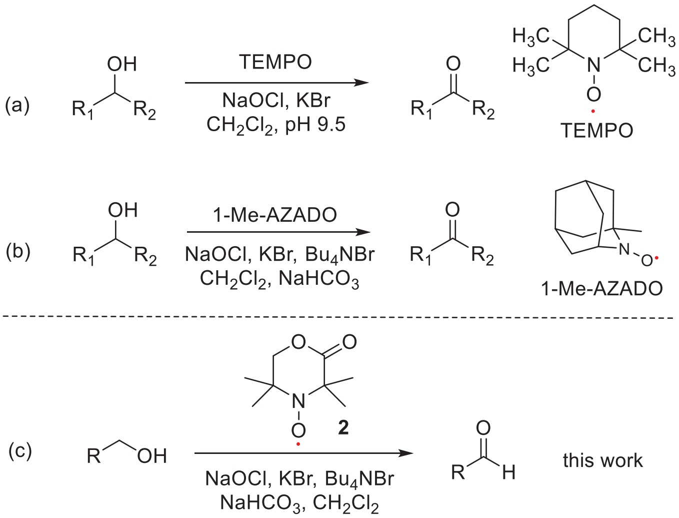
The oxidation of alcohol is one of the most common and crucial transformations in synthetic organic chemistry, especially in the fine chemicals and pharmaceutical industries.[1,2] Several methods have been developed for the oxidation of alcohols to aldehydes, ketones, or acids. Traditional methods include the using of chromium reagents, manganese reagents,[3] noble metal, [4] copper reagents,[5] or the periodinane reagents as well as the metal-free reaction condition.[6] Although such methods can promote the oxidation procedure efficiently, the demand of stoichiometric oxidants or the residual of metal are confronted with environmental stress. On the other hand, it remains a continuous challenging that chemoselective oxidation of primary alcohols to the aldehydes rather than the carboxylic acids.[7]

In the past decades, the oxidation of alcohols catalyzed by stable free radical TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and its derivations have been used for numerous

---

CONTACT Zhenhua Dong ✉ hautdong@foxmail.com College of Chemistry and Chemical Engineering, Henan University of Technology, Zhengzhou, 450001, PR China.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.
Supplemental data for this article is available online at on the publisher's website.



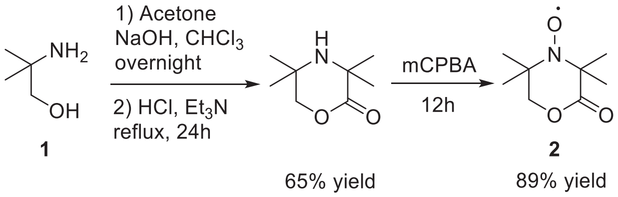
Scheme 1. The oxidation of alcohols using different oxidates.

transformation including the pharmaceutical industries and fine chemicals.[8–10] Comparing with other oxygenant, TEMPO and its derivations can be used in mild reaction condition such as short reaction time, low catalyst loading and green reaction medium.[11–16] The typically oxidation condition (known by Anelli's oxidation) by 4-methoxy-TEMPO with hypochlorite as the primary oxidant in water is showed, and the alcohols can be oxidized to aldehydes or ketones efficiently (Scheme 1(a)).[17–19] Except for the oxidation of alcohols, the TEMPO can be used for various transformation. However, a potential problem is that the expensive of TEMPO would restrict its application at an industrial scale. A series of TEMPO derivatives and analogs have been developed and applied to decrease the cost.[20–22] Such as Iwabuchi reported an azaadamantane nitroxyl radical which could be an efficient catalyst for oxidation of alcohols with shorted reaction time compared with TEMPO (Scheme 1(b)).[23] Nevertheless, the synthesis of azaadamantane nitroxyl radical (1-Me-AZADO) was difficult.[23] Hence, there is still significant room for the structural improvement in TEMPO analogs.

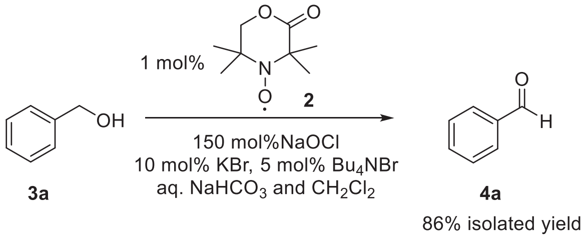
Furthermore, mostly of the TMEPO derivatives have the inferior capability for the selective oxidation of primary alcohols to aldehydes in the presence of secondary alcohols. We herein disclose that the morpholinone nitroxide **2**, which is served as TEMPO analog, has an outstanding catalytic capability for the selective oxidation of primary alcohols to aldehydes (Scheme 1(c)). The morpholinone nitroxide **2** was synthesized by Rychnovsky in 1998.[24,25] As far as we know, however, its catalytic ability as oxidation has never been examined.[26–28] Including Rychnovsky's work in 1999, they didn't find its oxidation ability.[28,29]]

Results and discussion

The study was started from the preparing of morpholinone nitroxide **2** as shown in Scheme 2. The synthesis was concise from cheap material **1** (2-amino-2-methyl-1-



Scheme 2. Synthesis of morpholinone nitroxide **2**.



Scheme 3. Optimized oxidation conditions.

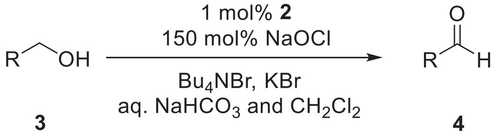
propanol), which was commercially available. The routes were concise and easy to operation.

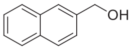
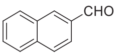
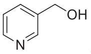
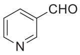
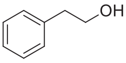
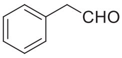
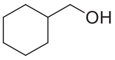
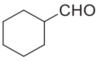
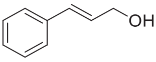
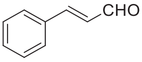
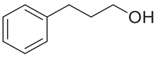
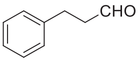
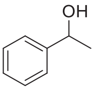
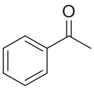
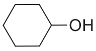
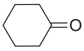
In the initiatory experiment, we found the morpholinone nitroxide **2** could promote the oxidation of benzyl alcohol to benzaldehyde efficiently under mild aqueous conditions. To our surprise, the morpholinone nitroxide **2** displayed efficient catalytic activity using only 1 mol% catalyst loading. The transformation could be completed entirely in 30 min as shown in Scheme 3. During the optimization of the reaction conditions, we found that other solvents and additives have poor influence for the transformation.

Under the optimized conditions, we tested the scope of this process and a number of primary alcohols were oxidized with morpholinone nitroxide **2** (Table 1). For diverse primary alcohols, including electron-withdrawing and electron-donating substitutional benzyl alcohol **3 b**-**3f**, condensed ring and heterocycle alcohols, **3 g** and **3 h**, excellent yields could be achieved. For the saturated alkyl alcohols and aryl alkyl substrates, the oxidation could also be proceeded smoothly. Unfortunately, when the secondary alcohols **3o** and **3p** were employed, no any products were obtained even though the reaction time was prolonged to 12 h. The results revealed this method could be a selective oxidation of primary alcohols to aldehydes.

Except for the NaOCl, $PhI(OAc)_2$ was also a common used oxidizing agent in TEMPO oxidation. In our exploration, the primary alcohols could be oxidized by using $PhI(OAc)_2$. However, it is obvious that the method using NaOCl was better than using $PhI(OAc)_2$. Because longer reaction times were needed. And the price of the $PhI(OAc)_2$ was considerably higher than NaOCl. However, the nitroxide-$PhI(OAc)_2$ system was also a chemoselective oxidant as shown by Table 2. Moreover, the method using $PhI(OAc)_2$ resulted in a little higher yields than the method using NaOCl. Because the washing by water was an indispensable operation in method using NaOCl. It was inevitably that the products, aldehydes, may be dissolved in water slightly. Comparing with the TEMPO- $PhI(OAc)_2$ system, morpholinone nitroxide **2** has a better catalytic activities under low catalytic loading (1 mol%).[30]

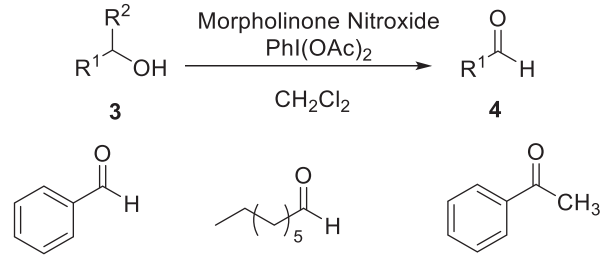
Table 1. The oxidation of different alcohols.[a]



Entry	Alcohol	Aldehyde	Yield%[b]
1	$PhCH_2OH$, **3a**	PhCHO, **4a**	86
2	2-Cl-$C_6H_4CH_2OH$, **3b**	2-Cl-C_6H_4CHO, **4b**	91
3	2-Me-$C_6H_4CH_2OH$, **3c**	2-Me-C_6H_4CHO, **4c**	89
4	4-Me-$C_6H_4CH_2OH$, **3d**	4-Me-C_6H_4CHO, **4d**	86
5	4-Cl-$C_6H_4CH_2OH$, **3e**	4-Cl-C_6H_4CHO, **4e**	90
6	4-OMe-$C_6H_4CH_2OH$, **3f**	4-OMe-C_6H_4CHO, **4f**	84
7	 ,**3g**	 ,**4g**	88
8	 ,**3h**	 ,**4h**	91
9	1-Octanol, **3i**	Octanal, **4i**	86
10	1-Hexanol, **3j**	Hexanal, **4j**	88
11	 ,**3k**	 ,**4k**	88
12	 ,**3l**	 ,**4l**	81
13	 ,**3m**	 ,**4m**	82
14	 ,**3n**	 ,**4n**	90
15	 ,**3o**	 ,**4o**	nr[c]
16	 ,**3p**	 ,**4p**	nr

[a] The reaction was carried out by morpholinone nitroxide **2** (1 mol %) with NaOCl (150 mol %), KBr (10 mol %), Bu_4NBr (5 mol %), aq. $NaHCO_3$ in CH_2Cl_2 at 0 °C for 30 min. [b] Isolated yield. [c] nr = no reaction.

Table 2. Comparison experiments under $PhI(OAc)_2$ condition[a].

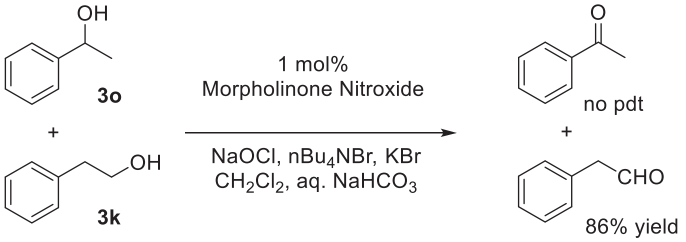


4a $R^2 = H$ (86%[b], 92%[c])

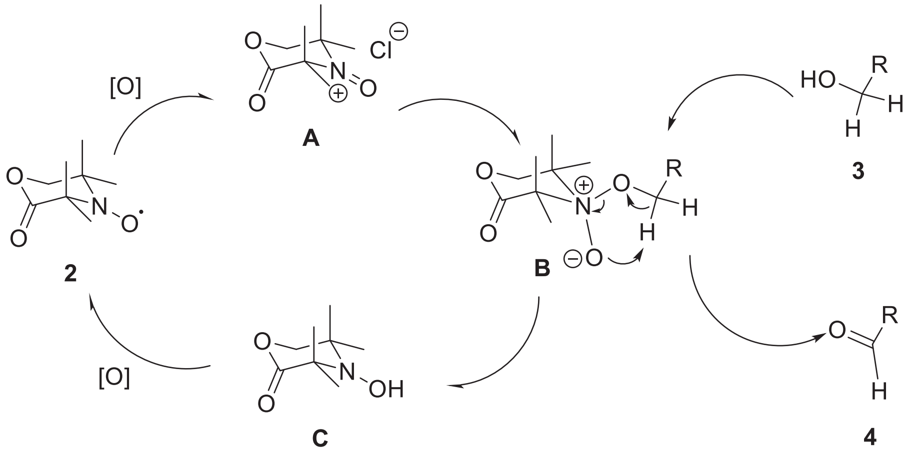
4i $R^2 = H$ (86%[b], 90%[c])

4n $R^2 = CH_3$ (0%[b], 0%[c])

[a] The reaction was carried out in CH_2Cl_2 using morpholinone nitroxide **2** (1 mol %) as a catalyst, the yields of products were isolated yields. [b] Using 1.5 equiv of NaOCl as an oxidation at 0 °C for 30 min. [c] Using 1.1 equiv of $PhI(OAc)_2$ as an oxidation at room temperature for 9 h.



Scheme 4. Selective oxidation experiment.



Scheme 5. A plausible reaction mechanism.

A control experiment was also tested for proving the exceptional chemoselectivity as shown in Scheme 4. The reaction of a 1:1 mixture of 1-phenethyl alcohol **3o** and 2-phenethyl alcohol **3k** was carried on under the standard reaction conditions. Only the phenylacetaldehyde was obtained after 30 mins and no any acetophenone was detected by TLC. The result revealed that the morpholinone nitroxide **2** could be used as a selective oxidant for primary alcohols.

Based on the results above, a probable reaction mechanism could be proposed (Scheme 5). The reaction occurred via the oxoammonium salt **A**, which was readily generated by the oxidation of morpholinone nitroxide **2** to provide salt intermediate **A**. Then a primary alcohol **3** reacted with oxoammonium salt **A** to form the intermediate **B**, which underwent fragmentation to generate the desired aldehyde **4** and hydroxylamine **C**. In this step, four methyl groups flanking the intermediate **B** played a key role in preventing secondary alcohol from generating the similar key intermediate **B**. This was the explanation why selective oxidation of primary alcohols in the presence of secondary alcohols occurred when morpholinone nitroxide **2** was used. Finally, hydroxylamine **C** was reoxidized to morpholinone nitroxide **2** in the presence of a stoichiometric co-oxidant. Then the catalytic cycle was closed.

Conclusion

In conclusion, we have disclosed the outstanding catalytic oxidation capacity of morpholinone nitroxide **2** which was synthesized easily and cheaply. The process could be a fast, selective, and high-yielding oxidation of the primary alcohols to aldehydes in the presence of secondary alcohols.

Experimental part

Reactions were carried out using commercial available reagents in over-dried apparatus. CH_2Cl_2 was commercially available and used directly. ^1H NMR spectra were recorded on commercial instruments.

Synthesis of morpholinone nitroxide 2

A 500 ml 3-neck-flask was equipped with an argon-inlet tube, a thermometer and a mechanical stirrer. Then 2-amino-2-methyl-1-propanol (26.74 g, 300 mmol), chloroform (36 mL, 450 mmol), and ketone (220 mL,3000 mmol) were added. The flask was cooled to 0 °C by ice-bath. Then the sodium hydroxide powder (60.0 g, 1500 mmol) was added in ten portions and the reaction temperature was kept below 5 °C. The reaction was stirred at 0 °C overnight after the addition. The mixture was then filtered, and the solid was washed by ketone. Then the white solid was stirred twice with 100 mL methanol and the combined filtrates were concentrated to afford the sodium carboxylate. Subsequently, the crude sodium carboxylate was refluxed with 250 mL concentrated HCl for 24 h. Then most of the HCl was removed by distilling. The residue was added 200 mL toluene and the residual water was depleted using a Dean-Stark trap. Et_3N (35.4 g, 350 mmol) was then added and the mixture was refluxed for 6 h under argon. After cooling to room temperature, the reaction was filtered and concentrated. Then the crude product was purified by flash column chromatography (Petroleum ether: Ethyl acetate = 5: 1) to give a colorless oil (3,3,5,5-tetramethyl-2-oxomorpholine, 30.6 g, 65% yield).

To a solution of 3,3,5,5-tetramethyl-2-oxomorpholine (1.571 g, 10 mmol) in 50 mL CH_2Cl_2 was added m-CPBA (3.45 g, 20 mmol) under 0 °C. Then the mixture was stirred at room temperature for 12 h. The reaction was then quenched by aq. $NaHCO_3$. The aqueous layer was extracted with 50 mL CH_2Cl_2 three times. The combined organic phases were washed by water and brine, dried by Na_2SO_4, filtered, and concentrated by rotary evaporators. The residue was purified by flash chromatography (Petroleum ether: Ethyl acetate = 2: 1) to furnish an orange solid (1.54 g, 89% yield).

General procedure for the oxidation using NaOCl

A 50 ml flask was charged with a solution of benzyl alcohol, morpholinone nitroxide **2** in CH_2Cl_2 and a sat. aqueous solution of $NaHCO_3$ containing KBr and n-Bu_4NBr. To this cooled to 0 °C by water-ice bath and well stirred mixture, a pre-mixed solution of aqueous NaOCl (6–14% Cl) and sat. aqueous solution of $NaHCO_3$ was added dropwise during 10 min. The reaction was stirred for 30 min at 0 °C, then quenched with sat. aqueous solution of $Na_2S_2O_3$. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash column chromatography to give benzaldehyd as a colorless oil.

Full experimental detail, ^1H NMR data of all compounds can be found via the"Supplementary material" section of this article's webpage. All the products are known compounds. Hence the products were identified by comparison of their ^1H NMR data with literature.[31]]

Funding

This work was generously supported by the Colleges and Universities Key Research Program Foundation of Henan Province [No. 17A150007], Doctor Fund of Henan University of Technology [No. 2015BS013].

References

[1] Gavriilidis, A.; Constantinou, A.; Hellgardt, K.; Hii, K. K.; Hutchings, G. J.; Brett, G. L.; Kuhn, S.; Marsden, S. P.Aerobic Oxidations in Flow: Opportunities for the Fine Chemicals and Pharmaceuticals Industries. React. Chem. *Eng.* **2016**, *1*, 595–612. DOI: 10.1039/C6RE00155F.

[2] Zhan, B.-Z.; Thompson, A. Recent Developments in the Aerobic Oxidation of Alcohols. *Tetrahedron* **2004**, *60*, 2917–2935. DOI: 10.1016/j.tet.2004.01.043.

[3] Dai, W.; Lv, Y.; Wang, L. Y.; Shang, S. S.; Chen, B.; Li, G. S.; Gao, S. Highly Efficient Oxidation of Alcohols Catalyzed by a Porphyrin-Inspired Manganese Complex. *Chem. Commun.* **2015**, *51*, 11268–11271. DOI: 10.1039/C5CC03657G.

[4] Imura, Y.; Akiyama, R.; Furukawa, S.; Kan, R.; Morita-Imura, C.; Komatsu, T.; Kawai, T. Au-Ag Nanoflower Catalysts with Clean Surfaces for Alcohol Oxidation. *Chem-Asian J.* **2019**, *14*, 547–552. DOI: 10.1002/asia.201801711.

[5] Hussain, M. I.; Feng, Y.; Hu, L.; Deng, Q.; Zhang, X.; Xiong, Y. Copper-Catalyzed Oxidative Difunctionalization of Terminal Unactivated Alkenes. *J. Org. Chem.* **2018**, *83*, 7852–7859. DOI: 10.1021/acs.joc.8b00729.

[6] Schilling, W.; Riemer, D.; Zhang, Y.; Hatami, N.; Das, S. Metal-Free Catalyst for Visible-Light-Induced Oxidation of Unactivated Alcohols using Air/Oxygen as an Oxidant. *ACS Catal.* **2018**, *8*, 5425–5430. DOI: 10.1021/acscatal.8b01067.

[7] Shibuya, M.; Furukawa, K.; Yamamoto, Y. Selective Aerobic Oxidation of Primary Alcohols to Aldehydes. *Synlett* **2017**, *28*, 1554–1557. DOI: 10.1055/s-0036-1588155.

[8] Sheldon, R. A. Recent Advances in Green Catalytic Oxidations of Alcohols in Aqueous Media. *Catal. Today* **2015**, *247*, 4–13. DOI: 10.1016/j.cattod.2014.08.024.

[9] Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245–251. DOI: 10.1021/op900059x.

[10] Studer, A.; Vogler, T. Applications of TEMPO in Synthesis. *Synthesis* **2008**, *2008*, 1979–1993. DOI: 10.1055/s-2008-1078445.

[11] Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. Aerobic Oxidation of Benzylic Alcohols Catalyzed by Metal-OrganicFrameworks Assisted by TEMPO. *ACS Catal.* **2011**, 1, 48–53. DOI: 10.1021/cs1000703.

[12] Hoover, J. M.; Stahl, S. S. Highly Practical Copper(I)/TEMPO Catalyst System for Chemoselective Aerobic Oxidation of Primary Alcohols. *J. Org. Chem.* **2011**, *133*, 16901–16910. DOI: 10.1021/ja206230h.

[13] Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M. Oxidation of Vic-Diols to.Alpha.-Dicarbonyl Compounds using the Oxoammonium Salt Derived from 4-Acetamido-TEMPO and p-Toluenesulfonic Acid. *J. Org. Chem.* **1994**, *59*, 6338–6343. DOI: 10.1021/jo00100a040.

[14] De Luca, L.; Giacomelli, G.; Masala, S.; Porcheddu, A. Trichloroisocyanuric/TEMPO Oxidation of Alcohols under Mild Conditions: A Close Investigation. *J. Org. Chem.* **2003**, *68*, 4999–5001. DOI: 10.1021/jo034276b.

[15] Rychnovsky, S. D.; Vaidyanathan, R. TEMPO-Catalyzed Oxidations of Alcohols Using m-CPBA: The Role of Halide Ions. *J. Org. Chem.* **1999**, *64*, 310–312. DOI: 10.1021/jo9819032.

[16] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. Oxidation of Primary Alcohols to Carboxylic Acids with Sodium Chlorite Catalyzed by TEMPO and Bleach. *J. Org. Chem.* **1999**, *64*, 2564–2566. DOI: 10.1021/jo982143y.

[17] Lucio Anelli, P.; Biffi, C.; Montanari, F.; Quici, S. Fast and Selective Oxidation of Primary Alcohols to Aldehydes or to Carboxylic Acids and of Secondary Alcohols to Ketones Mediated by Oxoammonium Salts under Two-Phase Conditions. *J. Org. Chem.* **1987**, *52*, 2559–2562. DOI: 10.1021/jo00388a038.

[18] Miyazawa, T.; Endo, T. Oxidation of Diols with Oxoaminium Salts. *J. Org. Chem.* **1985**, *50*, 3930–3931. DOI: 10.1021/jo00220a053.

[19] Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawara, M. Selective Oxidation of Alcohols by Oxoaminium Salts (R2N:O + X-). *J. Org. Chem.* **1985**, *50*, 1332–1334. DOI: 10.1021/jo00208a047.

[20] Doi, R.; Shibuya, M.; Murayama, T.; Yamamoto, Y.; Iwabuchi, Y. Development of an Azanoradamantane-Type Nitroxyl Radical Catalyst for Class-Selective Oxidation of Alcohols. *J. Org. Chem.* **2015**, *80*, 401–413. DOI: 10.1021/jo502426p.

[21] Furukawa, K.; Inada, H.; Shibuya, M.; Yamamoto, Y. Chemoselective Conversion from α-Hydroxy Acids to α-Keto Acids Enabled by Nitroxyl-Radical-Catalyzed Aerobic Oxidation. *Org. Lett.* **2016**, *18*, 4230–4233. DOI: 10.1021/acs.orglett.6b01964.

[22] Shibuya, M.; Doi, R.; Shibuta, T.; Uesugi, S-i.; Iwabuchi, Y. Organocatalytic One-Pot Oxidative Cleavage of Terminal Diols to Dehomologated Carboxylic Acids. *Org. Lett.* **2012**, *14*, 5006–5009. DOI: 10.1021/ol3021429.

[23] Shibuya, M.; Sasano, Y.; Tomizawa, M.; Hamada, T.; Kozawa, M.; Nagahama, N.; Iwabuchi, Y. Practical Preparation Methods for Highly Active Azaadamantane-Nitroxyl-Radical-Type Oxidation Catalysts. *Synthesis-Stuttgart* **2011**, 3418–3425. DOI: 10.1055/s-0030-1260257.

[24] Rychnovsky, S. D.; Beauchamp, T.; Vaidyanathan, R.; Kwan, T. Synthesis of Chiral Nitroxides and an Unusual Racemization Reaction. *J. Org. Chem.* **1998**, *63*, 6363–6374. DOI: 10.1021/jo9808831.

[25] Lai, J. T. Hindered Amines 1. 3,3,5,5-Tetrasubstituted-2-Oxomorpholines and Derivatives. *Synthesis* **1984**, *1984*, 122–123. DOI: 10.1055/s-1984-30746.

[26] Lai, J. T. Hindered Amines. Novel Synthesis of 1,3,3,5,5-Pentasubstitued 2-Piperazinones. *J. Org. Chem.* **1980**, *45*, 754–755. DOI: 10.1021/jo01306a025.

[27] Lai, J. T. Hindered Amines. 8. Hindered Monoazacrown Ethers. *J. Org. Chem.* **1985**, *50*, 1329–1330. DOI: 10.1021/jo00208a045.

[28] Zhang, K.; Noble, B. B.; Mater, A. C.; Monteiro, M. J.; Coote, M. L.; Jia, Z. Effect of Heteroatom and Functionality Substitution on the Oxidation Potential of Cyclic Nitroxide Radicals: Role of Electrostatics in Electrochemistry. *Phys. Chem. Chem. Phys.* **2018**, *20*, 2606–2614. DOI: 10.1039/c7cp07444a.

[29] Rychnovsky, S. D.; Vaidyanathan, R.; Beauchamp, T.; Lin, R.; Farmer, P. J. AM1-SM2 Calculations Model the Redox Potential of Nitroxyl Radicals Such as TEMPO. *J. Org. Chem.* **1999**, *64*, 6745–6749. DOI: 10.1021/jo990636c.

[30] Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. 2-Azaadamantane N-Oxyl (AZADO) and 1-Me-AZADO: Highly Efficient Organocatalysts for Oxidation of Alcohols. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413. DOI: 10.1021/ja0620336.

[31] Chen, T.; Cai, C. Selective Oxidation of Benzyl Alcohols to Aldehydes with a Salophen Copper(II) Complex and tert -Butyl Hydroperoxide at Room Temperature. *Synthetic Commun.* **2015**, *45*, 1334–1341. DOI: 10.1080/00397911.2015.1015034.