Efficient oxidation of alcohols electrochemically mediated by azabicyclo-*N*-oxyls

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Abstract- Preparation of azabicyclo-*N*-oxyls and the electrochemical oxidation of alcohols using them as mediators have been exploited. This oxidation was applicable to a transformation of sterically hindered *secondary* alcohols into the corresponding ketones in high yields.

The oxidation of *primary* or *secondary* alcohols to the corresponding aldehydes or ketones is an important transformation in organic synthesis. Recently, from the environmental and atom-economical point of view, a lot of catalytic methods using clean oxidants have been exploited.[1] A versatile organocatalyst 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) has been utilized in chemical[2] and electrochemical oxidation[3] of alcohols as a mediator. TEMPO is a stable but sterically hindered radical because of the four methyl groups adjacent to the nitroxyl group. Therefore TEMPO is not suitable for the oxidation of sterically hindered alcohols. In 2006, Iwabuchi and co-workers reported an excellent oxidation of sterically hindered alcohols using 1-methyl-2-azaadamantane-*N*-oxyl (1-Me-AZADO), which is one of the sterically less hindered class of nitroxyl radicals (Fig. 1).[4]

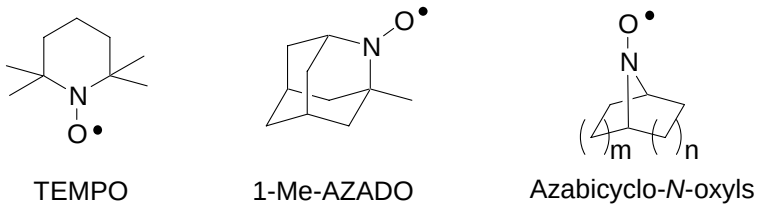

Figure 1. Structures of some *N*-oxyls.

Several azabicyclo-*N*-oxyls[5] (Fig. 1) have been reported. They exist as stable radicals

Key words: oxidation; alcohol; ketone; aldehyde; nitroxyl radical.

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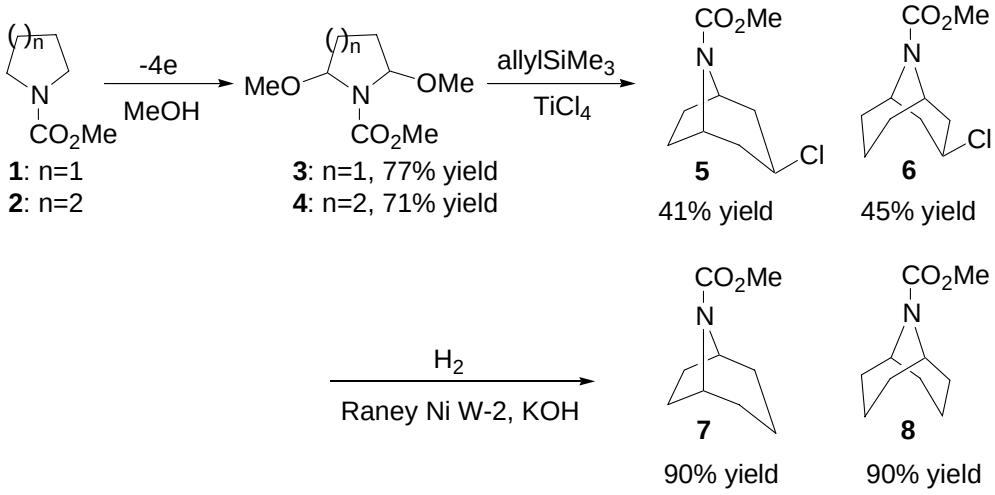
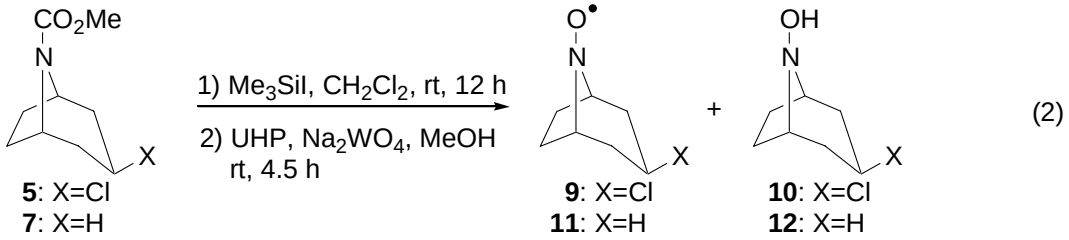
because of Bredt's rule.[6] Although their physicochemical properties were examined, the possibility for them acting as mediators for the oxidation of alcohols has hardly been known.[7] We wish to report herein an efficient electrochemical oxidation of various alcohols mediated by azabicyclo-*N*-oxyls. The azabicyclo skeletons were prepared according with the method reported by us as shown in Eq. 1. Namely, the electrochemical oxidation of *N*-methoxycarbonyl-pyrrolidine (**1**) and -piperidine (**2**) afforded dimethoxylated compounds **3** and **4**,[8] which were easily transformed into azabicyclo compounds **5** and **6**, respectively, by $TiCl_4$-catalyzed one-pot cyclization with allyltrimethylsilane. Finally, reductive dechlorination of **5** and **6** afforded **7** and **8**, respectively.[9]

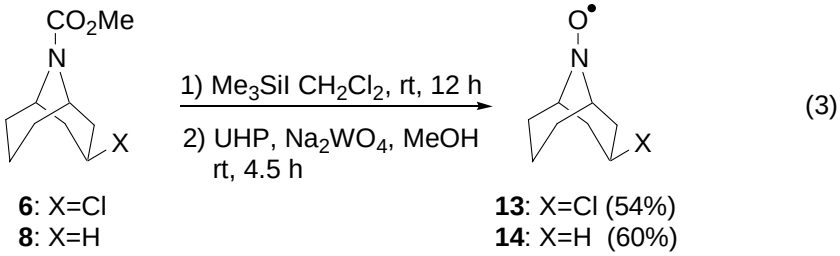


(1)

Preparation of 3-chloro-8-azabicyclo[3.2.1]octane-*N*-oxyl (**9**) is shown in Eq. 2. That is, deprotection of **5** by utilizing Me_3SiI followed by Na_2WO_4-catalyzed oxidation using urea hydrogen peroxide (UHP) afforded a mixture of **9** and the corresponding hydroxylamine **10**. Also, a mixture of 8-azabicyclo[3.2.1]octane-*N*-oxyl (**11**)[5a] and the corresponding hydroxylamine **12**[10] was synthesized from **7**. In a similar manner, 3-chloro-9-azabicyclo[3.3.1]octane-*N*-oxyl (**13**)[11,12] and 9-azabicyclo[3. 3.1]octane-*N*-oxyl (**14**)[5f] without any generation of the hydroxylamines were synthesized from **6** and **8** respectively (Eq. 3).



(2)



(3)

Cyclic voltammograms for a mixture of *N*-oxyl **9** and hydroxylamine **10** (**9**+**10**) showed reversible wave pattern similar to that for TEMPO. This strongly suggests that azabicyclo-*N*-oxyls could play the role of an oxidation mediator just like TEMPO (Fig. 2).[13]

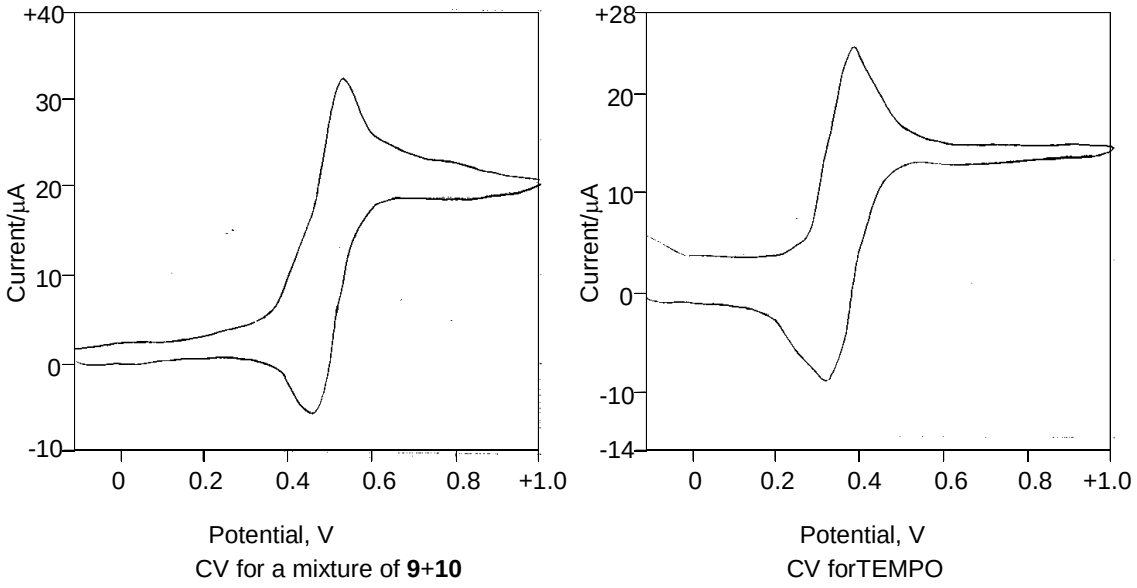
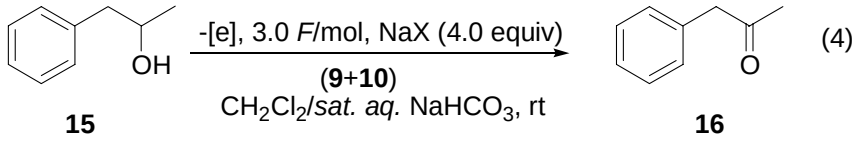


Figure 2. Cyclic voltammograms for **9**+**10** and TEMPO.

The electrochemical oxidation of 1-phenyl-2-propanol (**15**) using azabicyclo-*N*-oxyls as

a mediator was carried out under similar conditions used by Torii and co-workers for TEMPO (Eq. 4).[3c] That is, the oxidation was conducted using platinum electrodes in an undivided beaker-type cell, containing a catalytic amount of (**9**+**10**), sodium halides (NaX), and a mixture of CH_2Cl_2 and sat. aqueous $NaHCO_3$ as solvent, at a constant current (50 mA).[14] The results are summarized in Table 1. Oxidation of **15** did not proceed at all in the absence of (**9**+**10**) (Entry 1). In the presence of 0.1 equiv of (**9**+**10**) together with NaBr, the oxidation of **15** afforded 1-phenyl-2-propanone (**16**) quantitatively (Entry 2). Whereas using NaCl in place of NaBr did not promote the oxidation (Entry 3), use of NaI led to poor yield compared to that of NaBr (28%, Entry 4). These results mean that Br^- ion is the most suitable halogen mediator for this electrochemical oxidation. Using 0.02 to 0.01 equiv of (**9**+**10**) slightly reduced the yield of **16** (93%, Entries 5 and 6).

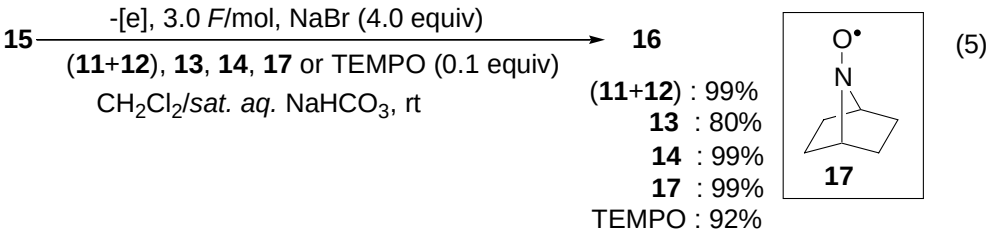


15 **16** (4)

Table 1. Electrochemical oxidation of 1-phenyl-2-propanol (**15**)

Entry	Equiv of (**9**+**10**)	Sodium halide	Yield of **16** (%)
1	0	NaBr	0
2	0.1	NaBr	99
3	0.1	NaCl	0
4	0.1	NaI	28
5	0.02	NaBr	93
6	0.01	NaBr	93

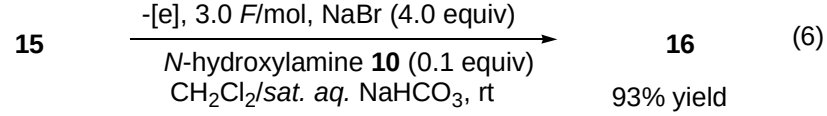
Other *N*-oxyls (**11**+**12**), **13**, **14**, and **17**[5d,15] were also good oxidation catalysts just like TEMPO (Eq. 5).



(5)

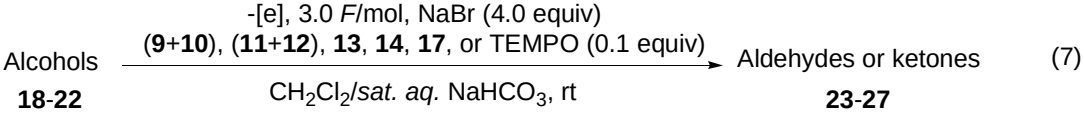
Moreover, isolated *N*-hydroxylamine **10** catalyzed the electrochemical oxidation of **15**

as efficiently as *N*-oxyl (**9**+**10**) (Eq. 6).



(6)

Table 2 shows the electrochemical oxidation of various *primary* and *secondary* alcohols **18**-**22** using azabicyclo-*N*-oxyls (**9**+**10**), (**11**+**12**), **13**, **14**, **17**, and TEMPO as mediators (Eq. 7). All *N*-oxyls had excellent catalytic activity just like TEMPO toward *primary* alcohols **18** and **19** (Entries 1 and 2), and *secondary* alcohols **20**-**22** (Entries 3-5) to afford the corresponding carbonyl compounds **23**-**27** in high yield, respectively.



(7)

Table 2. Electrochemical oxidation of various alcohols **18**-**22**

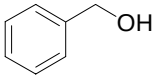
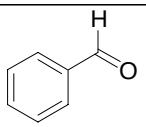
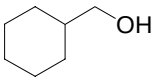
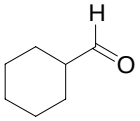
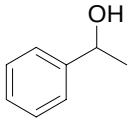
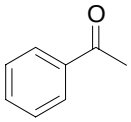
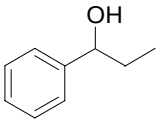
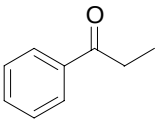
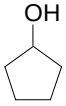
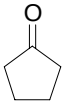
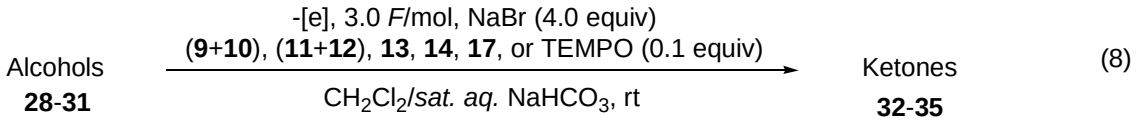
Entry	Alcohol	Product	Yield of product (%)					
			(**9**+**10**)	(**11**+**12**)	**13**	**14**	**17**	TEMPO
1	**18** 	**23** 	99	96	99	90	82	99
2	**19** 	**24** 	77	90	91	99	99	68
3	**20** 	**25** 	99	99	99	99	99	72
4	**21** 	**26** 	99	97	86	90	99	77
5	**22** 	**27** 	98	99	99	99	99	84

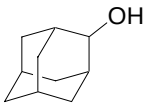
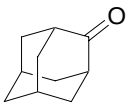
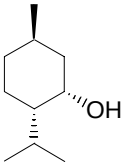
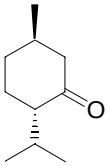
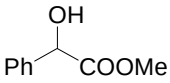
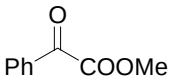
Table 3 summarizes the electrochemical oxidation of sterically hindered *secondary*

alcohols **28**-**31** (Eq. 8). In the case of TEMPO, the oxidized products **32**-**35** were obtained in low to moderate yield (23-61%), while *N*-oxyls (**9**+**10**), (**11**+**12**), **13, 14**, and **17** played a better role than TEMPO (Entries 1-4). These results prove that azabicylo-*N*-oxyls are efficient mediators for the oxidation of sterically hindered alcohols because they are less hindered than TEMPO.

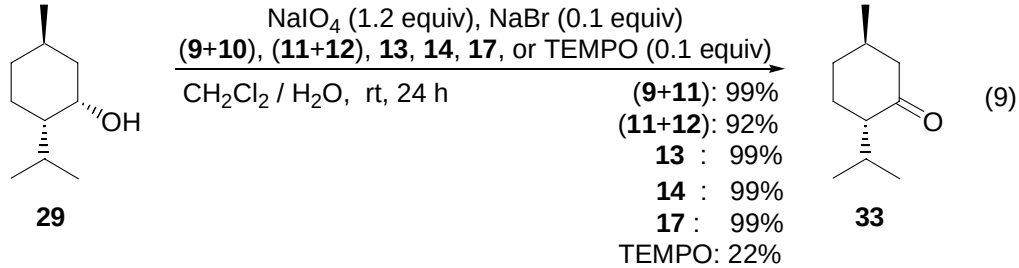


(8)

Table 3. Electrochemical oxidation of sterically hindered alcohols **28**-**31**

Entry	Alcohol	Product	Yield of product (%)					
			(**9+10**)	(**11+12**)	**13**	**14**	**17**	TEMPO
1	**28** 	**32** 	87	65	90	86	82	61
2	**29** 	**33** 	99	86	92	82	76	23
3	**30** 	**34** 	85	74	94	99	99	41
4	**31** 	**35** 	72	75	97	99	74	56

Azabicyclo-*N*-oxyls (**9**+**10**), (**11**+**12**), **13, 14**, and **17** were also effective in the chemical oxidation (Eq. 9).[17-19] That is, *l*-menthol (**29**) was almost quantitatively oxidized by using these *N*-oxyls, while in the case of TEMPO the yield of *l*-menthone (**33**) was only 22%.



(9)

In summary, azabicyclo-*N*-oxyls (**9**+**10**), (**11**+**12**), **13, 14**, and **17** were applicable to

electrochemical oxidation of various alcohols as mediators. Especially in the oxidation of sterically hindered *secondary* alcohols to the corresponding ketones, these *N*-oxyls were much more effective than TEMPO. Preparation of chiral azabicyclo-*N*-oxyls and enantiospecific oxidation of *secondary* alcohols using them as mediators are now underway.

Acknowledgements

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11. A typical procedure for preparation of *N*-oxyl **13**: A solution of **6** (218 mg, 1.0 mmol) and Me_3SiI (600 mg, 3.0 mmol) in CH_2Cl_2 (5.0 mL) was stirred for 12 hr at rt. The solution was added into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was dried over K_2CO_3 and the solvent removed under reduced pressure to afford a crude amine that was used for the next reaction without purification. A solution of amine and $Na_2WO_4 \cdot 2H_2O$ (33 mg, 0.1 mmol) in MeOH (2.0 mL) was stirred for 30 min at rt. To the solution was added urea hydrogen peroxide (470 mg, 5.0 mmol). After stirring for 4 h at rt, the solution was poured in saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (20 mL x 3). The combined organic layer was dried over K_2CO_3 and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 10 : 1) to afford *N*-oxyl **13** (175 mg, 54% yield) as an yellow solid. Mp : 69-70^oC. IR (neat): 2991, 1441, 1358, 1298 cm^{-1}. MS[HR-FAB(+)]: *m/z* calcd for $C_8H_{14}ClNO$ 175.0764 $[M+H]^+$ found 175.0781.
12. Relative stereoconfiguration of **13** was determined by the X-ray analysis. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 663222. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK; fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
13. Cyclic voltammogram for a mixture of **9**+**10** was measured in 0.1 M Et_4NBF_4/MeCN solution using glassy-carbon as a working electrode, platinum as a counter electrode, and Ag/0.01 M $AgNO_3$ as a reference electrode. Concentration of (**9**+**10**): 1.0 mM. Scan rate: 10 mV/s. Other *N*-oxyls (**11**+**12**), **13**, **14**, and **17** were represented by the similar reversible wave patterns.
14. Representative procedure for the electrochemical oxidation of alcohols: Anodic oxidation of **15** was carried out using platinum electrodes (1 cm x 2 cm) in an

undivided beaker-type cell. Alcohol **15** (68 mg, 0.5 mmol), a mixture of **9**+**10** (8.1 mg, 0.05 mmol) and NaBr (206 mg, 2.0 mmol) were added into a mixture of CH_2Cl_2 (2.5 mL) and saturated aqueous $NaHCO_3$ (2.5 mL). After passing through 3.0 *F*/mol of electricity at constant current (50 mA) at rt, the mixture was poured in water and extracted with AcOEt (20 mL x 3). The combined organic layer was dried on $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 20 : 1) to afford **16** (66 mg, 99% yield) as a colorless oil.

15. Azabicyclo-*N*-oxyl **17**[5d] was prepared from *N*-Cbz-7-azabicyclo[2.2.1]heptane.[16] Since isolated **17** was somewhat unstable, it gradually changed into the corresponding *N*-hydroxylamine even at -20^{o}C.
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17. A procedure for the chemical oxidation (ref. 18) of **29**: Under an aerobic atmosphere, **29** (78 mg, 0.5 mmol), a mixture of **9**+**10** (8.1 mg, 0.05 mmol), $NaIO_4$ (128 mg, 0.6 mmol), and NaBr (5.1 mg, 0.05 mmol) were added into a mixture of CH_2Cl_2 (1.0 mL) and water (1.0 mL). After stirring for 24 h at rt, the solution was poured in water and extracted with AcOEt (20 mL x 3). The combined organic layer was dried on $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 20 : 1) to afford **33** (77 mg, 99% yield) as a colorless oil.
18. Lei, M.; Hu. R-. J.; Wang, Y-. G. *Tetrahedron* **2006,** *62*, 8928-8932.
19. Recently, some methods for highly efficient chemical oxidation of sterically hindered *secondary* alcohols using TEMPO or its analogs have been reported. (a) Bobbitt, J. M. *J. Org. Chem.* **1998,** *63*, 9367-9374. (b) Zhao, X. -F.; Zhang, C. *Synthesis* **2007**, 551-557.

Graphical Abstract

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Efficient oxidation of alcohols electrochemically mediated by azabicyclo-*N*-oxyls

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