9-Azanoradamantane *N*-Oxyl (Nor-AZADO): A Highly Active Organocatalyst for Alcohol Oxidation

Masaki Hayashi,[a,b] Yusuke Sasano,[a] Shota Nagasawa,[a] Masatoshi Shibuya,[a] and Yoshiharu Iwabuchi*,[a]

[a] *Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University; 6–3 Aobayama, Sendai 980–8578, Japan: and* [b] *Process Technology Research Laboratories, Daiichi Sankyo Co., Ltd.; 1–12–1 Shinomiya, Hiratsuka, Kanagawa 254–0014, Japan.*

A highly active organocatalyst for alcohol oxidation has been developed. 9-Azanoradamantane *N*-oxyl (Nor-AZADO 4), constituting an unhindered, stable nitroxyl radical, exhibits superior catalytic activity to 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and AZADOs in the oxidation of alcohols to their corresponding carbonyl compounds.

Key words organocatalyst; nitroxyl radical; alcohol oxidation; aerobic oxidation; 2-azaadamantane *N*-oxyl AZADO

The oxidation of alcohols to their corresponding carbonyl compounds is one of the most fundamental transformations in both laboratory synthesis and industrial manufacturing, and numerous methods of such oxidation have been developed.[1,2] In recent years, a stable class of nitroxyl radicals, as exemplified by TEMPO [2,2,6,6-tetramethyl piperidinyl 1-oxyl (**1**); Fig. 1], has been extensively used as a catalyst for the oxidation of alcohols in a wide range of chemistry.[3—19] In particular, TEMPO-catalyzed alcohol oxidation has high priority in the pharmaceutical industry as an efficient, mild, and environmentally acceptable method. However, TEMPO is often inefficient in the oxidation of structurally hindered alcohols, posing a problem in the oxidation of secondary alcohols.

We have recently reported that a less-hindered class of nitroxyl radicals, namely, 2-azaadamantane *N*-oxyls [AZA-DOs; AZADO (**2a**) and 1-Me-AZADO (**2b**)] and 9-azabicyclo[3.3.1]nonane *N*-oxyl [ABNO (**3**)], exhibit significantly enhanced reactivity compared with TEMPO.[20—26] They exhibit extremely high activities toward a wide range of alcohols, including structurally hindered secondary alcohols that TEMPO fails to efficiently oxidize.[20,21] A structure–activity comparison indicated that the steric congestion near the active center exerts a critical impact on catalytic efficiency.[20]

In our continuous interest in nitroxyl-radical-based oxidation, we envisaged that the catalytic activity of nitroxyl radicals can further be enhanced by reducing the steric factors around their active center. We herein report the advanced catalytic activity of 9-azanoradamantane *N*-oxyl [Nor-AZADO (**4**); Fig. 1]. This new catalyst exhibits superior catalytic efficiency to AZADO, 1-Me-AZADO and ABNO as well as to TEMPO.

Nor-AZADO (**4**) was firstly synthesized in 1978 by Dupeyre and Rassat and reported to be a stable class of nitroxyl radicals.[27] To the best of our knowledge, however, no study of Nor-AZADO has been reported since then. We were particularly interested in determining whether Nor-AZADO, which is a constraint variant of AZADO, produces the oxoammonium ions, which are useful for alcohol oxidation.

Nor-AZADO was prepared in five steps from acetonedicarboxylic acid (**5**), glutaraldehyde, and benzylamine, by a previous method (Chart 1) with slight modification.[27,28]
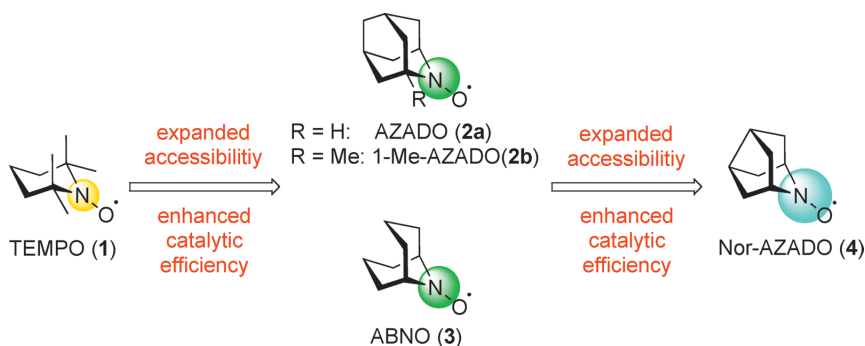
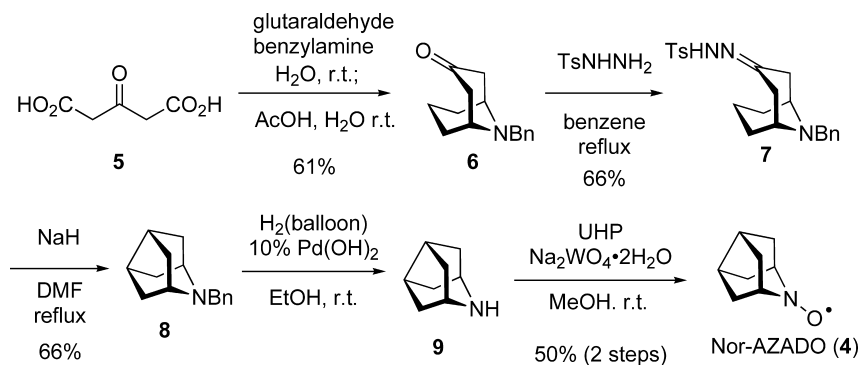

Fig. 1. Design Concept of Nor-AZADO

Chart 1. Preparation of Nor-AZADO

* To whom correspondence should be addressed.   e-mail: y-iwabuchi@m.tohoku.ac.jp

Table 1. Comparison of Catalytic Activities toward Secondary Alcohols under Anelli's Condition

nitroxy radicals
NaOCl (1.5 eq.)
KBr (10 mol%), TBAB (5 mol%)

alcohol ⟶ ketone

CH_2Cl_2–sat. aq. $NaHCO_3$ (1:1,0.2 M), 0 °C

Entry[a]	Substrates	Loading amount (mol%)	Yield				
			TEMPO	ABNO	1-Me-AZADO	AZADO	Nor-AZADO
1	OH Ph **10**	1	97%	100%	99%	99%	99%
2		0.01	28%	94%	97%	99%	99%
3		0.005	n.d.[a]	91%	76%	96%	96%
4		0.003	n.d.[a]	24%	67%	74%	92%
5	OH **11**	1	5%	94%	95%	99%	99%
6		0.01	n.d.[a]	95%	61%	98%	98%
7		0.005	n.d.[a]	92%	41%	96%	96%
8		0.003	n.d.[a]	8%	25%	87%	92%

a) Not determined.

Table 2. Comparison of Catalytic Activities toward Primary Alcohols under Anelli's Condition

nitroxy radicals
NaOCl (1.5 eq.)
KBr (10 mol%), TBAB (5 mol%)

Ph⌒⌒OH **12** ⟶ Ph⌒O **13**

CH_2Cl_2–sat. aq. $NaHCO_3$ (1:1,0.2 M), 0 °C

Entry[a]	Loading amount (mol%)	Yield				
		TEMPO	ABNO	1-Me-AZADO	AZADO	Nor-AZADO
1	1	89%	91%	91%	91%	92%
2	0.01	19%	83%	89%	88%	89%
3	0.003	n.d.[a]	59%	79%	82%	82%

a) Not determined.

The catalytic activity of Nor-AZADO was compared with those of TEMPO, AZADO, 1-Me-AZADO, and ABNO under Anelli's condition using NaOCl as the bulk oxidant[12,13] (Tables 1, 2). The catalytic activities toward secondary alcohols are shown in Table 1. Although almost the same results were obtained for the oxidation of 4-phenyl-butan-2-ol (**10**) when a 1 mol% catalyst load was used, apparent differences in catalytic efficiency were observed, when catalyst load was decreased. Nor-AZADO maintained its performance even with a 0.003 mol% catalyst load, whereas other nitroxyl radicals including AZADO showed a decline in performance (Table 1, entry 4). A similar result was obtained in the oxidation of L-menthol (**11**). A 0.003 mol% catalyst load was sufficient to complete the reaction with Nor-AZADO (Table 1, entry 8). Note that TEMPO failed to oxidize L-menthol (**11**) even with a 1 mol% catalyst load (Table 1, entry 5).

Nor-AZADO also exhibited efficient catalytic activity in the oxidation of primary alcohol (**12**) compared with TEMPO, although AZADO and 1-Me-AZADO also worked well in this case (Table 2).

We next examined the aerobic oxidation conditions[6—8,14—19] using the nitroxyl radical/NaNO2/Air/AcOH system,[29] which we have recently reported as versatile transition-metal-free and halogen-free conditions.
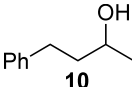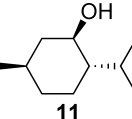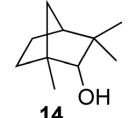
The secondary alcohols **10**, **11** and **14** were selected as the test substrates, and their reactions were carried out with 1 mol% catalyst load (Table 3). It was confirmed that Nor-AZADO exhibited superior catalytic efficiency to AZADO and 1-Me-AZADO particularly in terms of reaction rate. In all the cases, the reaction completed within several hours with Nor-AZADO, of which efficiency is comparable to that of 5-F-AZADO which exhibit the highest activity for aerobic oxidation in AZADO derivatives.[29] In fact, TEMPO failed to serve as an efficient catalyst in all the cases. Although the structural difference between Nor-AZADO and AZADO is only one methylene group in their skeletons, they exhibit different catalytic activities evidently.

The substrate applicability of Nor-AZADO-catalyzed aerobic oxidation is shown in Table 4. Various alcohols were oxidized to their corresponding carbonyl compounds efficiently with a 1 mol% catalyst load. The reaction proceeded under air atmosphere, and no significant effect on the catalytic performance was observed with the use of different reaction atmospheres, *i.e.*, O2 and air (data not shown). Aliphatic and benzylic secondary alcohols, including a sugar derivative (entry 6), a N-protected amine (entry 8), a nucleoside derivative (entry 9) and a pyridine derivative (entry 10), were effectively oxidized. An acid-labile isopropylidene protecting group remained in this reaction (entry 6).
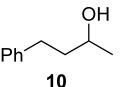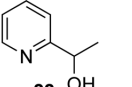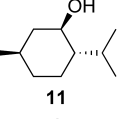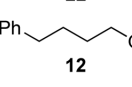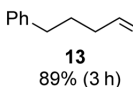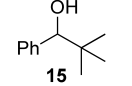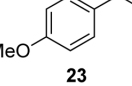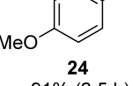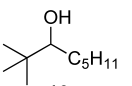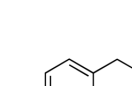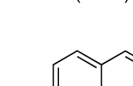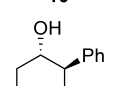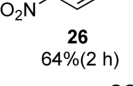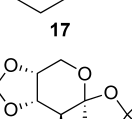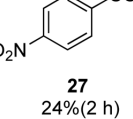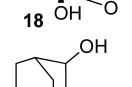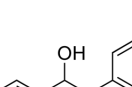
The primary alcohols **12** and **23** were also oxidized to their

Table 3. Comparison of Catalytic Activities under Aerobic Oxidation

$$\text{alcohol} \xrightarrow[\text{AcOH (1 M), Air (balloon), r.t.}]{\substack{\text{nitroxyl radical (1 mol\%)} \\ \text{NaNO}_2\text{(10 mol\%)}}} \text{ketone}$$

Entry	Substrates	Conversion (time)[a]				
		TEMPO	1-Me-AZADO	AZADO	5-F-AZADO	Nor-AZADO
1	**10**	10% (24 h)	79% (24 h)	97% (9 h)	100% (5 h)	100% (5 h)
2	**11**	0% (24 h)	46% (24 h)	92% (9.5 h)	100% (6 h)	100% (9.5 h)
3	**14**	1% (24 h)	99% (24 h)	100% (6 h)	100% (7 h)	100% (5 h)

a) Conversion was determined by GC.

Table 4. Scope of Nor-AZADO Catalyzed Aerobic Oxidation

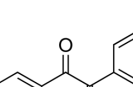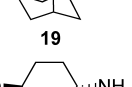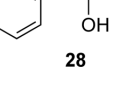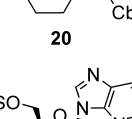| Entry	Substrates	Methods[a]	Yield (time)	Entry	Substrates	Methods[a]	Yield (time)
1	**10**	A	98% (4 h)	10	**22**	A	81% (3 h)
2	**11**	A	96% (6 h)	11	**12**	A	**13** 89% (3 h)
3	**15**	A	95% (7 h)	12	**23**	A	**24** 91% (2.5 h)
4	**16**	A	87% (12 h)	13	**25**	A	**26** 64% (2 h)
5	**17**	A	99% (4 h)				**27** 24% (2 h)
6	**18**	A	90% (5 h)				
7	**19**	B	92% (22 h)	14	**28**	A	**29** 99% (4 h)
8	**20**	B	73% (24 h)				
9	**21**	B	80% (6 h)	15[b]	**30**	A	**31** 92% (2.5 h)
				16[c]	**32**	B	34% (4 h)

a) Method A: Reactions were carried out with Nor-AZADO (1 mol%), NaNO₂ (20 mol%), and AcOH (2 eq) in MeCN (1 M) under air atmosphere (balloon) at room temperature. Method B: Reactions were carried out with Nor-AZADO (1 mol%), and NaNO₂ (20 mol%) in AcOH (0.3 M), under air atmosphere (balloon) at room temperature. *b*) 5 mol% Nor-AZADO was used. *c*) 10 mol% Nor-AZADO was used.

corresponding aldehyde **13** and **24** in high yield (entries 11, 12), although the oxidation of *p*-nitrobenzyl alcohol (**25**) to *p*-nitrobenzylaldehyde (**26**) resulted in moderate yield because of the overoxidation of (**26**) to the carboxylic acid (**27**) (entry 13). Note that the hydrobenzoin (**28**), which is prone to form benzaldehyde because of its easy carbon–carbon bond cleavage in some other oxidation systems,[30] was oxidized to benzil (**29**) in quantitative yield without oxidative cleavage (entry 14). This system is also effective for the 3-quinuclidinol (**32**), which contains an amine functionality, although a 10 mol% catalyst load is needed (entry 16).

In summary, we have disclosed the excellent catalytic oxidizing abilities of Nor-AZADO for alcohol oxidation. It is interesting to note that a slight difference in structure between Nor-AZADO and AZADO affects their catalytic abilities. Nor-AZADO can serve as an environmentally benign catalyst for the oxidation of wide range of alcohols owing to its superior catalytic activity and ready availability.

Representative Procedure for Oxidation of Alcohols under Anelli's Condition To a solution of 4-phenylbutan-2-ol (**10**) (103.7 mg, 0.690 mmol), Nor-AZADO (**4**) (0.95 mg, 0.00690 mmol), KBr (8.22 mg, 0.0690 mmol), and TBAB (11.1 mg, 0.0345 mmol) in CH_2Cl_2–saturated aqueous $NaHCO_3$ (3:2 v/v, 1.70 ml), 2.1 M NaOCl (0.50 ml, 1.04 mmol) in saturated $NaHCO_3$ (1.2 ml) at 0 °C was slowly added. After 20 min, the mixture was quenched with saturated aqueous Na_2SO_3 and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane–Et_2O (4:1 v/v)] to afford 2-phenylbutan-2-one (101.0 mg, 0.682 mmol, 99%) as a colorless oil.

Representative Procedure for Aerobic Oxidation of Alcohols (Method A) A solution of 4-phenylbutan-2-ol (**10**) (104.3 mg, 0.694 mmol), Nor-AZADO (**4**) (0.96 mg, 0.00694 mmol), AcOH (0.080 ml, 1.39 mmol), and $NaNO_2$ (9.58 mg, 0.139 mmol) in MeCN (0.69 ml) was stirred under air (balloon) atmosphere at rt for 4 h. Saturated aqueous Na_2CO_3 (2 ml) was added to the solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane–Et_2O (4:1 v/v)] to afford 2-phenyl-butan-2-one (101.1 mg, 0.682 mmol, 98%) as a colorless oil.

Representative Procedure for Aerobic Oxidation of Alcohols (Method B) A solution of 2-adamantanol (**19**) (101.1 mg, 0.664 mmol), Nor-AZADO (**4**) (0.92 mg, 0.00664 mmol), and $NaNO_2$ (9.16 mg, 0.133 mmol) in AcOH (2 ml) was stirred under air (balloon) atmosphere at rt for 22 h. Saturated aqueous Na_2CO_3 (10 ml) was added and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography [hexane–Et_2O (8:1 v/v)] to afford 2-adamantanone (91.8 mg, 0.611 mmol, 92%) as a colorless solid.

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