

2-Azaadamantane *N*-Oxyl (AZADO) and 1-Me-AZADO: Highly Efficient Organocatalysts for Oxidation of Alcohols

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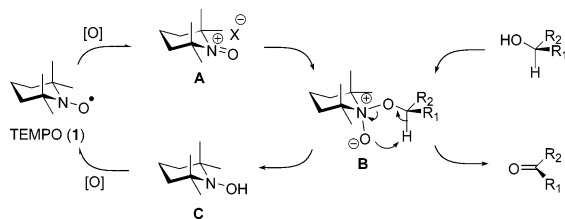
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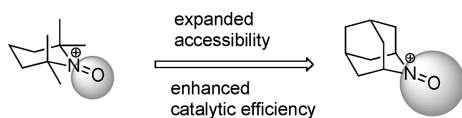
The oxidation of alcohols to their corresponding carbonyl compounds is a pivotal transformation in organic chemistry.¹ The recent global demand for attenuating environmental stress has spurred much effort directed toward the development of green oxidation processes that fulfill the requirements for practical applications.² The 2,2,6,6-tetramethyl-1-piperidinyloxy [TEMPO (1), a nitroxyl radical]-catalyzed oxidation method has attracted attention in many areas of synthetic organic chemistry because it enables the use of various safe bulk oxidants, thereby enabling a safe and extremely efficient oxidation of alcohols with considerable operational simplicity.^{3,4}

Of the reported nitroxyl radicals, the readily available TEMPO and its derivative have the highest potential for expanded use. One distinguishing feature of the TEMPO-based method is its capability for the selective oxidation of primary alcohols in the presence of secondary alcohols.⁵ The rationale behind such a feature is its reaction mechanism and the catalyst structure it uses, where four methyl groups flanking the nearby catalytic center play key roles in preventing bulky substrates from forming the key intermediate **B**, which collapses to a carbonyl compound and the hydroxylamine **C**^{3,5} (Scheme 1). Paradoxically, TEMPO is inefficient in the oxidation of structurally hindered secondary alcohols, posing a problem in the oxidation of alcohols.

Scheme 1



We envisaged that the use of a structurally less hindered class of nitroxyl radicals can solve this problem to expand the scope of the oxidation of alcohols. We herein disclose the excellent catalytic activity of the 2-azaadamantane *N*-oxyl (AZADO) class of nitroxyl radicals toward a variety of alcohols; this class has a superior catalytic proficiency to TEMPO.



AZADO (2) was synthesized in 1978 by Dupeyre and Rassat fueled by their interest in its physical properties as a stable radical. To the best of our knowledge, however, no study has been performed to examine its ability as oxidation catalyst.⁶ We then started preparing AZADO as described in the literature, but encountered a problem in terms of reproducibility in a crucial step

Table 1. Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO under Anelli's Conditions

loading amount (mol%)	yield (%)	
	TEMPO	1-Me-AZADO
0.1	96	95
0.01	23	91
0.004	n.d.	88 ^a
0.001	n.d.	62 ^b

^a The run time was 30 min. ^b The run time was 60 min.

Table 2. Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO under Margarita's Conditions

loading amount (mol%)	yield (%) / time (h)	
	TEMPO	1-Me-AZADO
10	95 / 1.5	96 / 0.1
1	42 / 6	93 / 0.7
0.1	n.d.	39 / 3

in constructing the azaadamantane skeleton.⁷ After considerable experimentations, we developed a 10-step synthesis route for AZADO⁸ and a 6-step synthesis route for 1-Me-AZADO (3),⁸ starting from 1,3-adamantanediol.

In a preliminary experiment, we found that AZADO as well as 1-Me-AZADO exhibited superior catalytic activities to TEMPO; interestingly, we found that AZADO and 1-Me-AZADO show similar catalytic efficiencies under the standard oxidation conditions developed by Anelli et al.^{4c,d,9} (data not shown). Considering its synthetic advantage, 1-Me-AZADO was chosen for further investigations. As shown in Tables 1 and 2, 1-Me-AZADO has high catalytic efficiencies under low catalytic loading conditions.

Importantly, 1 mol % of 1-Me-AZADO is sufficient for obtaining a high productivity in the preparation of ketones from a variety of secondary alcohols, for which TEMPO results in a low productivity^{4a,9,10} (Table 3, entries 1–10).^{4e,9–13} Note that 1,2:4,5-di-*O*-isopropylidene- β -D-fructopyranose is also efficiently oxidized on a 20 g scale to give Shi's catalyst in 90% yield.^{11,12} Unfortunately, 1-Me-AZADO does not efficiently oxidize a substrate containing amine functionality (entry 11).

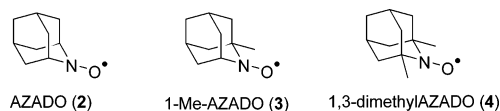








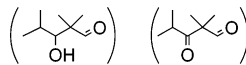





Table 3. Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO toward Various Secondary Alcohols^a

entry	substrate	method	yield ^b (%)	
			TEMPO	1-Me-AZADO
1		A	83	94
2		A	84	99
3		A	68	97
4		A	0	94
5		A	16	99
6		A	5	95
7		A	15	93
8		A	57	87
				
9		A A ^c	8	99 90
10		A B	n.d. ^d 12 ^e	19 100
11		A B	n.d. ^d 27 ^f	10 46 ^f

^a Method A: reactions were catalyzed by TEMPO or 1-Me-AZADO (1 mol %) with NaOCl (150 mol %), KBr (10 mol %), Bu₄NBr (5 mol %), aq. NaHCO₃ in CH₂Cl₂ at 0 °C for 20 min. Method B: reactions were catalyzed by TEMPO or 1-Me-AZADO (1 mol%) with 1.1 equiv of PhI(OAc)₂ in CH₂Cl₂ for 9 h at room temperature. ^b Isolated yield. ^c Reaction was run using 20 g of substrate. ^d Not determined. ^e Reaction was run using 3.3 equiv of PhI(OAc)₂ for 14 h at room temperature. ^f Reaction was run using 5.1 equiv of PhI(OAc)₂ for 30 h at room temperature.

To gain insight into the origin of the remarkable catalytic efficiency of AZADO-type nitroxyl radicals, we synthesized 1,3-dimethyl-AZADO (**4**)⁸ and examined its catalytic efficiency. 1,3-Dimethyl-AZADO exhibits an activity for the oxidation of 3-phenylpropanol comparable to those exhibited by AZADO (**2**) and 1-Me-AZADO (**3**). On the other hand, it does not efficiently oxidize *l*-menthol similarly to TEMPO (**1**), showing a remarkable difference from 1-Me-AZADO and AZADO. Cyclic voltammetric measurements revealed that **2**, **3**, and **4** show well-defined redox waves, of which the forms were unchanged after more than 100 cycle measurements, demonstrating their high durability as oxidation catalysts.⁸ The *E*^{o'} values of the nitroxyl radicals are in the order of **4** (136 mV) < **3** (186 mV) < **2** (236 mV) < **1** (294 mV).⁸ However, the total efficiencies of the nitroxyl radicals as catalyst are in the order of **1** ~ **4** < **3** ~ **2**.¹⁴ These observations support the notion that the aggressive catalytic natures of **2** and **3** are due to kinetic factors derived from decreased steric hindrance around the reaction center.

In summary, we have disclosed the excellent catalytic oxidizing abilities of AZADO and 1-Me-AZADO for the oxidation of alcohols, which offer complementary use with TEMPO-type nitroxyl radicals. Information on the structure–activity correlation of these compounds should inspire new designs of organocatalysts with increased catalytic efficiencies.

Acknowledgment. We thank Prof. Emeritus Kunio Ogasawara of Tohoku University for his encouragement and helpful discussion. This work was supported by JST, JSPS, and MEXT, Japan.

Supporting Information Available: Experimental procedures, spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- See Supporting Information.
- Representative procedure for oxidation of alcohols under Anelli's condition:^{4c} To a stirring mixture of 3-phenylpropanol (200 mg, 1.47 mmol), 1-Me-AZADO (**3**) (0.244 mg, 1.47 μmol) in CH₂Cl₂ (3.9 mL) and aqueous sat. NaHCO₃ (2 mL) containing KBr (17.5 mg, 0.074 M) and Bu₄NBr (23.7 mg, 0.037 M) was added dropwise a premixed solution of aqueous NaOCl (8% Cl) and aqueous sat. NaHCO₃ (3.3 mL, 1:1.4 v/v) at 0 °C over 6 min. The mixture was vigorously stirred for 20 min at 0 °C, then quenched with aqueous sat. Na₂S₂O₃ (4 mL). The aqueous layer was separated and extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by flash column chromatography (SiO₂, 1:6 Et₂O:hexane) to give 3-phenylpropanal (177 mg, 1.32 mmol, 90%) as colorless oil.
- Representative procedure for oxidation of alcohols under Margarita's condition:^{4e} PhI(OAc)₂ (720 mg, 2.24 mmol) was added to a solution of cinnamyl alcohol (200 mg, 1.49 mmol) and 1-Me-AZADO (**3**) (2.47 mg, 14.9 μmol) in CH₂Cl₂ (1.5 mL). The reaction mixture was stirred for 40 min, it was then diluted with Et₂O and quenched with aqueous sat. NaHCO₃ (4 mL), followed by aqueous sat. Na₂S₂O₃ (4 mL). The layer was separated, and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by flash column chromatography (SiO₂, 1:9 Et₂O:hexane) to give cinnamaldehyde (183 mg, 1.39 mmol, 93%) as colorless oil.
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JA0620336