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Highly Efficient, Organocatalytic Aerobic Alcohol Oxidation

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S Supporting Information

ABSTRACT: 5-Fluoro-2-azaadamantane *N*-oxyl (5-F-AZADO) realizes a simple, organocatalytic aerobic alcohol oxidation system that has a wide scope under mild conditions at ambient pressure and temperature and is weakly acidic and halogen- and transition-metal-free. The oxoammonium nitrate (5-F-AZADO$^+$$NO_3^-$) works as a bifunctional catalyst of 5-F-AZADO and NO_x that enables the catalytic aerobic oxidation of alcohols by itself (a metal-salt-free system).

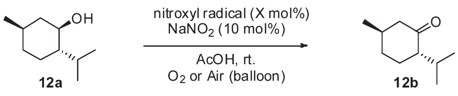
One important goal in modern chemistry is the development of sustainable and efficient processes capable of replacing hazardous classical reactions.[1] The oxidation of alcohols to the corresponding carbonyl compounds is a fundamental reaction in organic chemistry that depends on dangerous and harmful reagents.[2] Recent growing environmental concerns, however, have spurred research activities directed toward the development of greener oxidation methods in which the use of oxygen as the terminal oxidant has been the focus of significant attention; unfortunately, the state of the art remains immature.[3−6] Here we describe a metal-free system for conducting the practical oxidation of alcohols under mild reaction conditions that features the cooperative redox catalysis by azaadamantane-*N*-oxyl-type nitroxyl radicals[7]/oxoammonium ions and NO_x.

Our work was inspired by the seminal report of Hu and Liang on the first transition-metal-free aerobic oxidation system, consisting of 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) (**1**)/Br_2/$NaNO_2$/air, which demonstrated the successful mediation of electron transfer from alcohols to O_2 via NO_x and the organic nitroxyl radical **1** with the aid of bromine.[8,9] They recently reported a halogen-free oxidation system [TEMPO/*tert*-butyl nitrite (TBN)] in which inorganic and cheap $NaNO_2$ is preferable to the NO_x source. This system still needs heat and pressurized oxygen.[9a] The most important point that needs to be improved is the attenuation of the catalytic reactivity of TEMPO in these systems compared with that under conventional conditions using NaOCl as the bulk oxidant,[10−13] which narrows its applicability; the substrate scope of these aerobic oxidation systems is limited to benzylic and simple aliphatic alcohols. The desired aerobic oxidation system is a variant applicable to multifunctionalized complex molecules. We envisioned that the catalytic efficiency of alcohol oxidation could be improved by modifying the structure of the nitroxyl radicals to facilitate alcohol oxidation as well as to enhance the potency of electron transfer in the presence of oxygenated nitrogen species.

We started our study by comparing the activities of **1** and less hindered 1-Me-AZADO (**4**), which was previously developed by us,[7,14] using 5 mol % catalyst in acetic acid under an O_2 atmosphere (balloon) in the presence of 10 mol % $NaNO_2$ (Table 1; see Figure 1 for the catalyst structures).[15] Although the TEMPO-catalyzed reaction of menthol (**12a**) gave only 5% menthone (**12b**) in 1 week, the 1-Me-AZADO system afforded 71% **12b** together with 21% **12a** in 24 h (entries 1 and 2). Less hindered AZADO (**3**) showed a higher reactivity, producing **12b** in 88% yield in 9 h (entry 3). These results led us to carry out further modification of AZADOs to develop a more efficient aerobic oxidation catalyst. Assuming that the rate-determining step is the process by which the alcohol approaches an oxoammonium ion, we decided to introduce electron-withdrawing groups into the catalyst: the more electrophilic the oxoammonium ion, the stronger should be the electrostatic interaction between the oxoammonium ion and alcohol, which should accelerate the crucial process by which the alcohol approaches the oxoammonium ion. Among the various AZADO derivatives synthesized, 5-F-AZADO (**9**) was found to exhibit the highest activity, completing the reaction within 2 h at room temperature (entries 4−8). Fortunately, the use of an air balloon was also applicable to this oxidation (entry 9). At 1 mol %, **9** efficiently catalyzed the oxidation, affording **12b** in high yield within 9 h (entry 10). Notably, 5,7-diF-1-Me-AZADO (**10**) having an additional F atom showed attenuated reactivity (entry 11).[16] At the same time, we found that using *tert*-butyl nitrite instead of $NaNO_2$ was effective for aerobic oxidation in CH_2Cl_2,[9a,c] in which we noticed that a yellow solid precipitated in the flask at the end point of the reaction (entry 12). It was found that this yellow precipitate was 5-F-AZADO$^+$$NO_3^-$ (**11**), which consists of an oxoammonium ion and nitrate,[17−19] indicating that the electrons on **9** and 5-F-AZADOH (**32**) (the hydroxylamine of **9**) were transferred to the NO_x/O_2 system. We confirmed that **11** immediately oxidized **12a** to **12b** under Ar, suggesting that the oxoammonium ion is the active species in this reaction, as in conventional nitroxyl radical-catalyzed alcohol oxidation.[10,11] Moreover, since **11** also has an NO_x moiety in the same molecule, it was expected to serve as an aerobic oxidation catalyst by itself. In fact, use of 5 mol % **11** attained the oxidation of **12a** in high yield with only air and solvent and without any additives (entry 13). Ultimately, we identified two sets of catalytic conditions (entries 10 and 13) as the methods of choice: method A employing 5-F-AZADO (**9**) (1 mol %)[20] and $NaNO_2$ (10 mol %)[21] and method B employing 5-F-AZADO$^+$$NO_3^-$ (**11**) (5 mol %).[22,23]

Received: December 6, 2010
Published: April 07, 2011

Table 1. Evaluation of the Catalytic Efficiencies of Nitroxyl Radicals and Oxoammonium Salts for Aerobic Oxidation



entry	nitroxyl radical	X	oxidant	time (h)	yield (%)
1	TEMPO (**1**)	5	O_2	168	5 (90)
2	1-Me-AZADO (**4**)	5	O_2	24	71 (21)
3	AZADO (**3**)	5	O_2	9	88
4	5-OH-1-Me-AZADO (**5**)	5	O_2	21	82
5	5-MeO-1-Me-AZADO (**6**)	5	O_2	18	83
6	5-F-1-Me-AZADO (**7**)	5	O_2	4	94
7	1-F-AZADO (**8**)	5	O_2	3	90
8	5-F-AZADO (**9**)	5	O_2	2	92
9	5-F-AZADO (**9**)	5	Air	2	90
10	5-F-AZADO (**9**)	1	Air	9	90
11	5,7-diF-1-Me-AZADO (**10**)	5	O_2	9	91
12[a]	5-F-AZADO (**9**)	5	O_2	12	91
13[b]	5-F-AZADO$^+NO_3^-$ (**11**)	5	Air	2	96

[a] This reaction was run using *tert*-butyl nitrite (30 mol %) in CH_2Cl_2. [b] This reaction was run without $NaNO_2$.

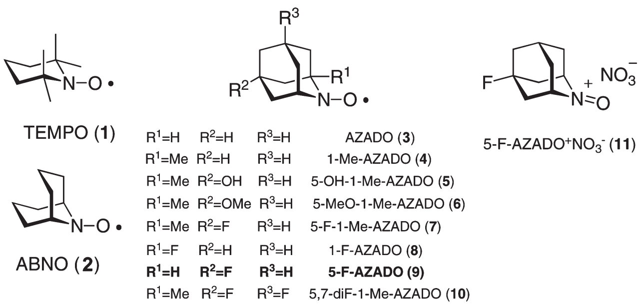
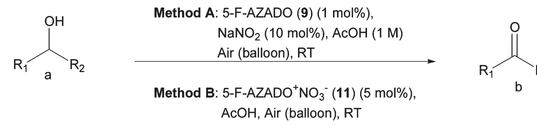


Figure 1. Catalyst structures.

Under each set of conditions, a wide range of alcohols can be readily oxidized to the corresponding carbonyl compounds (Table 2). 5-F-AZADO$^+NO_3^-$ (**11**) showed a markedly high reactivity, completing each of the secondary alcohol oxidations shown in Table 2 within 2 h. Primary alcohol **16a**, which often resists aerobic oxidation using transition-metal catalysts,[3] was also readily oxidized to the corresponding aldehyde in yields of 72% (method A) and 76% (method B), accompanied by a small amount of carboxylic acid under each set of conditions (entry 4); the use of 5 mol % 5-F-AZADO (**9**) gave the corresponding carboxylic acid **16c** in high yield (entry 5). These aerobic oxidation systems have sufficient compatibility to convert various alcohols to their corresponding carbonyl compounds.[24−30] Since nucleic acid derivatives as well as olefin substrates are difficult to oxidize under conventional NaOCl conditions, these results clearly demonstrate the advantage of these methods. It should be noted that 5 g of 1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (**22a**) was also effectively oxidized (entry 11).[25−27] The oxidation of prolinol **26a** and phenylalaninol **27a** proceeded without racemization (entries 15 and 16).[31] Unfortunately, 6-methylhept-5-en-2-ol having the trisubstituted olefin suffered from an ene-like reaction.[32] Envisioning recycling, we tried to recover **11** using 4-methoxybenzyl alcohol (**13a**). The inorganic-salt-free conditions greatly facilitated the operation,[33] and the **11**

Table 2. Scope of Aerobic Oxidation Using 5-F-AZADO (9)/ $NaNO_2$ and 5-F-AZADO$^+NO_3^-$ (11)

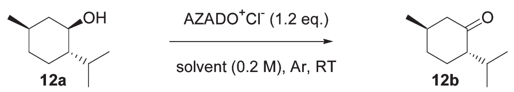


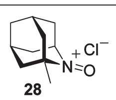
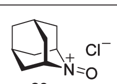
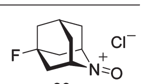
entry	alcohol	product	Method A[a] yield(%) / time	Method B[a] yield(%) / time
1	**13a**	**13b**	96 / 3 h	96 / 0.75 h
2	**14a**	**14b**	95 / 7 h	99 / 0.5 h
3	**15a**	**15b**	93 / 3 h[b]	95 / 2 h
4	**16a**	**16b**	72 / 5 h	76 / 2.5 h
5	**16a**	**16c**	76 / 2.5 h[c]	
6	**17a**	**17b**	85 / 9 h	84 / 2 h
7	**18a**	**18b**	98 / 3.5 h	98 / 2 h
8	**19a**	**19b**	100 / 2 h[b,d]	99 / 1.5 h
9[14a]	**20a**	**20b**	90 / 6 h[e]	96 / 2 h
10[24]	**21a**	**21b**	94 / 1 h[b]	96 / 0.5 h
11[25,26]	**22a**	**22b**	98 / 2 h 100 / 2 h[f]	97 / 0.5 h 99 / 5 h[f,g]
12[28]	**23a**	**23b**	97 / 2 h	91 / 0.5 h
13	**24a**	**24b**	93 / 1 h[b]	90 / 1 h[h]
14[29,30]	**25a**	**25b**	91 / 2 h[b]	90 / 0.5 h[i]
15	**26a**	**26b**	77 / 4 h[j]	74 / 8 h[k]
16	**27a**	**27b**	78 / 2.5 h[l]	71 / 5 h[m]

[a] Isolated yields are shown. [b] 3 mol % **9** was used. [c] The reaction used 5 mol % **9** and 10 mol % $NaNO_2$ in AcOH (0.1 M). [d] AcOH (0.4 M) was used. [e] 15 mol % **9** and 20 mol % $NaNO_2$ were used. [f] 5 g of alcohol **22a** was used. [g] 1 mol % **11** was used. [h] O_2 atmosphere (balloon). [i] 5 mol % $NaNO_2$ was added. [j] **9** (1 mol %), $NaNO_2$ (10 mol %), AcOH (2 equiv), MeCN (1 M). [k] 5-F-AZADO$^+NO_3^-$ (5 mol %), AcOH (2 equiv), MeCN (1 M). [l] **9** (3 mol %), $NaNO_2$ (20 mol %), AcOH (10 equiv), MeCN (0.5 M). [m] **11** (5 mol %), AcOH (10 equiv), MeCN (0.5 M).

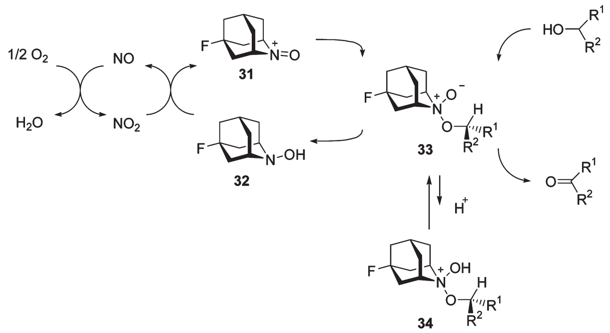
 dx.doi.org/10.1021/ja110940c | *J. Am. Chem. Soc.* 2011, 133, 6497–6500

Table 3. Reactivities of Oxoammonium Salts



solvent	 28	 29	 30
CH_2Cl_2	76% / 30 min	85% / 30 min	94% / 30 min
AcOH	27% / 300 min	37% / 180 min	86% / 90 min

Scheme 1. Reaction Mechanism for Aerobic Oxidation



recovered from the reaction mixture exhibited the same catalytic activity in the second oxidation as in its first use.[34]

To gain insight into the remarkable reactivity of **9** and **11**, we analyzed a series of newly synthesized AZADO derivatives by cyclic voltammetry,[7b,34−36] which revealed that fluoro-AZADOs [5-F-AZADO (**9**), +413 mV; 5-F-1-Me-AZADO (**7**), +363 mV; 1-F-AZADO (**8**), +471 mV; and 5,7-diF-1-Me-AZADO (**10**), +534 mV] had higher oxidation potentials ($E^{\circ\prime}$) than TEMPO (**1**) (+294 mV), AZADO (**3**) (+236 mV), and 1-Me-AZADO (**4**) (+186 mV). These values indicate that it is the electron-withdrawing effect of the fluorine atom that leads to the increase in the oxidation potential of fluoro-AZADOs.

We also investigated the reactivity of oxoammonium chlorides under stoichiometric oxidation conditions (Table 3). 5-F-AZADO$^+$Cl$^-$ (**30**) showed a higher reactivity than 1-Me-AZADO$^+$Cl$^-$ (**28**) and AZADO$^+$Cl$^-$ (**29**). Table 3 also shows a comparison of the reactivities in AcOH with those in CH_2Cl_2.

On the basis of all of the aforementioned results, the possible overall mechanism for these aerobic oxidations shown in Scheme 1 is proposed. Electrons are directly transferred from F-AZADOH (**32**) to NO_x/O_2. The oxoammonium ion **31** oxidizes the alcohol via a mechanism similar to a proposed mechanism for conventional TEMPO/NaOCl.[10,11] It is presumed that the basicity of the oxide moiety of the alcohol adduct **33** can be attenuated by the electron-withdrawing effect of the F group, protecting the intermediate from undesirable protonation to give **34** and thus promoting the oxidation of the alcohol by 5-F-AZADO$^+$ (**31**) in AcOH.

In summary, we have developed a reliable aerobic oxidation system using 5-F-AZADO (**9**) as a highly active oxidation catalyst. The introduction of a fluoro group at a position remote from the nitroxyl radical on AZADOs markedly increases their activities in aerobic oxidation. 5-F-AZADO (**9**) realized direct and efficient electron transfer with inorganic nitroxyl radicals (NO_x), indicating that not only the use of the less hindered class of nitroxyl radicals but also the suitable modulation of the nitroxyl radical nature is essential for an efficient aerobic oxidation system. In the 5-F-AZADO$^+NO_3^-$ (**11**) system, it is notable that the nitrate moiety of an oxoammonium salt works as an alternative electron carrier between molecular oxygen and 5-F-AZADO, which shows an advantage of the use of an oxoammonium salt as a catalyst. These systems are applicable to a wide range of alcohols, including olefin substrates to which the conventional NaOCl conditions cannot be applied as well as multifunctionalized molecules such as carbohydrates, nucleic acids, and aminoalcohols, enabling the replacement of harmful reagents used in alcohol oxidation. The system described here will greatly expand the scope of nitroxyl radical/oxoammonium salt-based organocatalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures for the preparation of catalysts, aerobic oxidation using methods A and B, and recycling of 5-F-AZADO$^+NO_3^-$; effects of AcOH and substituents of TEMPO; details of electrochemical measurements and DSC analysis; and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

This work was partially supported by a Grant-in-Aid for Scientific Research (B) (17390002) from the Japan Society for the Promotion of Science (JSPS) and a Grant-in-Aid for a Research Fellowship for Young Scientists (B) (19790005) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT).

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(15) 1-Me-AZADO (**4**) also catalyzed the oxidation of menthol with moderate efficiency under Liu and Liang's conditions ($FeCl_3/NaNO_2/O_2/CH_2Cl_2$).[9d] It was found that AcOH realizes nonmetal aerobic oxidation, while $FeCl_3$ is necessary to have the reaction proceed in CH_2Cl_2.

(16) It is presumed that the oxidation rate of 5,7-diF-AZADOH by NO_2 decreases because of the increasing oxidation potential.

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(18) 5-F-AZADO^{+}NO$_3^{-}$ (**11**): IR (neat) ν_{max}: 1628, 1372, 1333 cm^{-1}. ESI-MS(+): *m/z* 170 [5-F-AZADO]$^{+}$. ESI-MS(−): *m/z* 62 [NO$_3$]$^{-}$. Anal. Calcd for $C_9H_{13}FN_2O_4$: C, 46.55; H, 5.64; N, 12.06. Found: C, 46.26; H, 5.73; O, 11.86. The counteranion of 5-F-AZADO^{+} was also identified as NO_3^{-} by ion chromatography.

(19) In DSC analysis, the starting point of exothermic decomposition was 116 °C, and the amount of heat released was 1815 J/g. These data do not suggest the necessity of careful operation involving **11** to prevent explosion in laboratory-scale operation.[34]

(20) **9** was easily prepared from 2-azaadamantane by a five-step method that we have established as a kilogram-scale preparation procedure (WO 2009/066735).[34]

(21) Tables showing the effect of AcOH are provided in the Supporting Information. They indicate that the use of AcOH as a solvent is not essential for these aerobic oxidation systems: addition of 2−5 equiv of AcOH in MeCN completed the aerobic oxidation using 1 mol % **9** and 10 mol% $NaNO_2$, and 5 mol % **11** realized the aerobic oxidation under AcOH-free conditions.[34]

(22) **11** was easily prepared either by mixing **9** and HNO_3 in Et_2O or by treatment with NO_2 gas.[34]

(23) **11** was stable enough to handle in air.

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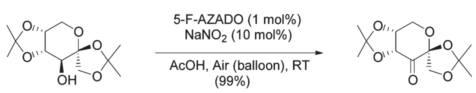
(27) In accordance with the comment of one of the reviewers, we attempted the 0.1 mol scale oxidation of 1,2:4,5-di-*O*-isopropylidene-*β*-D-fructopyranose (**22a**). Because of an efficient electron transfer system, the reaction proceeded smoothly to give the product in high yield without pressurized oxygen.[34]



22a (26.0 g)
0.1 mol
22b (25.6 g)

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(33) **11** was not obtained after the reaction under **9**/$NaNO_2$ conditions. Metal-salt-free conditions promoted the production of **11**.

(34) The details are provided in the Supporting Information.

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(36) The reference electrode was Ag/AgCl.