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Mechanistic Insight into Aerobic Alcohol Oxidation Using NO_x–Nitroxide Catalysis Based on Catalyst Structure–Activity Relationships

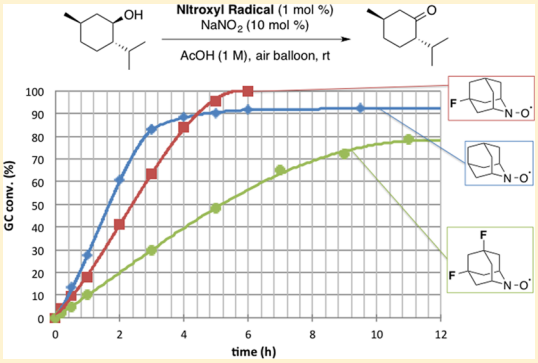
Masatoshi Shibuya,[†] Shota Nagasawa,[‡] Yuji Osada,[‡] and Yoshiharu Iwabuchi*[,‡]

[†]Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

[‡]Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama 6-3, Sendai 980-8578, Japan

Supporting Information

ABSTRACT: The mechanism of an NO_x-assisted, nitroxide(nitroxyl radical)-catalyzed aerobic oxidation of alcohols was investigated using a set of sterically and electronically modified nitroxides (i.e., TEMPO, AZADO (**1**), 5-F-AZADO (**2**), 5,7-DiF-AZADO (**3**), 5-MeO-AZADO (**4**), 5,7-DiMeO-AZADO (**5**), oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**)). The motivation for the present study stemmed from our previous observation that the introduction of an F atom at a remote position from the nitroxyl radical moiety on the azaadamantane nucleus effectively enhanced the catalytic activity under typical NO_x-mediated aerobic-oxidation conditions. The kinetic profiles of the azaadamantane-*N*-oxyl-[AZADO (**1**)-, 5-F-AZADO (**2**)-, and 5,7-DiF-AZADO (**3**)]-catalyzed aerobic oxidations were closely investigated, revealing that AZADO (**1**) showed a high initial reaction rate compared to 5-F-AZADO (**2**) and 5,7-DiF-AZADO (**3**); however, AZADO-catalyzed oxidation exhibited a marked slowdown, resulting in ∼90% conversion, whereas 5-F-AZADO-catalyzed oxidation smoothly reached completion without a marked slowdown. The reasons for the marked slowdown and the role of the fluoro group are discussed. Oxa-AZADO (**6**), Ts*N*-AZADO (**7**), and DiAZADO (**8**) were designed and synthesized to confirm their comparable catalytic efficiency to that of 5-F-AZADO (**2**), providing supporting evidence for the electronic effect on the catalytic efficiency of the heteroatoms under NO_x-assisted aerobic-oxidation conditions.



INTRODUCTION

The oxidation of alcohols to their corresponding carbonyl compounds is a fundamental transformation in organic chemistry, where quests for the realization of an efficient and selective oxidation method have continuously spurred active investigations to enrich the repertoire of useful reagents and methods.[1] In addition to such development processes, the recent social demand to evolve sustainable chemistry encourages the development of a catalytic alcohol-oxidation method that uses molecular oxygen (O_2) as the terminal oxidant, presenting a difficult, but rewarding, challenge: designing an aerobic-oxidation method that is the ideal chemical process, using the minimum amount of nontoxic catalyst under mild conditions and yielding H_2O as the only byproduct.[2]

Throughout the history of the development of aerobic alcohol oxidation processes, a class of stable nitroxyl radicals has played salient roles. In 1984, Semmelhack et al. disclosed the first catalytic aerobic alcohol oxidation using TEMPO with CuCl in DMF.[3] After their seminal report, significant progress in terms of catalytic efficiency and substrate applicability has been achieved by Sheldon and co-workers,[4] Kumpulainen and Koskinen,[5] and Stahl and co-workers,[6] resulting in TEMPO/Cu-catalyzed aerobic oxidation, a reliable method of choice in practical organic synthesis.[7,8] We also developed an AZADO/Cu system for a highly chemoselective aerobic oxidation of amino alcohols.[9] In 2004, Hu and Liang et al. developed the first transition-metal-free aerobic oxidation catalyzed by TEMPO, which employs Br_2 and NO_x as cocatalysts.[10] Subsequently, both they and Studer's group achieved TEMPO-catalyzed aerobic oxidation under a halogen- and transition-metal-free condition (TEMPO/*tert*-butyl nitrite, TEMPO/NH_2OH).[11,12] Unfortunately, the substrate applicability of the previously mentioned TEMPO/NO_x-catalyzed aerobic-oxidation methods is limited to benzylic alcohols and a few simple aliphatic alcohols. Thus, we have recently developed a highly efficient aerobic-oxidation method using AZADO-type nitroxides as catalysts. This method can be applied to a broad range of aliphatic alcohols including alkenyl alcohols,

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carbohydrates, and nucleic acid derivatives.[13] During our research on this aerobic-oxidation system, we found that fluorinated azaadamantane *N*-oxyl (5-F-AZADO, **2**) exhibits a higher efficiency than nonsubstituted AZADO (**1**). Although the F atom of 5-F-AZADO (**2**) is located at a remote position from the nitroxyl radical moiety, the introduction of the F atom significantly affects its catalytic behavior. Herein, we investigated the kinetic profile of a series of AZADOs to probe the role of F groups. New nitroxyl radicals oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**) have been developed with the above insight.

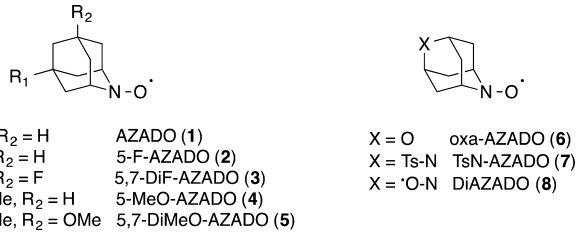

Figure 1. Structures of a series of AZADO derivatives.

RESULTS AND DISCUSSION

Our investigation commenced with the comparison of the temporal profiles of AZADO (**1**), 5-F-AZADO (**2**), and 5,7-DiF-AZADO (**3**),[14] using *l*-menthol (**9a**) as the substrate under conditions identical to those in our original report (1 mol % nitroxyl radical, 10 mol % $NaNO_2$, AcOH solvent, air balloon).[13a] The kinetic profile of TEMPO was also investigated for reference. 5-F-AZADO had completely oxidized **9a** within 6 h, whereas AZADO and 5,7-DiF-AZADO had not completely oxidized **9a** even after 12 h. Under TEMPO-catalyzed conditions, no oxidized products were detected after 12 h. The following results were also observed: (1) AZADO exhibited a higher initial rate than that of 5-F-AZADO, (2) AZADO-catalyzed oxidation reaction showed a marked slowdown, resulting in ~90% conversion, and (3) the introduction of a second F atom markedly attenuated the catalytic efficiency. These observations indicated that the introduction of one F atom into AZADO does not accelerate the reaction rate but prevents the slowdown (Figure 2). The reproducibility of this result is confirmed by repeated experiments. Similar profiles were also obtained from the oxidation of 4-phenyl-2-butanol (**10a**, Figure 3) and 2-octanol (**11a**, Figure 4). The temporal profiles of ABNO using these three alcohols were examined (Figures S1−S3). The initial rates were similar to those of AZADO; however, the marked slowdown of the reaction was observed at slightly lower conversion than that of AZADO.

We also investigated the temporal profiles of 5-MeO-AZADO (**4**) and 5,7-DiMeO-AZADO (**5**)[15] under identical conditions to probe the effect of the F atom on robust catalytic activity. Although 5-MeO-AZADO (**4**) showed a slightly lower catalytic activity than did 5-F-AZADO (**2**), the reaction went to completion without any marked slowdown. The introduction of a second MeO group attenuated the reaction rate in a manner similar to that of fluorinated AZADOs. Moreover, 5-MeO-AZADO (**4**) enabled the completion of the oxidation within 10 h without any marked slowdown, and the initial rate decreased in a manner dependent on the number of introduced MeO

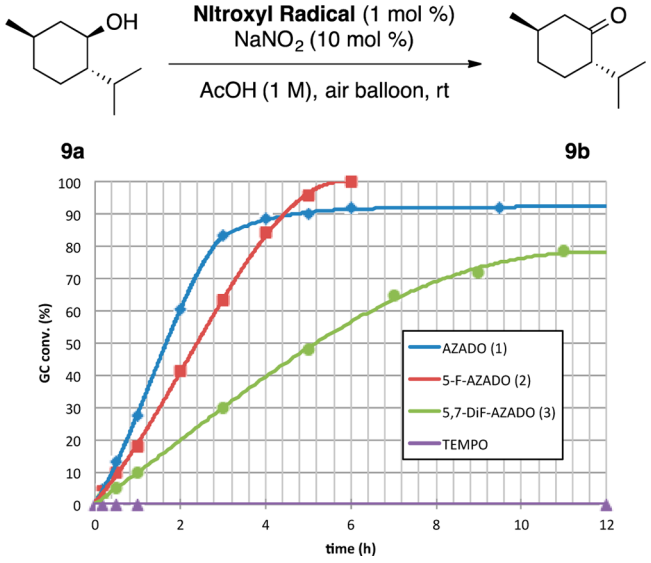

Figure 2. Temporal profiles of AZADO (**1**), 5-F-AZADO (**2**), 5,7-DiF-AZADO (**3**), and TEMPO. Substrate: *l*-menthol (**9a**).

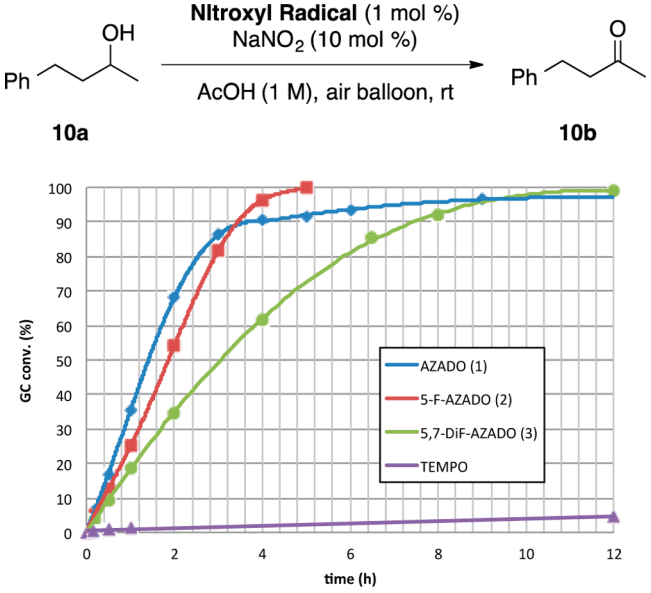

Figure 3. Temporal profiles of AZADO (**1**), 5-F-AZADO (**2**), 5,7-DiF-AZADO (**3**), and TEMPO. Substrate: 4-phenyl-2-butanol (**10a**).

groups (Figure 5). These results support the notion that an inductive effect of the heteroatoms plays an important role in preventing a marked slowdown of the reaction.

In the course of the development of a 5-F-AZADO-catalyzed aerobic-oxidation method, it was revealed that the acidity of AcOH plays an essential role. Therefore, we obtained the temporal profiles of AZADO (**1**) and 5-F-AZADO (**2**) for five different amounts of AcOH in MeCN to evaluate the effect of AcOH on the reaction rate. The results are shown in Figure 6. Under the 5-F-AZADO-catalyzed condition, the larger the amount of AcOH, the higher the reaction rate. However, two interesting catalytic behavioral features of AZADO (**1**) were also observed: (i) the initial rate increased as the loading amount of AcOH increased in a way that was similar to the 5-F-AZADO-catalyzed condition and (ii) a slowdown was evident when more than 10 equiv of AcOH was loaded. Regarding the possible reasons for the marked slowdown under the AZADO-

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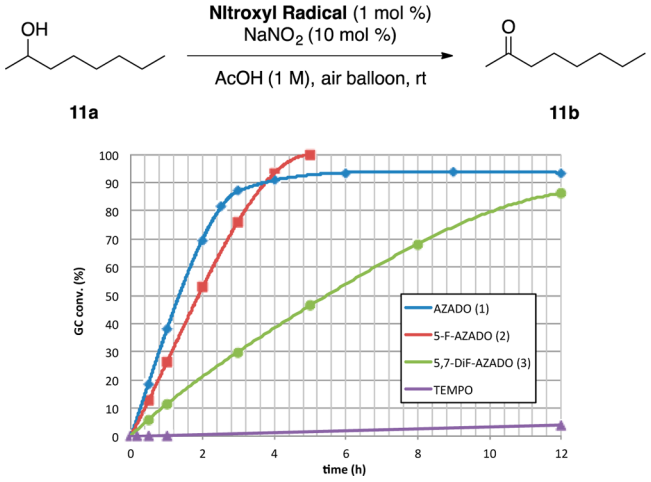

Figure 4. Temporal profiles of AZADO (**1**), 5-F-AZADO (**2**), 5,7-DiF-AZADO (**3**), and TEMPO. Substrate: 2-octanol (**11a**).

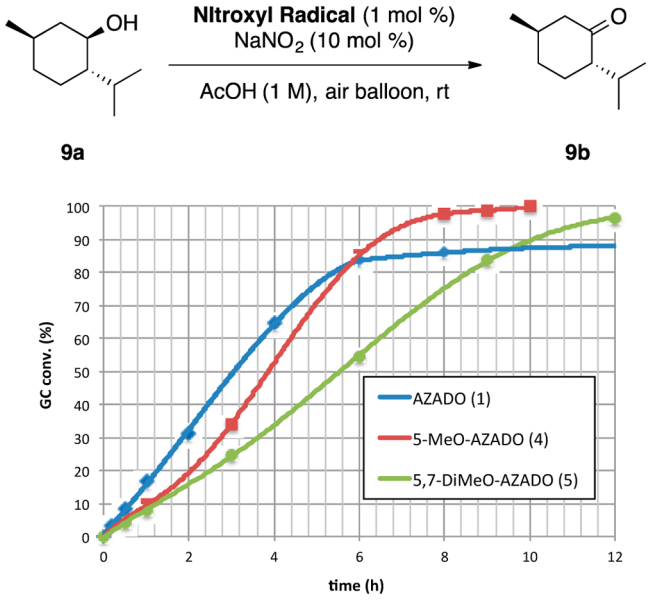

Figure 5. Temporal profiles of AZADO (**1**), 5-MeO-AZADO (**4**), and 5,7-DiMeO-AZADO (**5**).

catalyzed condition, we postulated the following: (i) AZADO (**1**) deactivation, (ii) the depletion of catalytically active NO_x, and (iii) the concomitant generation of catalytic poisons.

An additional 1 mol % AZADO (**1**) was added immediately after the slowdown was observed (Figure 7, 8 h) to examine the possibility of AZADO (**1**) deactivation. However, only a slight increase in the conversion rate was observed, indicating the presence of deactivating factors. However, the addition of 1 mol % 5-F-AZADO (**2**) led to the completion of the reaction (Figure 7).

Next, an additional 10 mol % $NaNO_2$ was added immediately after the slowdown was observed to examine the possibility of the depletion of catalytically active NO_x. The result showed that although a marginal increment in conversion was observed, the reaction did not reach completion (Figure 8). The formation of a small amount of menthyl nitrite was detected instead.[16]

The third possible cause of the marked slowdown is the concomitant generation of catalytic poisons; HNO_3 and H_2O

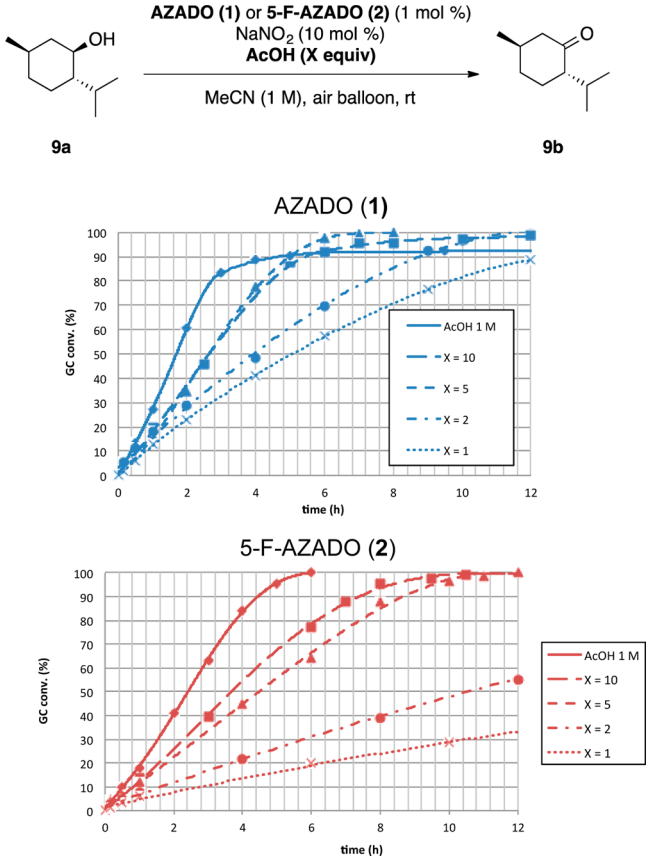

Figure 6. Effects of the amount of AcOH on catalytic efficiencies.

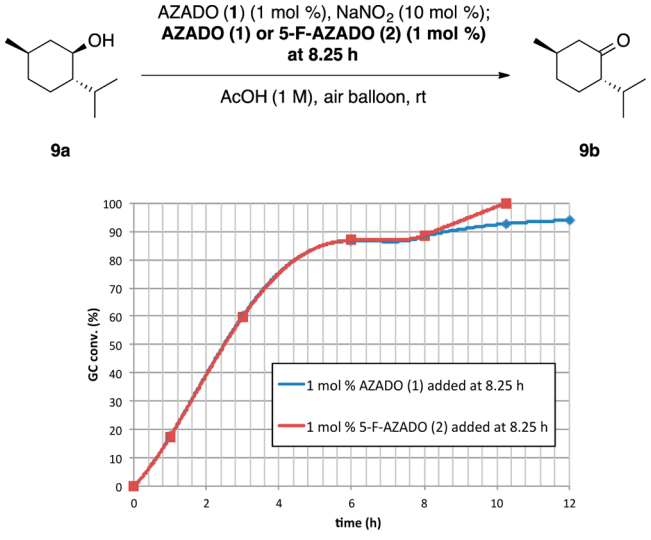

Figure 7. Effects of the addition of extra AZADO (**1**) and 5-F-AZADO (**2**) on temporal profiles.

were each considered to be candidate catalytic poisons. The results of the evaluation of the effect of AcOH have already suggested that AZADO-catalyzed oxidation is more sensitive to the acidity of the reaction mixture than is 5-F-AZADO-catalyzed oxidation (Figure 6). First, we postulated that HNO_3, which is generated via NO_x autoxidation, quenches the oxidation.[17] AZADO- and 5-F-AZADO-catalyzed aerobic oxidations in the presence of HNO_3 were examined to verify the possibility. The result showed that the addition of 1 mol %

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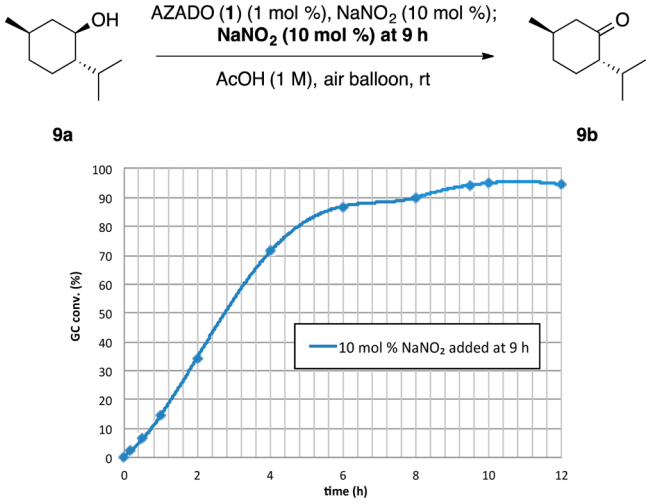

Figure 8. Effect of the addition of extra $NaNO_2$ on the temporal profile of AZADO-catalyzed oxidation.

HNO_3 decreased the conversion rate of the AZADO-catalyzed oxidation by about 5% but enabled the completion of the 5-F-AZADO-catalyzed oxidation with a slight deceleration. A similar slowdown was observed under the 5-F-AZADO-catalyzed condition in the presence of more than 10 mol % HNO_3 (Figure 9). These results are in agreement with the catalytic behavior of AZADO (**1**) and 5-F-AZADO (**2**).

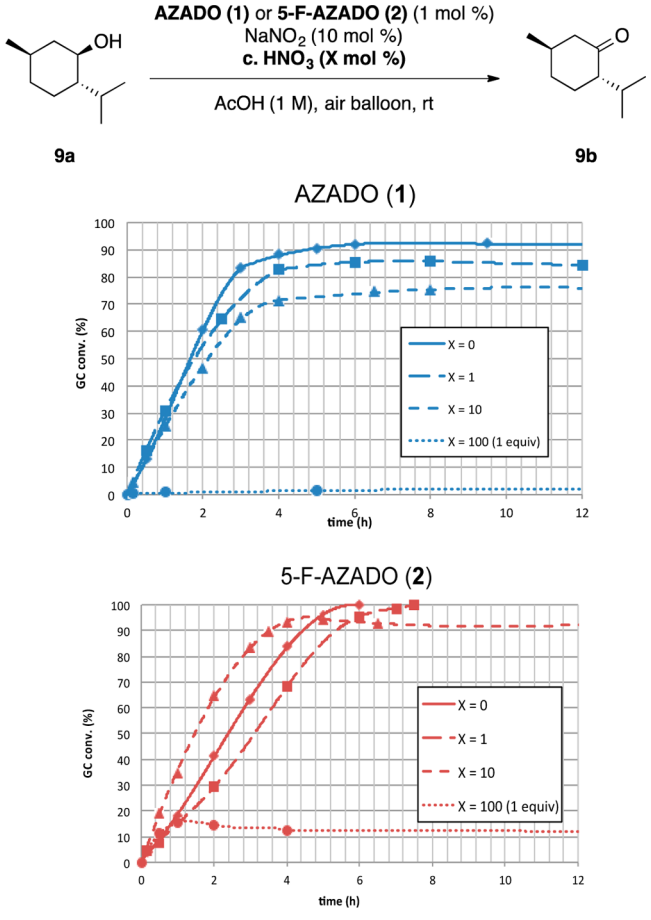

Figure 9. Effects of HNO_3 on the temporal profiles of AZADO- and 5-F-AZADO-catalyzed oxidations.

However, we observed no detectable pH change in the reaction mixture using conventional pH-indicator paper. The possibility of H_2O acting as a catalytic poison, which is a byproduct of the reduction of O_2 under aerobic oxidation, was investigated by determining the temporal profiles of the AZADO- and 5-F-AZADO-catalyzed oxidation in the presence of H_2O (Figure 10).[18] The result showed that 1 equiv of H_2O to substrate

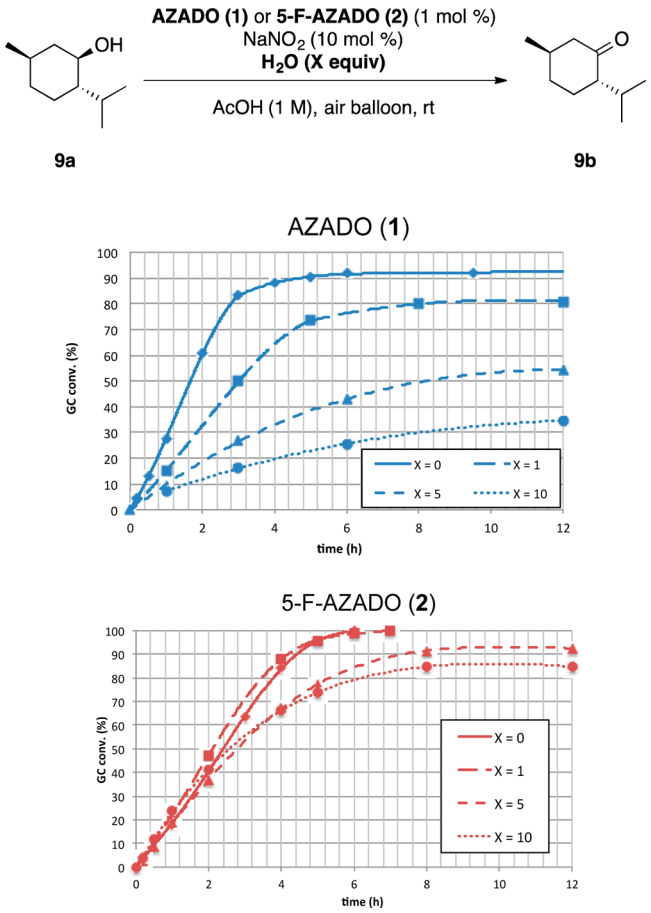

Figure 10. Effects of H_2O on the temporal profiles of AZADO- and 5-F-AZADO-catalyzed oxidations.

clearly decreased the conversion rate under the AZADO-catalyzed condition up to ~80%, although a slight extension of the reaction time was observed under the 5-F-AZADO-catalyzed condition. It was found that AZADO-catalyzed oxidation is clearly more sensitive to H_2O than 5-F-AZADO-catalyzed oxidation. These results suggest that H_2O generated from O_2 inhibits the catalytic cycles of AZADO oxidation.[19]

Two experiments were conducted to shed light on the shutdown event. In the first experiment, **9a** (0.96 mmol, 1.0 equiv) was subjected to 1 mol % AZADO-catalyzed oxidation, and an additional 0.5 equiv (0.48 mmol) of **9a** was added when the reaction reached ~70% conversion (Figure 11, just before the slowdown was observed). Interestingly, more than 1.0 equiv of **9a** (~1.2 equiv) was oxidized to menthone (**9b**), suggesting that the slowdown begins when the amount of remaining alcohol is critically decreased.

In the second experiment, **9a** (0.96 mmol, 1.0 equiv) was subjected to 1 mol % AZADO-catalyzed oxidation; after 8 h, an additional 0.5 equiv (0.48 mmol) of **9a** was added (Figure 12, just after the slowdown). No obvious progression of the

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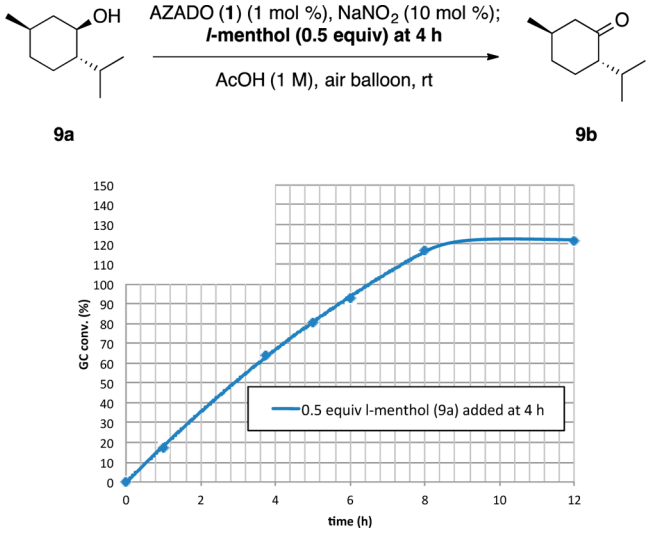


Figure 11. Effect of the addition of 0.5 equiv of *l*-menthol (**9a**) at approximately 70% conversion on the temporal profile of AZADO-catalyzed oxidation.

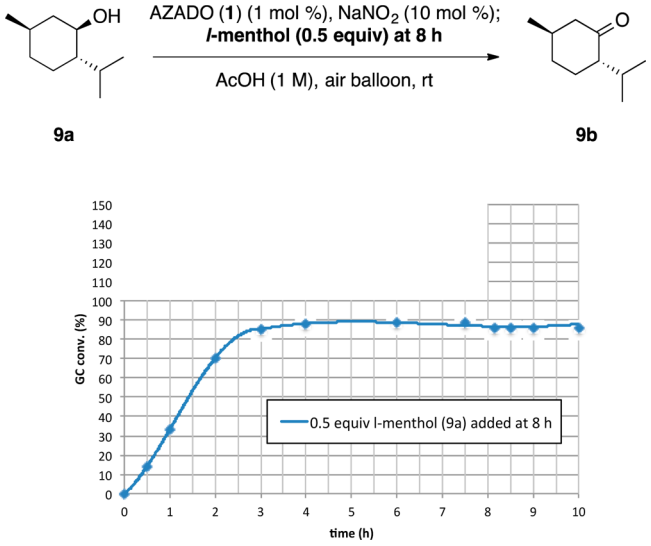


Figure 12. Effect of the addition of 0.5 equiv of *l*-menthol (**9a**) after 8 h on the temporal profile of AZADO-catalyzed oxidation.

reaction was observed, indicating that the observed slowdown results from a deactivation of the reaction rather than some kind of equilibrium being reached.

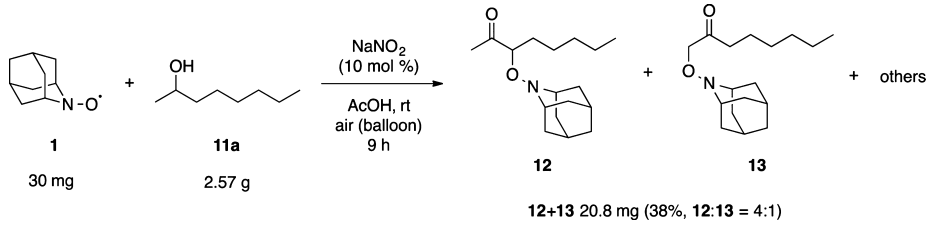
A large-scale oxidation of 2-octanol (**11a**, 2.57 g) using 30 mg of AZADO (**1**) was conducted to probe the deactivation pathway (Scheme 1). After a slowdown was observed (9 h), the reaction mixture was concentrated to give a dark residue, from which alkoxyamines **12** and **13** were isolated as major AZADO-derived products.

On the basis of all of the above results, the following are plausible explanations for the effect of the F atom and the marked slowdown of AZADO-catalyzed aerobic oxidation (Scheme 2). The oxoammonium species (**III**) forms a hydrate (**IV**) with H_2O in equilibrium, which is promoted by acids. As the amount of water increases with the advance of oxidation, the equilibrium between the catalytically active oxoammonium species (**III**) and the inactive hydrate (**IV**) shifts toward hydrate (**IV**) formation, thereby decreasing the probability of forming the alcohol adduct (**V**).[20] In this way, AZADO-catalyzed oxidation suffers from a slowdown, and AZADO is deactivated via an irreversible reaction between AZADO$^+$ (**III**, X = H) and the carbonyl compound. Because the oxygen atom of 5-F-AZADO$^+$ is slightly less basic than that of AZADO$^+$ (owing to the strong inductive effect of the F atom), 5-F-AZADO$^+$ is difficult to protonate and thereby eludes the hydrate (**IV**) formation reaction.[21] As such, 5-F-AZADO (**2**) efficiently catalyzes the aerobic oxidation without causing the fatal hydrate formation.

On the basis of the above kinetic study results, we are now interested in determining the reactivities of nitroxyl radical catalysts with a heteroatom in the azaadamantane nucleus. To examine the effect of the introduction of a heteroatom into the azaadamantane nucleus, we designed and synthesized three new catalysts ,i.e., oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**)[22] (Figure 13). These catalysts have a slightly more compact nucleus than AZADO (**1**) and 5-F-AZADO (**2**), resulting from the shorter bond lengths of C−O and C−N compared to that of C−C. We considered that these three catalysts were synthesized from their common intermediate *N*-Ts-9-azabicyclo[3.3.1]nonan-3-one (**14**), which can be readily prepared by the three-component condensation of acetonedicarboxylic acid, glutaraldehyde, and ammonia[23], followed by Ts protection. Oxa-AZADO (**6**) can be easily prepared in five steps from such an intermediate according to Tius's procedure (Scheme 3).[24] TsN-AZADO (**7**) and DiAZADO (**8**) were synthesized using modified Hofmann−Löffler−Freytag reaction conditions[25] in order to construct diazaadamantane skeletons

Figure 13. Structures of the newly synthesized aerobic-oxidation catalysts.

Scheme 1. Aerobic Oxidation of 2-Octanol (11a) on a Large Scale Using 30 mg of AZADO (1) and the Isolation of Azado-Derived Products



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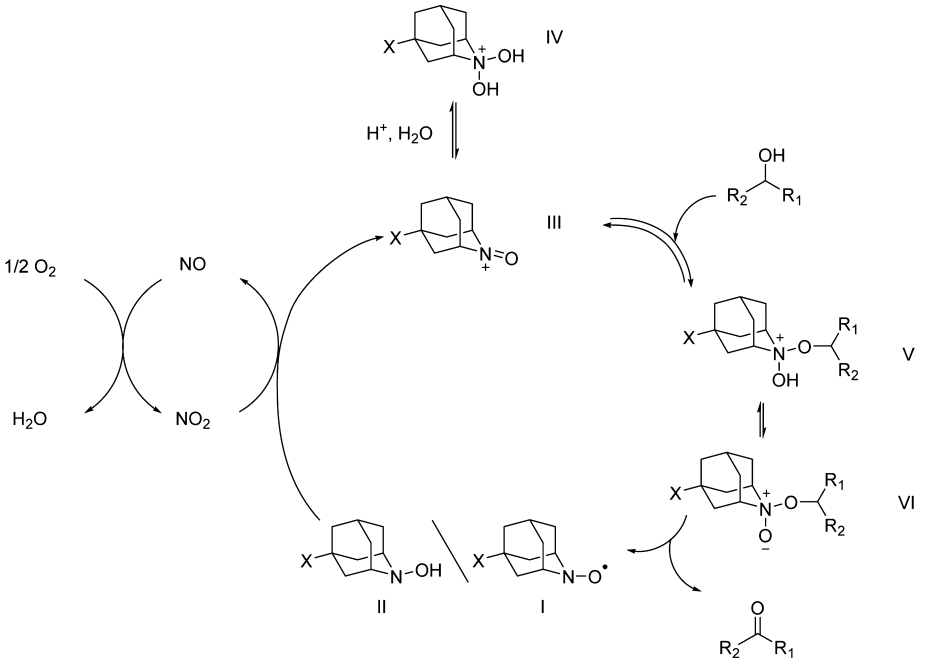
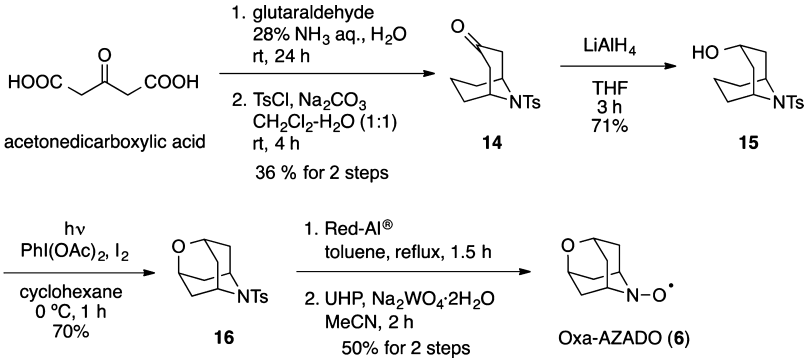
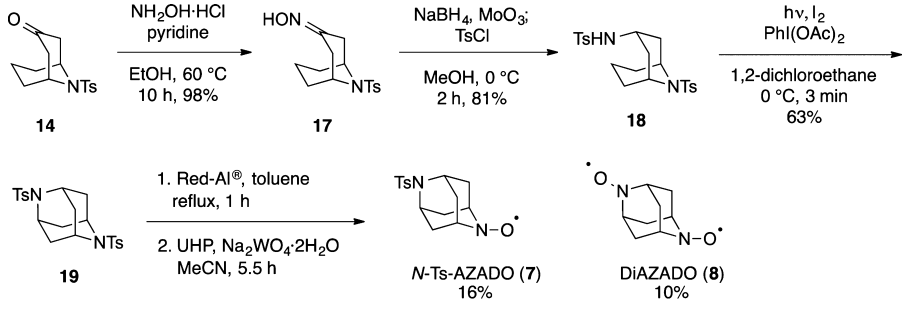
Scheme 2. Plausible Overall Mechanism of 5-F-AZADO- and AZADO-Catalyzed Oxidations



Scheme 3. Synthesis of Oxa-AZADO (6)



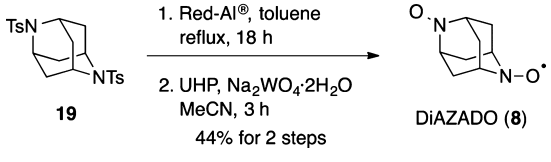
Scheme 4. Syntheses of TsN-AZADO (7) and DiAZADO (8)



(Scheme 4). DiAZADO (**8**) was obtained more efficiently by extension of the reaction time for the deprotection of Ts groups using sodium bis(2-methoxyethoxy)aluminum hydride (red-Al) (Scheme 5).

We examined the temporal profiles of oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**) (Figure 14). We found that these three catalysts are not markedly superior to 5-F-AZADO; however, they all enable the completion of the reaction without a marked slowdown. These catalysts also have a broad range of substrate applicabilities (Table 1).

Scheme 5. More Efficient Procedure for the Synthesis of DiAZADO (8)



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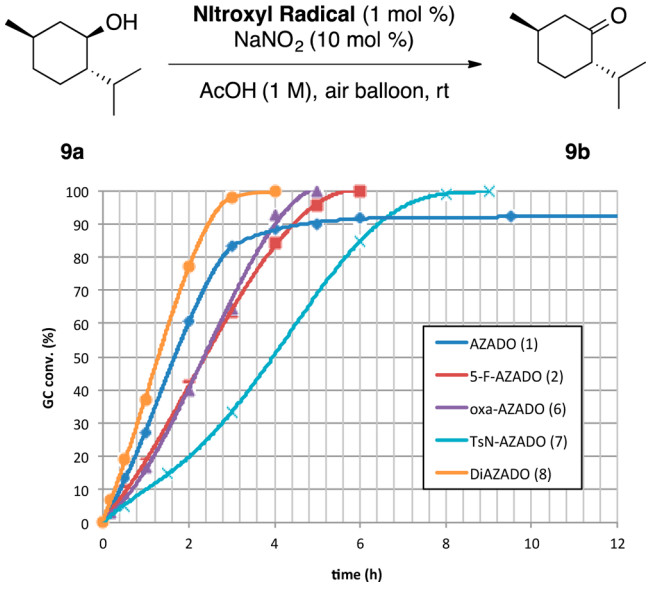


Figure 14. Temporal profiles of oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**) for the oxidation of *l*-menthol (**9a**).

CONCLUSIONS

We have investigated the kinetic behavior of AZADO, (Di)F-AZADO, and (Di)MeO-AZADO under NO_x-assisted aerobic alcohol-oxidation conditions. From the results, it became clear that AZADO (**1**) has the highest initial rate among these catalysts but suffers from a marked slowdown in its catalyzed reaction, resulting in only ~90% conversion. Although the introduction of an F atom and a MeO group decreases the reaction rate, the introduction of a monoheteroatom prevents such a marked slowdown. 5-F-AZADO (**2**) consequently shows the best performance as an aerobic-oxidation catalyst. Further kinetic studies suggested that H_2O works as a catalytic poison in NO_x-nitroxide aerobic-oxidation systems and that the deceleration effect of H_2O is promoted by acids. 5-F-AZADO (**2**) is less susceptible to such an effect than is AZADO (**1**) because of the less-basic oxygen atom in its nitroxide moiety. Newly synthesized oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**) all showed catalytic performance comparable to that of 5-F-AZADO (**2**).

EXPERIMENTAL SECTION

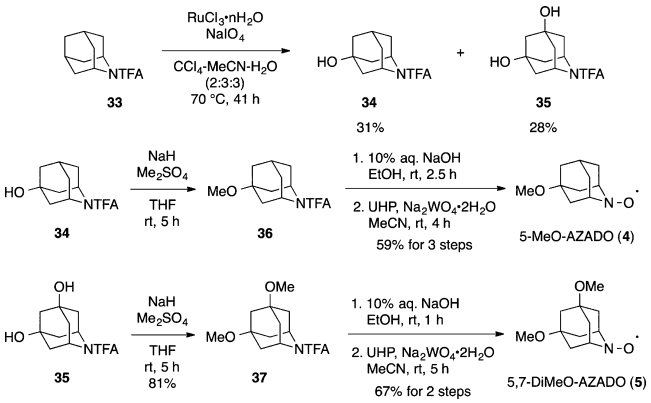
General Experimental Procedures. Aerobic oxidations were carried out under an air atmosphere (balloon). All reactions for the preparations of oxa-AZADO (**6**), TsN-AZADO (**7**), and DiAZADO (**8**) were carried out under an atmosphere of argon or N_2. Ethereal solvents and dichloromethane (anhydrous grade) were used without further purification. All solvents except AcOH were dried and distilled by standard procedures. Reagents were purchased from commercial suppliers and used without further purification. AZADO (**1**) was generously provided by Nissan Chemical Industries, Ltd. and purified with flash column chromatography (Et_2O–hexane = 1:1). 5-F-AZADO (**2**)[13a] and 5,7-DiF-AZADO (**3**)[14] were synthesized according to our previous reports.

Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates ($60F_{254}$) using a UV light as visualizing agent, *p*-anisaldehyde in ethanol–aqueous H_2SO_4–AcOH, phosphomolybdic acid in ethanol, and nynhydrin in AcOH–*n*-BuOH for staining. Column chromatography was performed with silica gel 60N (spherical, particle size 0.063–0.210 mm, neutral), silica gel 60N (spherical, particle size 0.040–0.050 mm, neutral), or CHROMATOREX-NH (spherical, particle size 0.040–0.075 mm or 0.075–0.200 mm, basic). The eluents employed are reported as volume/volume percentages.

Melting points were determined using a melting-point apparatus and are reported uncorrected. The recrystallization solvents are shown in parentheses after the melting point. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using 400 or 700 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.00 ppm). Coupling constants (J) are reported in hertz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, double doublet; dt, double triplet; dq, double quartet. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a 100 or 175 MHz spectrometer. The chemical shift is reported in parts per million (ppm) relative to the center line of the triplet of $CDCl_3$ (77.0 ppm). Infrared spectra were obtained at 4.0 cm^{-1} resolution and are reported in wavenumbers. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using an electron impact (EI) with magnetic sector time-of-flight mass analyzer or an electrospray ionization (ESI) with ion-trap mass analyzer. HPLC was performed using a UV/vistbl1 detector at 254 nm.

Syntheses of 5-MeO-AZADO (4) and 5,7-DiMeO-AZADO (5) (Scheme 6).[15]

Scheme 6. Syntheses of 5-MeO-AZADO (4) and 5,7-DiMeO-AZADO (5)



*N-Trifluoroacetyl-5-hydroxy-2-azaadamantane (**34**) and N-Trifluoroacetyl-5,7-dihydroxy-2-azaadamantane (**35**).* To a solution of *N*-trifluoroacetyl-2-azaadamantane (**33**) (6.00 g, 25.7 mmol) and $RuCl_3 \cdot nH_2O$ (1.60 g, 7.72 mmol) in a mixture of CCl_4–MeCN–H_2O (1.65 M, 15 mL; 1.1 M, 23 mL; 1.1 M, 23 mL) was added $NaIO_4$ (19.3 g, 90.1 mmol) at ambient temperature. The mixture was vigorously stirred for 41 h at 70 °C. After being cooled to room temperature, sat $NaHCO_3$ (aq) and 20% $Na_2S_2O_3$ (aq) were added to the mixture before filtering it through Celite. The filtrate was extracted with AcOEt (6×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with column chromatography (AcOEt–hexane = 1:4 to AcOEt) to afford *N*-trifluoroacetyl-5-hydroxy-2-azaadamantane (**34**) (1.98 g, 7.95 mmol, 31%) as a colorless solid and *N*-trifluoroacetyl-5,7-dihydroxy-2-azaadamantane (**35**) (1.93 g, 7.28 mmol, 28%) as a colorless solid, accompanied by recovered **33** (276 mg). **34**: colorless crystals; mp 95–96 °C ($CHCl_3$–Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.43 (s, 1H), 2.41 (s, 1H), 1.89–1.56 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (q, J = 35.2 Hz), 116.5 (q, J = 286.4 Hz), 66.6, 51.5 (q, J = 3.6 Hz), 48.3, 43.6, 43.1, 42.9, 34.9, 34.0, 28.8; IR (neat, cm^{-1}) 3425, 1681; MS m/z 249 (M^+), 249 (100%); HRMS (EI) calcd for $C_{11}H_{14}F_3NO_2$, 249.0977; found, 249.0956; Anal. calcd for $C_{11}H_{14}F_3NO_2$: C, 53.01; H, 5.66; N, 5.62; found: C, 52.88; H, 5.66; N, 5.62. **35**: colorless crystals; mp 167 °C (AcOEt); ^{1}H NMR (400 MHz, CD_3OD) δ 4.97 (s, 1H), 4.52 (s, 1H), 1.87–1.69 (m, 10H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.3 (q, J = 35.9 Hz), 118.1 (q, J = 274.2 Hz), 69.4, 53.2 (q, J = 3.8 Hz), 51.5, 50.3, 43.3, 42.5; IR (neat, cm^{-1}) 3335, 3197, 1686; MS m/z

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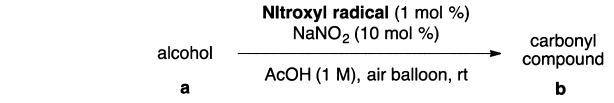
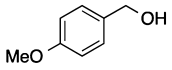
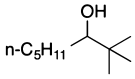
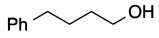
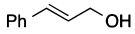
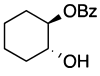
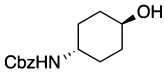
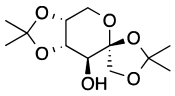
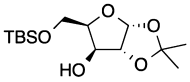
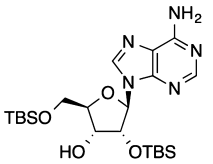
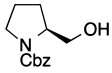
Table 1. Scope of Oxa-AZADO (6), TsN-AZADO (7), and DiAZADO (8)



entry	alcohol		isolated yield / time 5-F-AZADO (2)	Oxa-AZADO (6)	TsN-AZADO (7)	DiAZADO (8)
1		**20a**	96% / 3 h	93% / 3 h	86% / 2 h	100% / 2 h
2		**21a**	85% / 9 h	80% / 8 h	80% / 6.5 h	83% / 8.25 h
3		**22a**	96% / 6 h	98% / 6.5 h	93% / 4.5 h	93% / 7.5 h
4		**23a**	95% / 7 h	93% / 7.5 h	97% / 6.5 h	100% / 8 h
5		**24a**	86% / 10 h[a]	86% / 8 h[a]	91% / 7 h[a]	94% / 6 h[a]
6		**25a**	72% / 5 h	70% / 8 h	67% / 6 h	80% / 5 h
7		**26a**	93% / 3 h[a]	95% / 1.5 h[a]	90% / 2.5 h[a]	100% / 1.5 h[a]
8		**27a**	96% / 6.5 h	95% / 5.5 h	88% / 4 h	92% / 4.5 h
9		**28a**	86% / 6 h[b]	96% / 2.5 h[a,b]	98% / 2.5 h[a,b]	92% / 4 h[b]
10		**29a**	98% / 2 h	95% / 1.5 h	94% / 1.5 h	92% / 1.5 h
11		**30a**	97% / 2 h	90% / 2.5 h	85% / 2 h	98% / 2.5 h
12		**31a**	93% / 1 h[a,b]	88% / 1.5 h[b,c]	90% / 3 h[a,b]	86% / 2 h[a,b]
13		**32a**	77% / 4 h[d] (no racemization)	69% / 4 h[d] (no racemization)	74% / 4 h[d] (no racemization)	74% / 3.5 h[d] (no racemization)

[a]3 mol % nitroxyl radical was used. [b]AcOH (0.4 M) was used. [c]5 mol % nitroxyl radical was used. [d]MeCN (1 M), AcOH (2 equiv) were used.

265 (M^+), 265 (100%); HRMS (EI) calcd for $C_{11}H_{14}F_3NO_3$, 265.0926; found, 265.0925.

5-Methoxy-2-azaadamantane N-Oxyl (5-MeO-AZADO, 4). To a suspension of 60% NaH (241 mg, 6.02 mmol) in THF (1.8 mL) was slowly added via cannula a solution of *N*-trifluoroacetyl-5-hydroxy-2-azaadamantane (**34**) (500 mg, 2.01 mmol) in THF (4.9 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, Me_2SO_4 (571 μL, 6.02 mmol) was added dropwise to the reaction mixture. The mixture was stirred for 5 h at ambient temperature. The mixture was quenched with H_2O and extracted with Et_2O (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with flash column chromatography (AcOEt–hexane = 1:4) to afford *N*-trifluoroacetyl-5-methoxy-2-azaadamantane (**36**) (443 mg) containing some amount of Me_2SO_4. **36** was used without further purification. To a solution of **36** in EtOH (7.1 mL) was added NaOH (aq) (10%, 3.5 mL) at ambient temperature. After the reaction mixture was stirred for 2.5 h at ambient temperature, the mixture was concentrated under reduced pressure. The residue was extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was used in the next reaction without further purification. $Na_2WO_4{\cdot}2H_2O$ (333 mg, 1.01 mmol) was added to a solution of the residue in MeCN (0.2 M, 10 mL) at ambient temperature. The suspension was stirred at the same temperature for 30 min. UHP (760 mg, 8.08 mmol) was added to the reaction mixture

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at 0 °C. The mixture was stirred for 3 h at room temperature. Additional UHP (190 mg, 2.02 mmol) at 0 °C was added, and the mixture was stirred for an additional 1 h at room temperature. The mixture was diluted with sat $NaHCO_3$ (aq) and extracted with $CHCl_3$ (3×). The organic layer was dried over K_2CO_3 and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 1:1) to afford 5-methoxy-2-azaadamantane *N*-oxyl (**4**) (5-MeO-AZADO, 216 mg, 1.19 mmol, 59% for three steps) as a yellow solid. **36**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.45 (s, 1H), 3.25 (s, 3H), 2.42 (s, 1H), 1.95−1.69 (m, 10H). 5-MeO-AZADO (**4**): yellow prisms; mp 64 °C (hexane); IR (neat, cm^{-1}) 1443, 1350, 1115; MS *m*/*z* 182 (M^+), 182 (100%); HRMS (EI) calcd for $C_{10}H_{16}NO_2$, 182.1181; found, 182.1165; Anal. calcd for $C_{10}H_{16}NO_2$: C, 65.91; H, 8.85; N, 7.69; found: C, 65.97; H, 9.04 ; N, 7.71.

*N-Trifluoroacetyl-5,7-dimethoxy-2-azaadamantane (**37**).* To a suspension of 60% NaH (604 mg, 15.1 mmol) in THF (3.5 mL) was slowly added via cannula a solution of 5,7-dihydroxy-2-azaadamantane (**35**) (500 mg, 1.89 mmol) in THF (9.5 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, Me_2SO_4 (1.43 mL, 15.1 mmol) was added dropwise to the reaction mixture. After the reaction mixture was stirred for 5 h at ambient temperature, the mixture was quenched with H_2O and extracted with Et_2O (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 1:2) to afford *N*-trifluoroacetyl-5,7-dimethoxy-2-azaadamantane (**37**) (446 mg, 1.52 mmol, 81%) as a colorless oil. **37**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (s, 1H), 4.58 (s, 1H), 3.26 (s, 6H), 1.96−1.87 (m, 2H), 1.85−1.79 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7 (q, *J* = 36.5 Hz), 116.3 (q, *J* = 289.7 Hz), 77.2, 72.8, 72.7, 50.9, 50.8, 48.3 (q, *J* = 1.90 Hz), 47.8, 42.7, 38.9, 38.0; IR (neat, cm^{-1}) 1689, 1458, 1225, 1191, 1124; MS *m*/*z* 293 (M^+), 138 (100%); HRMS (EI) calcd for $C_{13}H_{18}F_3NO_3$, 293.1239; found, 293.1232.

*5,7-Dimethoxy-2-azaadamantane N-Oxyl (5,7-DiMeO-AZADO, **5**).* To a solution of *N*-trifluoroacetyl-5,7-dimethoxy-2-azaadamantane (**37**) (400 mg, 1.36 mmol) in EtOH (4.8 mL) was added NaOH (aq) (10%, 2.4 mL) at ambient temperature. After the reaction mixture was stirred for 1 h at ambient temperature, it was concentrated under reduced pressure. The residue was extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The crude product was used in the next reaction without further purification. $Na_2WO_4{\cdot}2H_2O$ (224 mg, 0.680 mmol) was added to the solution of the residue in MeCN (0.2 M, 6.8 mL). The suspension was stirred at ambient temperature for 30 min. UHP (512 mg, 5.44 mmol) at 0 °C was added to the reaction mixture, and the mixture was stirred at room temperature for 2 h. Additional UHP (128 mg, 1.36 mmol) at 0 °C was added, and the mixture was stirred for another 3 h at room temperature. The mixture was diluted with sat $NaHCO_3$ (aq) and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 2:1) to afford 5,7-dimethoxy-2-azaadamantane *N*-oxyl (5,7-diMeO-AZADO (**5**), 193 mg, 0.910 mmol, 67% for two steps) as a yellow solid. **5**: yellow prisms; mp 105−106 °C (Et_2O−hexane); IR (neat, cm^{-1}) 1444, 1305, 1119, 1108; MS *m*/*z* 212 (M^+), 212 (100%); HRMS (EI) calcd for $C_{11}H_{18}NO_3$, 212.1287; found, 212.1303; Anal. calcd for $C_{11}H_{18}NO_3$: C, 62.24; H, 8.55; N, 6.60; found: C, 62.07; H, 8.55; N, 6.53.

Experimental Procedures for the Aerobic Oxidation of Alcohols. *Experiments for the Temporal Profiles of AZADO Derivatives (Figures 2−5, 7−12, and 14).* To a solution of *l*-menthol (**9a**) (150 mg, 0.961 mmol) and AZADO (**1**) (1.44 mg, 9.61 μmol) in AcOH (0.961 mL) was added $NaNO_2$ (6.63 mg, 96.1 μmol) at room temperature. The mixture was stirred at the same temperature under an air atmosphere (balloon). The conversion of the reaction was monitored directly by GC analysis.

Experiments for the Evaluation of the Amount of AcOH (Figure 6). To a solution of *l*-menthol (**9a**) (150 mg, 0.961 mmol), AcOH (1, 2, 5, and 10 equiv), and AZADO (**1**) (1.44 mg, 9.61 μmol) in MeCN (0.961 mL) was added $NaNO_2$ (6.63 mg, 96.1 μmol) at room temperature. The mixture was stirred at the same temperature under an air atmosphere (balloon). The conversion of the reaction was monitored directly by GC analysis.

Conditions for GC Analysis. Sample, 5 μL of the reaction mixture in 1 mL of acetone; column, HP-5 (30 m × 0.32 mm, 0.25 μm); FID detector, 270 °C; injection, 250 °C; carrier gas, helium (3.0 mL/min); column temperature, *l*-menthol (**9a**): 70 °C for 2 min, raised to 140 °C at a rate of 10 °C/min, then 140 °C for 1 min or 70 °C for 2 min, raised to 210 °C at a rate of 20 °C/min, then 210 °C for 1 min; 4-phenyl-2-butanol (**10a**): 70 °C for 2 min, raised to 280 °C at a rate of 30 °C/min, then 280 °C for 1 min; 2-octanol (**11a**): 50 °C for 2 min, raised to 70 °C at a rate of 5 °C/min, then 70 °C for 1 min, raised to 130 °C at a rate of 30 °C/min, then 130 °C for 1 min.

Large-Scale Aerobic Oxidation for the Isolation of AZADO-Derived Products (Scheme 1). To a solution of 2-octanol (**11a**) (2.57 g, 19.7 mmol) and AZADO (**1**) (30.0 mg, 0.197 mmol) in AcOH (20 mL) in a 1 L recovery flask was added $NaNO_2$ (136 mg, 1.97 mmol) at room temperature. The mixture was stirred at the same temperature under an air atmosphere (balloon) for 9 h. The mixture was concentrated under reduced pressure to remove AcOH, 2-octanol, and 2-octanone (50 °C, 100 Pa). The residue was diluted with AcOEt and sat $NaHCO_3$ (aq) and extracted with AcOEt (3×). The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified with column chromatography (AcOEt−hexane = 1:8 to $CHCl_3$−MeOH = 4:1) to afford a mixture of alkoxyamines **12** and **13** (20.8 mg, 74.4 μmol, 38%, **12**−**13** = 4:1) and several unidentified products (total 9.72 mg) as a colorless oil. (In this experiment, AZADO and/or AZADOL (hydroxylamine form of AZADO) were not recovered.) 3-{(2-Azaadamantan-2-yl)-oxy}-octan-2-one (**12**) (major product): ^{1}H NMR (700 MHz, $CDCl_3$) δ 3.99 (s, 1H), 3.36 (s, 1H), 3.29 (s, 1H), 2.41 (d, *J* = 13.7 Hz, 1H), 2.34 (d, *J* = 13.7 Hz, 1H), 2.15 (s, 3H), 1.92 (s, 1H), 1.84 (s, 1H), 1.86−1.75 (m, 6H), 1.61−1.26 (m, 8H), 1.38 (t, *J* = 13.3 Hz, 2H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 212.4, 85.5, 55.5, 52.6, 36.6, 31.6, 30.7, 30.2, 26.5, 26.2, 25.3, 22.5, 14.0. 1-{(2-Azaadamantan-2-yl)-oxy}-octan-2-one (**13**) (minor product; only assignable signal given): ^{1}H NMR (700 MHz, $CDCl_3$) δ 4.23 (s, 2H), 3.40 (s, 2H), 2.48 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 210.4, 76.8, 54.4, 39.2, 29.0, 23.3. **12** + **13**: IR (neat, cm^{-1}) 2853, 1716; MS *m*/*z* 279 (M^+), 152 (100%); HRMS (EI) calcd for $C_{17}H_{29}NO_2$, 279.2198; found, 279.2200.

Synthesis of Oxa-AZADO (6) (Scheme 3). *N-p-Toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one (**14**).* To a solution of acetonedicarboxylic acid (8.00 g, 54.8 mmol) in H_2O (200 mL) was added over 15 min 28% NH_3 (H_2O solution, 19 mL, 274 mmol) at 0 °C. Glutaraldehyde (50% H_2O solution, 10 mL, 55.3 mmol) was added slowly (1 drop/4−5 s) to the mixture at the same temperature. After stirring for 24 h at room temperature, the mixture was freeze-dried to remove H_2O. The resulting orange solid was used in the next reaction without further purification. To a suspension of the orange solid and Na_2CO_3 (19.0 g, 178 mmol) in CH_2Cl_2 (31 mL)−H_2O (62 mL) was added dropwise a solution of TsCl (12.5 g, 65.8 mmol) in CH_2Cl_2 (31 mL) at 0 °C. The reaction mixture was stirred for 4 h at room temperature. The mixture was diluted with H_2O (100 mL). After the separation of the organic layer, the aqueous layer was extracted with AcOEt (2×). The organic extracts were combined, dried over $MgSO_4$, and evaporated. The residue was purified with column chromatography (AcOEt−hexane = 1:4) to afford *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one (**14**) (5.80 g, 19.8 mmol, 36% for two steps) as a colorless solid. **14**: colorless crystals; mp 139 °C ($CHCl_3$−hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.50 (s, 2H), 2.71 (dd, *J* = 17.2, 6.8 Hz, 2H), 2.43 (s, 3H), 2.35 (d, *J* = 16.8 Hz, 2H), 1.79−1.46 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 143.6, 137.8, 129.8, 126.9, 49.6, 45.4, 30.4, 21.5, 15.8; IR (neat, cm^{-1}) 1707, 1351, 1161, 1090; MS *m*/*z* 293 (M^+), 138 (100%); HRMS (EI) calcd for $C_{15}H_{19}NO_3S$, 293.1086; found, 293.1068.

*N-p-Toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-ol (**15**).* To a suspension of $LiAlH_4$ (194 mg, 5.12 mmol) in THF (25 mL) was slowly added *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one (**14**) (1.00 g, 3.41 mmol) at 0 °C. After stirring for 3 h at room temperature, the mixture was quenched with AcOEt and saturated

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aqueous potassium sodium tartrate was added. The biphasic solution was stirred vigorously at room temperature for 30 min. The mixture was extracted with AcOEt (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with column chromatography (AcOEt−hexane = 1:2) to afford *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-ol (**15**) (719 mg, 2.44 mmol, 71%) as colorless crystals. **15**: mp 99−100 °C ($CHCl_3$−hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.6 Hz, 2H), 4.25 (m, 2H), 3.72 (m, 1H), 2.42 (s, 3H), 2.36 (m, 2H), 2.13 (qt, J = 13.6, 4.8 Hz, 1H), 1.62−1.31 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 138.9, 129.6, 126.7, 63.6, 47.1, 34.6, 30.3, 21.4, 13.7; IR (neat, cm^{-1}) 3510, 1335, 1312, 1162; MS m/z 295 (M^+), 140 (100%); HRMS (EI) calcd for $C_{15}H_{21}NO_3S$, 295.1242; found, 295.1233.

*N-p-Toluenesulfonyl-6-oxa-2-azaadamantane (**16**).* To a suspension of *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-ol (**15**) (560 mg, 1.90 mmol) and I_2 (723 mg, 2.85 mmol) in cyclohexane (14 mL) was added $PhI(OAc)_2$ (950 mg, 2.95 mmol) at room temperature. After stirring with irradiation (light source: 100 V, 100 W filament lamp) for 1 h at 0 °C, the mixture was quenched with sat $NaHCO_3$ (aq) and 20% $Na_2S_2O_3$ (aq) and extracted with Et_2O (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 1:4) to afford *N*-*p*-toluenesulfonyl-6-oxa-2-azaadamantane (**16**) (389 mg, 1.33 mmol, 70%) as colorless crystals and to recover *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one (**14**) (47.5 mg, 160 μmol, 8.5%) as a colorless solid. **16**: mp 152−153 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.30 (s, 2H), 4.10 (s, 2H), 2.42 (s, 3H), 1.98 (d, J = 12.6 Hz, 4H), 1.75 (d, J = 12.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 138.3, 129.7, 127.0, 66.3, 47.2, 33.9, 21.5; IR (neat, cm^{-1}) 1345, 1165; MS m/z 293 (M^+), 293 (100%); HRMS (EI) calcd for $C_{15}H_{19}NO_3S$, 293.1086; found, 293.1083.

*2-Aza-6-oxaadamantane N-Oxyl (Oxa-AZADO, **6**).* To a solution of *N*-*p*-toluenesulfonyl-2-aza-6-oxaadamantane (**16**) (200 mg, 682 μmol) in toluene (1.5 mL) was added dropwise sodium bis(2-methoxyethoxy)aluminum hydride (red-Al, 70% toluene solution, 950 μL, 3.41 mmol) at 0 °C. The mixture was refluxed for 1.5 h. After being cooled to room temperature, the mixture was diluted with Et_2O and quenched with H_2O. The mixture was filtered through Celite. The filtrate was acidified with 10% HCl (aq) and washed with Et_2O (1×). The aqueous layer was basified with 10% NaOH (aq) and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was used in the next reaction without further purification. $Na_2WO_4{\cdot}2H_2O$ (112 mg, 341 μmol) was added to a solution of the residue in MeCN (3.4 mL) at ambient temperature. The mixture was stirred at the same temperature for 20 min. UHP (256 mg, 2.73 mmol) was added to the solution at room temperature. After stirring for 2 h at the same temperature, the mixture was diluted with sat $NaHCO_3$ (aq) and extracted with $CHCl_3$ (3×). The organic layer was dried over K_2CO_3 and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 1:1) to afford 2-aza-6-oxaadamantane *N*-oxyl (oxa-AZADO, **6**) (52.4 mg, 337 μmol, 50% for two steps) as a yellow solid. **6**: mp 115−116 °C (dec); 70 °C (hexane, color changed from yellow to red); IR (neat, cm^{-1}) 1442, 1338, 1284, 1057; MS m/z 154 (M^+), 154 (100%); HRMS (EI) calcd for $C_8H_{12}NO_2$, 154.0868; found, 154.0858; Anal. calcd for $C_8H_{12}NO_2$: C, 62.32; H, 7.84; N, 9.08; found: C, 62.14; H, 7.83; N, 8.96.

Syntheses of TsN-AZADO (7) and DiAZADO (8) (Scheme 4). *N-p-Toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one Oxime (**17**).* To a solution of *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one (**14**) (15.0 g, 51.2 mmol) and pyridine (17 mL, 205 mmol) in EtOH (85 mL) was added $NH_2OH{\cdot}HCl$ (11.0 g, 154 mmol) at ambient temperature. The mixture was stirred at 60 °C for 10 h. After being cooled to room temperature, EtOH was removed under reduced pressure. H_2O was added to the residue, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with column chromatography (AcOEt−hexane = 1:1) to afford *N*-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]nonan-3-one oxime (**17**) (15.5 g, 50.3 mmol, 98%) as a colorless solid. **17**: colorless crystals; mp 149−150 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (br s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.32 (s, 2H), 3.15 (d, J = 16.6 Hz, 1H), 2.58 (dd, J = 15.6, 6.4 Hz, 1H), 2.41 (s, 3H), 2.35 (d, J = 15.6 Hz, 1H), 2.21 (dd, J = 16.6, 6.4 Hz, 1H), 2.00 (s, 1H), 1.84−1.58 (m, 4H), 1.47−1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 143.3, 138.3, 129.8, 126.9, 48.8, 48.0, 35.2, 30.9, 30.0, 28.6, 21.4, 16.4; IR (neat, cm^{-1}) 3242, 1350, 1162; MS m/z 308 (M^+), 291 (100%); HRMS (EI) calcd for $C_{15}H_{20}N_2O_3S$, 308.1195; found: 308.1183.

*N-[N′-p-Toluenesulfonyl-9-azabicyclo[3.3.1]non-3-yl]-p-toluenesulfonamide (**18**).* To a solution of *N*-*p*-toluenesulfonyl-9-azabicyclo-[3.3.1]nonan-3-one oxime (**17**) (1.00 g, 3.25 mmol) in MeOH (16 mL) was added MoO_3 (792 mg, 4.88 mmol) at room temperature. The mixture was stirred at room temperature for 30 min. $NaBH_4$ (369 mg, 9.75 mmol) was added portionwise to the mixture at 0 °C. The mixture was stirred until the oxime was no longer detected (ca. 1 h). Then, TsCl (3.11 g, 16.3 mmol) was added to the mixture at 0 °C. After stirring for 1 h at the same temperature, the mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was diluted with H_2O and then extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with column chromatography (AcOEt−hexane = 1:1) to afford *N*-[*N*′-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]non-3-yl]-*p*-toluenesulfonamide (**18**) (1.18 g, 2.63 mmol, 81%) as colorless crystals: mp 146 °C (AcOEt−hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.29 (d, J = 8.4 Hz, 1H), 4.19 (s, 1H), 4.16 (s, 1H), 3.04 (m, 1H), 2.44 (s, 6H), 2.15 (td, J = 12.0, 6.4 Hz, 2H), 1.82 (m, 1H), 1.51−1.42 (m, 3H), 1.30 (d, J = 14.0 Hz, 2H), 1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 143.0, 138.7, 137.9, 129.8, 129.7, 126.9, 126.7, 46.9, 46.0, 33.0, 30.4, 21.53, 21.51, 13.4; IR (neat, cm^{-1}) 3279, 1331, 1162; MS m/z 448 (M^+), 293 (100%); HRMS (EI) calcd for $C_{22}H_{28}N_2O_4S_2$, 448.1490; found, 448.1494.

*N,N′-Di-p-toluenesulfonyl-2,6-diazaadamantane (**19**).* To a solution of *N*-[*N*′-*p*-toluenesulfonyl-9-azabicyclo[3.3.1]non-3-yl]-*p*-toluenesulfonamide (**18**) (1.00 g, 2.23 mmol) and I_2 (284 mg, 1.12 mmol) in 1,2-dichloromethane (15 mL) was added $PhI(OAc)_2$ (1.08 g, 3.35 mmol) at room temperature. After stirring with irradiation (light source: 100 V, 100 W filament lamp) for 3 min at 0 °C, the mixture was quenched with sat $NaHCO_3$ (aq) and 20% $Na_2S_2O_3$ (aq) and extracted with AcOEt (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was recrystallized from CH_2Cl_2-MeOH (1:1) to give *N*,*N*′-di-*p*-toluenesulfonyl-2,6-diazaadamantane (**19**) (630 mg, 1.41 mmol, 63%) as colorless needles. **19**: mp 248 °C (CH_2Cl_2−MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 4H), 7.27 (d, J = 8.4 Hz, 4H), 4.20 (s, 4H), 2.41 (s, 6H), 1.74 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.0, 129.8, 126.9, 47.0, 33.0, 21.5; IR (neat, cm^{-1}) 1341, 1166; MS m/z 446 (M^+), 446 (100%); HRMS (EI) calcd for $C_{22}H_{26}N_2O_4S_2$, 446.1334; found, 446.1320.

*N-p-Toluenesulfonyl-2,6-diazaadamantane N′-Oxyl (TsN-AZADO, **7**), 2,6-Diazaadamantane N,N′-Dioxyl (DiAZADO, **8**).* To a solution of *N*,*N*′-di-*p*-toluenesulfonyl-2,6-diazaadamantane (**19**) (2.00 g, 4.48 mmol) in toluene (10 mL) was added sodium bis(2-methoxyethoxy)aluminum hydride (red-Al, 70% toluene solution, 10 mL, 35.9 mmol) dropwise at 0 °C. The mixture was refluxed for 1 h. After being cooled to room temperature, the mixture was diluted with Et_2O and quenched with H_2O. The mixture was filtered through Celite. The filtrate was acidified with 10% HCl (aq) and washed with Et_2O (1×). The aqueous layer was basified with 10% NaOH (aq) and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was used in the next reaction without further purification. $Na_2WO_4{\cdot}2H_2O$ (739 mg, 2.24 mmol) was added to a solution of the residue in MeCN (22 mL) at room temperature. The suspension was stirred at the same temperature for 30 min. UHP (3.36 g, 35.8 mmol) was added to the suspension at room temperature. The mixture was stirred for 4 h at the same temperature. Additional UHP (842 mg, 8.96 mmol) was added to the solution at room temperature. After stirring for another 1.5 h at the same temperature, the mixture

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was diluted with sat $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was purified with column chromatography (CHROMATOREX-NH, $CHCl_3$−hexane = 2:3) to afford *N*-*p*-toluenesulfonyl-2,6-diazaadamanatne *N*′-oxyl (TsN-AZADO (**7**), 223 mg, 726 μmol, 16% for two steps) as a pale-yellow solid and 2,6-diazaadamantane-*N*,*N*′-dioxyl (DiAZADO, **8**) (79 mg, 470 μmol, 10% for two steps) as a yellow solid. TsN-AZADO (**7**): pale-yellow crystals; mp 173 °C ($CHCl_3$−hexane); IR (neat, cm^{-1}) 1343, 1161, 686; MS *m*/*z* 307 (M^+, 100%); HRMS (EI) calcd for $C_{15}H_{19}N_2O_3S$, 307.1116; found, 307.1098; Anal. calcd for $C_{15}H_{19}N_2O_3S$: C, 58.61; H, 6.23; N, 9.11; found, C, 58.61; H, 6.23; N, 8.91. DiAZADO (**8**): yellow needles; mp 243−245 °C (dec, $CHCl_3$); IR (neat, cm^{-1}) 1425, 1143; MS *m*/*z* 168 (M^+), 168 (100%); HRMS (EI) calcd for $C_8H_{12}N_2O_2$, 168.0899; found, 168.0891; Anal. calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66; found: C, 56.86; H, 7.13; N, 16.52.

*More Efficient Procedure for the Synthesis of DiAZADO (**8**) (Scheme 5).* To a solution of *N*,*N*′-di-*p*-toluenesulfonyl-2,6-diazaadamantane (**19**) (1.00 g, 2.24 mmol) in toluene (5.0 mL) was dropwise added sodium bis(2-methoxyethoxy)aluminum hydride (red-Al, 70% toluene solution, 6.2 mL, 22.4 mmol) at 0 °C. The mixture was refluxed for 18 h. After being cooled to room temperature, the mixture was diluted with Et_2O and quenched with H_2O. The mixture was filtered through Celite. The filtrate was acidified with 10% HCl (aq) and washed with Et_2O (1×). The aqueous layer was basified with 10% NaOH (aq) and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was used in the next reaction without further purification. $Na_2WO_4{\cdot}2H_2O$ (369 mg, 1.12 mmol) was added to a solution of the residue in MeCN (11 mL) at room temperature. The mixture was stirred at the same temperature for 30 min. UHP (1.69 g, 17.9 mmol) was added to the solution at room temperature. The mixture was stirred for 2 h at the same temperature. Additional UHP (422 mg, 4.48 mmol) was added to the solution at room temperature. After stirring for another 1 h at the same temperature, the mixture was diluted with sat $NaHCO_3$ (aq) and extracted with $CHCl_3$. The organic layer was dried over K_2CO_3 and evaporated. The residue was recrystallized from $CHCl_3$ to give 2,6-diazaadamantane *N*,*N*′-dioxyl (DiAZADO, **8**) (146 mg, 869 μmol, 39% for two steps) as a bright-yellow needles. The mother liquor was purified with column chromatography (CHROMATOREX-NH, $CHCl_3$−hexane = 2:3) to afford DiAZADO (**8**) (19 mg, 113 μmol, 5.0% for two steps) as a yellow solid.

Selected Examples for the Scope of Oxa-AZADO (6), TsN-AZADO (7), and DiAZADO (8) (Table 1). *Substrates.* *l*-Menthol (**9a**), 4-phenyl-2-butanol (**10a**), 2-octanol (**11a**), 4-methoxy benzylalcohol (**20a**), (−)-borneol (**21a**), 2,2-dimethyl-1-phenyl-1-propanol (**23a**), 2,2-dimethyl-3-octanol (**24a**), 4-phenyl-1-butanol (**25a**), and cinnamyl alcohol (**26a**) were purchased from commercial suppliers. 2-Phenyl-1-cyclohexanol (**22a**),[26] *trans*-2-benzoyloxy-1-cyclohexanol (**27a**),[27] *N*-carbobenzoxy-4-amino-1-cyclohexanol (**28a**),[28] 1,2:3,4-di-*O*-isoproliridene-D-fructopyranose (**29a**),[29] 5-*O*-*tert*-butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**30a**),[30] 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-adenosine (**31a**),[31] and *N*-carbobenzoxy-prolinol (**32a**)[32] were prepared according to the literature.

*Entry 1: 4-Methoxybenzyl Alcohol (**20a**) Using Oxa-AZADO (**6**).* To a solution of 4-methoxybenzyl alcohol (**20a**) (181 mg, 1.31 mmol) and oxa-AZADO (**6**) (2.02 mg, 13.1 μmol) in AcOH (1.3 mL) was added $NaNO_2$ (9.04 mg, 0.131 mmol) at ambient temperature. After stirring for 3 h at the same temperature under an air atmosphere (balloon), the reaction mixture was diluted with Et_2O and quenched with sat $NaHCO_3$ (aq) and 20% $Na_2S_2O_3$ aq. The mixture was extracted with Et_2O (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with flash column chromatography (Et_2O−hexane = 1:4) to afford 4-methoxybenzaldehyde (**20b**) (169 mg, 1.24 mmol, 93%) as a light-yellow oil.

*Entry 9: N-Carbobenzoxy-trans-4-aminocyclohexanol (**28a**) Using TsN-AZADO (**7**).* To a solution of *N*-Cbz-*trans*-4-aminocyclohexanol **28a** (43.4 mg, 174 μmol) and TsN-AZADO **7** (1.60 mg, 5.21 μmol) in AcOH (435 μL) was added $NaNO_2$ (1.20 mg, 17.4 μmol) at ambient temperature. After stirring for 2.5 h at the same temperature under an air atmosphere (balloon), the reaction mixture was diluted with AcOEt and quenched with sat $NaHCO_3$ (aq) and 20% $Na_2S_2O_3$ aq. The mixture was extracted with AcOEt (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 2:3) to afford *N*-carbobenzoxy-4-aminocyclohexanone (**28b**) (42.0 mg, 170 μmol, 98%) as a colorless solid.

*Entry 13: N-Carbobenzoxy-l-prolinol (**32a**) Using DiAZADO (**8**).* $NaNO_2$ (6.63 mg, 96.1 μmol) at ambient temperature was added to a solution of *N*-carbobenzoxy-*l*-prolinol (**32a**) (>99% ee) (226 mg, 0.961 mmol), AcOH (110 μL, 1.92 mmol), and DiAZADO (**8**) (1.62 mg, 9.61 μmol) in MeCN (961 μL). After stirring for 3.5 h at the same temperature under an air atmosphere, the mixture was diluted with AcOEt and quenched with sat $NaHCO_3$ and 20% $Na_2S_2O_3$. The mixture was extracted with AcOEt (3×). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified with flash column chromatography (AcOEt−hexane = 1:3) to afford *N*-carbobenzoxy-*l*-prolinal (**32b**) (>99% ee, 166 mg, 0.712 mmol, 74%) as a colorless oil. Enantiomeric excess was determined by HPLC with CHIRALPAK AD-H (5% iPrOH in hexane; flow rate, 0.5 mL/min).

*Entry 1: 4-Methoxybezaldehyde (**20b**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 164.6, 131.9, 129.9, 114.2, 55.5; IR (neat, cm^{-1}) 1683; MS *m*/*z* 136 (M^+), 135 (100%); HRMS (EI) calcd for $C_8H_8O_2$, 136.0524; found, 136.0518.

*Entry 2: (−)-Camphor (**21b**).* Colorless solid; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (dt, *J* = 18.4, 3.6 Hz, 1H), 2.09 (t, *J* = 4.4 Hz, 1H), 1.99−1.92 (m, 1H), 1.84 (d, *J* = 18.4 Hz, 1H), 1.72−1.65 (m, 1H), 1.44−1.31 (m, 2H), 0.96 (s, 3H), 0.91 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.5, 57.7, 46.8, 43.3, 43.1, 29.9, 27.0, 19.8, 19.1, 9.2; IR (neat, cm^{-1}) 1739; MS *m*/*z* 152 (M^+), 149 (100%); HRMS (EI) calcd for $C_{10}H_{16}O$, 152.1201; found, 152.1189.

*Entry 3: 2-Phenylcyclohexan-1-one (**22b**).* Colorless solid; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.13 (m, 5H), 3.62 (dd, *J* = 12.2, 5.4 Hz, 1H), 2.56−2.42 (m, 2H), 2.31−2.25 (m, 1H), 2.18−2.13 (m, 1H), 2.09−1.97 (m, 2H), 1.86−1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 138.7, 128.5, 128.3, 126.8, 57.3, 42.1, 35.0, 27.7, 25.2; IR (neat, cm^{-1}) 1698; MS *m*/*z* 174 (M^+), 174 (100%); HRMS (EI) calcd for $C_{12}H_{14}O$, 174.1045; found, 174.1033.

*Entry 4: 2,2-Dimethyl-1-phenylpropan-1-one (**23b**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.47−7.37 (m, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 138.6, 130.7, 128.0, 127.7, 44.1, 27.9; IR (neat, cm^{-1}) 1676; MS *m*/*z* 162 (M^+), 105 (100%); HRMS (EI) calcd for $C_{11}H_{14}O$, 162.1045; found, 162.1057.

*Entry 5: 2,2-Dimethyloctan-3-one (**24b**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, *J* = 7.2 Hz, 2H), 1.55 (m, 2H), 1.34−1.21 (m, 4H), 1.13 (s, 9H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 44.1, 36.4, 31.5, 26.4, 23.6, 22.5, 13.9; IR (neat, cm^{-1}) 1706; MS *m*/*z* 156 (M^+), 99 (100%); HRMS (EI) calcd for $C_{10}H_{20}O$, 156.1514; found, 156.1510.

*Entry 6: 4-Phenylbutanal (**25b**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 1.6 Hz, 1H), 7.31−7.16 (m, 2H), 7.22−7.17 (m, 3H), 2.66 (t, *J* = 7.4 Hz, 2H) 2.45 (t, *J* = 7.4 Hz, 2H), 1.96 (quint, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 141.2, 128.4, 126.0, 43.0, 34.9, 23.6; IR (neat, cm^{-1}) 1723; MS *m*/*z* 148 (M^+), 104 (100%); HRMS (EI) calcd for $C_{10}H_{12}O$, 148.0888; found, 148.0880.

*Entry 7: trans-Cinnamaldehyde (**26b**).* Yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 8.0 Hz, 1H), 7.58−7.56 (m, 2H), 7.49 (d, *J* = 16.4 Hz, 1H), 7.45−7.42 (m, 3H), 6.73 (dd, *J* = 16.4, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 152.6, 134.0, 131.2, 129.0, 128.5, 128.4; IR (neat, cm^{-1}) 1675; MS *m*/*z* 132 (M^+), 131 (100%); HRMS (EI) calcd for C_9H_8O, 132.0575; found, 132.0564.

*Entry 8: 2-Benzoyloxycyclohexan-1-one (**27b**).* Colorless solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 5.41 (dd, *J* = 11.8, 6.4 Hz, 1H), 2.57 (d, *J* = 11.8 Hz, 1H), 2.51−2.43 (m, 2H), 2.14−1.89 (m, 4H), 1.86−

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1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 165.5, 133.1, 129.8, 129.7, 128.3, 76.9, 40.7, 33.2, 27.2, 23.7; IR (neat, cm^{-1}) 1731, 1708; MS m/z 218 (M^+), 105 (100%); HRMS (EI) calcd for $C_{13}H_{14}O_3$, 218.0943; found, 218.0949.

*Entry 9: N-Carbobenzoxy-4-aminocyclohexan-1-one (**28b**).* Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 5.11 (s, 2H), 4.78 (s, 1H), 4.00 (br s, 1H), 2.42 (s, 4H), 2.24 (s, 2H), 1.75−1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 155.6, 136.3, 128.5, 128.2, 128.1, 66.8, 47.9, 38.8, 32.1; IR (neat, cm^{-1}) 1717, 1685, 1532. HRMS (ESI) calcd for $C_{14}H_{17}NO_3Na$ ([M + Na]$^+$), 247.1208; found, 247.1172.

*Entry 10: 1,2:4,5-Di-O-isopropylidene-β-D-erythro-2,3-hexodiulo-2,6-pyranose (**29b**).* Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (d, J = 5.8 Hz, 1H), 4.61 (d, J = 9.2 Hz, 1H), 4.55 (dd, J = 5.8, 2.0 Hz, 1H), 4.40 (dd, J = 13.6, 2.0 Hz, 1H), 4.12 (d, J = 13.6 Hz, 1H), 3.99 (d, J = 9.2 Hz, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 113.7, 110.5, 104.1, 77.8, 75.8, 69.9, 60.0, 27.1, 26.4, 26.0, 25.9; IR (neat, cm^{-1}) 1749; MS m/z 259 ([M + H]$^+$), 114 (100%); HRMS (EI) calcd for $C_{12}H_{19}O_6$, 259.1182; found, 259.1195.

*Entry 11: 5-O-tert-Butyldimethylsilyl-1,2-O-isopropylidene-α-D-erythro-3-pentulofuranose (**30b**).* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, J = 4.4 Hz, 1H), 4.35 (s, 1H), 4.27 (d, J = 4.4 Hz, 1H), 3.88 (dd, J = 11.2, 2.0 Hz, 1H), 3.81 (dd, J = 11.2, 2.0 Hz, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 0.86 (s, 9H) 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 114.1, 103.8, 81.7, 77.1, 63.9, 27.7, 27.2, 25.8, 18.1, −5.5, −5.7; IR (neat, cm^{-1}) 1776; MS m/z 245 ([M − tBu]$^+$), 245 (100%); HRMS (EI) calcd for $C_{10}H_{17}O_5Si$, 245.0845; found, 245.0849.

*Entry 12: 9-[2′,5′-Bis-O-(tert-butyldimethylsilyl)-β-D-erythro-pentofuranos-3′-ulosyl]-adenine (**31b**).* Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.15 (s, 1H), 6.15 (d, J = 8.0 Hz, 1H), 5.84 (s, 2H), 4.95 (d, J = 8.0 Hz, 1H), 4.31 (s, 1H), 3.98 (s, 2H), 0.93 (s, 9H), 0.73 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), −0.01 (s, 3H), −0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 155.6, 153.4, 150.4, 138.5, 119.7, 85.0, 82.4, 77.8, 62.4, 25.8, 25.2, 18.2, 18.0, −4.9, −5.5, −5.6, −5.8; IR (neat, cm^{-1}) 1787, 1647, 1595, 1577; MS m/z 436 ([M − tBu]$^+$), 301 (100%); HRMS (EI) calcd for $C_{18}H_{30}N_5O_4Si_2$, 436.1836; found, 436.1816

*Entry 13: N-Carbobenzoxy-l-prolinal (**32b**).* Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 0.5H), 9.49 (d, J = 2.4 Hz, 0.5H), 7.38−7.28 (m, 5H), 5.21−5.13 (m, 2H), 4.30 (t, 0.5 H, J = 5.8 Hz), 4.20 (t, 0.5 H, J = 5.8 Hz), 3.62−3.50 (m, 2H), 2.17−1.99 (m, 2H), 1.95−1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 155.4, 154.5, 136.5, 136.3, 128.5, 128.1, 128.0, 67.33, 67.29, 65.3, 64.9, 47.3, 46.7, 27.9, 26.6, 24.5, 23.8; IR (neat, cm^{-1}) 1734, 1699, 1415, 1356; MS m/z 204 ([M − CHO]$^+$), 91 (100%); HRMS calcd $C_{12}H_{14}NO_2$, 204.1025; found, 204.1033.

■ ASSOCIATED CONTENT

Supporting Information

Kinetic profile of the ABNO-catalyzed oxidation, raw data of figures, electrochemical measurement results, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: y-iwabuchi@m.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

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(19) Although we attempted to remove H_2O from the reaction mixture by adding MS4A or $MgSO_4$, no positive effect on the

conversion of AZADO-catalyzed oxidation was observed, most likely because of the hydrophilicity of acetic acid.
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