Review

Discovery and Exploitation of AZADO: The Highly Active Catalyst for Alcohol Oxidation

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The oxidation of primary and secondary alcohols to the corresponding aldehydes (or carboxylic acids) or ketones is a fundamental transformation in organic synthesis. Stable organic nitroxyl radicals as represented by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (1) have been used extensively to catalyze the oxidation of a number of alcohol substrates employing environmentally benign co-oxidants such as bleach (NaOCl) or $PhI(OAc)_2$. Although TEMPO oxidation is better known as a method for selective oxidation of primary alcohols to the corresponding aldehydes, the TEMPO-based method is not very efficient for the oxidation of structurally hindered secondary alcohols. We designed and synthesized 2-azaadamantane *N*-oxyl [AZADO (11)] and 1-Me-AZADO (20), a structurally less hindered class of nitroxyl radical. AZADOs were found to exhibit excellent catalytic activity enabling oxidation of a variety of alcohols with which TEMPO exhibits poor reactivity. Based on structure–activity relationships (SAR) employing AZADO (11), 1-Me-AZADO (20), 1,3-dimethyl-AZADO (33), 9-azabicyclo[3.3.1]nonane-*N*-oxyl [ABNO (34)] and 9-azanoradamantane *N*-oxyl [Nor-AZADO (37)], we concluded that the *α*-methyl group flanked nearby the nitroxyl group affects the reactivity for the oxidation of sterically hindered alcohols and the azaadamantane skeleton contributes to the high turnover of the catalyst. The highly active nature of AZADOs spurred us to exploit their further use in alcohol oxidations. A facile, green, one-pot oxidation of primary alcohols to carboxylic acids with broad substrate applicability has been developed by employing an expedient catalytic system consisting of the oxoammonium salt [1-Me-AZADO$^+$X$^-$ (X=Cl, BF_4)]/$NaClO_2$. The synthetic use of AZADOs and the related nitroxyl radicals/oxoammonium salts-based methods for alcohol oxidation have been demonstrated in several total syntheses of natural products. We also describe the development of a Nor-AZADO (37)/DIAD/AcOH method that offers exceptionally mild and highly chemoselective oxidation of alcohols.

Key words organocatalyst; nitroxyl radical; oxoammonium salt; alcohol oxidation; 2-azaadamantane *N*-oxyl

1. Introduction

The oxidation of alcohols to their corresponding carbonyl compounds is a fundamental transformation in organic chemistry,[1,2] leading synthetic chemists to a reliable entry to the fertile realm of carbonyl chemistry.[3] To attain this simple transformation, numerous reagents and methods have been developed so far, which unequivocally represents its prominent roles in organic chemistry: the history of alcohol oxidation should aptly reflect the state-of-the-art of organic synthesis. What about the current status of alcohol oxidation at the beginning decades of the second millennium? Alcohol oxidation still suffers from a substantial issue of chemoselectivtiy; electron-rich groups often compete with alcohols. Another issue arises, particularly in a large-scale oxidation, associated with safety, environmental and economical reasons: toxic, harmful reagents are used; rather harsh conditions are often required, spurring chemists to develop ecologically more sustainable methods.[4–11]

In recent years, a stable class of nitroxyl radicals,[12] as exemplified by 2,2,6,6-tetramethyl piperidinyl 1-oxyl (TEMPO) [(**1**); Chart 1], has extensively been used as a catalyst for oxidation of alcohols, because TEMPO is readily available from chemical suppliers at a reasonable price, and because the method allows the use of various safe bulk oxidants, thereby offering safe and extremely efficient oxidation of alcohols with considerable operational simplicity.[13–25] Today, TEMPO-catalyzed alcohol oxidation has high priority not only in academic laboratories, but also in the chemical industries, particularly in the pharmaceutical industry, as an efficient, mild, and environmentally acceptable method.

We discovered that 2-azaadamantane *N*-oxyl (AZADO) (**11**), a less-hindered class of stable nitroxyl radical, exhibits extraordinarily high catalytic activity and a wider substrate scope in alcohol oxidation compared with TEMPO (**1**). This review describes the discovery and exploitation of synthetic use of AZADO and its derivatives.

2. Discovery of AZADO as an Exceptionally Active Catalyst for Alcohol Oxidation

2.1. The Inception: Encounter with AZADO In ad-

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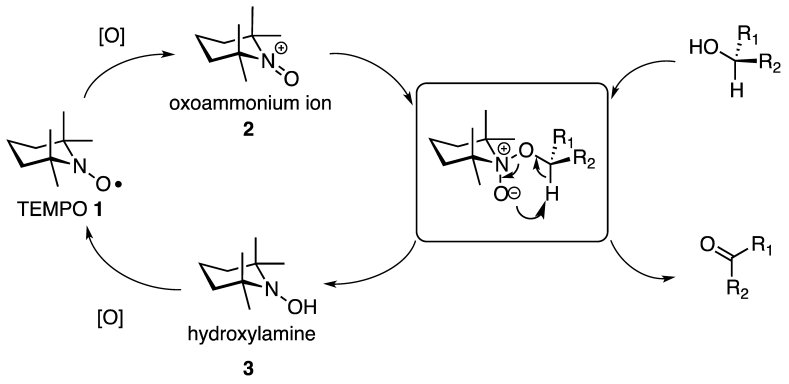

Chart 1. The Proposed Mechanism of TEMPO Oxidation

dition to its fascinating "green" features, TEMPO oxidation is distinguished from other oxidation methods by its ability to conduct the selective oxidation of primary alcohols in the presence of secondary alcohols.[13–16] The rationale behind such a feature is its reaction mechanism and its structure, in which four methyl groups flanking the nearby catalytic center $TEMPO^+$ (oxoammonium ion **2**) play key roles in preventing bulky substrates from forming the key intermediate (Chart 1). (Note: It is known that a nitroxyl radical having α-hydrogens is prone to isomerize to the corresponding nitrone and hydroxylamine *via* disproportionation; the four methyl groups are essential for TEMPO to be stable.[26–28]) As a result, TEMPO is inefficient in the oxidation of structurally hindered secondary alcohols, posing a problem in the oxidation of alcohols. Another weak point indicated for TEMPO oxidation is the less-stable nature of $TEMPO^+$ (**2**) that sometimes suffers from low catalytic efficiency and contamination of the product due to the decomposition of TEMPO[29] (Chart 2).

Such drawbacks of the TEMPO oxidation led us to imagine a "super" nitroxyl radical that can solve these problems and expand the scope of alcohol oxidation. It was a stroke of luck that we witnessed the birth of an elegant synthetic methodology coined "Chiral Modification of Adamantanes"[30] by Professor Kunio Ogasawara, featuring the ring-opening of 1,3-adamantanediol (**4**) to bicyclo[3.3.1]nonane (**5**), the subsequent σ-desymmetrization, and the following ring-closure to give the chirally modified adamantane **8** (Chart 3). This synthetic sequence inspired us to conceive 2-azaadamantane (**10**), and subsequently led to AZADO (**11**) as a possible superior alternative to TEMPO (Charts 3, 4).

AZADO (**11**) was first synthesized in 1975 by Dupeyre and Rassat as a result of their interest in its physical properties as a stable radical.[31,32] (It is important to note that AZADO-type nitroxyl radial is protected by the Bredt rule[33,34] from a destructive disproportionation to give the corresponding nitrone and hydroxylamine.) However, no study has been reported regarding AZADO since then. It was unknown whether AZADO generates the corresponding oxoammonium ion $\mathbf{11}^+$ that functions as an oxidation catalyst or not. Thus, significant challenges had remained to explore the use of AZADOs. We attempted preparation of AZADO (**11**) as described in the literature, but we encountered several problems in terms of reproducibility. First, the diketone **12** turned out to be intractable, giving a mixture with the highly polar hydrate form **13**, and second, complicated procedures for the $NaBH_3CN$-mediated reduction of the *in situ*-generated half-imine **9** hampered reliable production of the azaadamatanol **15**.[35,36] The major product we obtained was the oxaadamantane **14**, and the desired azaadamantanol **15** was secured in only a trace amount (Chart 5).

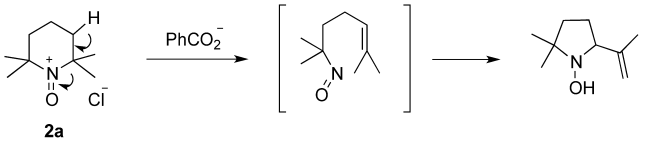

Chart 2. Decomposition of TEMPO-Derived Oxoammonium Salt

One compromise was made to avoid the difficulty in using the diketone **12**: we altered our target to 1-Me-AZADO (**20**),[37] which should be the second best catalyst having the advantage of the "one-methyl" downsized effect over TEMPO (**1**). We envisioned that 1-Me-AZADO (**20**) could be synthesized from the ketone **5** *via* the reductive amination and the subsequent intramolecular halo-amination (Chart 6). After considerable experimentation, we found that Ipaktschi's conditions[38] brought about the desired results; treatment of the oxime **16** with $NaBH_4$ in the presence of a stoichiometric amount of MoO_3 in MeOH at 0°C gave the *endo*-amine **17**

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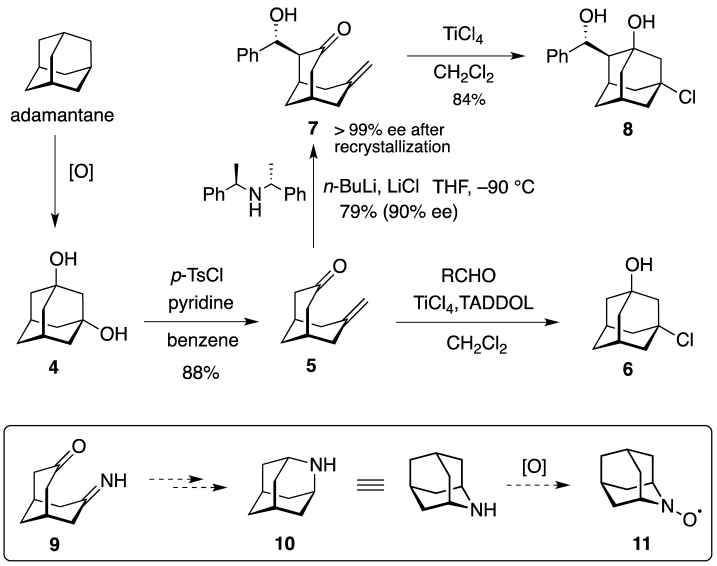


Chart 3. The Chiral Modification of Adamantane and Inspiration

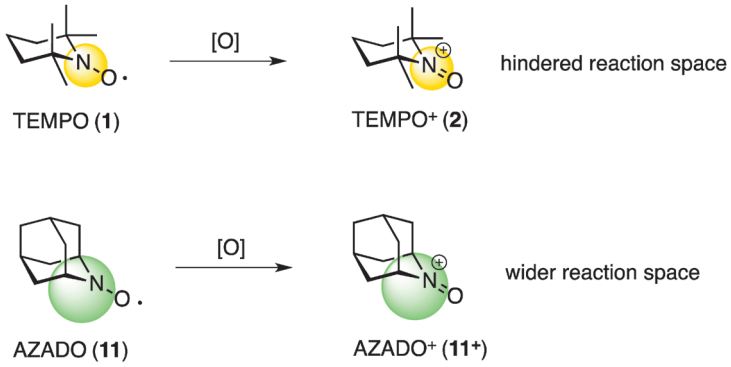


Chart 4. Structure of TEMPO and AZADO

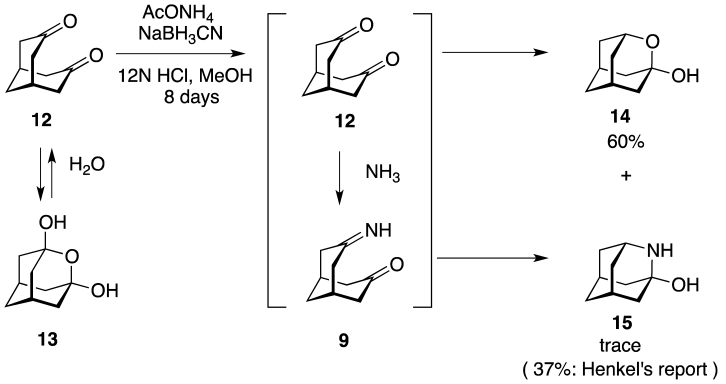


Chart 5. A Problem in Preparation of 2-Azaadamantane

diastereoselectively. The synthesis of 1-Me-AZADO (**20**) was achieved through a three-step sequence consisting of (i) the iodine mediated ring closure to **18**, (ii) subsequent $LiAlH_4$-mediated excision of iodine to give 1-methyl-2-azaadamantane (**19**), and (iii) the oxidation of **19** under conventional conditions (cat. Na_2WO_4, 30% H_2O_2) (Chart 6).

Encouraged by the finding that an oximation and Ipaktschi's reduction sequence affected the reductive amination of bulky ketones, we got back to AZADO with a slight modification of the original route. Prior to the reductive amination, selective mono protection was made on the diketone **12**: upon treatment with ethylene glycol (4 eq) in boiling toluene in the presence of *p*-TsOH, **12** was converted to the monoketone **21** in 94% yield. It is interesting to note that bis-ketalization was not observed, probably due to steric hindrance. The oximation of **21** and the subsequent Ipaktschi reduction of the oximie **22** proceeded nicely to give the corresponding amine, direct addition of Cbz-Cl and Et_3N to which the reaction mixture gave the *endo*-Cbz carbamate **23** in 75% yield. Treatment of **23** with 5% HCl allowed the deprotection of the ketal and the concomitant aminal formation to give the *N*-Cbz-1-hydroxy-2-azaadamantane (**24**). Subsequent deprotection of the Cbz

group afforded the known 1-hydroxy-2-azaadamantane, from which 2-azaadamantane (**10**) was prepared in a straightforward manner, as described by Henkel *et al.*[35,36] (Chart 7).

With 1-Me-AZADO (**20**) and AZADO (**11**) in hand, we carried out comparative evaluations of their catalytic activities with that of TEMPO (**1**) under two popular alcohol oxidation conditions, namely, Anelli's conditions using NaOCl as the bulk oxidant (Table 1) and Margarita's conditions using $PhI(OAc)_2$ as the bulk oxidant (Table 2). It was found that AZADO (**11**) as well as 1-Me-AZADO (**20**) exhibited superior (more than 20-fold higher!) catalytic activities to TEMPO (**1**), which was far beyond our expectation. Intriguingly, **11** and **20** showed *similar* catalytic efficiencies under both oxidation conditions. As shown in Table 3, both AZADO (**11**) and 1-Me-AZADO (**20**) exhibit surprisingly high catalytic efficiency for the oxidation of various secondary alcohols with which TEMPO (**1**) suffers from poor reactivity. It should be stressed 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 (Table 3, entry 6). The mild oxidizing nature of $PhI(OAc)_2$ allowed clean and selective oxidation of the nucleoside derivative to give the corresponding ketone in 95% yield (Table 3, entry 7).[37,39]

2.2. Structure–Activity Relationships (SAR) of AZADOs

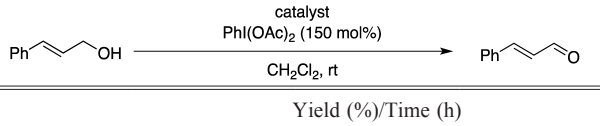
2.2.1. Synthesis of 1,3-Dimethyl-AZADO and Its Catalytic Activity

To gain insight into the origin of the remarkable catalytic efficiency of AZADO-type nitroxyl radicals, we decided to synthesize 1,3-dimethyl-AZADO (**33**) to compare its catalytic efficiency with those of AZADO (**11**) and 1-Me-AZADO (**20**). After considerable experimentation, we developed a synthesis route to 1,3-dimethyl-AZADO (**33**) as shown in Chart 8, in which the most problematic step was the installation of the second methyl group through reductive removal of the hydroxyl group from alcohol **30**. Almost all the conventional methods attempted failed, except for reaction of the iodide **31** with NaI in boiling isopropanol. The use of NaI was not the result of a capricious choice as we unexpectedly ob-

Table 1. Comparison of Catalytic Efficiency under Anelli's Condition

Loading amount (mol%)	Time (min)	Yield (%) 1	20	11
0.1	20	88	95	90
0.01	30	23	91	89
0.003	30	n.d.	81	83
0.001	60	n.d.	62	51

Table 2. Comparison of Catalytic Efficiency under Margarita's Condition



Loading amount (mol%)	Yield (%)/Time (h) 1	20	11
10	95/1.5	95/0.1	94/0.1
1	42/6.0	93/0.7	92/0.5
0.1	n.d.	39/3.0	45/3.0

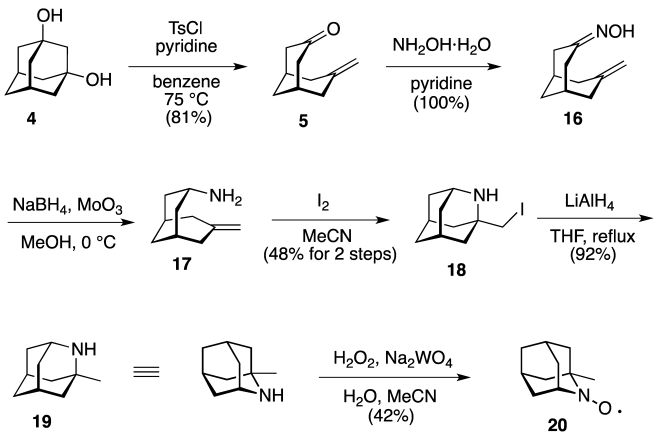


Chart 6. Synthesis of 1-Me-AZADO (**20**)

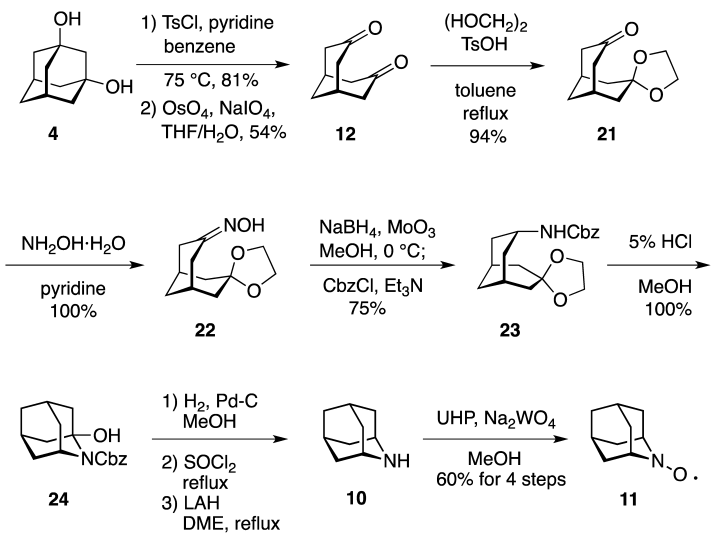


Chart 7. Synthesis of AZADO

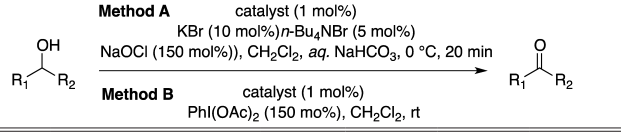
tained a trace amount of *N*-Ts-1,3-dimethyl-2-azaadamantane **32** during the Appel reaction of **30** to obtain **31**, suggesting the reducing potential of an iodide ion.

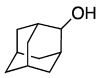
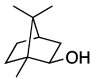
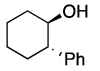
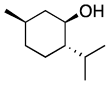
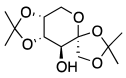
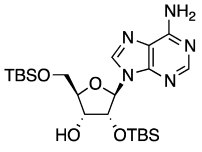
1,3-Dimethyl-AZADO (**33**) exhibited catalytic activity for the oxidation of 3-phenylpropanol that was comparable to those exhibited by AZADO (**11**) and 1-Me-AZADO (**20**). On the other hand, it does not efficiently oxidize *l*-menthol similarly to TEMPO (**1**), showing a remarkable difference from 1-Me-AZADO (**20**) and AZADO (**11**)[37,39] (Table 4).

2.2.2. Critical Comparison of AZADO and 1-Me-AZADO Having observed the huge impact of the "one methyl difference" on the catalytic activities between 1-Me-AZADO (**20**) and 1,3-dimethyl-AZADO (**33**), we became curious about the *similar* catalytic reactivity observed for 1-Me-AZADO (**20**) and AZADO (**11**) (*vide ante*). To understand the difference in catalytic activity between 1-Me-AZADO and AZADO, we set up a quick analytical system using NMR to monitor their performances in the oxidation of the particular alcoholic substrate [1-(adamantan-2-yl)-3-phenylpropan-1-ol] under Anelli's conditions. We surprisingly found that AZADO completed its reaction within a minute (just after addition of the bulk oxidant), while 1-Me-AZADO took ten minutes for the completion, highlighting again the huge impact of the "one methyl difference" (Chart 9). The conventional TLC analysis underestimated the catalytic activity of AZADO. Although the "one methyl difference" between AZADO and 1-Me-AZADO may not be so obvious all the time in standard laboratory-scale oxidation of alcohols, the ultra-high catalytic activity of AZADO will find a role in large-scale alcohol oxidation. On the other hand, 1-Me-AZADO will enjoy its expedient use when a particular stereoselective oxidation is required in a complex molecular system.

2.2.3. Redox Potentials of AZADOs Cyclic voltammetric measurements revealed that AZADO (**11**), 1-Me-AZADO (**20**), and 1,3-diMe-AZADO (**33**) show well-defined redox waves, the forms of which are unchanged after more than 100 measurement cycles, indicating their high durability as oxidation catalysts[37] (Chart 10). The $E^{\circ\prime}$ values of the nitroxyl radicals are in the order of **33** (136 mV)<**20** (186 mV)<**11** (236 mV)<TEMPO (**1**) (294 mV). However, the total efficiencies of the nitroxyl radicals as catalysts are in the order of **1**–**33**≪**20**<**11**. Based on these observations, we concluded

Table 3. Substrate Scope of TEMPO, 1-Me-AZADO and AZADO



Entry	Substrate	Method	Yield (%) 1	20	11
1		A	83	94	98
2		A	0	94	93
3		A	16	99	99
4		A	5	95	94
5		A	13	95	91
6		B	8	99	97
7		B	n.d.	—	95

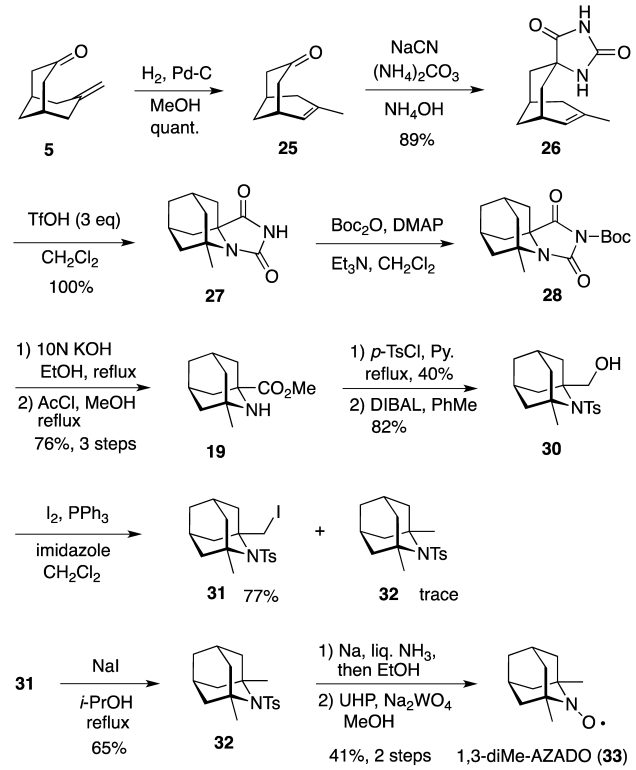
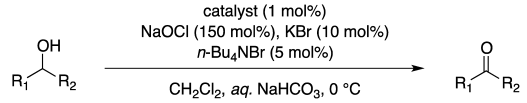
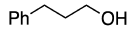
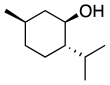


Chart 8. Synthesis of 1,3-Dimethyl-AZADO

Table 4. Comparison of Catalytic Efficiencies of TEMPO and AZADOs



Alcohol	Catalyst 11	20	33	1
	89%	91%	92%	90%
	94%	95%	Trace	Trace

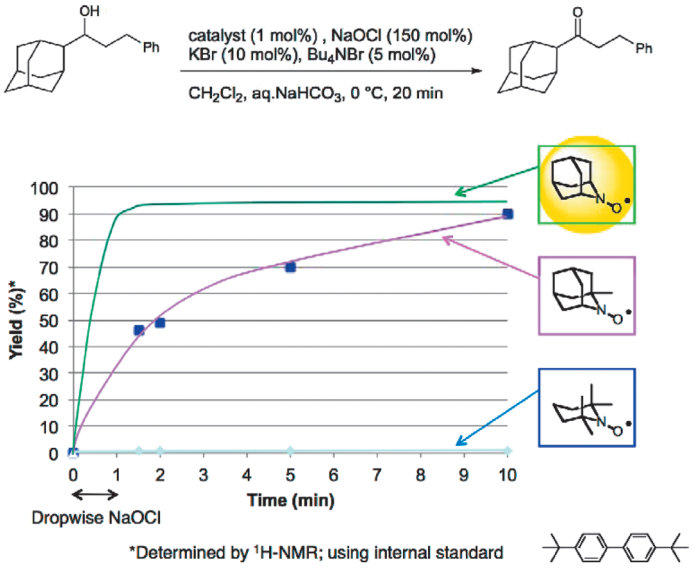
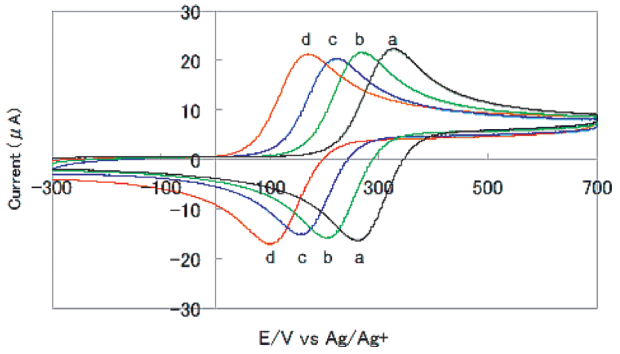


Chart 9. A Critical Comparison of Catalytic Efficiency of AZADO and 1-Me-AZADO



a: TEMPO, b: AZADO, c: 1-Me-AZADO, d: 1,3-diMe-AZADO)

Chart 10. Cyclic Voltammograms of Various Nitroxyl Radicals (2 mM) at a Scan Rate of 50 mV s^{-1}

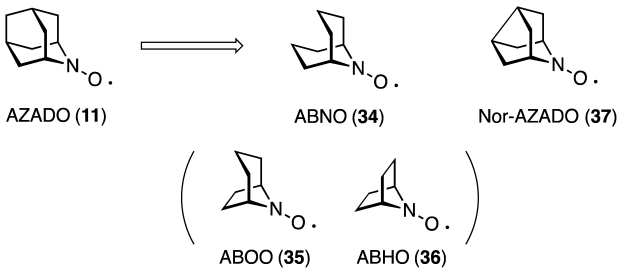


Chart 11

that the highly active catalytic nature of **11** and **20** is due to kinetic factors derived from decreased steric hindrance around the catalytic center.[37]

3. Development of ABNO and 9-Azanoradamantane *N*-oxyl(Nor-AZADO)

Although we have developed gram-scale routes to AZADO (**11**) and 1-Me-AZADO (**20**) starting from commercially available 1,3-adamantanediol (**4**) *via* a 10-step synthesis and a 6-step synthesis, respectively (Charts 6, 7), we inquired into more readily available alternatives to AZADOs for the further development of nitroxyl radical-based methodologies in organic chemistry. As a logical extension, we were interested in bicyclic unhindered nitroxyl radicals, such as 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO, **34**),[40] 8-azabicyclo[3.2.1]octane *N*-oxyl (ABOO, **35**),[40,41] and 7-azabicyclo[2.2.1]heptene *N*-oxyl (ABHO, **36**),[41] from which we chose ABNO in light of knowledge on the stability of bridged-bicyclo *N*-oxyls being in the order of ABNO>ABOO>ABHO. We were also interested in Nor-AZADO (**37**), which is a constraint variant of AZADO (Chart 11).

3.1. Shortest-Step Synthesis of ABNO With our intention to develop a protecting group-free synthesis route to ABNO (**34**), we have established the 3-step synthesis of ABNO as shown in Chart 12.[42] The use of 23% aqueous ammonia, instead of NH_4Cl, in the historical Robinson–Schöpf reaction was the main key to our success, which allowed us to obtain norpseudopelletierine (**40**) as a yellow powder after simple lyophilization of the reaction mixture. The subsequent adoption of the Huang–Minlon modification of the Wolff–Kishner reduction of **40** was the second key, facilitating the distillation of 9-azabicylco[3.3.1]nonane (**41**), together with water, from the reaction mixture. The chloroform extracts of the distillate were dried over K_2CO_3, concentrated, and subjected to conventional oxidation conditions to furnish ABNO in 42% yield after column chromatography (Chart 12).

3.2. Synthesis of Nor-AZADO Nor-AZADO (**37**) was first synthesized by Dupeyre and Rassat in 1978 and reported to be a stable class of nitroxyl radicals.[32] We prepared Nor-AZADO in 5 steps from acetonedicarboxylic acid (**38**), glutaraldehyde (**39**), and benzylamine (**40**), with slight modification of a previous method[43] (Chart 13).

3.3. Catalytic Activities of ABNO and Nor-AZADO The catalytic activities of ABNO (**34**) and Nor-AZADO (**37**) were compared with those of TEMPO (**1**), AZADO (**11**), and 1-Me-AZADO (**20**) under Anelli's conditions using NaOCl as the bulk oxidant (Tables 5, 6). The catalytic activities toward secondary alcohols are shown in Table 5. Although almost the same results were obtained for the oxidation of 4-phenylbutan-2-ol when a 1 mol% catalyst load was used, apparent differences in catalytic efficiency were observed when the catalyst load was decreased. A 0.003 mol% catalyst loading was sufficient to complete the reaction with Nor-AZADO. Nor-

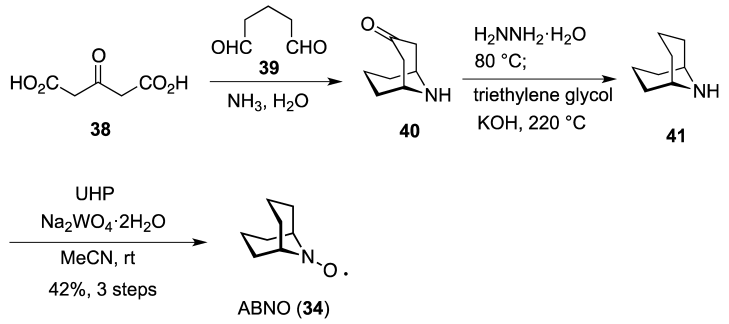


Chart 12. Synthesis of ABNO

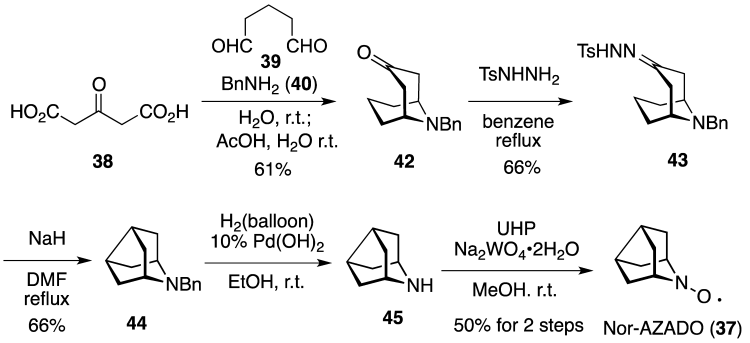
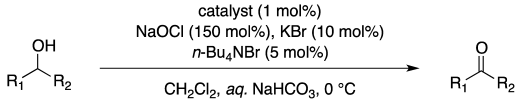


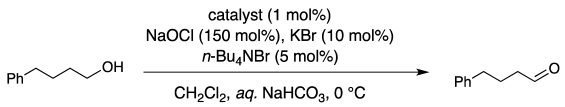
Chart 13. Synthesis of Nor-AZADO

Table 5. Comparison of Catalytic Efficiencies toward Primary Alcohol



Substrate	Loading amount (mol%)	1	20	11	34	37
	1	97%	99%	99%	100%	99%
	0.01	28%	97%	99%	94%	99%
	0.005	n.d.	76%	96%	91%	96%
	0.003	n.d.	67%	74%	24%	92%
	1	5	95%	99%	94%	99%
	0.01	n.d.	61%	98%	95%	98%
	0.005	n.d.	41%	96%	92%	96%
	0.003	n.d.	25%	87%	8%	92%

Table 6. Comparison of Catalytic Efficiencies of TEMPO and AZADOs



Loading amount (mol%)	1	20	11	34	37
1	89%	91%	91%	91%	92%
0.01	19%	89%	88%	83%	89%
0.003	n.d.	79%	82%	59%	82%

AZADO also exhibited efficient catalytic activity in the oxidation of primary alcohol compared with TEMPO, although AZADO and 1-Me-AZADO also worked well in this case[42,43] (Table 6). The operationally facile and scalable features in synthesizing ABNO and Nor-AZADO should make their use applicable in many types of alcohol oxidation.

4. Exploitation of AZADOs: Development of Large-Scale Preparation Methods

In recognition of the excellent catalytic activities of AZADOs, we hope they will be listed in future textbooks as standard reagents for alcohol oxidation. As the first step to this end, we set about to develop improved syntheses of AZADO (**11**) and 1-Me-AZADO (**20**).[39]

4.1. Second Generation Synthesis of 1-Me-AZADO To improve the preparation of 1-Me-AZADO (**20**), we considered the following two points. One is avoiding isolation of the polar amine **17**, which requires tedious handling. The other is the pursuit of redox economy; if direct intramolecular hydroami-

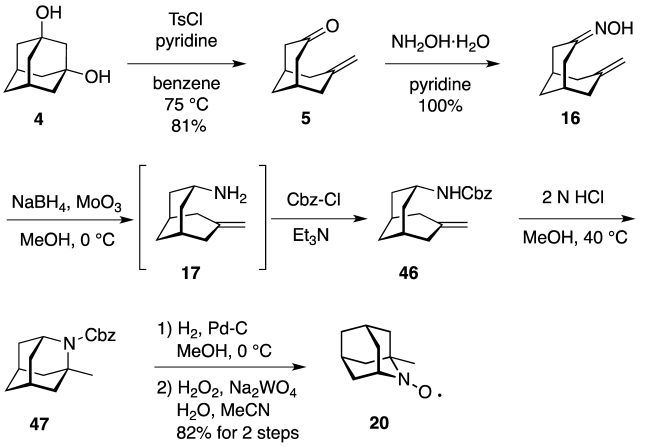


Chart 14. The Second-Generation Synthesis of 1-Me-AZADO

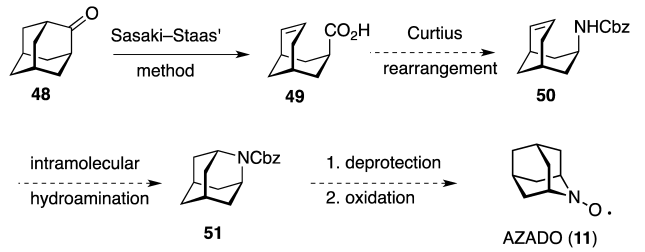


Chart 15. A Blueprint for the Second-Generation Synthesis of AZADO

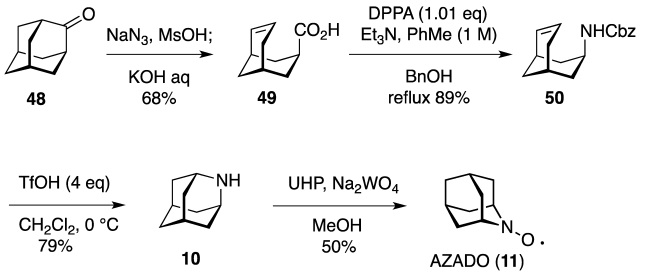


Chart 16. The Second-Generation Synthesis of AZADO

nation is adoptable, instead of iodoamination for ring closure (Chart 6), we would be liberated from extraneous redox sequences.

We commenced with examining the *in situ* protection of the amine **17**. CbzCl was directly added to the mixture just after completion of the Ipaktschi reduction of the oxime **16**. The protection proceeded smoothly, and the Cbz carbamate **46** was isolated in good yield. The projected hydroamination proceeded facilely on treatment of **46** with 2 N HCl at 40°C to give **47** quantitatively. In the final oxidation, urea hydrogen peroxide (UHP) instead of H_2O_2 yielded a better result. In this way, an improved preparation of 1-Me-AZADO was achieved (Chart 14).

4.2. Second Generation Synthesis of AZADO Having achieved the facile hydroamination in the second-generation synthesis of 1-Me-AZADO, we envisaged a short-step synthesis of AZADO (**11**) by applying hydroamination to the intermediate (**50**) (Chart 15).

According to Sasaki and Staas' procedure using HN_3 (Caution! HN_3 is explosive), the carboxylic acid **49** was prepared from the commercially available 2-adamantanone (**48**) in good yield[44,45] (Chart 16). The subsequent Curtius rearrangement

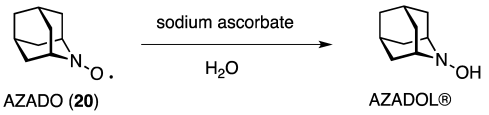


Chart 17. Preparation of AZADOL®

was successively promoted using 1.01 eq of diphenyl phosphoryl azide (DPPA) in 1 M toluene upon heating to reflux with the addition of benzyl alcohol to produce the *N*-Cbz carbamate **50**. However, the attempted hydroamination of **50** by applying 2 N HCl conditions, which successfully induced hydroamination of **46** to give **47**, did not give the azaadamantane **51**. It was found that an anhydrous condition using 4 eq of TfOH achieved the key intramolecular hydroamination, accompanied by the concomitant deprotection of the Cbz group to furnish 2-azaadamantane (**10**) in 79% yield. The subsequent oxidation of the 2-azaadamantane (**10**) with Na_2WO_4 and UHP afforded AZADO (**11**) in 50% yield (Chart 16). The second generation synthesis of AZADO thus developed has currently been applied to kilogram synthesis by Nissan Chemical Co., Ltd., which enabled commercialization of AZADO and AZADOL®[39] (Chart 17).

5. Exploitation of Synthetic Use of AZADOs

5.1. Application of AZADOs to One-Pot Oxidation of Primary Alcohols to Carboxylic Acids 5.1.1. Use of 1-Me-AZADO The oxidation of primary alcohols to the corresponding carboxylic acids is a popular transformation in organic synthesis.[1,2] The straightforward appearance of this transformation, consisting of simple, two-step oxidations (primary alcohol to aldehyde, then aldehyde to carboxylic acid) has encouraged many organic chemists to develop efficient one-pot oxidation methods. To date, a number of useful methods have been developed, *i.e.*, CrO_3/H_2SO_4,[46] PDC/*N*,*N*-dimethylformamide (DMF),[47] CrO_3/H_5IO_6,[48] $RuCl_3/H_5IO_6$,[49] $RuCl_3/K_2S_2O_8$,[50] Na_2WO_4/H_2O_2,[4] and PhIO/KBr.[51,52] Unfortunately, the task often suffers from several drawbacks, such as limited substrate applicability, toxic and hazardous nature of the reagents, and the harsh conditions required.

Regarding the nitroxyl radical/oxoammonium ion-based method, useful extensions have been reported, such as TEMPO/NaOCl,[19] TEMPO/PhI(OAc)$_2$–H_2O,[53] and TEMPO/NaOCl/$NaClO_2$[54] systems. However, further improvement is still required to address issues in terms of chemoselectivity: electron-rich alkenes and aromatic rings are damaged under the reaction conditions. It is assumed that an oxoammonium ion requires an aldehyde to form the corresponding hydrate prior to oxidation, where the less-hindered 1-Me-AZADO$^+$ (**20**$^+$) would exhibit superior activity to TEMPO. The chemoselectivity should be improved by alleviating substrates from the oxidative stress (Chart 18).

Preliminary experiments employing the conditions developed by Anelli *et al.* revealed the superiority of 1-Me-AZADO (**20**) to TEMPO (**1**), although substrates that did not readily form the corresponding hydrate gave disappointing results[55] (Table 7). As shown in Table 8, 1-Me-AZADO gave better use of PhI(OAc)$_2$/H_2O than TEMPO, showing improved chemoselectivity.

5.2. Oxoammonium Salt/$NaClO_2$ Method During our preliminary investigation, we were encouraged by Merck's method using cat. TEMPO/cat. NaOCl/$NaClO_2$,[54] in which

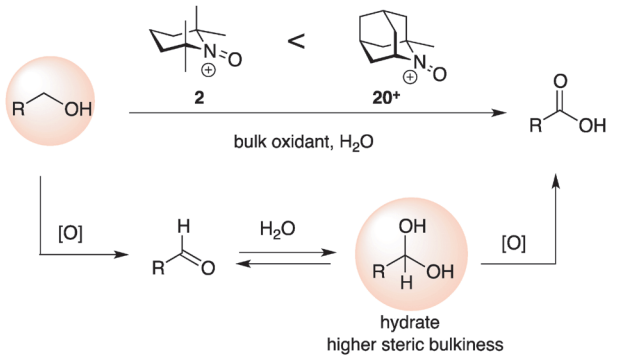
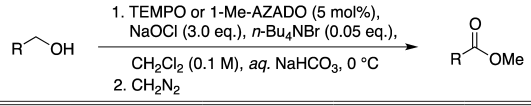
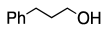
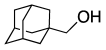
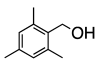


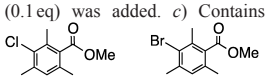
Chart 18. Oxidation of Primary Alcohols to Carboxylic Acids

Table 7. Comparison of Catalytic Efficiency of TEMPO and 1-Me-AZADO under Anelli's Conditions



Entry	Alcohol	Time	Yield (yield of aldehyde) (%)[a] 1	20
1[b]		15 min	42 (12)	84
2		20 min	91	93
3		1 h	46 (31)	84
4		1 h	<5[c] (70)	<5[b] (61)

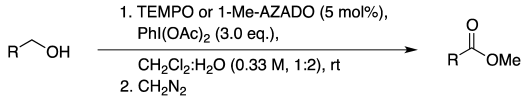
a) Isolated yield as a methyl ester after treatment with CH_2N_2. *b*) KBr (0.1 eq) was added. *c*) Contains halogenated byproducts as inseparable mixture.

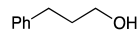
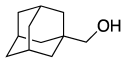
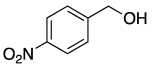
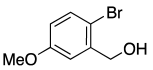
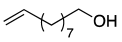
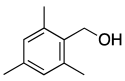


the *in situ* generation of TEMPO$^+$ **2** and the use of $NaClO_2$ as the bulk oxidant bring about significant improvement. We expected that use of oxoammonium salt as an initial catalyst would allow a "*virtually* NaOCl-free" catalytic cycle featuring the following steps: (i) oxoammonium ion reacts with alcohols to give hydroxylamine and aldehyde; (ii) the aldehyde generated reacts with $NaClO_2$ to give a carboxylic acid and NaOCl; (iii) NaOCl generated *in situ* is *immediately* consumed by hydroxylamine to regenerate an oxoammonium ion, thereby establishing a catalytic cycle (Chart 19). It was hoped that the less-hindered structure of 1-Me-AZADO-derived hydroxylamine should exhibit *kinetic* superiority to TEMPO-derived hydroxylamine in quenching the destructive NaOCl and would reasonably improve the net productivity.

To verify the feasibility of the above-mentioned scenario, two types of 1-Me-AZADO-derived oxoammonium salts, namely, 1-Me-AZADO$^+$Cl$^-$ (**20a**) and 1-Me-AZADO$^+$BF$_4^-$ (**20b**), were prepared, along with TEMPO$^+$Cl$^-$ (**2a**) and TEMPO$^+$BF$_4^-$ (**2b**) and examined them for the one-pot oxidation. We confirmed that the oxoammonium salt/$NaClO_2$ system exhibited an optimized performance in MeCN-aq. sodium phosphate buffer (1.0 M, pH 6.8) to convert primary alcohols to

Table 8. Comparison of Catalytic Efficiency of TEMPO and 1-Me-AZADO under Widlanski's Conditions.



Entry	Alcohol	Time	Yield (yield of aldehyde) (%)[a] 1	20
1		2	48	86
2		1	76	85
3		20	80	97
4		23	46 (46)	69 (22)
5		20	15	84
6		10	3 (90)	8 (77)

a) Isolated yield as a methyl ester after treatment with CH_2N_2.

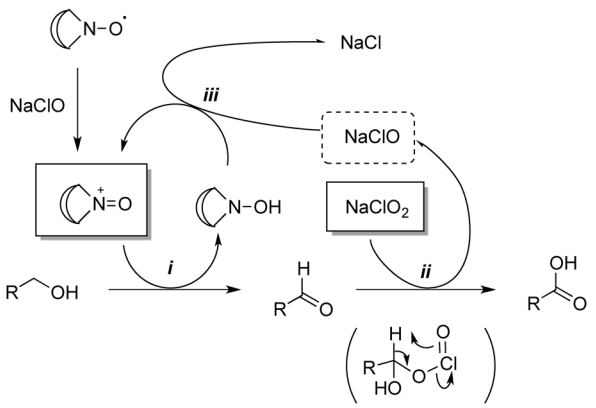
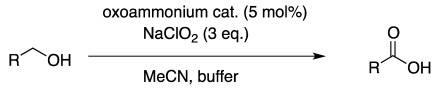


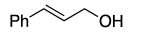
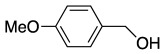
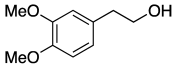
Chart 19. The Merck Method for One-Pot Oxidation of Primary Alcohols to Carboxylic Acids

the corresponding carboxylic acids in a 10 g-scale experiment, with which cat. TEMPO/cat. NaOCl/$NaClO_2$ (Merck's method) failed to afford a carboxylic acid product in good yield due to damage to the electron-rich functionalities. In addition to the superiority of 1-Me-AZADO over TEMPO, it should be noted that direct investment of the substantial catalyst, the oxoammonium salt, brought about a marked productivity[56] (Table 9).

The scope of the oxoammonium salt/$NaClO_2$ method for the one-pot oxidation of primary alcohols to carboxylic acids is shown in Table 10, where 1-Me-AZADO$^+$ exhibited better catalytic performance than TEMPO$^+$. It should be noted that 1-Me-AZADO$^+$Cl$^-$ successfully oxidized alkenyl alcohols to afford the corresponding carboxylic acids, where TEMPO$^+$ suffered from side reactions, such as oxidative cleavage and chlorination (entry 7). The admirably clean transformations

Table 9. Catalytic One-Pot Oxidation of Primary Alcohols Having Electron-Rich Groups Employing $NaClO_2$ as the Terminal Oxidant



Entry	Substrate	Method	Yield (%)[a]/Time 2+X−	Yield (%)[a]/Time 20+X−
1		A	79/5 h[b]	82/6 h[b]
		B	82/8 h	97/5 h[b]
2		A	92/40 h	92/23.5 h
		B	96/40 h	97/26 h
		C	86/3 h	99/2 h
3		A	64/7 h	92/10 min

Method A: Reactions were catalyzed by $TEMPO^+Cl^-$ (**2a**) or 1-Me-$AZADO^+Cl^-$ (**20a**) (5 mol%) with $NaClO_2$ (5 eq) in sodium phosphate buffer and MeCN 25°C. Method B: Reactions were catalyzed by $TEMPO^+BF_4^-$ (**2b**) or 1-Me-$AZADO^+BF_4^-$ (**20b**) (5 mol%) with $NaClO_2$ (3 eq) in sodium phosphate buffer and MeCN at 25°C. Method C: Reactions were catalyzed by 1-Me-$AZADO^+Cl^-$ (**20a**) (5 mol%) with $NaClO_2$ (3 eq) in CH_3CO_2H/CH_3CO_2Na buffer and MeCN. *a*) Isolated yield as a methyl ester after treatment with CH_2N_2. *b*) Reaction was performed at 50°C.

attained by 1-Me-$AZADO^+$ should be attributed to the highly reactive nature of 1-Me-AZADOH in consuming NaClO, quenching the destructive pathway of reacting π-electrons of the substrates. No epimerizations were observed in the oxidation of *N*-protected α-amino alcohols (entries 9, 10). In some cases, a more acidic buffer produced a faster reaction rate (entry 8; Method C). It would be useful to point out that 1-Me-$AZADO^+BF_4^-$ is advantageous over 1-Me-$AZADO^+Cl^-$ in terms of its less hygroscopic nature as well as its selectivity in suppressing undesired chlorination to under 5%[56] (entry 7).

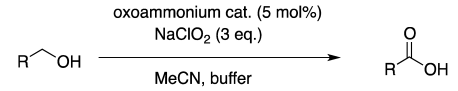
6. Application of AZADOs in Total Synthesis of Natural Products

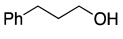
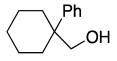
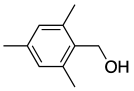
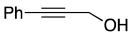
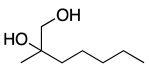
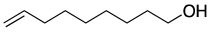
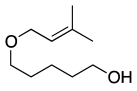
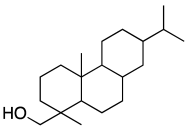
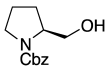
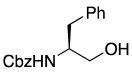
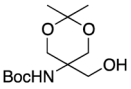
Natural products are children of *Mother Nature* whose structures and biological activities pose considerable challenges to organic chemists, providing intellectual platforms for discovery and invention that will lead to sustainable development of our society. Thanks to natural products, chemical sciences and technology have steadily been stimulated to continue their further development. Paralleled with these activities, the size and complexity of molecules we can synthesize have continuously been increasing. As a natural consequence, the structures of future medicines are expected to become more complex in our pursuit of better pharmaceutical efficiencies. Not only to verify the practicality of AZADOs and the related nitroxyl radicals/oxoammonium salts-based methods in alcohol oxidation, but also to identify issues associated with alcohol oxidation in complex systems, we have positively been applying AZADOs oxidation to our natural product synthesis projects. We describe below some instructive examples of AZADOs and related oxidations.

6.1. 1-Me-AZADO/$PhI(OAc)_2$ in Total Synthesis of (+)-Juvabione During our research program on the development of bicyclo[3.3.1]nonane-type chiral building block, we were in need of selective oxidation of the secondary alcohol **55** to the corresponding ketone **56** with the α,β-unsaturated aldehyde moiety intact. Although treatment of **55** with Dess–Martin periodinane gave the desired ketone **56** in a satisfying yield of 85% after 1 h, use of 5 mol% 1-Me-AZADO and $PhI(OAc)_2$ allowed us to obtain the same in a better yield of 94% after 7.5 h. The ketone **56** was successfully converted to (+)-juvabione (**57**) by applying Corey's condition using NaCN, MnO_2, and AcOH in MeOH[57] (Chart 20).

6.2. $TEMPO^+Cl^-$ and 1-Me-AZADO/$PhI(OAc)_2$ in Total Synthesis of Cylindrocyclophanes Intrigued by the

Table 10. Scope of One-Pot Oxidation Employing Oxoammonium Ion/$NaClO_2$



Entry	Substrate	Method	Yield (%)[a]/Time 2+X−	Yield (%)[a]/Time 12+X−
1		A	98/30 min	98/30 min
		B	98/1.5 h	93/30 min
2		A	79/10 h	93/10 h
		B	97/10 h	97/10 h
3		A	100/9.5 h	98/7 h
		B	83/8 h	98/7 h
4		A	86/4 h	100/4 h
5		A	93/9.5 h	92/30 min
6		A	74/24 h[b]	94/1 h
		B	77/24 h[b]	93/3 h
7		A	<10/48 h	73/24 h[c]
		B	<10/48 h	78/18 h[d]
8		A	32/70 h	64/58 h
		C	73/7 h	90/4 h
9		A	100/9 h	100/3 h
		B	100/8.5 h	100/1.5 h
10		A	13/42 h	100/18 h
		B	8/42 h	94/24 h
11		A	42/24 h	100/1 h

Method A: Reactions were catalyzed by $TEMPO^+Cl^-$ (**2a**) or 1-Me-$AZADO^+Cl^-$ (**20a**) (5 mol%) with $NaClO_2$ (5 eq) in sodium phosphate buffer and MeCN 25°C. Method B: Reactions were catalyzed by $TEMPO^+BF_4^-$ (**2b**) or 1-Me-$AZADO^+BF_4^-$ (**20b**) (5 mol%) with NaClO2 (3 eq) in sodium phosphate buffer and MeCN at 25°C. Method C: Reactions were catalyzed by 1-Me-$AZADO^+Cl^-$ (5 mol%) with $NaClO_2$ (3 eq) in CH_3CO_2H/CH_3CO_2Na buffer and MeCN. *a*) Isolated yield as a methyl ester after treatment with CH_2N_2. *b*) *ca.* 10% of starting material was still remained. *c*) *ca.* 18% chlorinated product was obtain as inseparable mixture. *d*) *ca.* 3% of chlorinated product was obtained as inseparable mixture.

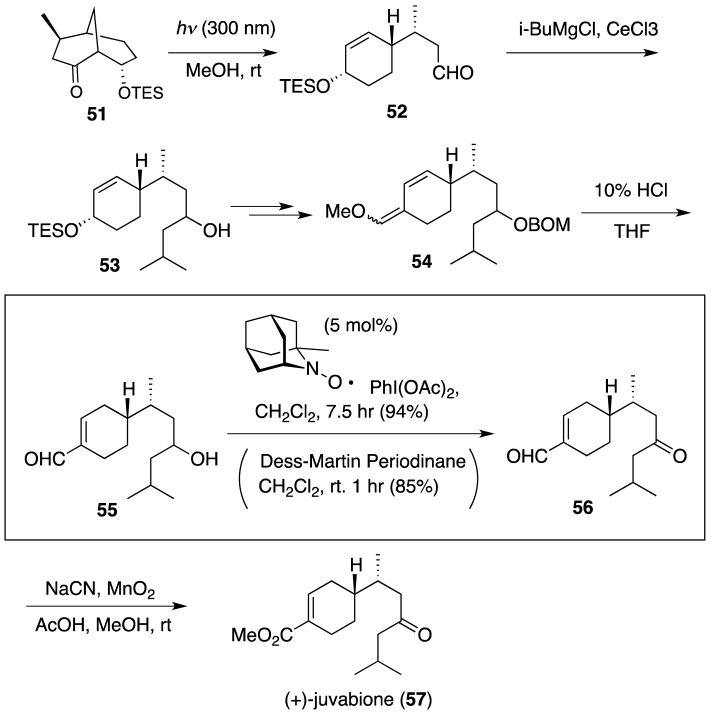


Chart 20. 1-Me-AZADO/PhI(OAc)$_2$ in the Total Synthesis of (+)-Juvabione

novel structures of cylindrocyclophanes, introduced as the first naturally occurring [m.n]cyclophanes isolated from extracts of the terrestrial blue green algae *Cylindrospermum licheniforme*, and their high *in vitro* cytotoxicity, we planned a preliminary SAR study based on a collective synthesis of both enantiomers of cylindrocyclophane A [(−)- and (+)-**58**] and the half-sized analogue **64**. We attempted chemoselective oxidation of the benzyl alcohol **59** to the corresponding benzaldehyde **60** with the resorcinol moiety intact. Due to the highly reactive nature, all the catalytic oxidation methods examined resulted in complex mixtures. MnO_2 gave **60** with a reproducible but low yield of around 30%. It is noteworthy that oxidation of **59** using a stoichiometric amount of TEMPO$^+$Cl$^-$ (**2a**) gave **60** in 69% yield. The related substrates **62** equipped with a suitable protecting group on the catecohol moiety underwent facile oxidation to give the corresponding aldehyde **63** without any problem. The biological evaluation of the synthetic compounds indicated that 2,5-resorcinol functionality is essential for eliciting the cytotoxicity and the [7.7]paracyclopnane framework enhances the potency of the resorcinol toxicophore[58] (Chart 21).

6.3. 1-Me-AZADO$^+$BF$_4^-$/PhI(OAc)$_2$ in Total Synthesis of Irciniastatin A Fascinated with the promising therapeutic potential coupled with the limited availability of (+)-irciniastatin A (**65**), which was originally isolated from the marine sponge *Ircinia ramose* as a new perderin-type natural product, with its absolute and partial relative structure undetermined status, we embarked on its total synthesis with extensive adoption of the Sharpless AE methodology. During our synthetic effort to isolate the substance from *Ircinia ramose*, we needed to undertake chemoselective oxidation of primary alcohols **67**, **69**, and **71** to the corresponding carboxylic acids **68**, **70**, and **72**, respectively, in the advanced stages. AZADOs-catalyzed methods, especially the oxoammonium salt/$NaClO_2$ methods, were extremely useful, as highlighted in Chart 22.[59]

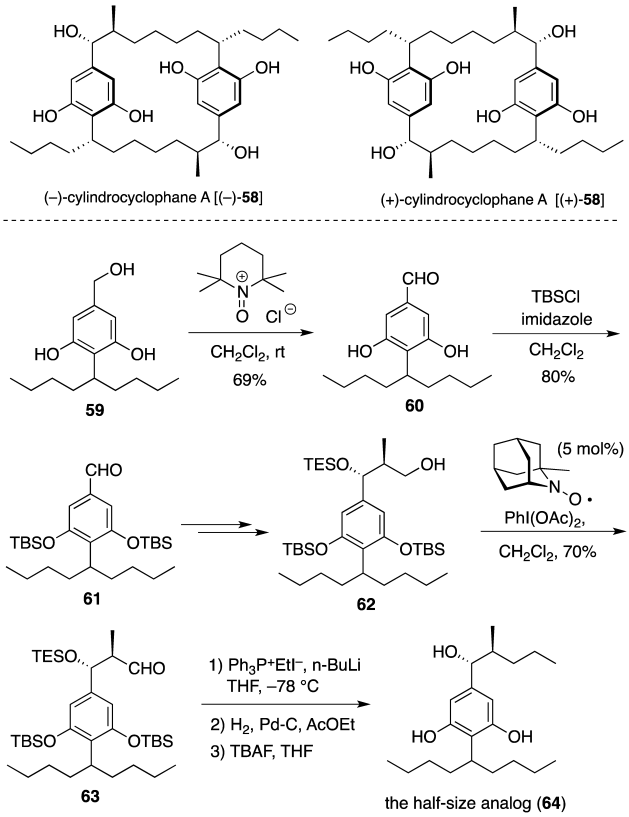


Chart 21. Application of TEMPO$^+$Cl$^-$ and 1-Me-AZADO/PhI(OAc)$_2$ to the Collective Total Synthesis of Cylindrocyclophanes

6.4. AZADO/PhI(OAc)$_2$ in Total Synthesis of Salinosporamide A Salinosporamide A (**85**) is a cytotoxic principle produced by the marine actiomycete *Salinospora tropicana*, and has been shown to be a potent inhibitor of the 20S proteasome as well as exhibit *in vitro* cytotoxicity against many cancer cell lines with IC_{50} values less than 10 nM. Cur-

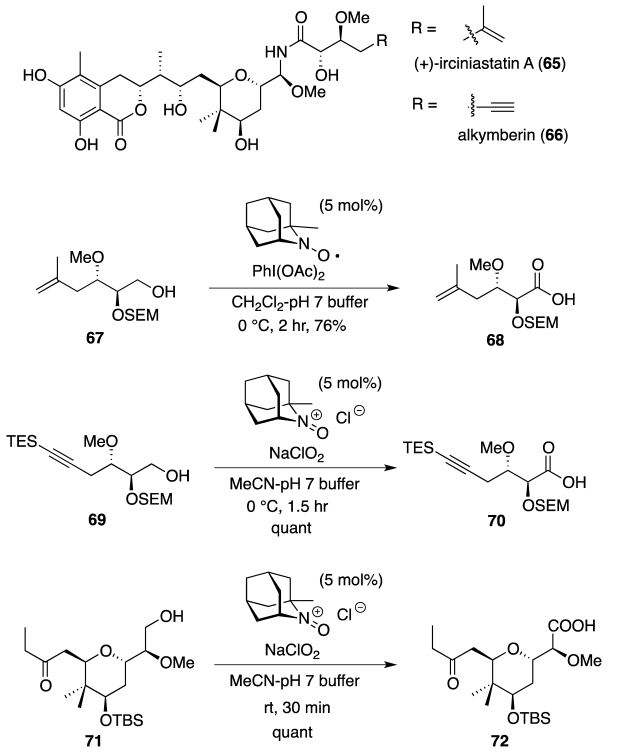


Chart 22. Applications to the Total Synthesis of Irciniastatin A and Its Analogue

rently, salinosporamide A is being tested as an anticancer drug candidate. In addition to its potent biological activity, the densely functionalized architecture has attracted the attention of many synthetic chemists. We embarked on its total synthesis *via* the extensive adoption of aldol and related reactions. The most promising use of AZADO/PhI(OAc)$_2$ was the unexpected, one-pot oxidative β-lactonization of the diol **83** to furnish **84** in a satisfying yield. The TEMPO and AZADOs oxidation methods helped us to complete the complicated total synthesis[60] (Chart 23).

6.5. AZADO/Polymer Supported PhI(OAc)$_2$ in Total Synthesis of Idesolide Having gained experience in using nitroxyl radicals/oxoammonium salt-based oxidation methods, we have learned that PhI(OAc)$_2$ offers a mild and chemoselective oxidation, particularly being tolerant to electron-rich double bonds, and such positive features led it to become the first-choice reagent in a serious synthetic situation. In some cases, PhI(OAc)$_2$ was found to realize chemoselective oxidation of alcohol functionalities of aminoalcohol substrate (in which the amino group must be tertiary) although substoichiometric amounts of AZADO are required to promote the reaction. With the above-mentioned know-how in mind, we attempted the oxidation of the 1,2-diol **86** to obtain the corresponding hydroxyl-ketone **88** using AZADO/PhI(OAc)$_2$, in which we observed glycol cleavage to give **87**. Dess–Martin periodinane also gave the same cleavage product. After considerable experimentation, we overcome the problem by using polymer-supported PhI(OAc)$_2$. We reasoned that the sterically less-accessible nature of PS-PhI(OAc)$_2$ suppressed the direct reaction between the 1,2-diol **86** and the iodine(III) center, while sterically accessible AZADO was able to reach there to give the active oxidant AZADO$^+$ (**11**$^+$) that expediently oxidized the diol to give the hydroxyl ketone **88**[61] (Chart 24).

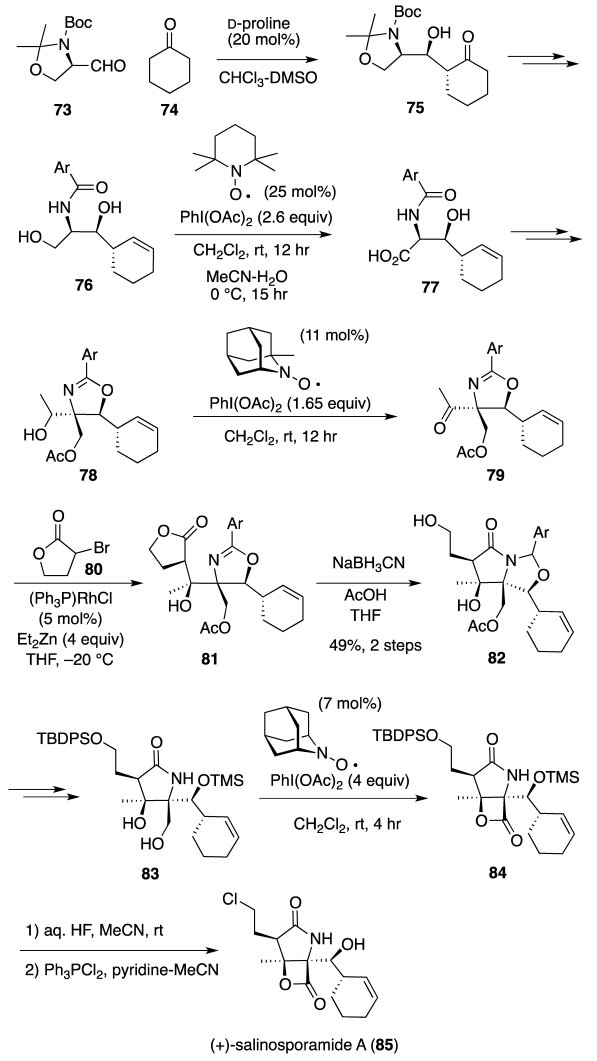


Chart 23. Applications in the Total Synthesis of (+)-Salinosporamide A

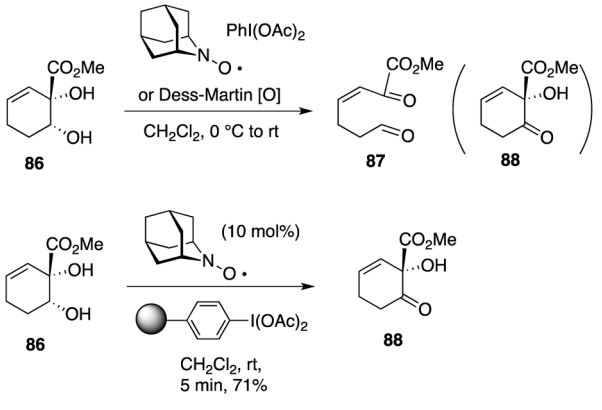


Chart 24. AZADO/PS-AZADO in the Total Synthesis of (−)-Idesolide

6.6. Miscellaneous As described above, AZADOs oxidation plays important roles in alcohol oxidation, but, at this juncture, it should be pointed out that they do not always yield a satisfactory output. During our final approach towards the total synthesis of the neurotrophic diterpene scabronine G, we were in need of the tricyclic ketone **90** *via* oxidation of the alcohol **89**. Dess–Martin periodinane resulted in spot-to-spot oxidation, but AZADO/PhI(OAc)$_2$ gave a disappointing multi-spot TLC[62] (Chart 25).

In relation to this failure, we encountered an unexpected reaction in the attempted α-oxyamination of the silyl enol ether **91** to obtain **93** using AZADO^{+}BF$_4^{-}$, in which we obtained cyclohexenone **92** as the major product.[63] A careful set of experiments revealed that the unexpected product came from the adduct **94** which was generated *via* "ene"-like addition of AZADO-derived oxoammonium ion to the silyl enol ether. The novel reactivity of AZADO^{+}BF$_4^{-}$ is now understood to be a substrate-dependent reaction: cyclic enol ethers are prone to give the ene-like adducts, but acyclic silyl enol ethers give α-adducts preferentially (Chart 26). The novel reactivity of the less-hindered oxoammonium salts led us eventually to develop a new oxidative transformation[63] (Table 11).

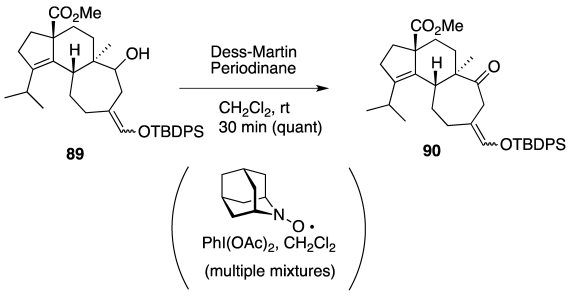


Chart 25. An Unsuccessful AZADO/PhI(OAc)$_2$ Oxidation in the Total Synthesis of (−)-Scabronine G

7. Recent Update: Development of AZADO (Nor-AZADO)/DIAD Method as an Extremely Mild Oxidation Method

During our continuous effort to develop a chemoselective, more specifically, alcohol-selective oxidation method that meets practical needs in synthesizing complex molecules, we discovered an interesting use of Mitsunobu reagents as the terminal oxidant for AZADOs oxidation[64] (Chart 27).

Besides their exceptional use in the Mitsunobu reaction, di-

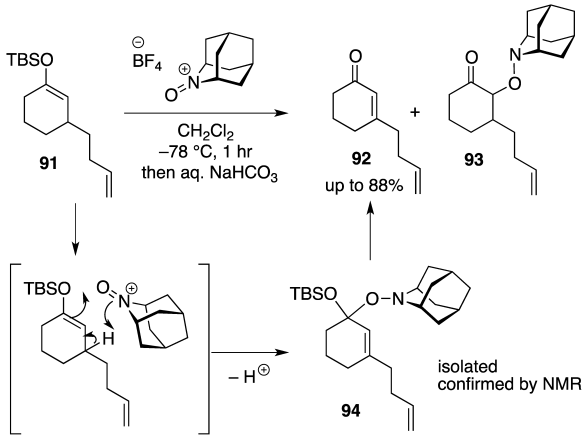
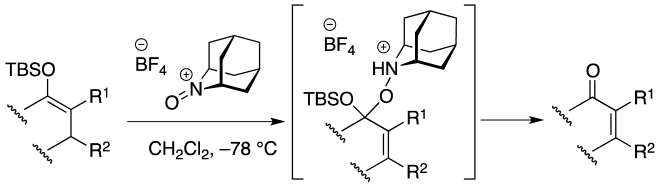
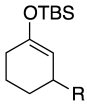
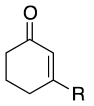
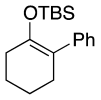
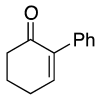
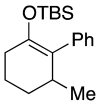
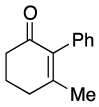
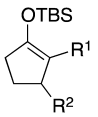
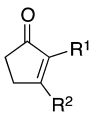
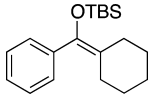
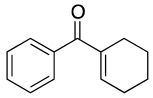
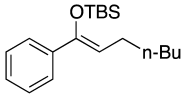
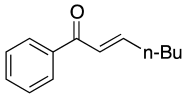


Chart 26

Table 11. Oxidative Conversion of Silyl Enol Ethers to α,β-Unsaturated Ketones by Oxoammonium Salts



Entry[a]	Substrates	Products	Yield
1			R=Ph, 88%
2			R=*n*-Bu, 88%
3			R=vinyl, 80%
4			83%
5			88%
6			R^1=H, R^2=Ph, 85%
7			R^1=Ph, R^2=H, 71%
8			R^1=Ph, R^2=*n*-Bu, 77%
9			R^1=Ph, R^2=Me, 82%
10			87%
11			6%

a) All reactions were carried out using 1 eq of AZADO^{+}BF$_4^{-}$ in CH_2Cl_2 at −78°C for 1 h, followed by treatment with sat. aqueous $NaHCO_3$ at rt.

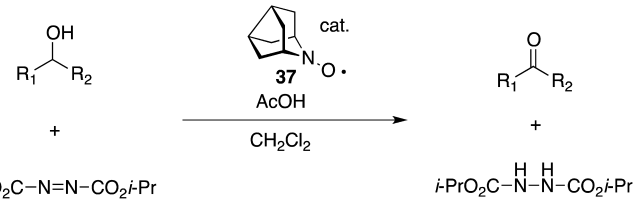
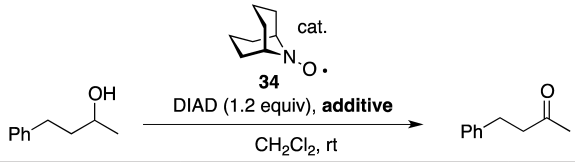


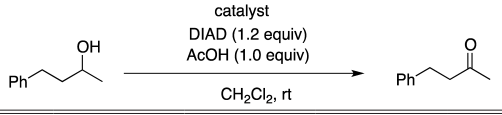
Chart 27. Oxidation of Alcohols to Carbonyl Compounds with DIAD Catalyzed by Nitroxyl Radicals

Table 12. Investigation of the Reaction Conditions



Entry	ABNO (**34**) (mol%)	Additive (eq)	CH_2Cl_2 (M)	Time (min)	Yield (%)
1	1	None	0.5	48 h	Trace
2	None	AcOH (1.0)	0.5	48 h	1
3	1	AcOH (1.0)	0.5	48 h	80
4	1	AcOH (1.0)	1.0	48 h	88
5	1	AcOH (2.0)	1.0	48 h	86
6	3	AcOH (1.0)	1.0	24 h	88

Table 13. Comparison of Catalytic Efficiency of Nitroxyl Radicals



Catalyst loading amount	Yield			
	34	**11**	**37**	**1**
3 mol%	88% (24 h)	96% (24 h)	99% (24 h)	n.d.
1 mol%	88% (48 h)	81% (24 h)	97% (24 h)	n.d.

alkyl azodicarboxylates, as exemplified by diisopropyl azodicarboxylate (DIAD) and diethyl azodicarboxylate (DEAD), are known as versatile reagents to promote several particular transformations including alcohol oxidation, azo-ene reaction, and hetero-Diels–Alder reaction. Alcohol oxidation by DEAD was first reported by Yoneda *et al.* in 1966 with a limited number of examples.[65] Recently, alcohol oxidation by a combination of DEAD and a Lewis acid has been reported.[66] Unfortunately, the method could not be applied to allylic or propargylic alcohols due to undesired side reactions. We are encouraged by a paper describing that hydroxylamines were oxidized to the corresponding nitroso-compounds by DEAD under low temperatures.[67] Thus, we envisioned that dialkyl azodicarboxylate should function as an oxidant converting a nitroxyl radical into oxoammonium ion, which would be a selective and efficient oxidant for alcohols.

We started with searching for an enabling additive that bridges the redox reactions between ABNO and DIAD at room temperature. It was eventually found that acetic acid was such an additive (Table 12).

We next compared the catalytic efficiencies of some nitroxyl radicals in this system. Nor-AZADO (**37**) and AZADO (**11**) gave comparable results with a loading amount of 3 mol%, showing superior catalytic efficiency to ABNO (**34**). Note that TEMPO did not work as a catalyst in this system. The difference between Nor-AZADO and AZADO became apparent when the loading amount was decreased to 1 mol%; the reaction was completed within 24 h with 1 mol% Nor-AZADO (**37**) to give 4-phenyl-2-butanone in excellent yield, whereas the oxidation using 1 mol% AZADO (**11**) was not completed (Table 13).

We also tested azo-compounds other than DIAD, such as diphenyl azodicarboxylate (DPAD), 1,1′-(azodicarbonyl)-dipiperidine (ADD), azodicalboxamide, azobenzene, and 2,2′-azopyridene, however, none of them worked effectively.

With the optimum reaction conditions in hand, the substrate applicability to the oxidation system using Nor-AZADO (**37**) as the catalyst was explored (Table 14).

A variety of alcohols were efficiently oxidized to their corresponding carbonyl compounds with 1 to 10 mol% catalyst. Aliphatic and benzylic secondary alcohols, including a sugar derivative, a nucleoside derivative, and a pyridine derivative, were effectively oxidized (entries 8–10). Relatively acid-labile isopropylidene and a TBS-protecting group remained after the reaction (entries 8, 9). Primary alcohols were also oxidized to their corresponding aldehydes in high yield without overoxidation to carboxylic acids. It is interesting to note that 4-methylthiobenzyl alcohol having a sulfide group was oxidized chemoselectively to its corresponding aldehyde (entry 4). We also tested some substrates containing amine functionalities. In the case of 3-quinuclidinol, its corresponding ketone was obtained in high yield, although 10 mol% catalyst was needed (entry 11).

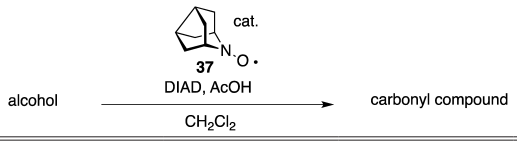
We then tested double- and triple-bond-containing substrates and diols (Table 15). A variety of double-and triple-bond-containing alcohols were selectively oxidized in high yield at room temperature (entries 1 to 6). It should be stressed that 1,2-diol was oxidized to a hydroxyl ketone or a diketone depending on the amount of DIAD used (entries 7–9). Primary alcohol was oxidized selectively over secondary alcohol in the case of the diol **49**, which has both primary and secondary alcohols (entry 10).

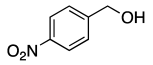
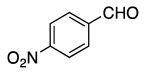
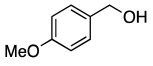
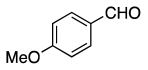
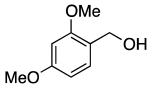
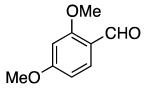
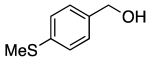
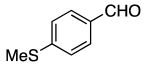
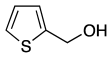
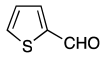
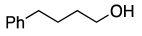
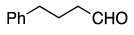
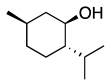
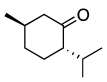
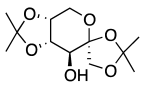
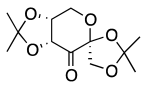
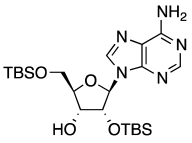
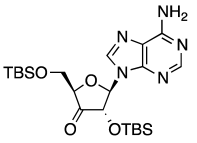
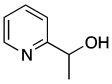
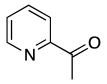
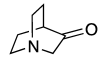
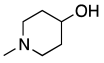
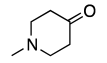
The described procedure is simple, mild, and applicable to a variety of alcohols including 1,2-diol. This mild system would find good use in the alcohol oxidation of complicated substrates that cannot tolerate conventional oxidants.

8. Conclusion

My naive interest and quest for improving the catalytic activity of TEMPO met timely with adamantane chemistry, which inspired me to conceive AZADO. The acquisition of AZADO required a great deal of trial and error, but the discovery of the ultra-high catalytic activity of AZADO, which

Table 14. Scope of the Nor-AZADO/DIAD/AcOH System



Entry[a)]	Substrate	Catalyst loading (mol%)	Time (h)	Temp.	Product	Yield (%)
1		3	5	rt		95
2		3	2.5	rt		98
3		3	3	rt		95
4		1	1.5	Reflux		93
5		3	5	rt		86
6		3	5	rt		95
7		3	48	rt		95
8		1	10	Reflux		91
9		10	24	rt		68
10		3	8	rt		87
11		10	8	rt		87
12		10	24	rt		0

a) The reactions were carried out with DIAD (1 eq) and AcOH (1 eq) in CH_2Cl_2 (1 M).

was far beyond our estimate, encouraged us to investigate the chemistry of a less-hindered class of nitroxyl radicals and oxoammonium salts, enabling us to exploit several useful catalysts, synthetic methods, and new oxidative reactions. The synthetic use of AZADO and the related nitroxyl radicals/oxoammonium salts/hydroxylamines have been successfully demonstrated in many synthetic studies that rely on alcohol oxidation. AZADO and the corresponding hydroxylamine, coined AZADOL®, are currently being manufactured at a kg-scale by Nissan Chemical Co., Ltd. and delivered globally. Wako Pure Chemical Industries, Ltd. has just recently started the manufacture of 1-Me-AZADO and Nor-AZADO.

The oxidation of alcohols is intimately connected to the chemistry of carbonyl groups where we hope AZADOs will find their use.

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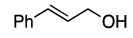
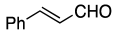
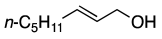
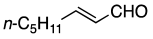
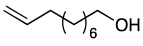
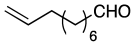
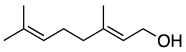
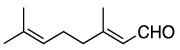
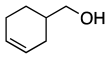
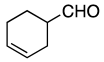
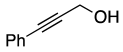
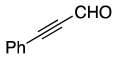
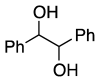
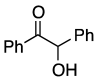
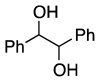
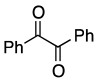
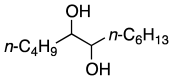
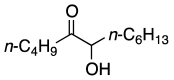
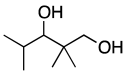
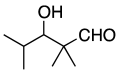
Table 15. Scope of the Nor-AZADO/DIAD/AcOH System

Entry[a)]	Substrate	Catalyst loading (mol%)	Time (h)	Temp.	Product	Yield (%)
1[b)]		1	10	rt		97
2		3	8	rt		87
3		3	5	rt		85
4[c)]		3	3	rt		87
5		3	8	rt		81
6		3	4	rt		90
7		3	6	rt		89
8[d)]		3	6	Reflux		92
9[d)]		3	24	rt		81
10		3	5.5	rt		83

a) The reactions were carried out with DIAD (1 eq) and AcOH (1 eq) in CH_2Cl_2 (1 M) unless otherwise noted. *b*) 1.2 eq DIAD was used. *c*) 1.1 eq of DIAD was used. *d*) 2 eq of DIAD was used.

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