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Methyl-Selective α-Oxygenation of Tertiary Amines to Formamides by Employing Copper/Moderately Hindered Nitroxyl Radical (DMN-AZADO or 1-Me-AZADO)

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Abstract: *Methyl-selective α-oxygenation of tertiary amines is a highly attractive approach for synthesizing formamides while preserving the amine substrate skeletons. Therefore, the development of efficient catalysts that can advance regioselective α-oxygenation at the N-methyl positions using molecular oxygen (O_2) as the terminal oxidant is an important subject. In this study, we successfully developed a highly regioselective and efficient aerobic methyl-selective α-oxygenation of tertiary amines by employing a Cu/nitroxyl radical catalyst system. The use of moderately hindered nitroxyl radicals, such as 1,5-dimethyl-9-azanoradamantane N-oxyl (DMN-AZADO) and 1-methyl-2-azaadamanane N-oxyl (1-Me-AZADO), was very important to promote the oxygenation effectively mainly because these N-oxyls have longer life-times than less hindered N-oxyls. Various types of tertiary N-methylamines were selectively converted to the corresponding formamides. A plausible reaction mechanism is also discussed on the basis of experimental evidence, together with DFT calculations. The high regioselectivity of this catalyst system stems from steric restriction of the amine-N-oxyl interactions.*

Introduction

Tertiary amines are recognized as important structural motifs in versatile compounds, such as pharmaceuticals, agricultural chemicals, bioactive compounds, and natural alkaloids.[1,2] New functional molecules can be designed by functionalization of tertiary amines while preserving their skeletons. Functionalization of the C–H bond adjacent to the nitrogen atom through cross-dehydrogenative coupling is gaining considerable attention as a powerful method of transforming tertiary amines to various valuable products.[3–5] Particularly, the development of oxidative functionalization of tertiary amines using molecular oxygen (O_2) is highly meaningful because traditional stoichiometric oxidants cause undesirable oxidation of sensitive functional groups in bioactive and natural compounds. As a continuation of our interest in developing aerobic oxidative functionalization of tertiary amines,[6,7] we focused on methyl-selective α-oxygenation of tertiary amines. Formamides, products of α-methyl-selective oxygenation of *N*-methylamines, are useful intermediates for transforming to versatile functional groups[8–12] and important building blocks for biologically active molecules.[13–16] Furthermore, demethylation of *N*-methylamines can be realized via the deformylation of formamides.[17,18] Therefore, methyl-selective α-oxygenation would be a practical strategy for transforming *N*-methylamines to various value-added compounds.

However, the presence of three α-carbons with different intrinsic chemical environments made it difficult to selectively produce desired amides from tertiary amines by α-oxygenation. Particularly, regioselective methyl-selective α-oxygenation is extremely difficult for the following reasons (i)–(iii). i) C–H bonds of α-methyl groups are strong with high bond dissociation energies compared with other α-alkyl groups, such as α-benzyl groups.[19] For instance, α-benzyl positions are reported to be regioselectively oxygenated by photocatalytic aerobic α-oxygenation of tertiary amines.[20] ii) Iminium cation intermediates produced by oxidation at the α-methyl groups are thermodynamically unstable compared with the multi-substituted iminium cations. Previously, we reported that cyclic and linear α-methylene positions are selectively oxygenated in aerobic α-oxygenation of tertiary amines catalyzed by supported gold nanoparticles.[21] iii) Unlike cross-dehydrogenative coupling, α-oxygenation requires additional oxidation of hemiaminal intermediates, produced by hydration of the iminium cations. We previously developed regioselective α-cyanation and α-alkynylation at *N*-methyl positions of tertiary amines by MnO_2-based catalysts.[6,7] However, a MnO_2-catalyzed methyl-selective α-oxygenation strategy failed because of the poor catalytic activity of MnO_2 for the hemiaminal oxidation. In previous Fe-[22–25] and Co-based catalytic[26] and oxoammonium-oxidizing reactions,[27,28] the formamide yields were also unsatisfactory, because the unstable hemiaminal intermediates mainly decomposed to undesired demethylated byproducts. Although formamides are effectively synthesized by oxoammonium-mediated electrochemical oxidation, the substrate scope is limited to aniline

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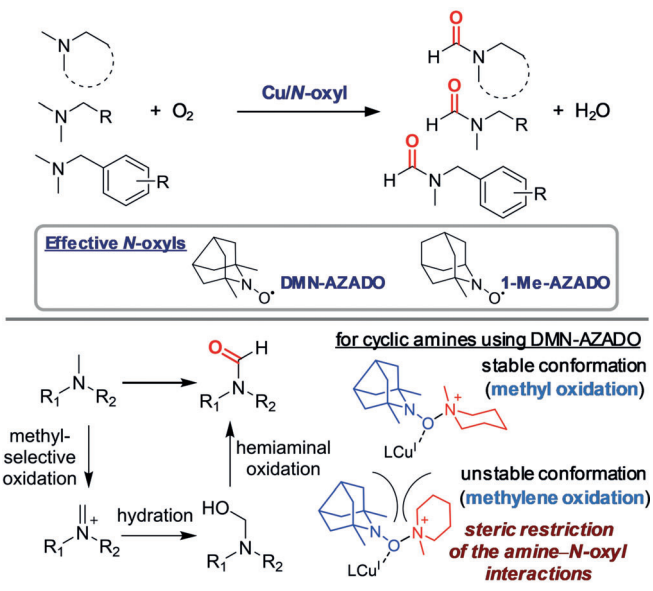
derivatives only.[29] As far as we know, there have been only a few good reports on the methyl-selective α-oxygenation. For example, the Pt black-catalyzed method showed preferential *N*-methyl oxygenation in the presence of benzylic groups though large amounts of expensive Pt were required.[30] A CuI-catalyzed oxygenation of dimethylamines under relatively harsh conditions (120 °C) was also reported.[31] However, the development of regioselective aerobic α-oxygenation of tertiary amines at the *N*-methyl positions with a broad substrate scope is still an extremely challenging task.

Cu/nitroxyl radical (*N*-oxyl) catalyst systems have gained attention for various aerobic oxidation reactions under mild conditions, particularly for alcohol oxidation.[32–39] Stahl et al. recently reported that Cu/*N*-oxyl catalysts promoted hemiaminal oxidation in the aerobic oxidative acylation of amines with primary alcohols.[40] Cu/*N*-oxyl-catalyzed oxidation of primary amines[41] and secondary amines[42–46] has also been reported so far. However, to the best of our knowledge, there is no precedent for Cu/*N*-oxyl-catalyzed oxidation of tertiary amines. Since Cu/*N*-oxyl-catalyzed alcohol oxidation is believed to proceed in a bulky closed-shell nitroxyl-Cu adduct,[47–50] we expected that tertiary amine oxidation would proceed regioselectively at *N*-methyl-positions due to such steric restriction.

In this study, we developed a practical route to various formamides through regioselective α-oxygenation of tertiary *N*-methylamines, using O_2 (open air atmosphere) as the terminal oxidant at room temperature, by employing the Cu/*N*-oxyl catalyst system (Scheme 1). The reaction proceeded efficiently in the presence of moderately hindered caged *N*-oxyls, such as 1,5-dimethyl-9-azanoradamantane *N*-oxyl (DMN-AZADO) and 1-methyl-2-azaadamanane *N*-oxyl (1-Me-AZADO). Although the *N*-methyl-selective oxygenation essentially proceeded even when using less hindered *N*-oxyls, the reactions stopped at the early stage most likely due to the deactivation of these *N*-oxyls. Additionally, the catalytic activity was significantly improved by precisely controlling the amounts of an appropriate counter anion, such as Cl^- or Br^-. With the optimized CuCl/$Cu(OTf)_2$/bpy/DMN-AZADO (or 1-Me-AZADO) catalyst system (OTf = triflate, bpy = 2,2′-bipyridyl), various tertiary aliphatic amines, including cyclic *N*-methylamines, *N*,*N*-dimethylamines, a natural alkaloid (pseudopelletierine), and pharmaceutical drugs (such as *N*-methylparoxetine and amitriptyline), could be highly regioselectively converted to the corresponding formamides (30 examples). On the basis of several pieces of experimental evidence, together with DFT calculations, we concluded that the high regioselectivity of the proposed catalyst system stemmed from steric restriction of the amine-*N*-oxyl interactions.



Scheme 1. Regioselectivity of α-oxygenation of tertiary amines.

Results and Discussion

Optimization of Reaction Conditions

Initially, we carried out the oxygenation of 1-methylpiperidine (**1a**) using 10 mol% of the $CuBr_2$/bpy/9-azanoradamantane *N*-oxyl (nor-AZADO) catalyst system at room temperature (≈23 °C) in non-dehydrated acetonitrile (MeCN) under open air conditions. Under these conditions, the desired α-methyl-oxygenated product 1-formylpiperidine (**1b**) was obtained selectively in 9% yield after 2 h, and *N*-methylpiperidone (**1c**) formation was negligible (Figure 1, Table S1, entry 1). Unfortunately, the formation of **1b** almost stopped within 2 h, and no significant increase in the yield of **1b** was observed even when the reaction time was increased to 24 h (Figure 1, Table S1, entry 2). Even after 24 h, **1c** was not detected. The undesirable termination of the reaction was considered to be due to the deactivation of nor-AZADO.[51] Then, other *N*-oxyls, such as 2-azaadamantane *N*-oxyl (AZADO), 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO), 9-

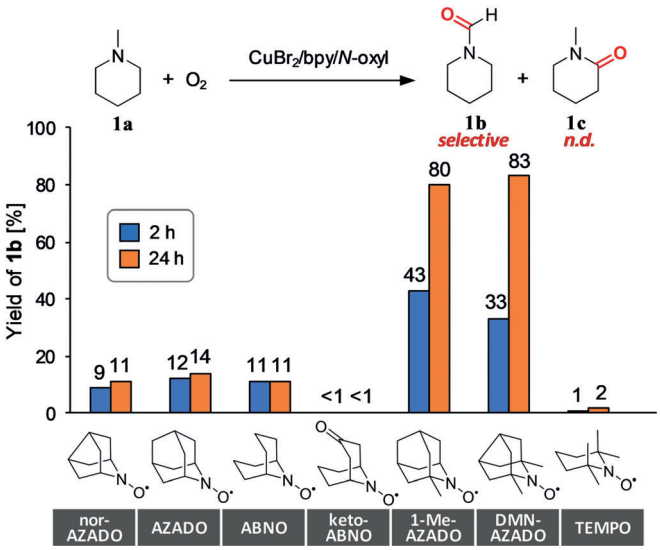


Figure 1. Effect of *N*-oxyls. Reaction conditions: **1a** (0.25 mmol), $CuBr_2$/bpy/*N*-oxyl (10/10/10 mol%), MeCN (1 mL), air (open), room temperature. Yields were determined by GC analysis. See also in Table S1.

azabicyclo[3.3.1]nonane-3-one *N*-oxyl (keto-ABNO), 1-Me-AZADO, DMN-AZADO, and 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO), were also investigated for the oxygenation of **1a** rather than nor-AZADO. When using AZADO or ABNO, the reactions were also *N*-methyl-selective and stopped within 2 h, affording **1b** in only ≈10% yield after 24 h (Figure 1, Table S1, entries 3–6). Therefore, these less hindered *N*-oxyls were also found to be ineffective from the viewpoint of increasing the yield of **1b**. Fortunately, we found that moderately hindered caged *N*-oxyls, such as 1-Me-AZADO and DMN-AZADO, exhibited high catalytic performances and that **1b** was produced effectively (Figure 1, Table S1, entries 3–6). In the case of DMN-AZADO and 1-Me-AZADO, byproducts due to the deactivation of these *N*-oxyls were not detected.[51] Thus, steric hindrance of *N*-oxyls is considered to be highly important for avoiding deactivation. DMN-AZADO showed a higher turnover number (TON) (25.5) than 1-Me-AZADO (11.8) after 24 h, even when the amount of *N*-oxyl was decreased to 2.5 mol% (Figure S1). The reaction hardly proceeded with keto-ABNO or TEMPO, possibly due to the high redox potential of keto-ABNO[42,52] and the bulkiness of TEMPO (Figure 1, Table S1, entries 7, 8, 13, and 14). Hereafter, we mainly used the effective moderately hindered DMN-AZADO or 1-Me-AZADO for further detailed investigations.

The effect of Cu sources was then examined. In this oxygenation, divalent Cu sources, such as $CuBr_2$, $CuCl_2$, and $Cu(OTf)_2$ (Table 1, entries 1–3), were more effective than monovalent CuBr, CuCl, CuI, and Cu(OTf)·4 MeCN (Table 1, entries 4–7). Among the divalent Cu sources examined, $CuBr_2$ showed the highest catalytic activity (Table 1, entry 1). To investigate the effect of Br^- in detail, **1a** was oxygenated at various Br^-/Cu molar ratios by fixing Cu at 10 mol%. When the Br^-/Cu molar ratios were controlled in the range 0.6–1.4 by changing the amounts of $Cu(OTf)_2$ and $CuBr_2$, the yield of **1b** was significantly higher than that obtained with $Cu(OTf)_2$ (Br^-/Cu = 0) (Figure 2a, Table 1, entries 8–10 vs. entry 3). The oxygenation also proceeded efficiently when LiBr or CuBr was added to $Cu(OTf)_2$ with a Br^-/Cu ratio in the range

Table 1: Effect of Cu catalysts on the oxygenation of **1a**.[a]

Entry	Catalyst (mol%)	Yield [%]	
		1b	**1c**
1	$CuBr_2$ (10)	33	n.d.
2	$CuCl_2$ (10)	14	n.d.
3	$Cu(OTf)_2$ (10)	26	n.d.
4	CuBr (10)	2	n.d.
5	CuCl (10)	n.d.	n.d.
6	CuI (10)	1	n.d.
7	Cu(OTf)·4 MeCN (10)	16	n.d.
8	$Cu(OTf)_2$ (7) + $CuBr_2$ (3)	83	n.d.
9	$Cu(OTf)_2$ (5) + $CuBr_2$ (5)	88	n.d.
10	$Cu(OTf)_2$ (3) + $CuBr_2$ (7)	78	n.d.
11	$Cu(OTf)_2$ (10) + LiBr (5)	83	n.d.
12	$Cu(OTf)_2$ (10) + LiBr (10)	87	n.d.
13	$Cu(OTf)_2$ (10) + LiBr (15)	71	n.d.
14	$Cu(OTf)_2$ (10) + LiBr (20)	45	n.d.
15	$Cu(OTf)_2$ (5) + CuBr (5)	91	n.d.
16	$Cu(OTf)_2$ (7) + $CuCl_2$ (3)	92	n.d.
17	$Cu(OTf)_2$ (5) + $CuCl_2$ (5)	96	n.d.
18	$Cu(OTf)_2$ (3) + $CuCl_2$ (7)	52	n.d.
19	$Cu(OTf)_2$ (5) + CuCl (5)	98	n.d.
20	$Cu(OTf)_2$ (5) + CuI (5)	14	n.d.

[a] Reaction conditions: **1a** (0.25 mmol), Cu/bpy/DMN-AZADO (10/10/10 mol%), MeCN (1 mL), air (open), room temperature, 2 h. Yields were determined by GC analysis.

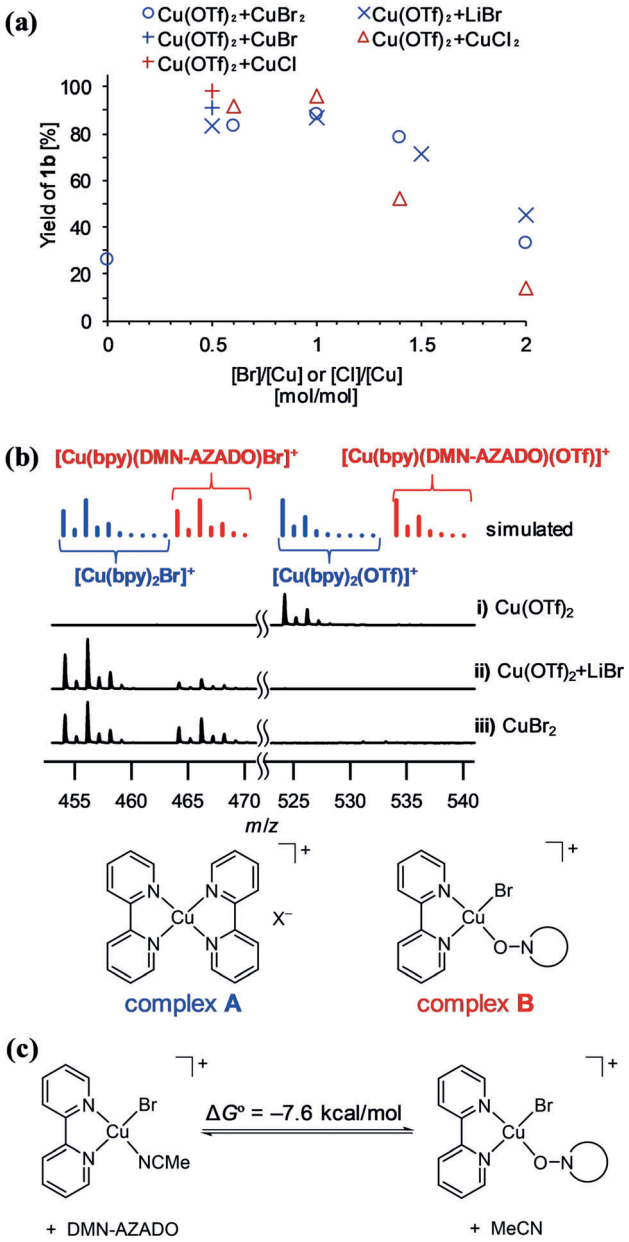


Figure 2. a) Effect of counter anions on the yield of **1b**. Reaction conditions: **1a** (0.25 mmol), Cu source/bpy/DMN-AZADO (10/10/10 mol%), MeCN (1 mL), air (open), room temperature, 2 h. Conversions and yields were determined by GC analysis. Detailed values are shown in Table 1. b) Positive-ion CSI-MS spectra of catalyst solution. Conditions: Cu/bpy/DMN-AZADO (1:1:1) in MeCN for (i) and (iii), $Cu(OTf)_2$/LiBr/bpy/DMN-AZADO (1:1:1:1) in MeCN for (ii). X = Br or OTf. c) Formation of complex **B**.

0.5–1.5 (Figure 2a, Table 1, entries 11–13 and 15). When the reaction was performed in the presence of $Cu(OTf)_2$ and LiBr with a Br^-/Cu ratio of 2.0, the result was similar to that using $CuBr_2$ (Figure 2a, Table 1, entry 14 vs. entry 1).

To gain a mechanistic insight into the role of Br^-, the reaction solutions were characterized by cold spray ionization mass spectrometry (CSI-MS, positive mode). The CSI-MS spectrum of a MeCN solution of $Cu(OTf)_2$, bpy, and DMN-AZADO ($Cu(OTf)_2$/bpy/DMN-AZADO = 1:1:1) presents a series of signals at m/z 524.2, assignable to $[Cu(bpy)_2(OTf)]^+$ (calcd 524.0, complex **A**) (Figure 2b,i). Thus, without Br^-, a Cu^{II} species coordinated by two bpy molecules was mainly observed, with no species coordinated by DMN-AZADO. Conversely, the CSI-MS spectrum of a MeCN solution of $Cu(OTf)_2$, LiBr, bpy, and DMN-AZADO ($Cu(OTf)_2$/LiBr/bpy/DMN-AZADO = 1:1:1:1) exhibited series of signals at m/z 456.2 and 466.2, assignable to $[Cu(bpy)_2Br]^+$ (calcd 456.0, complex **A**) and $[Cu(bpy)(DMN\text{-}AZADO)Br]^+$ (calcd 466.0, complex **B**), respectively (Figure 2b,ii). The computational calculation indicated that the formation of $[Cu(bpy)(DMN\text{-}AZADO)Br]^+$ (complex **B**) by replacement of MeCN in $[Cu(bpy)(MeCN)Br]^+$ is thermodynamically favorable by 7.6 kcal mol^{-1} (Figure 2c)[53] The CSI-MS spectrum of a MeCN solution of $CuBr_2$, bpy, and DMN-AZADO ($CuBr_2$/bpy/DMN-AZADO = 1:1:1) also exhibited series of signals at m/z 456.2 and 466.2 (Figure 2b,iii). Consequently, it is considered that Br^- acts as a monodentate ligand to inhibit coordination of two bpy ligands and allow coordination of DMN-AZADO.[53] As mentioned above, the reaction proceeded efficiently with Br^-/Cu = 0.5–1.5, and as the Br^-/Cu ratio was increased further, the reaction rate decreased. Excess Br^- presumably inhibits the coordination of the amine substrate, reducing the efficiency of the reaction.

Furthermore, we found that Cl^- was more effective than Br^-; when Cl^-/Cu was controlled in the range 0.5–1.0 by using $Cu(OTf)_2$ and $CuCl_2$, or $Cu(OTf)_2$ and CuCl, **1b** was obtained in almost quantitative yields (Figure 2a, Table 1, entries 16, 17, and 19). The yield of **1b** was more drastically decreased when the Cl^-/Cu ratio exceeded 1.0 (Figure 2a, Table S1, entry 18 vs. entry 10). CuI was ineffective for this oxygenation (Table S1, entry 20). On the basis of the above-mentioned investigations, we mainly used $Cu(OTf)_2$/CuCl (5 mol%/5 mol%) as the most effective copper catalyst for further detailed investigations.

Next, various ligands were examined for the oxygenation of **1a**. The reaction proceeded effectively in the presence of bpy, 4,4′-dimethyl-2,2′-bipyridyl (^{4Me}bpy), 4,4′-dimethoxy-2,2′-bipyridyl (^{4MeO}bpy), 1,10-phenanthroline (phen), and tetramethylethylenediamine (TMEDA) (Table S2, entries 1–5). However, bulky 6,6′-dimethyl-2,2′-bipyridyl (^{6Me}bpy) and electron-deficient 4,4′-dibromo-2,2′-bipyridyl (^{4Br}bpy) were inferior to bpy (Table S2, entries 6 and 7). Whichever bidentate ligand was used, **1b** was selectively obtained without formation of **1c**. We also examined the effect of monodentate ligands. 2,4,4-Trimethyl-2-oxazoline and pyridine were not effective (Table S2, entries 8 and 9). 4-Dimethylaminopyridine and 1-methylimidazole gave **1b** in 79% and 70% yields, respectively (Table S2, entries 10 and 11). Therefore, it is likely that ligands that coordinate strongly to Cu center are effective. The reactions did not proceed when other metal sources such as $MnCl_2{\cdot}4H_2O$, $FeCl_3$, and $CoCl_2$ were used (Table S3). The yield of **1b** also drastically decreased when the solvent was changed from MeCN to tetrahydrofuran or 1,2-dichloroethane (Table S4).

The yield of **1b** drastically decreased without a Cu source, ligand, or *N*-oxyl (Table 2, entries 2–4 vs. entry 1). When the reaction was performed under an Ar atmosphere, the yield of **1b** was only 3%, which was below the amount of catalyst used (10 mol%) (Table 2, entry 5). Therefore, O_2 in air functioned as the terminal oxidant in this α-oxygenation. Under the optimized $Cu(OTf)_2$/CuCl/bpy/DMN-AZADO reaction conditions (standard conditions), the oxygenation of **1a** was completed within 2 h, affording 98% yield of **1b** (Figure S2, Table 2, entry 1). The reaction solution was dark red during the catalytic turnover and became green when **1a** was completely converted to **1b**. Even when the amount of DMN-AZADO catalyst was reduced to 1 mol%, **1b** was obtained quantitatively after 24 h (Table 2, entry 6).

Table 2: Control experiments.[a]

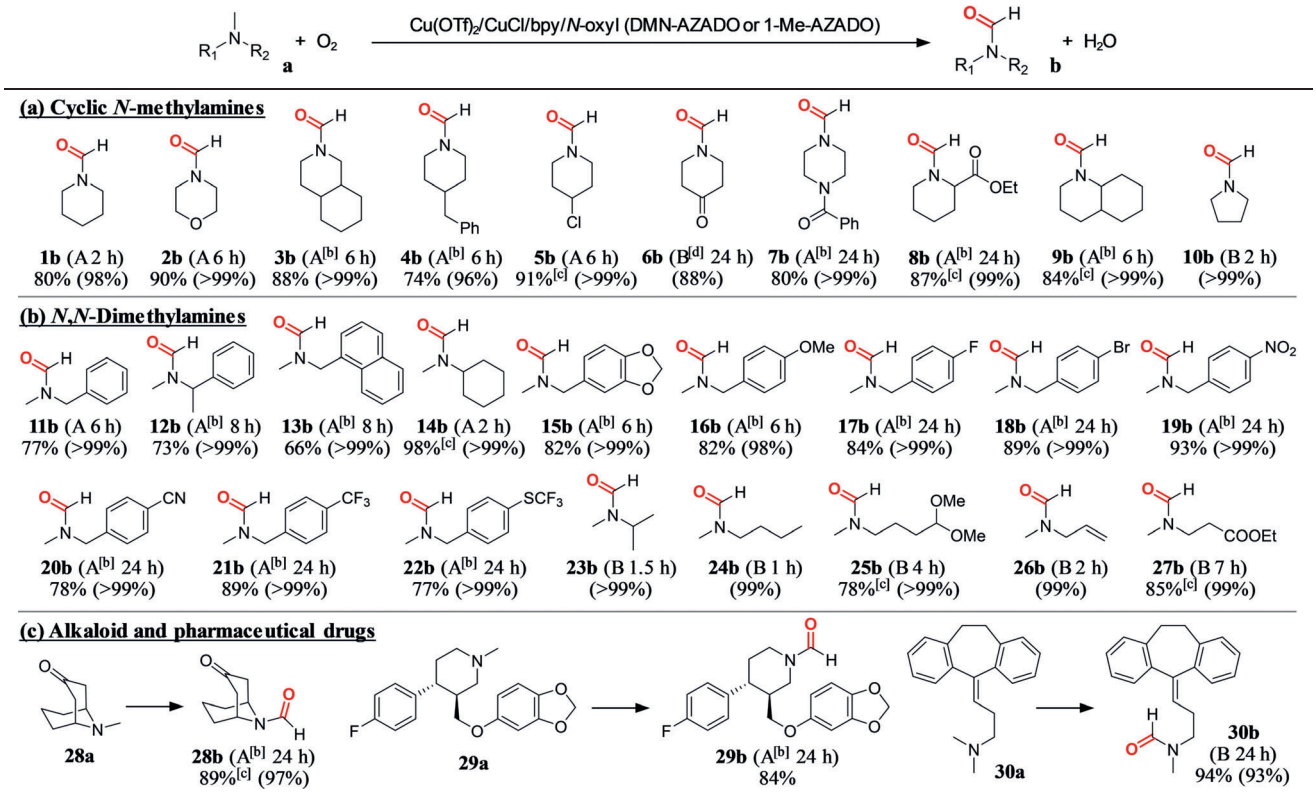
Entry	Deviation from standard conditions	Yield [%]	
		1b	**1c**
1	No changes (standard conditions)	98	n.d.
2	Without Cu	n.d.	n.d.
3	Without bpy	11	n.d.
4	$CuBr_2$ (10 mol%), without DMN-AZADO	n.d.	n.d.
5	Ar atmosphere	3	n.d.
6	DMN-AZADO (1 mol%), 24 h	94	n.d.

[a] Reaction conditions: **1a** (0.25 mmol), Cu/bpy/DMN-AZADO (10/10/10 mol%), MeCN (1 mL), air (open), room temperature, 2 h. Yields were determined by GC analysis.

Substrate Scope for Formamide Synthesis

Under the optimized conditions, we examined the substrate scope for the proposed Cu/*N*-oxyl-catalyzed methyl-selective α-oxygenation of tertiary amines. It was confirmed by NMR analyses of the isolated products or the crude reaction mixtures (after removal of the catalysts by short silica column) that all reactions in Table 3 occurred highly regioselectively at the *N*-methyl positions. We first examined the applicability to cyclic *N*-methylamines (Table 3a). Six-membered cyclic *N*-methylamines, such as 1-methylpiperidine and 4-methylmorpholine, were oxygenated to the corresponding formamides in high yields (Table 3a, **1** and **2**). Various six-membered cyclic *N*-methylamines with substituents at the 3- or 4-positions reacted efficiently to afford the corresponding formamides in high yields (Table 3a, **3** and **4**). Chloro, ketone, and amide groups were tolerated in this oxygenation (Table 3a, **5**–**7**). Although DMN-AZADO showed poor catalytic activity for six-membered cyclic *N*-methylamines with substituents at the 2-positions, the reaction proceeded effectively with less bulky 1-Me-AZADO (Table 3a, **8** and **9**). The reaction of a five-membered *N*-

Table 3: Substrate scope for α-methyl-selective oxygenation of tertiary amines.[a]



[a] Reaction conditions **A**: Amine substrate **a** (0.25 mmol), $Cu(OTf)_2$/CuCl/bpy/DMN-AZADO (5/5/10/10 mol%), MeCN (1 mL), air (open), room temperature; Conditions **B**: Amine substrate **a** (0.25 mmol), $Cu(OTf)_2$/CuCl/bpy/2,4,4-trimethyl-2-oxazoline/DMN-AZADO (10/10/20/50/20 mol%), MeCN (1 mL), air (open), room temperature. Isolated yields and GC yields (the values in parentheses) are shown. Limitation of substrate is described in Table S5. [b] 1-Me-AZADO (10 mol%) rather than DMN-AZADO. [c] 0.5 mmol scale (two-fold scale-up). [d] Without the oxazoline ligand.

methylamine, 1-methylpyrrolidine, under the conditions A was failed. When the amount of Cu/bpy/DMN-AZADO was increased from 10 mol% to 20 mol%, and 2,4,4-trimethyl-2-oxazoline was used, *N*-formylpyrrolidine was produced in a quantitative yield (Table 3a, **10**).[54] As previously mentioned, 2,4,4-trimethyl-2-oxazoline was not an effective ligand (Table S2, entry 11). It is possible that 2,4,4-trimethyl-2-oxazoline functions as a suitable base and promotes the deprotonation (and/or protonation).[54] However, the details are unclear and thus further studies are required. In all cases, no byproducts derived from oxygenation at the ring positions were detected.

This catalytic system was also applicable to the α-oxygenation of *N*,*N*-dimethylamines (Table 3b). For *N*,*N*-dimethylamines, both DMN-AZADO and 1-Me-AZADO were effective. Various *N*,*N*-dimethylamines with benzyl, naphthylmethyl, and cyclohexyl groups reacted efficiently, affording the corresponding formamides in high yields (Table 3b, **11**–**14**). The reaction proceeded smoothly when *N*,*N*-dimethylbenzylamine derivatives with electron-donating groups were used as the substrates, and the corresponding formamides were obtained in high yields (Table 3b, **15** and **16**). Although *N*,*N*-dimethylbenzylamine derivatives with electron-withdrawing groups were less effective, the oxygenation was almost complete when the reaction time was increased to 24 h (Table 3b, **17**–**22**). The yields of formamides were unsatisfactory with some kinds of *N*,*N*-dimethylamines, such as *N*,*N*-dimethylisopropylamine and *N*,*N*-dimethylbutylamine, under the standard conditions. For these substrates, the corresponding formamides were obtained in good yields by using 2,4,4-trimethyl-2-oxazoline and increasing the amount of catalyst as with 1-methylpyrrolidine (Table 3b, **23** and **24**). The ester, acetal-protected aldehyde, and olefinic groups were also tolerated, affording the corresponding formamides in excellent yields (Table 3b, **25**–**27**). Whichever *N*,*N*-dimethylamine substrates were used, the oxygenation occurred regioselectively at the *N*-methyl positions with *N*-methylene, *N*-methine, and *N*-benzyl groups remaining intact, as shown in Table 3b.

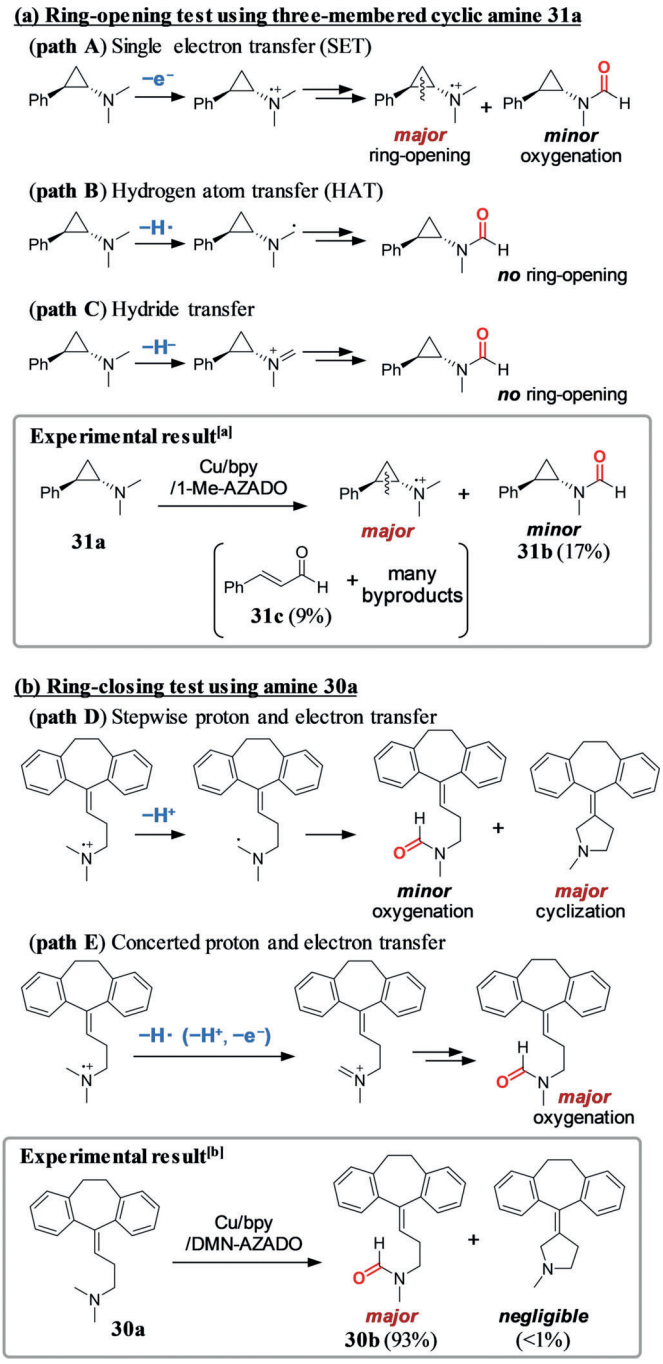
Notably, this catalyst system could be applied to a natural alkaloid and commercially available pharmaceutical drugs (Table 3c). Pseudopelletierine (**28a**), an alkaloid derived from the pomegranate tree, was efficiently converted to the corresponding formamide in a high yield (Table 3c, **28**). Furthermore, *N*-methylparoxetine (**29a**) and amitriptyline (**30a**), medicines for mental illness, reacted smoothly, giving the corresponding formamides (Table 3c, **29** and **30**). Thus, this catalyst system would enable a useful reaction for functionalizing *N*-methyl groups of bioactive compounds while preserving the original amine substrate skeletons.

Reaction Mechanism and Origin of Regioselectivity

Various experiments were conducted to elucidate the reaction mechanism. Firstly, to better understand the origin of the formamide oxygen, a series of ^{18}O-labeling experiments was conducted. The α-oxygenation of **1a** with 30 mol% of $H_2{}^{18}O$ under $^{16}O_2$ (purified air, 1 atm) afforded ^{18}O-labeled **1b** and unlabeled **1b** in 23% and 74% yields, respectively (Figure S3a). The ^{18}O-labeled **1b**/total **1b** ratio was 0.52 at the initial stage of the reaction (after 15 min) and gradually decreased as the yield of **1b** increased (Figure S3b). When α-oxygenation of **1a** was performed with 500 mol% of $H_2{}^{18}O$ under $^{16}O_2$ (purified air, 1 atm), 67% ^{18}O incorporation in the product was observed after 24 h. These results suggest that the formamide oxygen originates from water; thus, in the early stages of the reaction, formamide is considered to be produced from water ($H_2{}^{18}O$) originally contained in the reaction system, and water produced by $^{16}O_2$ reduction is also used in the later stage of the reaction.

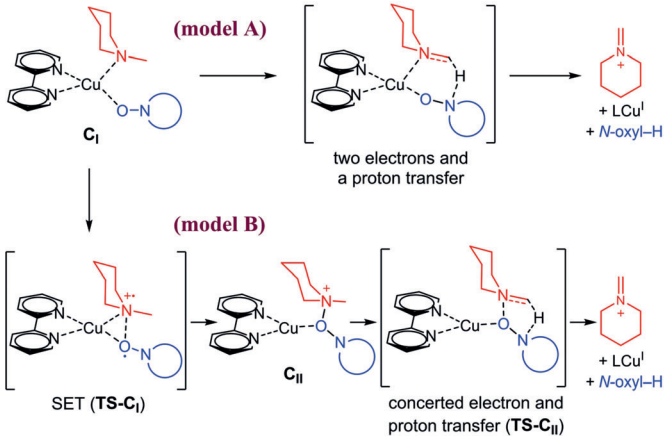
In this α-oxygenation, two electrons and one proton of the amine substrate are believed to transfer to the catalyst to form an iminium cation intermediate which is subsequently reacted with water to produce a hemiaminal intermediate. The following investigations were performed to gain insight into electron and proton transfer mechanisms. It is known that ring-opening proceeds when radical species are generated adjacent to a three-membered ring.[42,55,56] Among the following three possible amine-oxidation mechanisms, path **A**: single electron transfer (SET) from the nitrogen atom; path **B**: hydrogen atom transfer (HAT) from the α-methyl position; and path **C**: hydride transfer from the α-methyl position, the ring-opening of three-membered cyclic amine **31a** would proceed only via path **A** (Scheme 2a). In this $Cu(OTf)_2$/CuCl/bpy/1-Me-AZADO system, the conversion of **31a** reached >99% after 4 h, and α-methyl-oxygenated product **31b** was obtained in only 17% yield with the concomitant formation of many byproducts derived from ring-opening including cinnamaldehyde (9% yield) (Scheme 2a). Therefore, path **A** (SET) is considered to be dominant. Furthermore, the reaction of **31a** hardly proceeded when using DMN-AZADO (Scheme S1). Considering that the *N*-oxyl-Cu adduct (complex **B**; see Figure 2) was detected by CSI-MS as the possible active species, bulky **31a** was difficult to coordinate to the adduct when DMN-AZADO was used rather than less bulky 1-Me-AZADO. Neither did the reactions proceed without *N*-oxyls (Scheme S1), suggesting that the reaction was initiated through SET by Cu only when both the substrate and *N*-oxyl coordinated to the Cu center.

The mechanism of electron and proton transfer from a radical cation species formed through the SET was then investigated. In stepwise proton and electron transfer (path **D**), 5-*exo*-cyclization of amine **30a** mainly proceeds via formation of the carbon radical at the α-position (Scheme 2b).[55–57] However, when an electron and a proton are concertedly transferred (path **E**), the 5-*exo*-cyclization of **30a** would be less likely to occur (Scheme 2b). In this $Cu(OTf)_2$/CuCl/bpy/DMN-AZADO system, the α-methyl-oxygenation of **30a** mainly proceeded without 5-*exo*-cyclization (Scheme 2b), suggesting that electron and proton transfer from the radical cation would proceed concertedly (path **E**). This concerted abstraction of the electron and proton from the radical cation is considered to proceed soon after the initial SET, since a small amount of **31b** was produced even though the ring-opening of **31a** proceeded rapidly (Scheme 2a).[42,55,56]



Scheme 2. Mechanistic investigation of the radical intermediate. [a] Reaction conditions: **31a** (0.25 mmol), $Cu(OTf)_2$/CuCl/bpy/*N*-oxyl (5/5/10/10 mol%), MeCN (1 mL), air (open), room temperature, 4 h. [b] Reaction conditions: **30a** (0.25 mmol), $Cu(OTf)_2$/CuCl/bpy/2,4,4-trimethyl-2-oxazoline/DMN-AZADO (10/10/20/50/20 mol%), MeCN (1 mL), air (open), room temperature, 24 h.

On the basis of the above-mentioned experimental evidence, two amine-oxidation models were proposed (Scheme 3): model **A**: SET and subsequent electron and proton transfer in a closed-shell Cu complex coordinated by



Scheme 3. Possible amine-oxidation models. L = bpy, *N*-oxyl = DMN-AZADO or 1-Me-AZADO, *N*-oxyl-H = hydroxylamine.

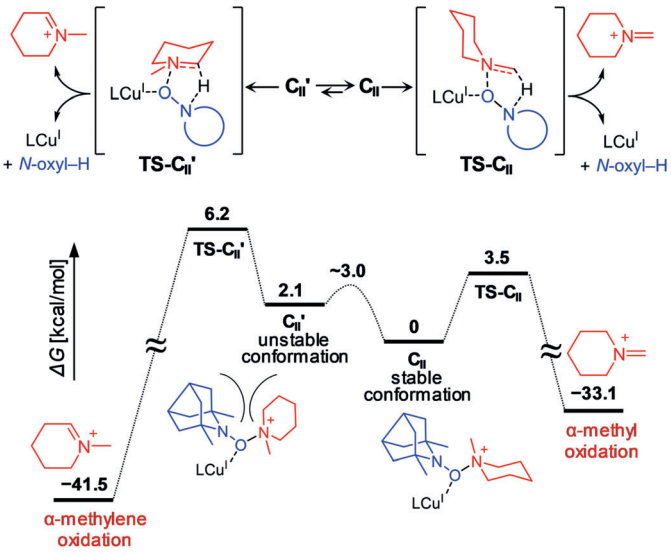


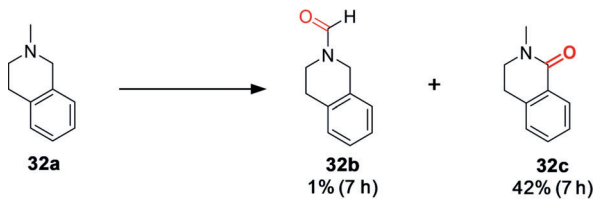
Figure 3. Investigation into the regioselectivity of α-oxygenation of tertiary amine **1a** by DFT calculation based on amine-oxidation model **B**. L = bpy, *N*-oxyl = DMN-AZADO, *N*-oxyl-H = hydroxylamine.

both the amine and the *N*-oxyl (complex $\mathbf{C_I}$); and model **B**: SET in a closed-shell Cu complex $\mathbf{C_I}$ and subsequent electron and proton transfer in a *N*-oxyl-amine adduct (complex $\mathbf{C_{II}}$) produced by radical-radical coupling of the *N*-oxyl and radical cation derived from the amine substrate. These two amine-oxidation mechanisms were examined by DFT computational studies. Firstly, model **A** was found to be inappropriate; α-methylene oxidation of five-membered cyclic amine **10a** was calculated to be favorable compared with α-methyl oxidation with a difference exceeding 5 kcal mol^{-1}, though the experimental result revealed that α-oxygenation of **10a** took place regioselectively at the α-methyl position only (Scheme S2). In computational studies based on model **A**, it was considered that the steric hindrance of the amine and bpy ligand mainly determined the regioselectivity of oxygenation of **10a** at the α-methylene position (Scheme S2, model **A**).

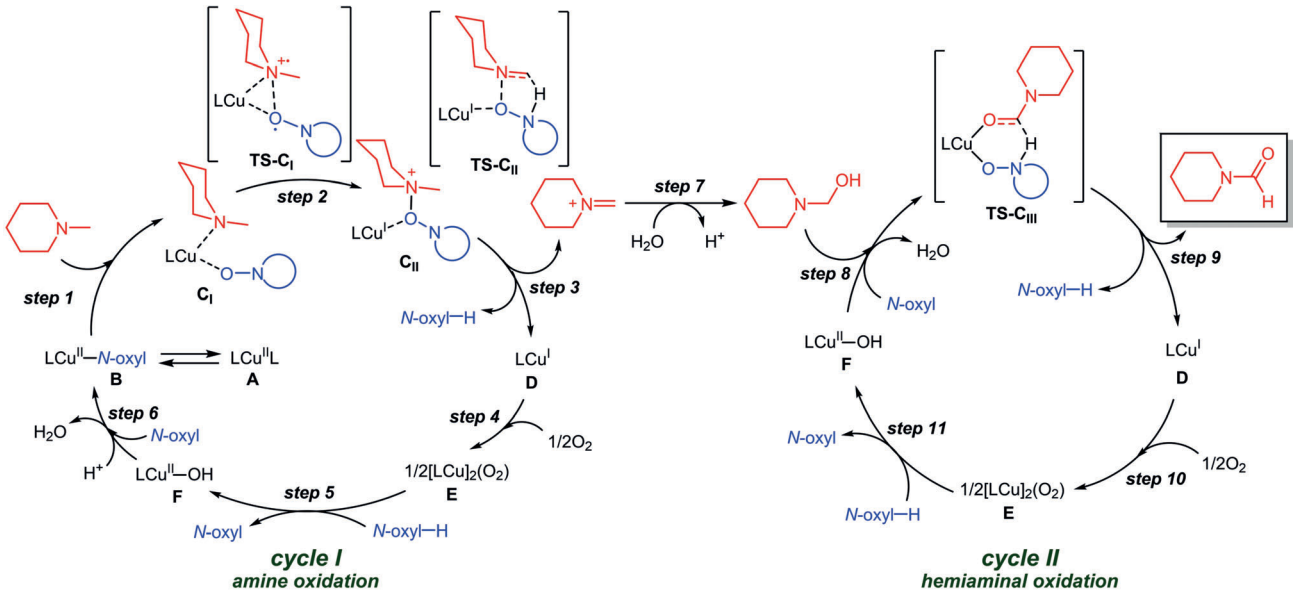
On the other hand, the experimental result was well-supported by model **B**; α-methyl oxidation was calculated to be more favorable than α-methylene oxidation (Figure 3, Scheme S3a). As shown in Figure 3, the energy barrier of α-methyl oxidation of **1a** via the speculated intermediate $\mathbf{C_{II}}$ was calculated as 3.5 kcal mol^{-1}. However, α-methylene oxidation of **1a** would require formation of the relatively unstable conformation $\mathbf{C_{II}}'$ (2.1 kcal mol^{-1} higher than intermediate $\mathbf{C_{II}}$) due to the steric hindrance originating from the *N*-oxyl and six-membered ring structure of amine **1a**. Thus, the energy barrier for α-methylene oxidation was 6.2 kcal mol^{-1}. In the oxygenation of **10a**, α-methyl oxidation was also calculated to be favourable because of the steric hindrance of the amine substrate and *N*-oxyl compared with α-methylene oxidation (Scheme S2, model **B**). Furthermore, we also performed the DFT computational studies for the nor-AZADO-catalyzed oxygenation of **1a** using model **B**. The calculation results well reproduced the experimental fact that the reaction proceeded in a methyl-selective manner even when using nor-AZADO (Figure 1, Table S1, entries 1 and 2); α-methyl oxidation was calculated to occur preferentially by 1.6 kcal mol^{-1} compared to α-methylene oxidation, and the amine-*N*-oxyl interaction also determined the methyl selectivity (Scheme S3b).

The regioselectivity of this α-oxygenation was then further tested on the basis of computational model **B**. Unlike amine **1a** and **10a**, α-methylene oxidation was calculated as 3.2 kcal mol^{-1} more favorable than α-methyl oxidation with 2-methyl-1,2,3,4-tetrahydroisoquinoline (**32a**), possibly because **32a** has no proton that protrudes into the bulky *N*-oxyl due to the aromatic ring (Scheme S3c). Experimental examination revealed that amide **32c**, an α-methylene-oxygenated product, was obtained regioselectively in 42% yield with this Cu(OTf)$_2$/CuCl/bpy/1-Me-AZADO system, and formamide **32b** was hardly obtained (Scheme 4, Scheme S3c). Consequently, we concluded that the regioselectivity of amine oxidation was determined by the steric constraints of the amine-*N*-oxyl interaction.

On the basis of the aforementioned experimental evidence, DFT calculations, and reported literatures,[39,47–50] a possible oxygenation mechanism is proposed as shown in Scheme 5. A tertiary amine initially coordinates to complex **B** to form complex $\mathbf{C_I}$ (Scheme 5, step 1). A radical cation intermediate formed through SET oxidation (**TS-C$_I$**) is then



Scheme 4. Oxygenation of **32a**. Reaction conditions: **32a** (0.25 mmol), Cu(OTf)$_2$/CuCl/1-Me-AZADO/*N*-oxyl (5/5/10/10 mol%), MeCN (1 mL), air (open), room temperature, 7 h. See also Scheme S3.



Scheme 5. Plausible reaction mechanism. L = bpy, *N*-oxyl = DMN-AZADO or 1-Me-AZADO, *N*-oxyl-H = hydroxylamine.

immediately trapped by an *N*-oxyl to form complex $\mathbf{C_{II}}$ (Scheme 5, step 2) followed by the formation of an iminium cation intermediate and a hydroxylamine (*N*-oxyl-H) through concerted proton and electron transfer ($\mathbf{TS\text{-}C_{II}}$) (Scheme 5, step 3). The regioselectivity of this oxidation is determined by step 3. Reduced copper species **D** is then oxidized by O_2 to form species **E** followed by its reduction by *N*-oxyl-H to generate Cu^{II}-OH species **F** (Scheme 5, steps 4 and 5). Complex **B** is regenerated by the reaction of **F** with *N*-oxyl to complete catalytic cycle I (Scheme 5, step 6). Meanwhile, a hemiaminal intermediate is formed by nucleophilic addition of water to the iminium cation species generated in catalytic cycle I (Scheme 5, step 7). We believe that oxidation of the hemiaminal intermediate proceeds according to the mechanism proposed by Stahl and co-workers (Scheme 5, steps 8 and 9), in which two electrons and one proton transfer concertedly in closed-shell transition state $\mathbf{TS\text{-}C_{III}}$.[47–50] Reduced copper species **D** is regenerated to form active Cu^{II}-OH species **F** by the reaction with O_2 and *N*-oxyl-H as in catalytic cycle I (Scheme 5, steps 10 and 11).

Conclusion

In this study, we successfully developed a highly regioselective and efficient aerobic α-oxygenation of tertiary *N*-methylamines catalyzed by a Cu/bpy/*N*-oxyl catalyst system. Various types of tertiary *N*-methylamines, including a natural alkaloid and pharmaceutical drugs, could be transformed to the corresponding formamides by the proposed method. The key to realizing this efficient oxygenation system is the use of caged *N*-oxyls with moderate steric hindrance together with an appropriate amount of anion, such as Cl^- or Br^-, as the monodentate ligand to enhance the coordination of the *N*-oxyls. We concluded that the steric constraints of the amine and *N*-oxyl during amine oxidation determine the regioselectively at the *N*-methyl positions. This catalytic oxygenation proceeds under extremely mild conditions (e.g., room temperature and open air atmosphere), enabling excellent functional group tolerance and a user-friendly protocol. We hope that this α-oxygenation system will find wide application, especially in fine chemical synthesis.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: copper · formamides · methyl-selective α-oxygenation · nitroxyl radical · tertiary amines

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[51] We confirmed by GC-MS analysis that a byproduct possibly derived from nor-AZADO ($m/z = 151$, assignable to *N*-formyl-9-azanoradamantane) was formed during the reaction albeit in a small amount (below 5%). There is no clear evidence for the formation mechanism of this byproduct, but it is considered to be generated from the cleavage of the N–O bond of nor-AZADO. In contrast, such byproducts were not detected when using DMN-AZADO and 1-Me-AZADO.
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[53] Stahl and co-workers reported that coordination of an *N*-oxyl to form a $[Cu(bpy)(N\text{-oxyl})(OR)]^+$ species is quite unfavorable.[49] In contrast, our DFT computational studies revealed that the formation of $[Cu(bpy)(DMN\text{-}AZADO)Br]^+$ was thermodynamically favorable. Therefore, as one of the reviewers pointed out, the replacement of an alkoxy ligand with Br^- could change the thermodynamics for binding of the *N*-oxyl.
[54] Even when the amount of 2,4,4-trimethyl-2-oxazoline was reduced to 20 mol% for the oxygenation of **10a**, **10b** was obtained quantitatively after 2 h. Furthermore, the oxygenation of **10a** was carried in the presence of bpy together with 1,8-diazabicyclo[5.4.0]undec-7-ene (20 mol%). However, in this case, the reaction hardly proceeded.
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[57] Coupling reactions of carbon radical at α-methyl position with O_2 would be ignorable, considering that the main oxygen source was water, rather than O_2.

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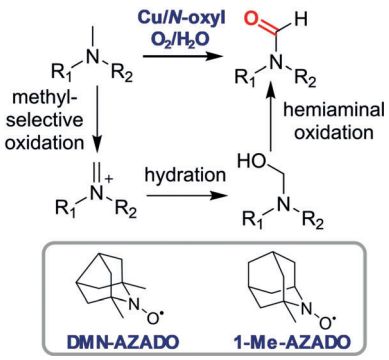
Research Articles

Oxygenation Reactions

S. Nakai, T. Yatabe, K. Suzuki, Y. Sasano, Y. Iwabuchi, J. Hasegawa, N. Mizuno, K. Yamaguchi* _____ ■■■■–■■■■

Methyl-Selective α-Oxygenation of Tertiary Amines to Formamides by Employing Copper/Moderately Hindered Nitroxyl Radical (DMN-AZADO or 1-Me-AZADO)



Mild and selective: The methyl-selective α-oxygenation of various tertiary amines to the corresponding formamides (30 examples) is achieved by employing copper and a moderately hindered nitroxyl radical (DMN-AZADO or 1-Me-AZADO) under mild conditions. The high regioselectivity of this catalyst system stems from steric restriction of the amine–*N*-oxyl interactions.