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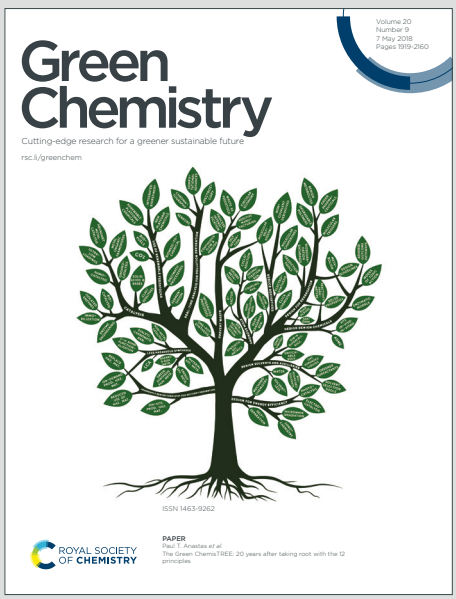

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ARTICLE

Copper Catalyzed *N*-Formylation of α-Silyl-Substituted Tertiary *N*-Alkylamines by Air

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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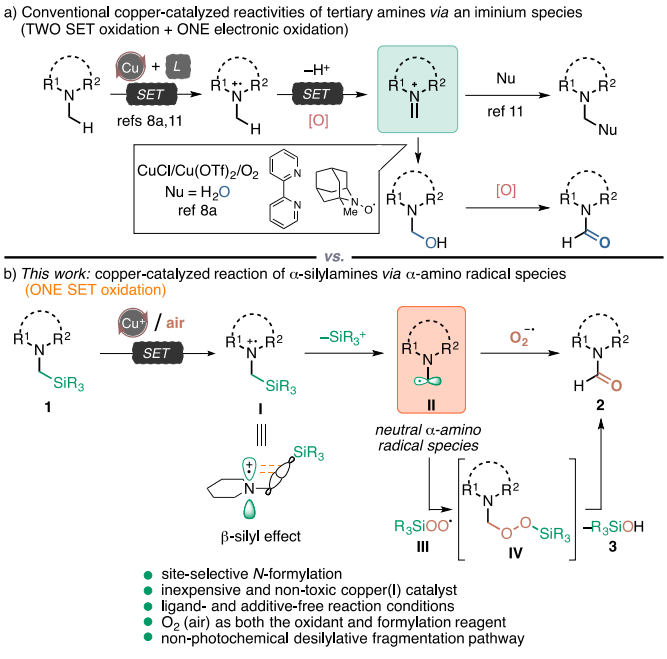
A site-selective method to prepare *N*-formyl amines efficiently that relies on the copper(I)-catalyzed oxidation of α-silyl-substituted tertiary *N*-alkylamines by air at room temperature is described. The oxidative protocol was shown to exhibit excellent functional group tolerance as it was applicable to a wide variety of amine substrates and a number of bioactive molecules and natural products. Moreover, it delinates a ligand- and additive-free amine oxidation process mediated by a low-cost metal salt with oxygen from air taking on the role of both the terminal oxidant and as part of the formylation reagent, which is unprecedented in copper catalysis. It also offers the first synthetic method that can selectively generate α-amino radical species as reactive intermediates from α-silylamines under non-photochemical reaction conditions.

Introduction

N-Formyl amines are a key structural motif in many bioactive natural products and pharmaceutical compounds as well as biological intermediates.[1,3] The compound class is also a versatile solvent, protecting group, reagent or chiral Lewis base organocatalyst in chemical synthesis.[4–7] For this reason, the development of new efficient synthetic methods for formamide synthesis continues to be actively pursued.[2,8–11] In recent years, this has been further fuelled by the demand for new synthetic tools that can streamline routes to synthetically and medicinally valuable small molecules.[8] Along with this is the growing demand for sustainable synthetic methods that can minimize or eliminate various reagent and energy resources such as ligands, additives, high reaction temperatures and pressurized gases such as CO and CO_2, and use low-cost metal catalysts and renewable oxidants such as oxygen from air.[9]

Copper-catalyzed α-functionalization of tertiary amines using oxygen as the oxidant has established itself in recent years as one of the most powerful synthetic tools to rapidly increase molecular complexity in a single step (Scheme 1a).[8a,11] From a mechanistic perspective, the reactions rely on the propensity of the electron-rich amine substrate to undergo single electron transfer (SET) oxidation to give the corresponding nitrogen-radical centered cation species.[11c–e] This is often followed by a second SET oxidation event to give the iminium species, which can subsequently engage in addition reactions with weak nucleophiles such as those of an alkyne, methyl ketone or phosphine. A recent example of this is the *N*-formylation of tertiary *N*-methylamines by a sterically demanding Cu(I)/Cu(II)/bipyridyl catalytic system activated by O_2 and with adamantyl *N*-oxyl as the sacrificial oxidant (Scheme 1a).[8a] The iminium species formed *in situ* during the course of the reaction was delineated to undergo a hydrolysis/hemiaminal oxidation cascade. In contrast, a single oxidation process involving tertiary amines in which oxygen from air acts as both the terminal oxidant and the formylation reagent to chemoselectively give *N*-formyl amines has so far remained unrealized. Presumably, this could be due to the challenge of supressing preferential formation of the iminium adduct as the α-amino radical species



Scheme 1 Iminium vs α-amino radical species as reactive intermediates.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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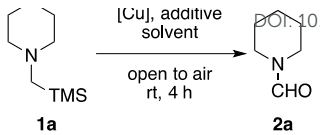
has been shown to be more readily oxidized than the starting amine under reaction conditions involving an excess amount of oxidant.[12] As a consequence, this makes the precise control of the oxidation process key to exploiting the α-amino radical species as a reactive intermediate. In this regard and as part of an ongoing program examining the utility of oxidative copper catalysis in organic synthesis, we became interested in the potential reactivity of bench-stable α-silyl-substituted tertiary *N*-alkylamines (Scheme 1b).[13] We anticipated that the compound class would readily undergo SET oxidation to give the nitrogen-centered species **I** due to the comparable redox potentials of the substrate and Cu(II)-Cu(I) systems.[14] With the possibility of β-silyl hyperconjugative stabilization, this may lead to facile desilylative fragmentation to afford the corresponding α-amino and peroxysilyl radical fragments **II** and **III**.[15,16] Radical recombination of the two reactive intermediates followed by a rapid deprotonation/desilylation cascade of the ensuing peroxide adduct **IV** might then be envisaged to deliver the formamide product.[17] Herein, we disclose the details of this *N*-formylation chemistry which offers an efficient and chemoselective route a synthetically valuable member of the amide compound family in good to excellent yields from α-silylamines. It provides a site-selective *N*-formylation protocol with key features that include: (a) the use of inexpensive and non-toxic CuBr as the catalyst; (b) a catalytic system that did not require ligands and/or additives; (c) oxygen from air acting as both the terminal oxidant and as part of the formylation reagent that is, to our knowledge, an extremely rare mode of reactivity in copper catalysis;[10] (d) extremely mild reaction conditions at ambient temperature and pressure that enabled exceptional functional group tolerance as exemplified by the late-stage modification of 13 bioactive molecules; (e) generation of a stoichiometric amount of silanol as potentially the only byproduct. Added to this, it realizes the first example in organic chemistry that can generate α-amino radical species as reactive intermediates from α-silylamines under non-photochemical reaction conditions.[15,16]

Results and discussion

We began our studies by examining the *N*-formylation of α-silylamine **1a**, prepared from chlorotrimethylsilane and piperidine, mediated by a variety of copper salts and air to determine the optimum reaction conditions (Table 1). This initially revealed treating a neat solution of the substrate with 20 mol % of CuBr under ambient reaction conditions at room temperature for 4 h gave a mixture of piperidine-1-carbaldehyde **2a** and the starting material in 55% yield (entry 1). In contrast, the use of toluene, diethyl ether, THF, ethyl acetate or acetone as the solvent was found to lead to lower product yields of 6–37% (entries 2–6). We were pleased to find a higher product yield of 70% was subsequently obtained on repeating the control experiment in acetonitrile in place of methanol as the solvent (entry 7). With acetonitrile as the solvent, the introduction of CsF, $NaHCO_3$ or Et_3N as an additive was found to result in lower product yields of 19–58% (entries 8–10). On the other hand, reducing the catalyst loading from 20 to 10 mol %

Table 1 Optimization of the reaction conditions[a]



1a **2a**

Entry	[Cu] (mol %)	Solvent (M)	Additive (equiv)	Yield (%)[b]
1	CuBr (20)	-	-	55
2	CuBr (20)	toluene (0.2)	-	37
3	CuBr (20)	Et_2O (0.2)	-	6
4	CuBr (20)	EtOAc (0.2)	-	29
5	CuBr (20)	acetone (0.2)	-	35
6	CuBr (20)	MeOH (0.2)	-	18
7	CuBr (20)	MeCN (0.2)	-	70
8	CuBr (20)	MeCN (0.2)	CsF (2)	19
9	CuBr (20)	MeCN (0.2)	$NaHCO_3$ (2)	58
10	CuBr (20)	MeCN (0.2)	Et_3N (2)	45
11	CuBr (10)	MeCN (0.2)	-	70
12	CuBr (10)	MeCN (0.4)	-	89[d]
13	CuBr (10)	MeCN (0.4)	1,10-phen (0.2)	-[c]
14	CuCl (10)	MeCN (0.4)	-	50
15	CuI (10)	MeCN (0.4)	-	50
16	$Cu(MeCN)_4PF_6$ (10)	MeCN (0.4)	-	-[c]
17	$CuBr_2$ (10)	MeCN (0.4)	-	61
18	$CuBr_2$ (10)	MeCN (0.4)	1,10-phen (0.2)	-[c]
19	$CuCl_2$ (10)	MeCN (0.4)	-	57
20	-	MeCN (0.4)	-	-[c]

[a] All reactions were performed with 0.1 mmol of **1a** with the catalyst system stated in the Table and exposed to open to air at room temperature for 4 h. [b] All product and recovered substrate yields were determined by ^{1}H NMR measurements using 2-(bromomethyl)naphthalene as the internal standard. [c] Substrate recovered in 3 to >99% yield. [d] Isolated product yield.

was found to have no influence on the outcome of the reaction, with the product afforded in 70% yield (entry 11). Our investigations next found lowering the reaction concentration from 0.2 and 0.4 M at a catalyst loading of 10 mol % gave the best result, providing an isolated product yield of 89% (entry 12). Under these latter reaction conditions, slightly lower product yields of 50–61% were furnished in the analogous control reactions mediated by CuCl, CuI, $CuCl_2$ or $CuBr_2$ (entries 14, 15, 17 and 19). However, no reaction could be observed by either TLC analysis or ^{1}H NMR measurements of the crude mixtures of control experiments with $Cu(MeCN)_4PF_6$ and the 1,10-phenanthrolinyl complexes of CuBr and $CuBr_2$ (entries 13, 16 and 18). Similarly, a final control reaction in the absence of the Group 11 metal salt was found to lead to the detection of only the starting material by TLC analysis and ^{1}H NMR measurements of the crude mixture (entry 20). On the basis of the above results, the *N*-formylation of **1a** with CuBr (10 mol %) as the catalyst in acetonitrile (0.4 M) and open to air at room temperature for 4 h was deemed to provide the optimum reaction conditions.

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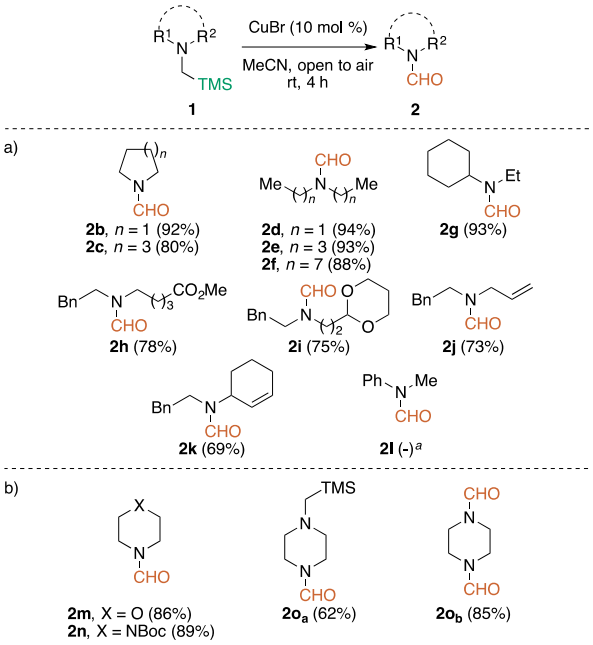
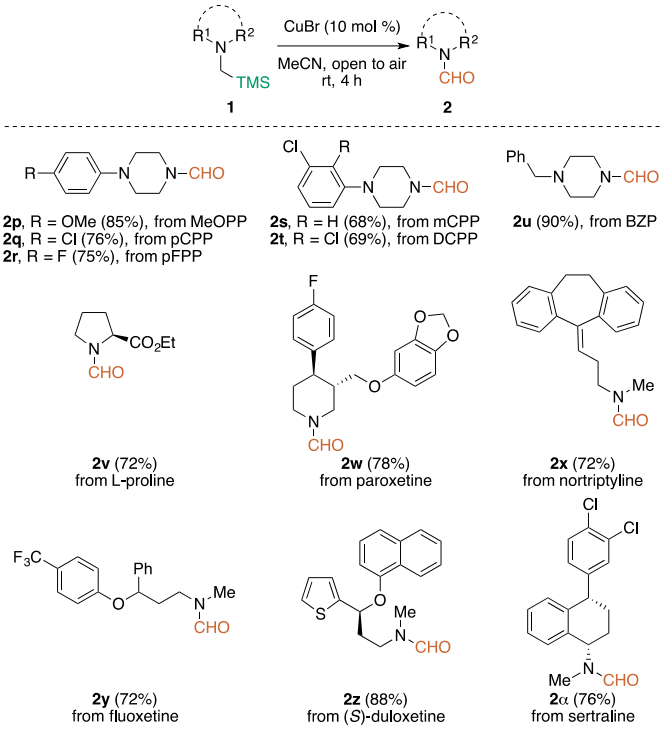
Attention was next turned to assessing the scope of the present procedure with a series of *N*,*N*-dialkyl *α*-silylamines **1b–l** prepared from the corresponding secondary amine and chlorotrimethylsilane, and the results are summarized in Scheme 2a. In general, these experiments showed that the oxidative CuBr-mediated reaction conditions were broad, furnishing a variety of substituted formamides **2b–k** in 62–94% yield from the corresponding substrates. Experiments of *α*-silylamines containing a pyrrolidinyl (**1b**) or azepanyl (**1c**) ring system instead of a piperidinyl motif were observed to proceed well to produce the corresponding *N*-formyl amines **2b** and **2c** in respective yields of 92 and 80%. Starting materials in which the nitrogen heterocycle was replaced with an acyclic amine with pendant *N*-alkyl substituents of varying chain lengths (**1d–f**) or an ethyl and cyclohexyl moiety (**1g**) were found to have no influence on the course of the reaction. In these experiments, the corresponding acyclic *N*-formylation adducts **2d–g** were furnished in 88–94% yield. *N*-Phenylethyl-substituted *α*-silylamines containing a pendant methyl ester (**1h**), 1,3-dioxanyl (**1i**), allyl (**1j**) or cyclohexenyl (**1k**) side-chain were also observed to provide the corresponding formamides **2h–k** in 69–78% yield. The oxidation of the *N*-methyl-*N*-phenyl substrate **1l** was found to be the only exception, which gave a mixture of unidentifiable decomposition products under the standard reaction conditions at room temperature or –10 °C based on ^{1}H NMR measurements.



Scheme 2 CuBr-mediated *N*-formylation of **1b–o** by air. All reactions were performed with 0.2 mmol of **1** and 10 mol % of CuBr in 0.5 mL of acetonitrile exposed to air at room temperature for 4 h. Values in parentheses denote isolated product yield. *a* Unknown decomposition products observed based on ^{1}H NMR measurements of the crude reaction mixture.

In view of their role as privileged scaffolds in many bioactive compounds such the fungicide fenpropimorph, antidepressant amoxapine and anti-ischemic metabolic agent trimetazidine, we next sought to define the scope of the present Cu(I)-mediated method to access *N*-formylated morpholine and piperazine derivatives (Scheme 2b). With this in mind, the *N*-formylation of *α*-silyl-substituted morphine (**1m**) under the CuBr-catalyzed standard reaction conditions was first examined and found to give the corresponding cyclic formamide **2m** in 86% yield. Likewise, the analogous reactions with the mono- and bis-*α*-silyl-substituted piperazine substrates **1n** and **1o** afforded the corresponding *N*-formyl amine products **2n** and **2o$_a$** in respective yields of 89 and 62%. Notably, we were also pleased to find repeating the experiment of **1o** under the CuBr-mediated standard reaction conditions for 8 h provided the diformylated adduct **2o$_b$** in 85% yield. This suggested the possibility to selectively *N*-formylate compounds containing more than one nitrogen center by fine-tuning the reaction time.

To further illustrate the synthetic utility of the present Cu(I)-catalyzed *N*-formylation protocol, the late stage modification of a variety of *α*-silyl-substituted natural products and bioactive molecules were evaluated (Scheme 3). Under the CuBr-mediated standard reaction conditions, the reaction of the *α*-silyl-functionalized synthetic stimulants MeOPP (**1p**), pCPP (**1q**), pFPP (**1r**), mCPP (**1s**), DCPP (**1t**) and BZP (**1u**) gave the corresponding formamides **2p–u** in 68–90% yield. The analogous transformation with the L-proline ethyl ester (**1v**) and antidepressants paroxetine (**1w**), nortriptyline (**1x**) and fluoxetine (**1y**) were likewise found to provide the corresponding aldehyde-containing products **2v–y** in 72–78%



Scheme 3 Late-stage CuBr-mediated *N*-formylation of modified natural products and bioactive molecules **1p–α** by air. All reactions were performed with 0.2 mmol of **1** and 10 mol % of CuBr in 0.5 mL of acetonitrile exposed to air at room temperature for 4 h. Values in parentheses denote isolated product yield.

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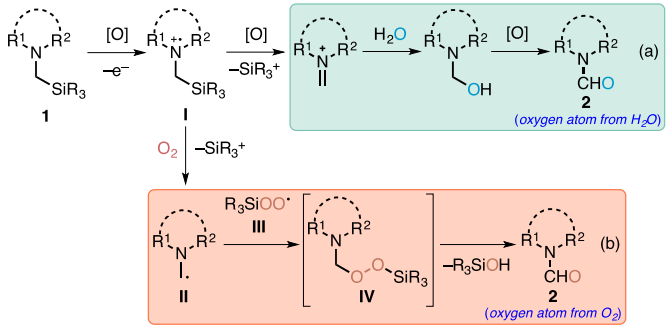
yield. Finally, the analogous Cu(I)-catalyzed *N*-formylations of (*S*)-duloxetine (**1z**), a serotonin-norepinephrine reuptake inhibitor, and sertraline (**1*α***), a selective-serotonin reuptake inhibitor, were found to afford the corresponding *N*-formyl amine adducts **2z** and **2*α*** in yields of 88 and 76%, respectively.

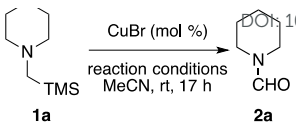
To gain a better understanding of whether the *N*-formylation protocol was more likely to proceed *via* pathways *a* or *b* illustrated in Scheme 4, the following control reactions were performed (Table 2). In a first set of control experiments, the surmised involvement of a radical pathway was supported by the introduction of TEMPO (0.5 equiv) to the copper(I)-catalyzed *N*-formylation of **1a** under the standard reaction conditions for 17 h, which was found to give **2a** in 38% yield (entry 1). This was further corroborated by repeating the control experiment of **1a** with 1 or 2 equiv of the radical scavenger and obtaining the *N*-carbaldehyde in lower yields of 25 and 19% (entries 2–3). The role of air providing oxygen as the terminal oxidant was supported by subjecting **1a** to the CuBr-mediated standard reaction conditions under a nitrogen or oxygen atmosphere (entries 4 and 5). Under a nitrogen atmosphere, this led to the recovery of the *α*-silylamine in near quantitative yield based on ^{1}H NMR measurements. In contrast, the analogous control reaction under an oxygen atmosphere was observed to produce **2a** in 50% yield. In a second set of control reactions, the CuBr-mediated control reaction of **1a** with 1,4-benzoquinone as an additive gave **2a** in 12% yield, which implied the presence of the superoxide radical anion (entry 6).[18] With BHT (0.5 equiv) in place of 1,4-benzoquinone as the additive, a similar outcome was found, giving a product yield of 17% along with a derivative of the additive containing a molecule of oxygen in 12 mg (entry 7). Although the structure of the latter could not be elucidated by NMR measurements, it's detection along with the low product yield provided further evidence of the involvement of the superoxide radical anion and a radical pathway.[19]



Scheme 4 Mechanistic investigation of the possible *N*-formylation reaction pathways.

In a final set of control reactions, the proposed elimination of the silyl motif as the silanol adduct on generation of the *N*-formylated product was shown to be likely by subjecting the PhMe$_2$Si-substituted substrate **1*β*** to the CuBr-mediated standard reaction conditions for 17 h (Table 3, entry 1). Monitoring the control experiment by ^{1}H NMR analysis showed the gradual formation of the *N*-formyl amine and PhMe$_2$SiOH **3*β*** in 75 and 80% yield, respectively, with the latter isolated in

Table 2 Control experiments with **1a**[a]



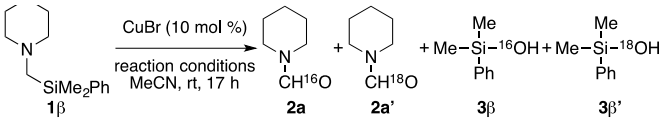
1a **2a**

Entry	Catalyst loading (mol %)	Reaction conditions	Yield (%)[b]
1	20	TEMPO (0.5 equiv)/air	38
2	20	TEMPO (1 equiv)/air	25
3	20	TEMPO (2 equiv)/air	19
4	10	N_2 atmosphere	-
5	10	O_2 atmosphere	50
6	10	1,4-benzoquinone (1 equiv)/air	12
7	10	BHT (0.5 equiv)/air	17[c]

[a] All reactions were performed with 0.2 mmol of **1a** and CuBr at a catalyst loading and reaction conditions stated in the Table in acetonitrile (0.5 mL) at room temperature for 17 h. [b] ^{1}H NMR product yield with 2-(bromomethyl)naphthalene as the internal standard. [c] Unknown structure of a BHT derivative containing a molecule of oxygen obtained in 12 mg based on NMR measurements and mass spectrometry.

82% yield. Moreover, our hypothesis that the succeeding role of air providing oxygen as part of the formylation reagent was supported by repeating control reaction with 4 Å molecular sieves (MS) in distilled acetonitrile and air pre-dried through a plug of H_2SO_4, which afforded **2a** and **3*β*** in 43 and 46% yield (entry 2). This was further augmented by performing the control experiment for a third and fourth time in distilled acetonitrile containing 1.25 or 10 equiv of $H_2{}^{18}O$ in place of 4 Å MS (entries 3 and 4).[20] These tests gave **2a** and **3*β*** with no incorporation of the isotope in respective yields of 57 and 48%, or no reaction, which also indicated that the elimination of the silyl group was unlikely to occur through nucleophilic attack by water. Consistent with this are the product yields obtained in the Cu(I)-catalyzed *N*-formylations of **1a** in methanol, ethyl acetate,

Table 3 Control experiments with **1*β***[a]



1β **2a** **2a'** **3β** **3β'**

Entry	Reaction conditions	Yield (%)[b]	
		2a/2a'	**3*β*/3*β***
1	air[c]	75/-	80 (82)[d]/-
2	4 Å MS (20 mg)/air (dried)	43/-	46/-
3	$H_2{}^{18}O$ (1.25 equiv)/air (dried)	57/-	48/-
4	$H_2{}^{18}O$ (10 equiv)/air (dried)	-/-	-/-

[a] All reactions were performed with 0.2 mmol of **1*β*** and 10 mol % of CuBr under reaction conditions stated in the Table in distilled acetonitrile (0.5 mL) at room temperature for 17 h. Air was dried by passing it through conc. H_2SO_4 prior to use. [b] ^{1}H NMR product yield with 2-(bromomethyl)naphthalene as the internal standard. [c]

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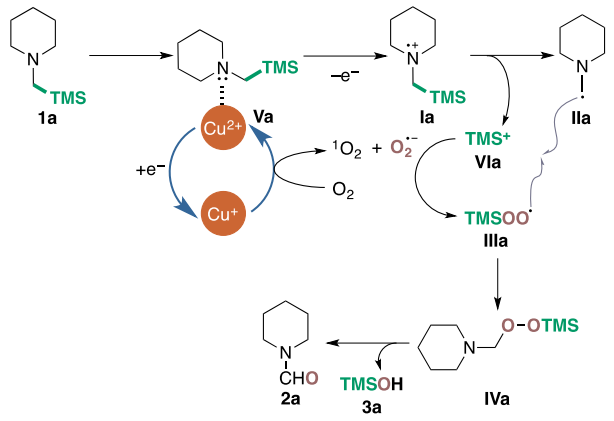
Reaction performed in non-distilled acetonitrile. [d] Value in parenthesis denotes isolated product yield.

acetone and acetonitrile described in Table 1, entries 2–8. It might be anticipated that an increase in substrate conversion or product yield might be expected as the solubility of oxygen from air increases on going from methanol ($[O_2]_{calc}$ = 1.99 mM) to ethyl acetate ($[O_2]_{calc}$ = 2.06 mM) to acetone ($[O_2]_{calc}$ = 2.55 mM) to acetonitrile ($[O_2]_{calc}$ = 2.60 mM).[21]

On the basis of the above results, a tentative mechanism for the present Cu(I)-mediated *N*-formylation of *α*-silylamines is outlined in Scheme 5.[11,15–17] This could involve the initial oxidation of CuBr by molecular oxygen to give the higher oxidation state [Cu^{II}] species along with singlet-state oxygen and the superoxide radical anion. With **1a** as a representative example, a one-electron redox reaction of the ensuing posited [Cu^{II}]-substrate complex **Va** *via* a SET pathway might produce the nitrogen-centered radical cation **Ia** and regeneration of the Cu(I) catalyst. For the analogous reactions catalyzed by $CuBr_2$ and $CuCl_2$ described in Table 1, entries 17 and 19, formation of the Cu(I) catalyst might arise from coordination of the substrate with the Cu(II) salt. Subsequent desilylative fragmentation of this amine radical cation would afford the carbon-centered radical species **IIa** and trimethylsilyl cation **VIa**, which can react further with the superoxide radical anion to give the peroxysilyl radical species **IIIa**. Coupling of this latter radical species with **IIa** would deliver the peroxide adduct **IVa**, which on deprotonation and desilylation, would provide the product **2a** and release of a molecule of trimethylsilanol **3a**.



Scheme 5 Proposed mechanism for the CuBr-mediated *N*-formylation of *α*-silylamines represented by **1a**.

Conclusions

In summary, we have exploited the intriguing reactivities of *α*-silyl-substituted tertiary *N*-alkylamines in the presence of an inexpensive copper(I) salt and oxygen from air to prepare *N*,*N*-dialkyl formamides. Achieved under mild reaction conditions at room temperature with a catalytic system that did not require a ligand or additives, the *N*-formylation protocol was demonstrated to be chemoselective and tolerate substrates containing a variety of functional groups such as an acetal, alkene, and carboxylic ester. The potential usefulness of the operationally straightforward synthetic approach was further exemplified by the selective *N*-formylation of a symmetrical bis(silyl)-substituted substrate and the late-stage functionalization of a series of modified bioactive compounds and natural products. Our studies additionally hint at the role of oxygen from air in the aldehyde forming process to be that of both the terminal oxidant and as part of the formylation reagent, a mode of reactivity which has remained conspicuously rare in copper catalysis. We envision that the present synthetic method will not only provide a practical, sustainable and low-cost tactic to install the *N*-formyl group that complements other amine oxidation strategies to access the compound class but also a non-photochemically-driven route to access *α*-amino radical species as reactive intermediates.

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Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

This work was supported by a Discovery Project Grant (DP160101682) from the Australian Research Council (to P. W. H. C.) and a China Scholarship Council Visiting Scholar Award (to B. X.).

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