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Bis(trialkylsilyl) Peroxides as Alkylating Agents in the Copper-catalyzed Selective Mono-*N*-alkylation of Primary Amides

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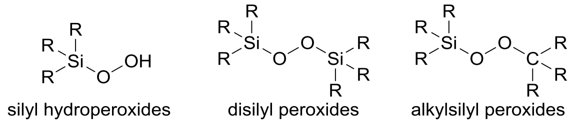
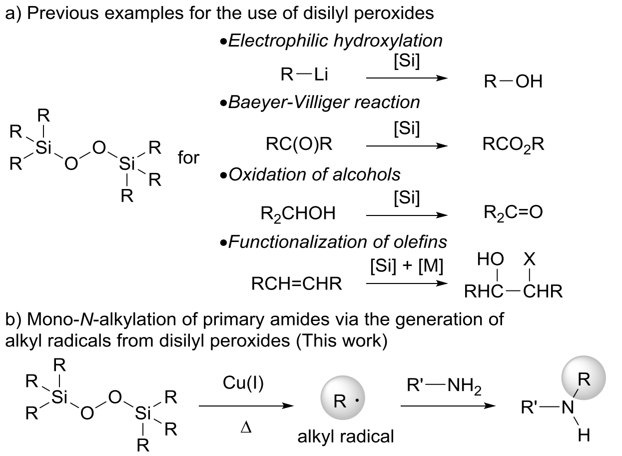
The copper-catalyzed selective mono-*N*-alkylation of primary amides with bis(trialkylsilyl) peroxides as alkylating agents was reported. The results of a mechanistic study suggest that this reaction should proceed via a free radical process that includes the generation of alkyl radicals from bis(trialkylsilyl) peroxides.

Organic peroxides are highly versatile and can be used as oxidants, radical initiators, polymerization initiators, cross-linking agents, and as synthetic building blocks.[1] In contrast, organosilicon peroxides, in which the peroxy group (-O-O-) is directly bound to at least one silicon atom, have received less attention.[2] Depending on their structures, organosilicon peroxides can be categorized into three classes, i.e., silyl hydroperoxides, disilyl peroxides, and alkylsilyl peroxides.



Among these, disilyl peroxides ($R_3SiOOSiR_3$) have found a few applications in organic synthesis (Scheme 1a).[3-7] For example, a commercially available bis(trimethylsilyl) peroxide has been employed as an equivalent of the hydroxyl cation in electrophilic hydroxylations.[3] In the Baeyer-Villiger oxidation, bis(trialkylsilyl) peroxides have been infrequently used as oxidants,[4] while combinations of bis(trimethylsilyl) peroxides and metal catalysts based on rhenium, zirconium, vanadium, or chromium have been used for the oxidation of alcohols and for the functionalization of olefins.[5-7] These early studies revealed a unique reactivity and synthetic utility for disilyl peroxides as oxidants in organic synthesis. However, applications beyond the use as oxidants have rarely been investigated. In this context, we report herein an unprecedented application of disilyl peroxides as alkylating agents, demonstrated by a copper-catalyzed selective mono-*N*-alkylation of primary amides (Scheme 1b). The corresponding mechanistic study suggested that the reaction should proceed via a free radical process that includes the generation of alkyl radicals from disilyl peroxides. This is, to the best of our knowledge, the first example for the use of disilyl peroxides as a source of alkyl radicals.



Scheme 1 Examples for the use of disilyl peroxides in organic synthesis.

In recent years, dialkyl peroxides such as di-*tert*-butyl or dicumyl peroxide, have frequently been used as methylating agents for e.g. the direct methylation of aryl C-H bonds, the methylation/cyclization of *N*-arylacrylamides, and the *N*-methylation of amides.[8-11] These routes facilitate efficient methylations through the generation of a methyl radical from the peroxides. However, the introduction of alkyl groups other than methyl via a similar radical process has been rarely reported, most likely due to the limited access to the corresponding dialkyl peroxides.[12] In this context, we became interested in the potential of bis(trialkylsilyl) peroxides (**1**), which can be readily synthesized from the reaction of a chlorosilane with a hydrogen peroxide-amine complex,[13] as an alternative source of alkyl radicals. As **1** can be substituted on the silicon atom with various alkyl groups, we envisioned that

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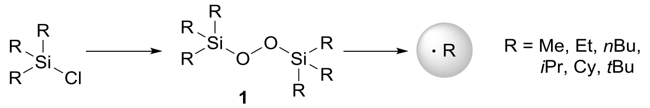
the introduction of alkyl groups other than methyl via a radical process could be realized if alkyl radicals could be generated from such bis(trialkylsilyl) peroxides (Scheme 2).



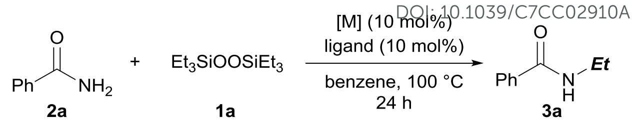
Scheme 2 Generation of alkyl radicals from disilyl peroxides.

Initially, we examined a metal-catalyzed *N*-alkylation of amides as a model reaction.[9a,14] When the reaction between benzamide (**2a**) and bis(triethylsilyl) peroxide (**1a**) was conducted at 100 °C in the presence of copper iodide and 2,2'-bipyrimidine (**L1**), the desired *N*-ethylbenzamide (**3a**) was obtained in 60% yield (entry 1) under concomitant formation of triethylsilanol. To rule out silanols as a possible source of the alkyl radicals, the same reaction was carried out using **2a** and triethylsilanol instead of **1a**. However, under otherwise identical conditions, the formation of **3a** was not observed (entry 2). A screening of several copper catalysts showed that copper iodide is the most efficient metal source (entries 3-6). In contrast, the use of several iron salts as catalysts did not afford the desired products, even though the decomposition of peroxide **1a** was observed (entries 7-9). We then examined the effect of the ligand on this reaction. A survey of several ligands demonstrated that the use of 1,10-phenanthroline (**L2**) improved the yield of **3a** (71%; entry 10).[15] Moreover, we discovered that the reaction time can be substantially reduced (24 h → 1 h) without affecting the product yield (entry 11). A further improvement of the yield was accomplished by addition of two further equivalents of **1a** after 1 h of stirring (entry 12). It should be noted that mono-*N*-alkylated product **3a** was obtained selectively in all cases, while *N,N*-dialkylation was not observed. Indeed, the reaction between **3a** and **1a** in the presence of a copper catalyst did not furnish any *N*,*N*-diethylamide, and **3a** could be recovered.

With optimized reaction conditions in hand, we examined the scope of silyl peroxides **1** (Scheme 3). The reaction between benzamide (**2a**) and bis(trimethylsilyl) peroxide (**1b**) afforded **3b** in 37% yield, while bis(tributylsilyl) peroxide (**1c**) furnished **3c** in 57% yield. The transfer of secondary alkyl groups was also possible using appropriate silyl peroxides. When bis(dimethylisopropylsilyl) peroxide (**1d**) was used, *N*-isopropyl amide **3d** was obtained in 63% yield. Similarly, the use of bis(dimethylcyclohexylsilyl) peroxide (**1e**) afforded *N*-cyclohexyl amide **3e** in 61% yield. Subsequently, we attempted the transfer of *tert*-butyl groups to the amides. However, the reaction of **2a** with bis(dimethyl-*tert*-butylsilyl) peroxide (**1f**) afforded **3f** in 9% yield, together with **3b** in 28% yield.[14g,16]

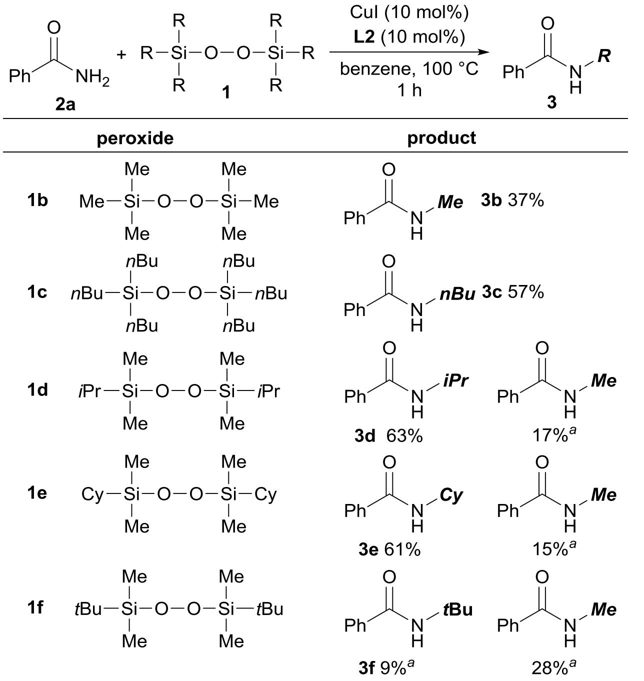
Then, we examined the reaction scope with respect to amides (Scheme 4). In the presence of bis(triethylsilyl) peroxide (**1a**) and copper iodide, the *N*-ethylation of various types of aryl amides **2** proceeded smoothly to furnish the corresponding secondary amides **4a**-**h** in moderate to good yields. The reaction with alkenyl and alkyl amides afforded the corresponding *N*-ethylated amides **4i** and **4j** in 40% and 51% yield, respectively.

Table 1 Optimization of reaction conditions using ethylbenzene **2a**.[a]



entry	[M]	Ligand	**3a** Yield (%)[b]	**2a** (%)[b]
1	CuI	**L1**	60	23
2[c]	CuI	**L1**	0	100
3	CuCl	**L1**	55	39
4	Cu(OAc)	**L1**	41	47
5	$Cu(acac)_2$	**L1**	36	50
6	$Cu(OAc)_2$	**L1**	43	51
7	$FeCl_2$	**L1**	0	98
8	$Fe(OAc)_2$	**L1**	0	74
9	$Fe(acac)_3$	**L1**	0	95
10	CuI	**L2**	71	18
11[d]	CuI	**L2**	69	21
12[e]	CuI	**L2**	81	4

[a] Performed with **2a** (0.1 mmol), **1a** (2.0 equiv), metal catalyst (10 mol%), and ligand (10 mol%) in benzene (0.4 M) for 24 h at 100 °C under an atmosphere of argon. [b] Yields were determined by ^1H NMR spectroscopy using DMF as an internal standard. [c] Triethylsilanol (2.0 equiv) was used instead of **1a**. [d] t = 1 h. [e] **1a** (2.0 equiv) was added after stirring for 1 h, and the reaction mixture was stirred for another hour. **L1**; 2,2'-Bipyrimidine, **L2**; 1,10-Phenanthroline



Scheme 3 Reaction scope with respect to bis(trialkylsilyl) peroxides **1**. [a] NMR yield.

Reactions using carbamate- or urea-based substrates were also successful, and furnished **4k** and **4l** in 47% and 44% yield, respectively. For the expansion of the substrate scope, we additionally tested reactions with primary anilines. Although the reaction between aniline and **1a** did not afford any product, the use of electron-deficient aryl amines such as pyridyl-2-amine, pyrimidyl-2-amine or pentafluoroaniline furnished ethylated products **4m-o** in low to modest yields.

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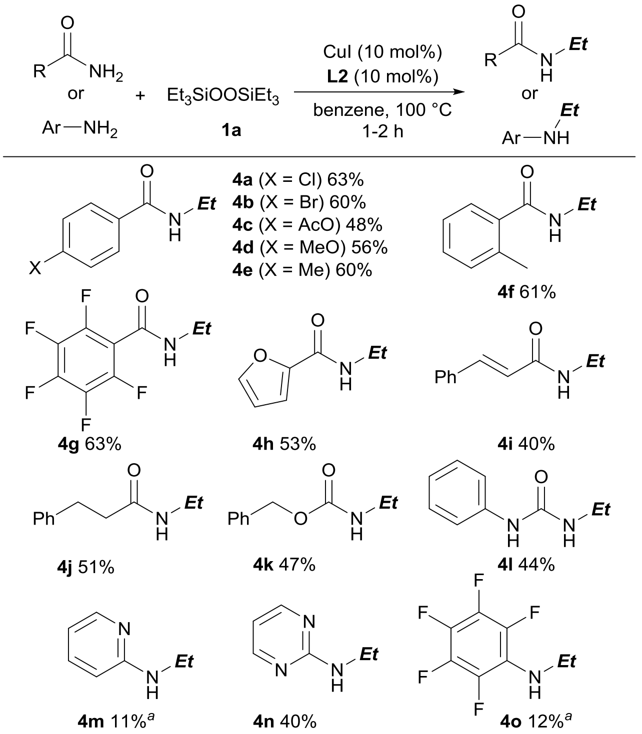
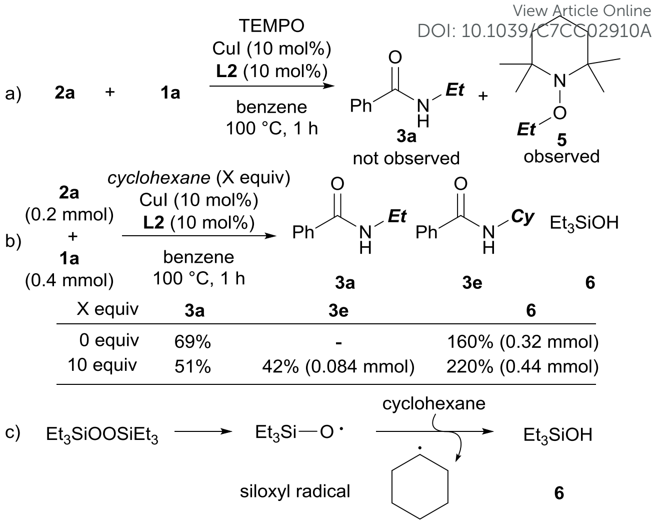
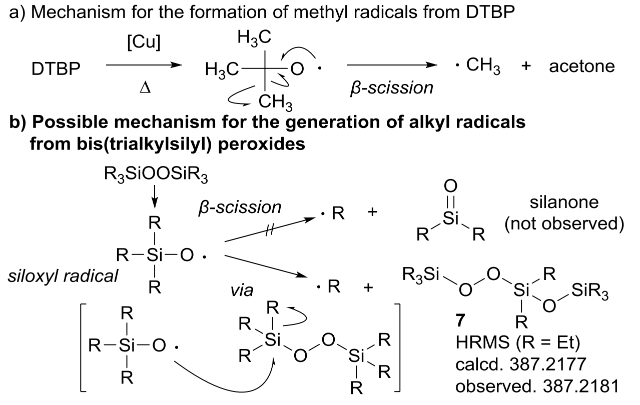


Scheme 4 Reaction scope with respect to amides or arylamines. [a] NMR yield.



X equiv	3a	3e	6
0 equiv	69%	-	160% (0.32 mmol)
10 equiv	51%	42% (0.084 mmol)	220% (0.44 mmol)

Scheme 5 Control experiments.



Scheme 6 Mechanisms for the generation of alkyl radicals from peroxides.

In order to elucidate the underlying reaction mechanism, we initially tested a radical trapping experiment with the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO). Addition of TEMPO to the standard reaction between **1a** and **2a** inhibited the formation of **3a**, while the formation of 1-ethoxy-2,2,6,6-tetramethylpiperadine (**5**) was detected by mass spectrometry and ^{1}H NMR spectroscopy, suggesting that a free radical process with the formation of an alkyl radical should be involved in this reaction (Scheme 5a). Conversely, in the presence of cyclohexane, the reaction afforded *N*-cyclohexyl benzamide (**3e**) in 42% yield, together with *N*-ethyl benzamide (**3a**) in 51% yield (Scheme 5b). Additionally, the amount of triethylsilanol (**6**) that was formed as a side product, increased compared to the reaction without cyclohexane. This result suggests the formation of a siloxyl radical, which should abstract a hydrogen atom from cyclohexane to generate a cyclohexyl radical and **6** (Scheme 5c).[14g]

We subsequently examined the mechanism for the generation of alkyl radicals from silyl peroxides. Previous research on methylations using di-*tert*-butyl peroxide (DTBP) has suggested that methyl radicals should be formed from the β-scission of *tert*-butoxy radicals under concomitant formation of acetone (Scheme 6a).[9,10] To the best of our knowledge, there appears to be no evidence for such a β-scission in trialkylsiloxyl radicals to afford alkyl radicals and the corresponding dialkylsilanone ($R_2Si{=}O$).[2d,17] Attempts to trap such silanones by the addition of methoxytrimethylsilane or hexamethyldisiloxane as trapping agents remained unsuccessful,[18] and the formation of silanone dimers and/or oligomers was not observed.[19] Instead, we detected the formation of **7** by high-resolution mass spectrometry (HRMS), indicating that the addition of a siloxyl radical to the silicon center of another peroxide could generate an alkyl radical under concomitant formation of **7** (Scheme 6b).

In order to reveal a potential involvement of the copper catalyst in the decomposition of silyl peroxides **1**, we carried out further experiments.[20] When **1a** was heated to 100 °C in the presence or absence of catalytic copper iodide, the silyl peroxide persisted almost quantitatively. In contrast, in the presence of copper iodide with **L1** or amide **2a**, decomposition of the peroxide was observed. These experiments indicate that a nitrogen-coordinated copper species should be necessary for the decomposition of **1**.

Based on these experiments, we would like to propose a plausible mechanism for the observed reactions in Figure 1. Initially, nitrogen-coordinated copper species **8** should cleave the silyl peroxide heterolytically, thus affording the corresponding siloxyl radical (**9**) and copper-silanoxide complex **10**. Subsequently, **9** should react with another silyl peroxide (**1**) to furnish alkyl radical **11**, while the ligand exchange on the copper center of **10** between an amide and a silanoxide would generate intermediate **12** and a silanol. Finally, the reaction between **12** and alkyl radical **11** should furnish the *N*-alkylated amide via intermediate **13**.

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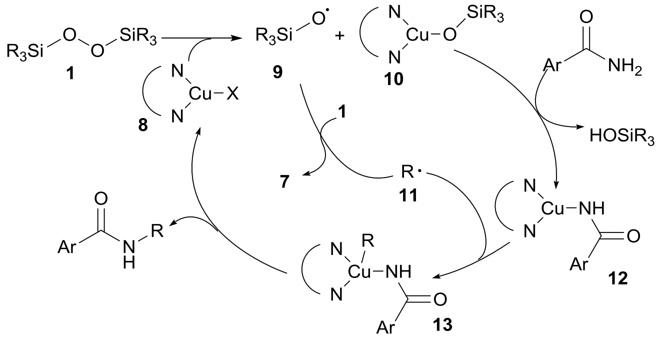

Figure 1 Proposed plausible reaction mechanism.

In conclusion, we have reported the unprecedented use of bis(trialkylsily) peroxides as a source of alkyl radicals. By using bis(trialkylsilyl) peroxides, various alkyl radicals can be generated efficiently, which has been demonstrated in the context of a copper-catalyzed selective mono-*N*-alkylation of primary amides. Our mechanistic studies suggest that the present reaction proceeds via a free-radical process that includes the generation of alkyl radicals from bis(trialkylsilyl) peroxides. Further investigations into the unequivocal determination of the underlying mechanism and further applications of these bis(trialkylsilyl) peroxides are currently in progress in our laboratory.

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