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Copper-catalyzed Electrophilic Amination of Alkoxyarylsilanes

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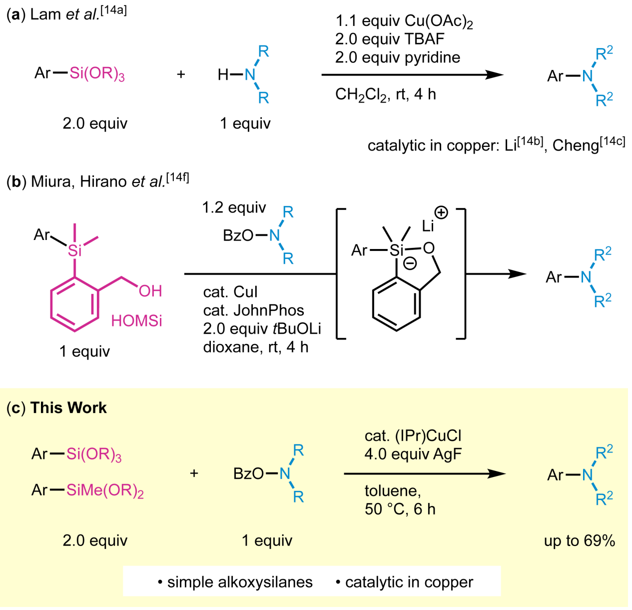
Abstract: We report a copper-catalyzed amination reaction between simple alkoxyarylsilanes and *N*-benzoyloxyamines. Silver fluoride serves as a stoichiometric base as well as an indispensable activator that allows the catalytic process to proceed. Multiply alkoxylated arylsilanes, such as trialkoxyarylsilanes, dialkoxyarylsilanes were transformed into the corresponding tertiary anilines under mild reaction conditions.

Arylamines constitute one of the most fundamental structural units found broadly in bioactive natural products and important pharmaceuticals.[1] Among diverse preparative methodologies known for these molecules, C(sp^2)–N bond-forming reactions, especially the ones using transition metals, represent an increasingly significant proportion. Continuous pursuits of amination reaction of aryl halides culminated in the development of Buchwald–Hartwig amination[2] and the Ullmann-type copper-catalyzed amination[3] that has broadened the applications of nitrogen-containing molecules. Besides these established methodologies, copper-promoted oxidative amination of arylboronic acids, namely, the Chan–Lam coupling,[4] has also proven to be a powerful method for C–N bond formation. The source of the nucleophiles developed for the related Chan–Lam-type amination were initially arylleads[5] or arylbismuths,[6] and were later expanded to other arylmetal species,[7] such as arylmagnesiums,[8] -zincs,[9] -stannanes,[10] -titaniums,[11] -zirconiums,[12] arylaluminums,[13] as well as arylsilanes.[14]

Our continuing interest in utilizing silicon functional groups for efficient transformation inspired us to develop our new conditions for a new repertoire of Chan–Lam-type amination of arylsilanes. The pioneering work of this transformation was reported by Lam *et al.*[14a] They described trialkoxyarylsilanes are viable as an alternative to arylboronic acids for the synthesis of arylamines using a stoichiometric amount of copper(II) acetate (Scheme 1a). Copper-catalyzed variants under oxygen atmosphere were later reported by Li[14b] and Cheng.[14c] Recently, Miura and Hirano reported copper-catalyzed electrophilic amination with *N*-benzoyloxyamines, which in turn required the use of HOMSi[14d, 14e] functional group for an efficient transmetalation via a cyclic silanolate intermediate (Scheme 1b).[14f] Smith also studied a closely related transformation directly from aryllithium as a one-pot transformation.[14g] The elaborate silyl group was necessary for these copper-catalyzed aminations with *N*-acyloxyamines as a nitrogen source,[14f] leaving simple alkoxysilanes inapplicable for the reactions. Herein, we describe electrophilic amination of simple arylalkoxysilanes with *N*-benzoyloxyamines and a catalytic amount of (IPr)CuCl in the presence of AgF as an indispensable stoichiometric base that serves as an activator for the generation of catalytic species as well.

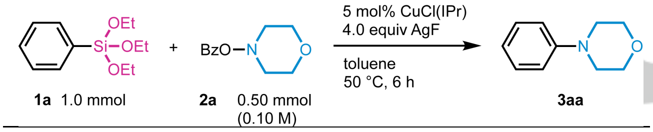


Scheme 1. Copper-mediated Electrophilic Amination of Arylsilanes.

As a result of our optimization of copper-catalyzed amination of triethoxyphenylsilane (**1a**) with *N*-benzoyloxymorpholine (**2a**), we eventually devised the standard conditions for the reaction: **2a** as the limiting agent (0.1 M), 2.0

equiv **1a**, 4.0 equiv AgF, 5 mol% (IPr)CuCl, toluene, 50 °C, 6 h. Table 1 shows the results associated with differences based on the deviations listed. Under the standard conditions (entry 1), arylamine **3aa** was obtained in 67% NMR yield (69% isolated yield). In the cases of other solvents, lower yields were observed (entries 2–4). Interestingly, a substantial amount of biphenyl was observed as an only obsevable byproduct, which would be due to the formation of arylsilver species followed by the known oxidative dimerization.[15] Regarding the source of the copper catalyst, a slightly lower yield (54%) was observed with CuCl(IMes), and the yield dropped with dppe or with no ligand (entries 5–7). The choice of AgF as a base was indispensable for this catalytic reaction.[16] Thus, other bases including other silver salts (entries 8 and 9), CsF (entry 10), Et_3N (entry 11), and *t*BuOK (entry 12) did not provide any of the desired product. Reducing the amount of the base resulted in the lowered yield (Table S5). The reaction was sluggish at room temperature (entry 13) while no significant change was observed at 70 °C (entry 14). Our attempt to set triethoxyphenylsilane (**1a**) as the limiting agent with a slight excess of **2a** gave the product **3aa** in substantially lower yield for an unclear reason (Scheme S1). Therefore, the conditions in entry 1 were confirmed to be optimal.

Table 1. Optimization of Amination Conditions.

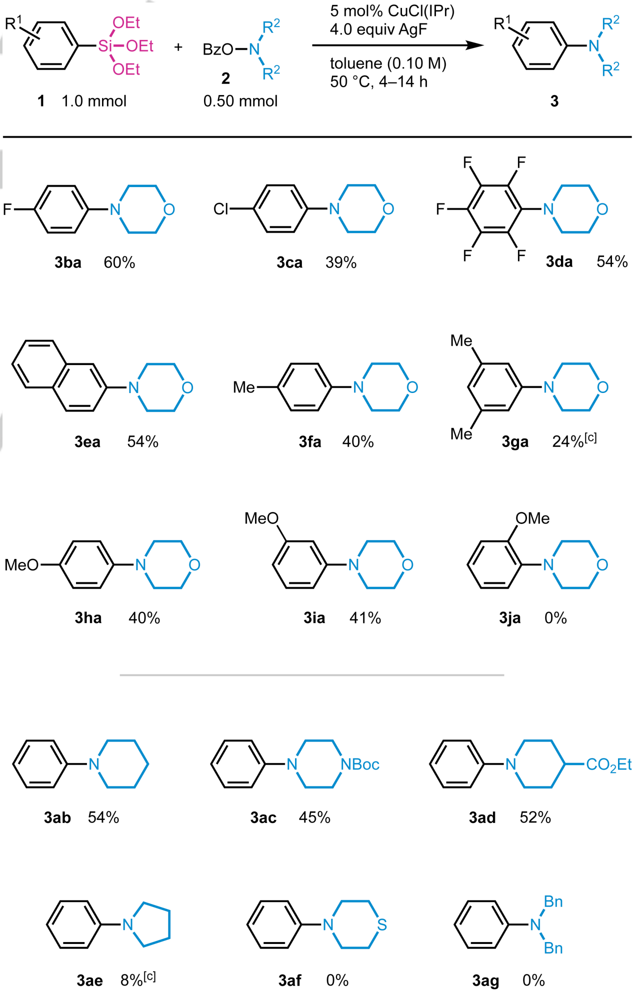


Entry	Deviation from the standard conditions	Yield (%)[a]	
		3aa	Biphenyl[c]
1	none	67 (69[b])	0
2	THF instead of toluene	47	74
3	MeCN instead of toluene	37	66
4	DMF instead of toluene	14	99
5	CuCl(IMes) instead of CuCl(IPr)	54	0
6	CuCl(dppe) instead of CuCl(IPr)	23	0
7	CuCl instead of CuCl(IPr)	39	0
8	AgOAc instead of AgF	0	0
9	Ag_2O[d] instead of AgF	0	0
10	CsF instead of AgF	0	0
11	Et_3N instead of AgF	0	0
12	*t*BuOK instead of AgF	0	0
13	rt	35	0
14	70 °C	64	0

[a] Determined by ^1H NMR analysis using mesitylene as an internal standard. [b] Isolated yield. [c] The theoretical maximum yield is 200%. [d] 2.0 equiv was used.

Table 2 shows the scope of the reaction between **1** and **2** with respect to the aryl group and the amine moiety under the optimized conditions. Anilines **3** were obtained in moderate yields when the para position of the aryl group was substituted with an electron-withdrawing group such as fluoro (**3ba**) and chloro (**3ca**) groups. Pentafluorophenyl (**3da**) or 2-naphthyl group (**3ea**) was also aminated. Electron-donating *p*-tolyl (**3fa**) was tolerated, but 3,5-dimethylphenyl (**3ga**) was not obtained in good yield. *p*-Anisyl (**3ha**), *m*-anisyl (**3ia**) aniline products were obtained in moderate yields. Under the same conditions, *ortho*-substituted product **3ja** was not obtained. The low reactivity of ortho-substituted substrates would be ascribed to the steric hindrance exerted by the substituent. The scope of the copper-catalyzed amination of **1a** with respect to different *N*-benzoyloxyamines **2b**–**2g** were also investigated. A piperidine unit could be introduced by the current reaction to give *N*-phenyl piperidine (**3ab**) in moderate yield. *N*-Boc-4-phenylpiperazine (**3ac**) and ethoxycarbonyl-substituted piperidine derivative (**3ad**) were also installed in moderate yields. Meanwhile, *N*-phenylpyrrolidine (**3ae**) was observed only in a trace amount, and *N*-phenylthiomorpholine (**3af**) and *N*,*N*-dibenzylaniline (**3ag**) were not obtained at all.

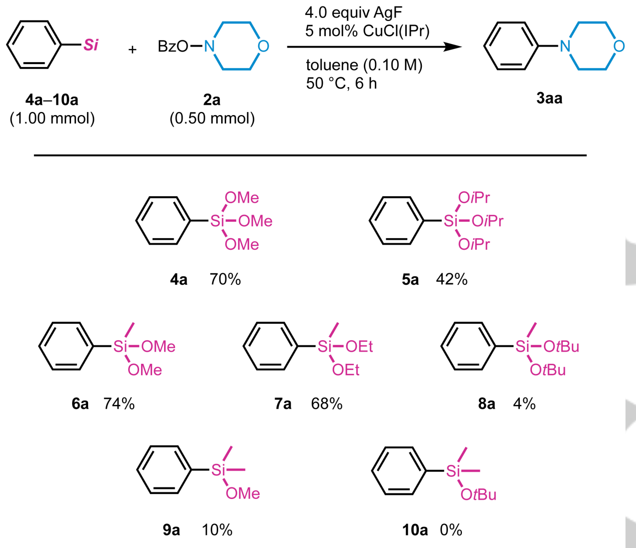
Table 2. Substrate Scope with Respect to Aryl Groups and Amines.[a],[b]



[a] Isolated yield. [b] Conditions: **2** (0.50 mmol, 0.10 M), **1** (2.0 equiv), AgF (4.0 equiv), CuCl(IPr) (5 mol%), toluene, 50 °C, 4–24 h. [c] Determined by ^1H NMR analysis using mesitylene as an internal standard.

The generality of the current reaction conditions was examined with variably *Si*-substituted alkoxyphenylsilanes **4a**–**10a** (Table 3). In the cases of trialkoxyphenylsilanes, Ph–Si(OMe)$_3$ (**4a**) were transformed to **3aa** in a competitive yield (70%), though the conversion of Ph–Si(O*i*Pr)$_3$ (**5a**) to **3aa** was not efficient probably because of the bulkiness around the silicon atom to hamper the approach of a fluoride. In the cases of dialkoxymethylphenylsilanes, Ph–SiMe(OMe)$_2$ (**6a**) and Ph–SiMe(OEt)$_2$ (**7a**) were converted to **3aa** in 74% and 68% respective yields. In turn, Ph–SiMe(O*t*Bu)$_2$ (**8a**) seemed to be too bulky for an efficient conversion and gave **3aa** only in 4% yield. The reactivity dropped in the case of mono-alkoxydimethylsilanes. Thus, Ph–SiMe$_2$(OMe) (**9a**) gave **3aa** in only 10% yield, and Ph–SiMe$_2$(O*t*Bu) (**10a**) showed no conversion under the same conditions. The utility of other reactive silicon functional groups are the issues to be examined in the following studies.

Table 3. Substrate Scope with Respect to Silyl Groups.[a],[b],[c]

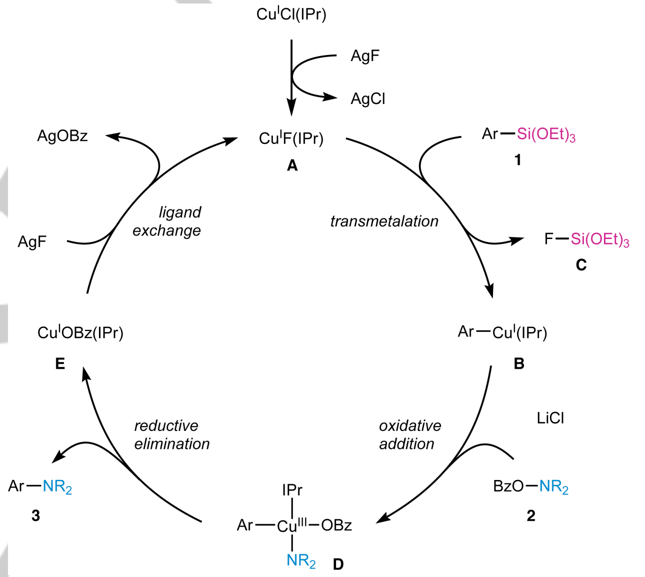


[a] Isolated yield. [b] Conditions: **2a** (0.50 mmol, 0.10 M), **1** (2.0 equiv), AgF (4.0 equiv), CuCl(IPr) (5 mol%), toluene, 50 °C, 6 h. [c] Determined by ^{1}H NMR analysis using mesitylene as an internal standard.

A tentative mechanistic proposal for the copper(I)-catalyzed amination of **1** with **2** is depicted in Figure 1. Initially, CuCl(IPr) would be transformed to the corresponding fluoride CuF(IPr) (**A**) that would then undergo transmetalation with **1** to give arylcopper species **B** with concomitant formation of fluorosilane **C** as previously depicted by Ball *et al.*[17] Oxidative addition of **2** to **B** would form copper(III) species **D**, and the subsequent reductive elimination would afford the desired arylamine **3** along with copper benzoate **E**. The following transmetalation with AgF would give AgOBz and regenerate **A** to maintain the catalytic cycle. Because of the absence of biphenyl byproduct in the case of toluene as a solvent, the formation of an arylsilver intermediate is not considered in the current mechanistic sketch. The necessity of the stoichiometric amount of AgF could be ascribed not only to the initial formation of CuF(IPr) (**A**), but to the efficient regeneration of **A** from intermediate CuOBz(IPr) (**E**). A mechanism involving an S$_N$2 reaction on the nitrogen atom[8b] or a mechanism via radical-mediated amination[18] could not be denied for this transformation.

In summary, we have developed copper-catalyzed electrophilic amination between alkoxyarylsilanes **1** and *N*-benzoyloxyamines **2** enabled by a stoichiometric amount of AgF that is not only a base but an essential activator. Triethoxyarylsilanes bearing an electron-withdrawing or -donating substituent on the aromatic rings could be transformed to tertiary aniline derivatives **3**. Also, various di-, and trialkoxysilyl groups on arenes were confirmed to be reactive except for the ones bearing sterically demanding alkoxy substituents. A broad range of reactivities of silyl groups with regard to the size of the substituents and the numbers of alkoxy groups are worth further investigation. More detailed studies of the use of variably substituted silyl groups will be reported in due course.

Figure 1. Tentative Mechanism for Amination of Arylsilanes.



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Keywords: alkoxysilane • arylamine • copper • catalyst • silver fluoride

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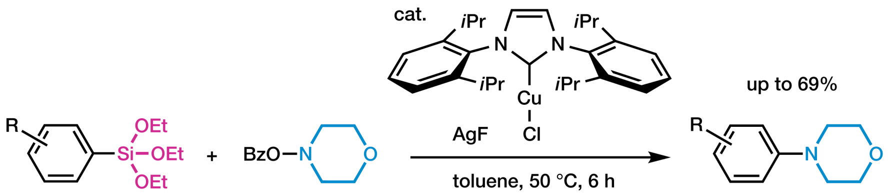
Entry for the Table of Contents

Key Topic: Amination



A stoichiometric amount of silver fluoride that serves as a base as well as an essential activator enabled a copper-catalyzed C–N-bond-forming reaction between simple alkoxyarylsilanes and *N*-benzoyloxyamines. This method allows the amination of simple arylsilanes bearing two or three alkoxy groups on the silicon atom.

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