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Copper-Catalyzed Electrophilic Amination of Arylsilanes with Hydroxylamines

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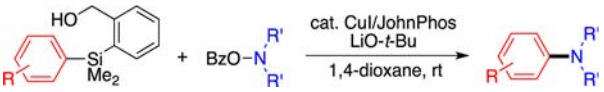
ABSTRACT



A copper-catalyzed electrophilic amination of aryl[(2-hydroxymethyl)phenyl]dimethylsilanes with *O*-acylated hydroxylamines has been developed to afford the corresponding anilines in good yields. The catalytic reaction proceeds very smoothly under mild conditions and tolerates a wide range of functional groups.

Arylamines are privileged structural motifs in many biologically active compounds, pharmaceutical targets, and functional materials.[1] Metal-promoted aromatic C–N cross-coupling reactions provide a powerful and convergent approach to the above amines. Among them, the copper-mediated oxidative coupling of arylmetals with amines (Chan–Lam-type coupling) ranks as one of the most useful protocols in synthetic chemistry.[2] So far, arylboronic acids and their derivatives have been mainly employed as the aryl source. On the other hand, there are a few successful reports of arylsilanes, despite their low toxicity and abundance which are similar to those of organoboron compounds.[3]

Meanwhile, an umpolung,[4] electrophilic amination[5] using a reagent of type R_2N^+ such as chloro- and hydroxylamines has recently received significant attention and enabled the effective amination of not only organometallic reagents based on Mg,[6] Zn,[7] Ti,[8] Zr,[9] and B[10] but also (hetero)aromatic C–H bonds.[11] Our group also focused on this type of transformation and succeeded in the copper-catalyzed electrophilic aminations of heteroarenes,[12a−e] arylboronates,[12f] and ketene silyl acetals.[12g] In the course of this study, we envisioned that the umpolung strategy could be applied to the amination of arylsilanes. Herein, we

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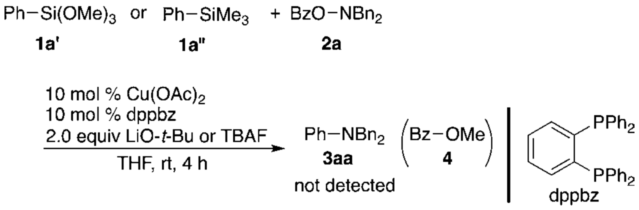
describe a copper-catalyzed electrophilic amination of aryl[(2-hydroxymethyl)phenyl]dimethylsilanes with *O*-acylated hydroxylamines. The copper catalysis tolerates a diverse set of functional groups and allows various arylsilanes to be adopted efficiently in the amination reaction for the synthesis of arylamines.

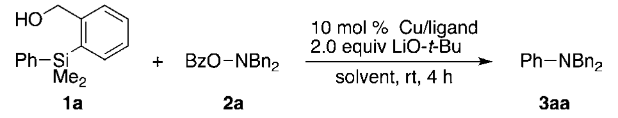
On the basis of our previous work with arylboronates,[12f] we initially attempted the amination of trimethoxyphenylsilane (**1a′**) with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**) in the presence of a $Cu(OAc)_2$/dppbz (dppbz = 1,2-bis(diphenylphosphino)benzene) catalyst and LiO-*t*-Bu in THF at room temperature (Scheme 1). Unfortunately, no desired aniline **3aa** was formed, and methyl benzoate (**4**) was instead detected as a byproduct, the methoxy group of which apparently came from **1a′**.[13] The use of tetrabutylammonium fluoride (TBAF) as a base also gave a similar result, while trimethylphenylsilane (**1a″**) in place of **1a′** showed no conversion.

Scheme 1. Initial Attempts on Copper-Catalyzed Electrophilic Amination of Trimethoxyphenylsilane (**1a′**) or Trimethylphenylsilane (**1a″**) with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**)



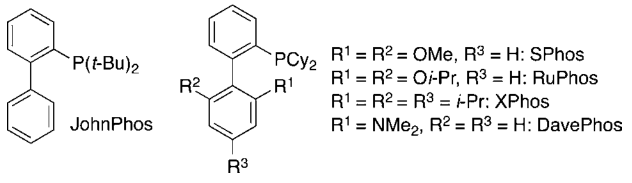
Thus, we turned our attention to [(2-hydroxymethyl)phenyl]dimethylphenylsilane (**1a,** Table 1), which was originally developed by Nakao and Hiyama,[14,15] because such an arylsilane is capable of selective aryl group transfer through facile formation of an intramolecularly pentacoordinated arylsilicate, despite its high stability associated with a tetraorganosilane structure. Additionally, **1a** is readily prepared and now commercially available from some suppliers. To our delight, **3aa** was obtained in 12% yield under the same catalytic conditions as those for Scheme 1 (entry 1). With the preliminary but intriguing results in hand, we screened copper salts (entries 2−4), and CuI showed higher catalytic activity (entry 2). Among various phosphine ligands tested, some Buchwald biarylphosphines[16] improved the yield of **3aa** (entries 5−9), with 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos) proving to be optimal (entry 5). Subsequent investigation of the solvent system (entry 10−12) revealed that 1,4-dioxane furthermore increased the reaction efficiency (entry 10). Finally, we could isolate **3aa** in 77% yield in the presence of 5 mol % of CuI and 10 mol % of JohnPhos (entry 13). On the other hand, other bases such as K_3PO_4, Cs_2CO_3, and NaO-*t*-Bu did not furnish **3aa** at all (data not shown). Notably, the present amination could be carried out on a 5-fold larger scale, indicating the good reproducibility and

Table 1. Optimization Studies for Copper-Catalyzed Electrophilic Amination of [(2-Hydroxymethyl)phenyl]dimethylphenylsilane (**1a**) with *O*-Benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**)[a]



entry	Cu/ligand	solvent	yield of **3aa** (%)[b]
1	$Cu(OAc)_2$/dppbz	THF	12
2	CuI/dppbz	THF	40
3	$CuBr•SMe_2$/dppbz	THF	21
4	CuCl/dppbz	THF	trace
5[c]	CuI/JohnPhos	THF	68
6[c]	CuI/SPhos	THF	37
7[c]	CuI/RuPhos	THF	50
8[c]	CuI/XPhos	THF	32
9[c]	CuI/DavePhos	THF	47
10[c]	CuI/JohnPhos	1,4-dioxane	81
11[c]	CuI/JohnPhos	CPME	69
12[c]	CuI/JohnPhos	DME	43
13[d]	CuI/JohnPhos	1,4-dioxane	90 (77)
14[d,e]	CuI/JohnPhos	1,4-dioxane	(71)

[a] Reaction conditions: Cu (0.025 mmol), ligand (0.025 mmol), LiO-*t*-Bu (0.50 mmol), **1a** (0.25 mmol), **2a** (0.30 mmol), solvent (1.5 mL), rt, 4 h, N_2. [b] The yields are determined by GC method. Yield of isolated product is in parentheses. [c] With 0.050 mmol of ligand. [d] With 0.013 mmol of CuI and 0.025 mmol of JohnPhos. [e] On a 1.25 mmol scale.



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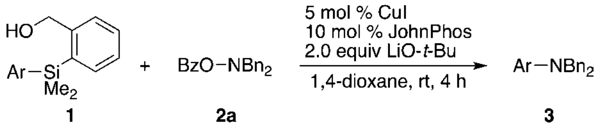
reliability of the copper catalysis (entry 14). Moreover, in this case, the resultant oxasilacyclopentane was recovered in 65% yield (98% purity by GC analysis) by Kugelrohr distillation, which can be recycled for the starting **1a**.[17]

We next performed the electrophilic amination of various aryl[(2-hydroxymethyl)phenyl]dimethylsilanes **1** with **2a** under conditions employed for entry 13 in Table 1 (Table 2). The catalytic reaction was compatible with an electron-donating methoxy group as well as an electron-withdrawing chloride function to afford the corresponding anilines **3ba** and **3ca** in good yields (entries 1 and 2). Particularly notable is that the aryl–Br moiety remained intact in the amination system, providing an opportunity for additional transformations by conventional palladium chemistry (entry 3). The mildness of the reaction conditions accommodated carbonyl groups including ester and nitrile functions (entries 4 and 5). In addition, *ortho*- and *meta*-substituted **1g** and **1h** could be employed (entries 6 and 7). Moreover, the bulky 1-naphthylsilane **1i** also coupled with **2a** without any difficulties (entry 8). The current limitation of the present copper catalysis is inaccessibility to 2-thienylamine (entry 9).

Table 2. Copper-Catalyzed Electrophilic Amination of Various Aryl[(2-hydroxymethyl)phenyl]dimethylsilanes **1** with *O*-Benzoyl-*N,N*-dibenzylhydroxylamine (**2a**)[a]

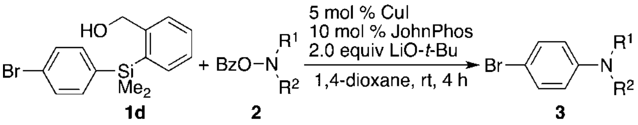


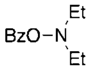
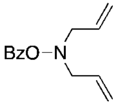
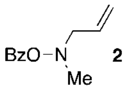
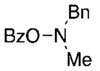
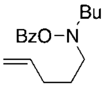
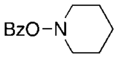
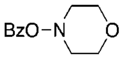
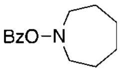
entry	Ar **1**	**3**, yield (%)[b]
1	Ar = 4-MeOC$_6$H$_4$ (**1b**)	**3ba**, 73
2	Ar = 4-ClC$_6$H$_4$ (**1c**)	**3ca**, 81
3	Ar = 4-BrC$_6$H$_4$ (**1d**)	**3da**, 77
4	Ar = 4-EtO$_2$CC$_6$H$_4$ (**1e**)	**3ea**, 76
5	Ar = 4-NCC$_6$H$_4$ (**1f**)	**3fa**, 88
6	Ar = 2-MeC$_6$H$_4$ (**1g**)	**3ga**, 43
7	Ar = 3-ClC$_6$H$_4$ (**1h**)	**3ha**, 76
8	Ar = 1-naphthyl (**1i**)	**3ia**, 79
9	Ar = 2-thienyl (**1j**)	**3ja**, 0

[a] Reaction conditions: CuI (0.013 mmol), JohnPhos (0.025 mmol), LiO-*t*-Bu (0.50 mmol), **1** (0.25 mmol), **2a** (0.30 mmol), 1,4-dioxane (1.5 mL), rt, 4 h, N$_2$. [b] Yield of isolated product.

With the Br-substituted arylsilane **1d** as the aryl source, the scope of hydroxylamines **2** was evaluated (Table 3). Acyclic amines with *N,N*-diethyl, *N,N*-diallyl, *N*-ally-*N*-methyl, and *N*-benzyl-*N*-methyl substituents underwent the coupling with **1d** very smoothly to form the corresponding 4-bromoanilines **3db**–**de** in synthetically useful yields (entries 1–4). The resultant *N*-allyl and *N*-benzyl moieties can work as a useful synthetic handle for further manipulations.[18] These successful examples deserve significant attention because such secondary acyclic alkylamines are an inaccessible substrate class in the conventional Chan–Lam-type coupling with arylsilanes.[3] The reaction with **2f** that contains the pendant olefin gave the usual aminated product **3df** exclusively, and any pyrrolidine derivatives were not detected at all (entry 5). Thus, an aminyl radical-promoted pathway is less likely.[19] On the other hand, cyclic amines showed somewhat lower efficiency: the reaction of six-membered piperidine **2g** and morpholine **2h** provided the corresponding anilines **3dg** and **3dh** in moderate yields, whereas the seven-membered azepane **2i** was transformed into **3di** in 78% yield.[20]

Table 3. Copper-Catalyzed Electrophilic Amination of Bromo-substituted Arylsilane **1d** with Various *O*-Benzoyl-hydroxylamines **2**[a]



entry	2		3, yield (%)[b]
1		**2b**	**3db**, 77
2		**2c**	**3dc**, 82
3		**2d**	**3dd**, 60
4		**2e**	**3de**, 74
5		**2f**	**3df**, 71
6		**2g**	**3dg**, 58
7		**2h**	**3dh**, 40
8		**2i**	**3di**, 78

[a] Reaction conditions: CuI (0.013 mmol), JohnPhos (0.025 mmol), LiO-*t*-Bu (0.50 mmol), **1d** (0.25 mmol), **2** (0.30 mmol), 1,4-dioxane (1.5 mL), rt, 4 h, N$_2$. [b] Yield of isolated product.

To attain some insight into the mechanism and intermediates of the reaction, we prepared the mesitylcopper complex **5**[21] and investigated its reactivity (Scheme 2). Upon treatment with a stoichiometric amount of *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**2a**) and JohnPhos, the

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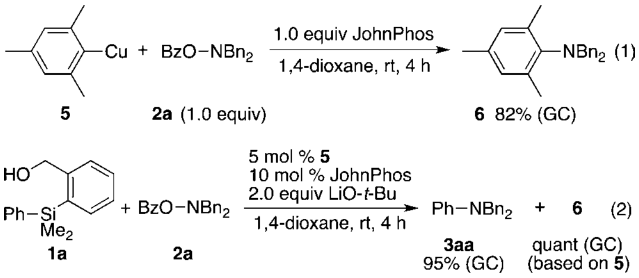
(20) The reaction with *O*-benzoyl-*N*-phenylamine was unsuccessful.

Scheme 2. Stoichiometric and Catalytic Reactions with Mesitylcopper Complex **5**



corresponding C–N coupling product **6** was formed in 82% yield (GC, eq 1). In addition, **5** catalyzed the amination of **1a** with **2a** effectively to furnish **3aa** in 95% yield (GC, eq 2), with concomitant formation of **6** (quantitative based on **5** employed). These findings suggest that a monoarylcopper species such as **5** would be formed in the catalytic cycle and responsible for the C–N bond forming step.[10e,12c] However, given that in our previous work[12f] the mesitylcopper **5** did not react with **2a** at all in the presence of dppbz, the reactivity profile of the arylcopper toward *O*-benzoylhydroxylamines would be dramatically influenced by the ancillary ligand coordinated to the copper center.

Based on the above considerations, a plausible mechanism involves (1) base-assisted transmetalation[22] of a Cu(I) complex with the arylsilane **1**, generating a JohnPhos-ligated neutral monoarylcopper species, and (2) electrophilic amination with the hydroxylamine **2** to form the observed aniline **3**.[6b,10e,12c,12e] An alternative is the involvement of a Cu(III) intermediate prior to the C–N bond formation.[23] Further efforts to clarify the detailed mechanism are ongoing.

In conclusion, we have developed a copper-catalyzed electrophilic amination of aryl[(2-hydroxymethyl)phenyl]-dimethylsilanes with *O*-acylated hydroxylamines. The umpolung, electrophilic amination strategy allows arylsilanes to serve as an efficient aryl source for the synthesis of aniline derivatives. Moreover, the high halogen compatibility of the process can provide a facile access to bromide-substituted arylamines and complement the conventional Pd-based amination chemistry. Further developments of related electrophilic aminations are currently underway.

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Supporting Information Available. Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Some copper salts are often added as a cocatalyst in the palladium-catalyzed Hiyama cross-coupling with aryl[(2-hydroxymethyl)phenyl]-dimethylsilanes **1**. They can mediate an aryl group transfer from Si to Pd through formation of an arylcopper intermediate; see ref 14.

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