

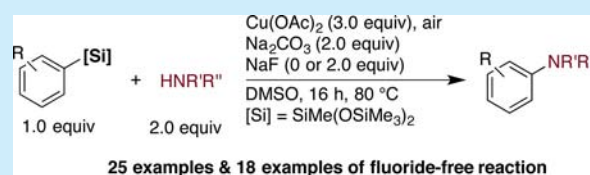
Copper-Mediated C–N Coupling of Arylsilanes with Nitrogen Nucleophiles

Johannes Morstein, Eric D. Kalkman, Chen Cheng, and John F. Hartwig*

Department of Chemistry, University of California, Berkeley, California 94720, United States

S Supporting Information

ABSTRACT: A method for the oxidative coupling of arylsilanes with nitrogen nucleophiles is reported. This method occurs with a broad range of heptamethyltrisiloxyarenes and nitrogen nucleophiles, proceeds with the arylsilane as limiting reagent, and does not require a fluoride activator with electron-poor arylsilanes. The combination of this method with C–H silylation generates arylamines from unactivated arenes with site selectivity controlled by steric effects. This combination of steps gives direct access to many compounds that cannot be accessed via alternative C–H functionalization methods, including direct C–H amination or the combination of C–H borylation and amination.



Pharmaceuticals, agrochemicals, and natural products often contain arylamine units or derivatives of arylamines (Figure 1). The C–N bonds in these molecules are frequently constructed through transition metal-catalyzed amination of functionalized arenes, including Pd-catalyzed coupling of aryl halides with nitrogen nucleophiles¹ or Cu-mediated oxidative coupling of arylboronic acids with nitrogen nucleophiles.² These methods are reliable and tolerate a broad scope of reagents. However, the substitution pattern of the arenes is intrinsically limited by the regioselectivity of the halogenation of arenes to prepare the electrophilic partner in cross-coupling to form C–N bonds or to prepare the arylboronic acids used in oxidative coupling.

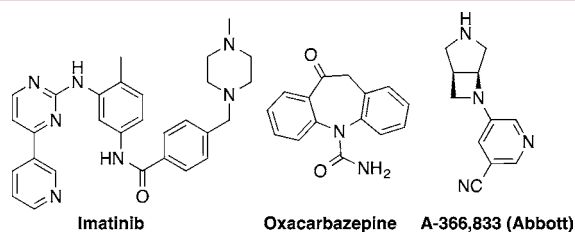


Figure 1. Biologically active molecules, which can be conveniently synthesized by coupling of a prefunctionalized arene with an N-nucleophile.^{2d}

Undirected, intermolecular amination of the C–H bonds in arenes is an alternative to more common aminations of prefunctionalized arenes (Figure 1).³ Recent methods reported by Nicewicz^{3b} and Falck^{3c} generate arylamines directly from simple arenes with the arene as limiting reagent. However, these methods occur with a limited range of nitrogen nucleophiles, with limited compatibility of auxiliary functional groups, and only with arenes that are electron-rich. Moreover, the regioselectivities of these methods are controlled by the electronic properties of the arene (*ortho/para* to electron-donating substituents). A

method for the amination of functionalized arenes to form products possessing substitution patterns different from those created by electrophilic aromatic substitutions would complement the arylamine derivatives generated by the aforementioned methods.

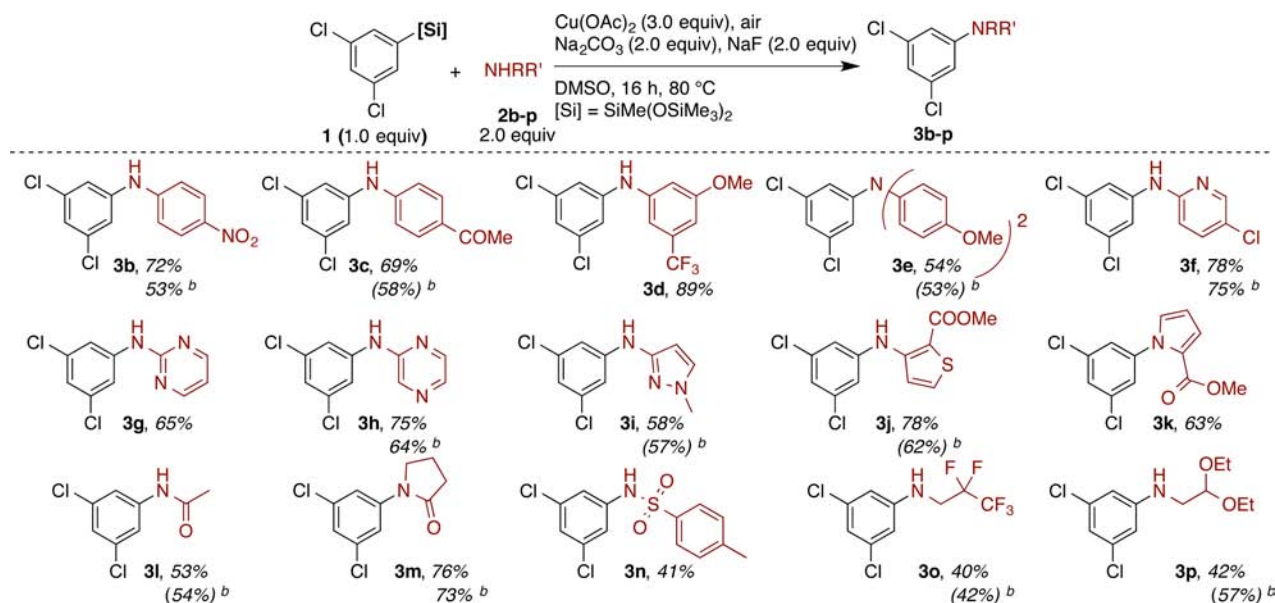
Arylboronates can be conveniently accessed by transition-metal catalyzed C–H-borylation with sterically controlled regioselectivity and are therefore attractive alternative substrates for oxidative coupling with nitrogen nucleophiles. However, in published procedures, the yields of coupling of nitrogen nucleophiles with arylboronate esters that can be accessed by C–H-borylation are moderate.⁴ Recently, a modification of the coupling of arylboronates with nitrogen nucleophiles with good yields of arylamines was reported (average yield = 65%).⁵ However, the reported scope of nucleophiles is limited to aryl- and alkylamines as nitrogen nucleophiles and uses different conditions for the coupling of arylamines and alkylamines.

Organosilanes are attractive alternatives to arylboronates.⁶ The catalytic silylation of aryl C–H bonds forms arylsilanes with regioselectivities that are higher than, and in some cases distinct from those of C–H borylation.^{6a,7} Moreover, arylsilanes are inexpensive, nontoxic,⁸ and more stable⁹ than their arylboronate analogues. The greater stability of arylsilanes than of arylboronates and the greater selectivity of C–H silylation than of C–H borylation creates the capability to functionalize heteroarenes and complex molecules that cannot be functionalized by C–H borylation.

Initial studies by Lam demonstrated that phenyltrimethoxysilanes undergo Cu-mediated oxidative amination with five different nitrogen nucleophiles with TBAF as a fluoride additive.¹⁰ Although these reactions showed that arylsilanes could be converted to arylamines, the aryltrimethoxysilanes used in this process have not been accessed by C–H silylation.

Received: August 25, 2016

Published: September 30, 2016

Scheme 1. Scope of the Coupling of Nitrogen Compounds with **1**^a

^aReaction conditions: **1** (0.3 mmol), **2b–p** (0.6 mmol), Cu(OAc)₂ (0.9 mmol), Na₂CO₃ (0.6 mmol), NaF (0.6 mmol), and dry DMSO (2.0 mL). Air atmosphere, heated at 80 °C for 16 h. Yields are isolated yields and yields in parentheses are yields by NMR. ^bReactions conducted in the absence of a fluoride source.

Aryltrimethoxysilanes are typically prepared from aryl halides; thus, this amination does not significantly expand the scope of substituted arenes that undergo oxidative amination beyond those of typical arylboronic acids. Moreover, the reported method requires an excess (2 equiv) of the arylsilane, and the arylsilane is often the more valuable component of the coupling reaction. A catalytic amination of arylsilanes was also reported,¹¹ but the high cost of the phosphine ligand [(C₆F₅)₃P] and high ligand loading (10%) as well as the limited scope of arylsilanes that underwent this reaction make it unclear if the existing method could be made more broadly applicable.^{10–12}

Because of the potential of arylsilanes derived from C–H bond functionalization to serve as intermediates for the synthesis of arylamines, we sought a practical method for the oxidative amination of heptamethyltrisiloxylarenes (HMTS-arenes), which are readily accessible by C–H silylation. Herein, we report the coupling of HMTS-arenes with nitrogen nucleophiles that occurs with broad scope of the nitrogen nucleophiles and arylsilanes and is the first amination of arylsilanes with the arylsilane as limiting reagent. Reactions without a fluoride additive give the arylamine products in yields that are similar to those with a fluoride additive, thereby overcoming one of the major limitations of the functionalization of arylsilanes.^{9b}

Our initial studies to develop the oxidative coupling of arylsilanes with nitrogen nucleophiles were guided by several features of the mechanism of Chan–Lam type coupling.¹³ Mechanistic studies have shown that transmetalation of the aryl group from the boronate to Cu(II) is the rate-limiting step of the common Chan–Lam reactions of arylboron derivatives.¹⁴ In general, transmetalation of an organic group from silicon to a transition metal is slower than transmetalation from boron to a transition metal. Thus, our studies focused on identifying conditions that could facilitate transfer of the aryl group from the silane to copper. We reasoned that the polarity of the solvent and the additives that can mediate transfer of the aryl group by creating a hypervalent silicon derivative or a bridge to the

transition metal¹⁵ could be critical factors to increase the rates of transmetalation.

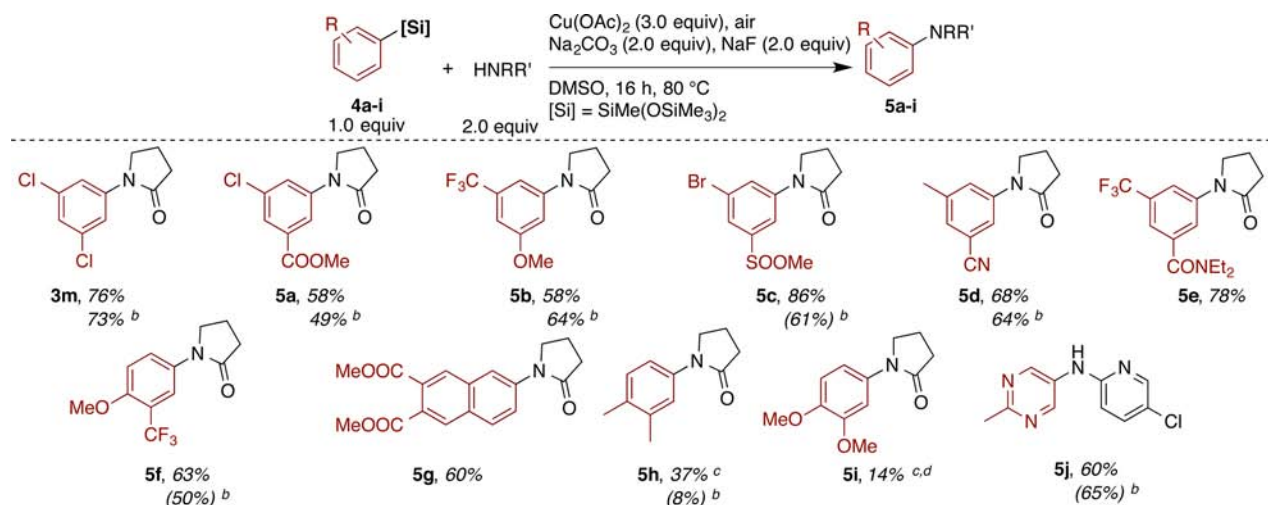
We selected arylsilane **1** as the substrate for our initial evaluation of conditions because this compound can be formed easily by the silylation of 1,3-dichlorobenzene on a 20 mmol (3.0 g) scale. Moreover, we considered that **1** was likely to be one of the least reactive arylsilanes because it is electron deficient.¹⁶

Testing a series of additives to activate the silane (entry 2–7) revealed that the ratio of diarylamine product **3a** to homocoupling product **6** is strongly dependent on the identity of the activator. Reactions conducted with TBAF, which is a typical activator for the coupling of **2** with aryltrimethoxysilanes, gave the coupled, diarylamine product **3a** in only a modest yield (26%). This reaction, as well as reactions with CsF, formed significant amounts of product from homocoupling of the arylsilane (53–70%). Reactions conducted with fluoride sources that are less activating than CsF predominantly formed **3a**. The highest yield (79%) was obtained with NaF (entry 3).

The amount of the two minor side products (arene from desilylation and phenol from oxidation) was higher at 100 °C (entry 12) than at 80 °C, resulting in a lower yield (61%) of **3a** at this higher temperature than was observed at 80 °C (84%) (entry 11).¹⁷

Further evaluation of the reaction conditions showed that stoichiometric amounts of copper are required (entry 9). However, the yields of **3a** from the reaction with equimolar amounts of copper and **1** were similar to those with excess copper (3 equiv) (78% vs 79%). We decided to explore this reaction with excess copper further because the yield of **3a** was slightly higher under these conditions, and the price of anhydrous copper acetate (about \$1/gram, or \$0.18/mmol) is negligible for reactions on laboratory scale. The highest yields of **3a** were obtained with a 2-fold excess of aniline at 80 °C with Na₂CO₃ as the base (entry 10).

The scope of nitrogen nucleophiles that couple with **1** is shown in Scheme 1. Anilines containing a range of functional groups and substitution patterns gave the arylamine products in

Scheme 2. Scope of the Coupling of Arylsilanes with N-Nucleophiles^a

^aReaction conditions: **4a-i** (0.3 mmol), N-nucleophile (0.6 mmol), $\text{Cu}(\text{OAc})_2$ (0.9 mmol), Na_2CO_3 (0.6 mmol), NaF (0.6 mmol), and dry DMSO (2.0 mL). Air atmosphere, heated at 80 °C for 16 h. Yields are isolated yields, and yields in parentheses are yields by NMR. ^bReactions conducted in the absence of a fluoride source. ^c KHF_2 was used as fluoride source. ^dReaction was conducted at 100 °C for 2 d.

high yields (**3b-d**). The reaction of a diarylamine (**2e**) also gave the triarylamine product, although the yield for this reaction was lower than that for the reaction of the primary arylamines. Reactions of aminopyridines (**2f**), -pyrimidines (**2g**), -pyrazines (**2h**), -pyrazoles (**2i**), and -thiophenes (**2j**) also led to the coupled products in good to excellent yields. Furthermore, pyrrole **2k** coupled directly with **1**.

The reaction also occurred at the N-H bond of a series of amides (**2l-m**) and sulfonamides (**2n**). In previous studies, amides reacted with phenyltrimethoxysilane to give only moderate yields of the coupled product.^{10-12,18}

Aliphatic amines (**2o-p**) also coupled with the arylsilane, although in lower yields than the reactions of less basic nitrogen nucleophiles. During the reaction with aliphatic amines, a change of color from green blue to deep blue was observed upon the addition of the amine. This change in color suggests that the amine coordinated to the copper. This coordination could interfere with the transmetalation of the aryl group from Si to Cu and cause the yields for reactions of alkylamines to be moderate.¹⁴ The robustness of the presented method was demonstrated by running a gram-scale reaction with a yield of 1.19 g (76%) of **3m**.

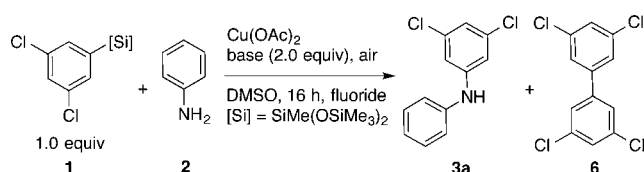
The scope of arylsilanes that undergo this process is shown in Scheme 2. For these studies, 2-pyrrolidone was used as the nucleophile because copper-catalyzed oxidative couplings of lactams have been used extensively for the synthesis of PPAR agonists,¹⁹ and the yield of **3m** (77%) is in the middle of the range of yields from reactions of the various nitrogen nucleophiles (Scheme 1). The results in Scheme 2 show that the conditions we developed for the coupling of the 3,5-dichlorophenylsilane are suitable for the coupling of a broad array of arylsilanes. Substrates containing halide, ester, trifluoromethyl, ether, sulfonyl, cyano, and amide functional groups (**4a-e**) gave the coupled products in good yields. In addition to arylsilanes, heteroarylsilanes, such as silylpyrimidines (**4j**), underwent coupling with **2f** under the conditions we developed.²⁰ Thus, the reported method gives access to arylamines, such as **5f** and **5j**, from substrates that are inaccessible through C-H borylation.⁷ The yield of **5h** under the reported condition was lower (8% yield by NMR spectroscopy) than

those of the amination products from the C-N couplings of electron-poor substrates. We reasoned that a more activating fluoride source could facilitate conversion of the electron-rich substrates **4h** and **4i** and therefore tested KHF_2 as activator. These reactions formed **5h** in a moderate yield (37%) and **5i** in a low yield (14%) after 16 h.

The fluoride additive in the functionalizations of arylsilanes can deter the use of these reactions in some settings and scales. The need to activate the silicon reagents with a fluoride has been addressed by Denmark and co-workers, who developed protocols for cross-coupling to form C-C bonds that do not require fluorides.^{9b} However, arylsilanes have not been shown to undergo coupling with nitrogen nucleophiles without a fluoride additive. Our initial evaluation of conditions for the results of Schemes 1 and 2 revealed that the reaction of **1** with **2** at 65 °C proceeded without a fluoride source (Table 1; entry 1), but the yield of arylamine from the reaction without fluoride was lower than that from the reaction with NaF (57% vs 79%).

Comparison of the reaction profile of the reaction without NaF with that of the reaction with NaF revealed that the reaction proceeds faster in the presence of NaF, most likely due to acceleration of the transmetalation step (see the Supporting Information). On the basis of this observation, we investigated opportunities for a fluoride-free reaction variant and ran reactions with representative amines (**3b,c,e,f,h,i,j,l,m,o,p**) and HMTS-arenes and heteroarylsilanes (**5a,b,c,d,f,j**) at 80 °C in the absence of a fluoride source. Because of acceleration of the reaction at this temperature, the yields of coupled products without fluoride were similar to those of reactions with NaF (Schemes 1 and 2). Electron-rich arylsilanes still require a fluoride additive to generate the product in acceptable yields.

In conclusion, we developed a method for the coupling of HMTS-arenes with a wide range of nitrogen nucleophiles to form the C-N bond in arylamines and their derivatives. This process, in combination with the silylation of C-H bonds, gives access to a broad scope arylamines directly from unactivated arenes and heteroarenes. Unlike other methods for coupling of arylsilanes to form C-N bonds, this method proceeds with the arylsilane as limiting reagent. This stoichiometry is valuable because the arylsilanes obtained from C-H silylation are often

Table 1. Evaluation of Conditions for the Cu-Mediated Coupling of 1 with 2^a


entry	conditions	fluoride (1.0 equiv)	yield (%) 3a	yield (%) 6
1	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C		57	
2	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	LiF	67	
3	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	NaF	79	
4	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	KF	66	15
5	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	CsF	15	70
6	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	TBAF	26	53
7	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	KOTMS	57	
8	Cu(OAc) ₂ (1.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	NaF	78	
9	Cu(OAc) ₂ (0.1 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 65 °C	NaF	9	
10	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (1.2 equiv), 80 °C	NaF	65	3
11	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 80 °C	NaF	84	
12	Cu(OAc) ₂ (3.0 equiv), Na ₂ CO ₃ , 2 (2.0 equiv), 100 °C	NaF	61	
13	Cu(OAc) ₂ (3.0 equiv), NEt ₃ , 2 (2.0 equiv), 80 °C	NaF ^b	56	19
14	Cu(OAc) ₂ (3.0 equiv), 2 (2.0 equiv), 80 °C	NaF ^b	63	7

^aReactions conducted on a 0.05 mmol scale. Yields were determined by gas chromatography (GC) with dodecane as standard. The GC-yields were calibrated by ¹H NMR with 1,3,5-trimethoxybenzene as NMR-standard. ^bReaction conducted with 2.0 equiv of NaF.

more valuable than the nitrogen nucleophile, especially in the late stage functionalization of complex molecules. We also found that fluoride is not required for the reaction to occur. This method should begin to broaden the applications of arylsilanes, which are nontoxic, less expensive, and more stable than their boronate analogues, in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02543.

Detailed experimental procedures and characterization of products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jhartwig@berkeley.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIH (GM-115812) for support of this work. J.M. thanks the German National Academic Foundation (Studienstiftung) for supporting his research in the Hartwig lab.

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