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Copper-Catalyzed Silylation of C(sp^3)−H Bonds Adjacent to Amide Nitrogen Atoms

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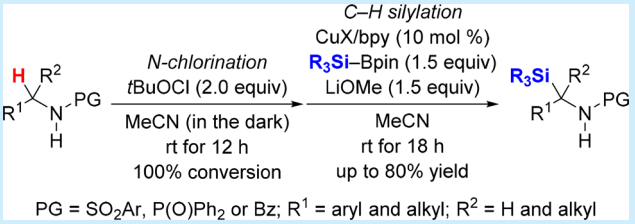
Supporting Information

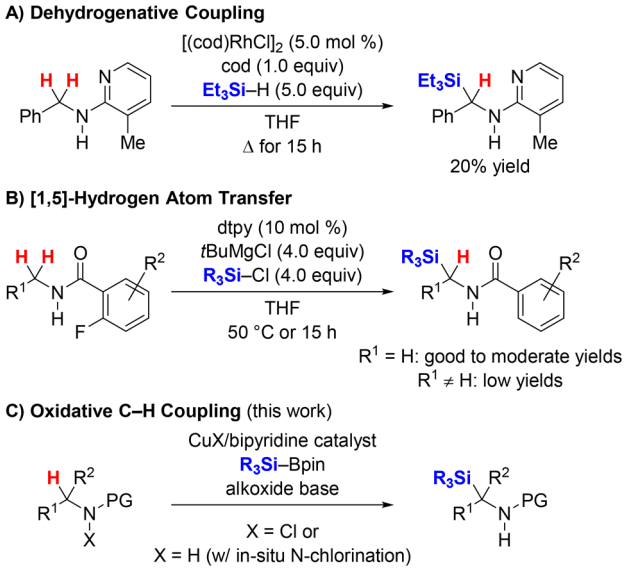
ABSTRACT: A copper-catalyzed C−Si bond formation between N-halogenated amides and Si−B reagents is described. This oxidative coupling enables the silylation of C(sp^3)−H bonds α to an amide nitrogen atom. The utility of the new method is demonstrated for sulfonamides, and N-chlorination with *t*BuOCl and C−H silylation employing CuSCN/4,4′-dimethoxy-2,2′-bipyridine as catalyst can be performed without purification of the N−Cl intermediate.



Catalytic oxidative functionalization of C(sp^3)−H bonds adjacent to the nitrogen atom of amines is an important way of diversifying their substitution pattern.[1] While C−C bond formation in this position is now relatively well established,[1] the related installation of heteroatoms α to the nitrogen atom is less developed.[2] To the best of our knowledge, there is no report on the formation of a C−Si bond by this strategy. Aside from the conventional preparation of α-silylated amines from amides by directed metalation−electrophilic silylation,[3] there are just a few catalytic approaches known.[4,5] Mita and Sato recently disclosed a rhodium-catalyzed dehydrogenative coupling of mainly Me_2N groups and Et_3SiH directed by a pyridin-2-yl donor; further substitution at the methyl group is detrimental (Scheme 1A).[4] Similar observations were made by Zeng and co-workers in their [1,5]-hydrogen atom transfer strategy starting from *ortho*-fluorinated benzamides with different alkyl groups attached to the nitrogen atom (Scheme 1B).[5] We therefore targeted an oxidative procedure that would convert those C(sp^3)−H into C(sp^3)−Si bonds without the structural bias of the aforementioned examples (Scheme 1C). Our approach is intended to complement the existing methods for the catalytic preparation of α-silylated amines,[6] particularly the addition of silicon nucleophiles to imines[7] and carbon nucleophiles to silylated imines,[8] respectively.[9,10]

Our plan was to make use of copper/bipyridine catalysts[11] and alkoxide-mediated activation of the Si−B bond[12,13] in Si−B reagents[14] (Scheme 1C). To avoid the use of oxidants in the presence of Si−B reagents,[15] we decided to transform the amine substrates into the readily available[16] N-chlorinated derivatives. The N−Cl linkage could serve as a traceless activating group in the coupling of the C(sp^3)−H bond α to the nitrogen atom by engaging in single electron transfer (SET) processes.[17] To demonstrate the feasibility of our proposal, we began with the optimization of the reaction using *N*-chlorosulfonamide **1a** as the model substrate and Me_2PhSi−Bpin[14a] as the silicon source (Table 1). After screening of various reaction parameters, we found that the desired bond

Scheme 1. Catalytic Approaches to α-Silylated Amines and Amides by Silylation of α-C(sp^3)−H Bonds[a]



[a]PG = protective group.

formation occurred with CuSCN/4,4′-dimethoxy-2,2′-bipyridine as catalyst and LiOMe as alkoxide base in CH_3CN at room temperature; the α-silylated amide **2a** was obtained in 78% NMR yield along with 22% NMR yield of amide **3a** resulting from hydrodechlorination at the nitrogen atom (entry 1; see the Supporting Information for the complete set of optimization data). Control experiments showed that both the copper salt and the alkoxide are essential (entries 2 and 3). Of note, when CuSCN was not employed, 42% NMR yield of hydrodechlorinated **3a** as well as a similar amount of the

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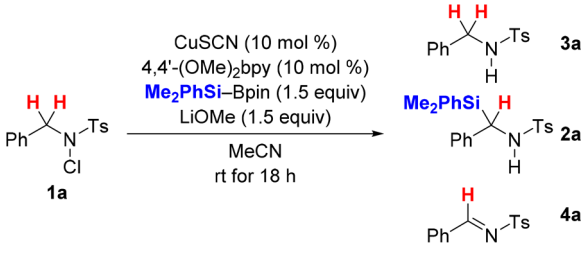
Table 1. Selected Examples of the Optimization of the C(sp^3)−H Silylation[a]



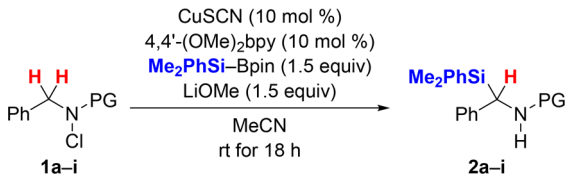
entry	variation	yield[b] of **2a** (%)	yield[b] of **3a** (%)
1	none	78	22
2[c]	w/o CuSCN	15	42
3[d]	w/o LiOMe	0	94
4	w/o 4,4′-(OMe)$_2$bpy	60	40
5	1,4-dioxane/DMF (9:1) instead of MeCN	76	23
6	1,4-dioxane instead of MeCN	67	33
7	DMF instead of MeCN	33	48
8	THF instead of MeCN	37	62

[a]All reactions performed on a 0.10 mmol scale. [b]NMR yield with CH_2Br_2 as an internal standard. [c]43% NMR yield of the **4a** observed. [d]5% NMR yield of **4a** observed.

corresponding aldimine **4a** were produced (entry 2); moreover, the formation of the α-silylated amide **2a** in 15% NMR yield suggests that LiOMe alone is able to mediate the Si−B bond activation and the subsequent silyl transfer onto **4a**.[18] The combination of CuSCN and 4,4′-(OMe)$_2$bpy is crucial to secure high yield (entry 4). The solvent also had substantial effect on the product distribution but no improvement over acetonitrile was seen (entries 5−8).

With the optimized conditions in hand, we evaluated different protecting groups on the nitrogen atom (Table 2). It was found that the electronic situation of the sulfonamide had a significant impact on the reaction outcome. Electron-rich **1a**, **1b**, and **1d** afforded relatively better results than electron-deficient **1c** and **1e** (entries 1−5). Ms-protected **1f** furnished **2f** in moderate yield whereas **1g** bearing a strongly electron-withdrawing Tf group did not lead to C−Si bond formation (entries 6 and 7). Aside from sulfonamides, phosphinamide **1h** and benzoylamide **1i** are also suitable substrates (entries 8 and 9).

Table 2. Assessment of Different Amides[a]

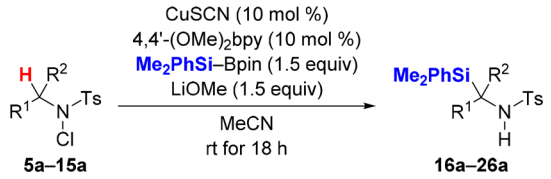


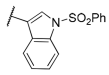
entry	amide	PG	amine	yield[b] (%)
1	**1a**	Ts	**2a**	77
2	**1b**	*p*-MeOPhSO$_2$	**2b**	80
3[c]	**1c**	*p*-NO$_2$PhSO$_2$	**2c**	50
4	**1d**	*o*-MePhSO$_2$	**2d**	80
5	**1e**	*o*-BrPhSO$_2$	**2e**	72
6	**1f**	MeSO$_2$	**2f**	66
7	**1g**	CF$_3$SO$_2$	**2g**	0
8	**1h**	Ph$_2$P(O)	**2h**	78
9	**1i**	Bz	**2i**	60

[a]All reactions performed on a 0.20 mmol scale. [b]Isolated yield after flash chromatography on silica gel. [c]Performed in 1,4-dioxane/DMF (9:1) instead of MeCN for better solubility.

Before examining the substrate scope with Ts as protective group, we tested silicon pronucleophiles other than Me$_2$PhSi−Bpin in the model reaction. MePh$_2$Si−Bpin[14a] led to a comparable result (70% versus 77% yield, see the Supporting Information for characterization data and NMR spectra) while Et$_3$Si−Bpin[14b] did not react;[15] degradation of **1a** to **3a** (65%) and **4a** (35%) was detected. The substrate scope is summarized in Table 3. The reaction of sulfonamides **5a**−**11a** bearing various benzyl groups with substituents in the *para*, *meta*, and *ortho* positions proceeded smoothly, and the corresponding α-silylated amines **16a**−**22a** were obtained in moderate yields (entries 1−7). In general, substrates with electron-withdrawing substituents on the aryl moiety showed lower yields than those bearing an electron-donating group (entry 1 versus 4). The phenyl unit in **1a** could be replaced by an α-naphthyl (**12a** → **23a**, entry 8) and a heteroaryl group (**13a** → **24a**, entry 9), still maintaining decent yields. However, the yield dropped to 29% for R^1 = alkyl (**14a** → **25a**, entry 10). Conversely, fully substituted **15a** with R^1 = Ph and R^2 = Me yielded α-silylated amine **26a** with a "quaternary" carbon atom in acceptable yield (entry 11).

Table 3. Scope of Copper-Catalyzed Silylation of C(sp^3)−H Bonds Adjacent to an Amide Nitrogen Atom[a]



entry	amide	R^1	R^2	amine	yield[b] (%)
1	**5a**	*p*-MeC$_6$H$_4$	H	**16a**	76
2	**6a**	*p*-ClC$_6$H$_4$	H	**17a**	71
3	**7a**	*p*-BrC$_6$H$_4$	H	**18a**	51
4	**8a**	*p*-CF$_3$C$_6$H$_4$	H	**19a**	56
5	**9a**	*m*-MeC$_6$H$_4$	H	**20a**	69
6	**10a**	*o*-MeC$_6$H$_4$	H	**21a**	63
7	**11a**	*o*-BrC$_6$H$_4$	H	**22a**	60
8[c]	**12a**	naphth-1-yl	H	**23a**	69
9	**13a**		H	**24a**	50
10	**14a**	Et	H	**25a**	29
11	**15a**	Ph	Me	**26a**	35

[a]All reactions performed on a 0.20 mmol scale. [b]Isolated yield after flash chromatography on silica gel. [c]Performed in 1,4-dioxane/DMF (9:1) instead of MeCN for better solubility.

As mentioned above, the *N*-chlorosulfonamides are easily accessible from the corresponding sulfonamides by oxidation with *t*BuOCl,[17c] e.g., **3a** → **1a** (Scheme 2). This procedure is in fact compatible with the formal C−H silylation, and the α-silylated amine **2a** was isolated in 70% yield after subjecting crude **1a** to the standard protocol (Scheme 2).

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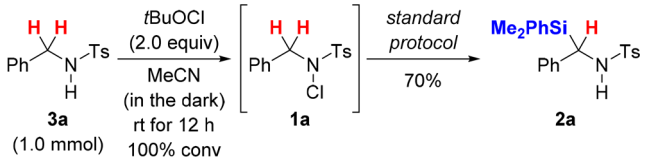
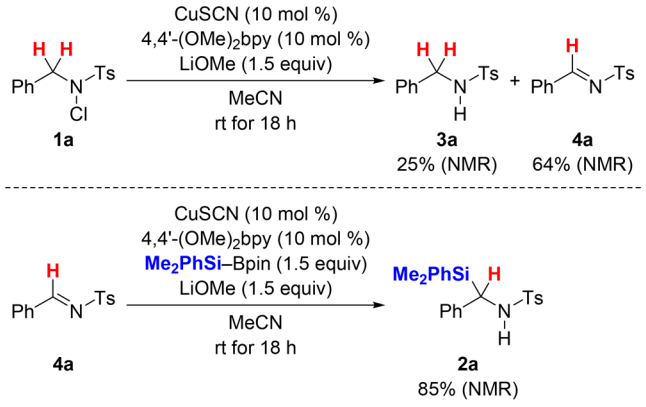
Scheme 2. Procedure on Larger Scale without Purification of the *N*-Chlorosulfonamide



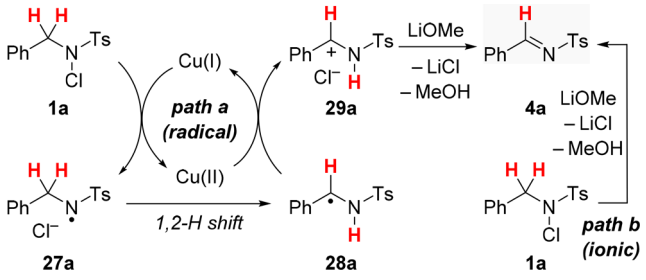
To gain preliminary insight into the reaction mechanism, specifically the formation of the imine **4a**, we performed two control experiments (Scheme 3). The reaction of **1a** in the absence of the Si–B reagent did form imine **4a** in 64% NMR yield along with amine **3a** in 25% NMR yield (top). Treatment of **4a** with the standard setup then gave α-silylated amine **2a** in 85% NMR yield (bottom).[7a]

Scheme 3. Control Experiments



On the basis of these control experiments and previous experimental observations, we believe that the catalysis proceeds through the imine (gray box, Scheme 4) that, in turn, undergoes conventional copper-catalyzed 1,2-addition of the silicon nucleophile (not shown).[7] That would also explain the higher yields seen with aldimines compared to the ketimine (see Table 3, entry 11). Two pathways explain the formation of the imine (Scheme 4):[17c] Path a is radical with Cu(I)-mediated N–Cl cleavage to generate the corresponding sulfonamidyl radical and Cu(II) (**1a** → **27a**);[19] **27a** then converts into carbon-centered radical **28a** by a 1,2-H shift[20] followed by Cu(II)-promoted oxidation to **29a**. Deprotonation of iminium ion **29a** yields the imine **4a**. Path b cannot be excluded as **4a** is also formed from **1a** by base-mediated β-elimination[21] (cf. Table 1, entry 2).

Scheme 4. Proposed Mechanism of Imine Formation



In summary, we have introduced here a new approach to the synthesis of synthetically valuable[6,22] α-silylated amines. The method allows for the silylation C(sp^3)–H bonds adjacent to amide nitrogen atoms at room temperature. The starting material, that is, the N-halogenated amide, can be prepared in situ and used without further purification in the subsequent copper-catalyzed silylation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01698.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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