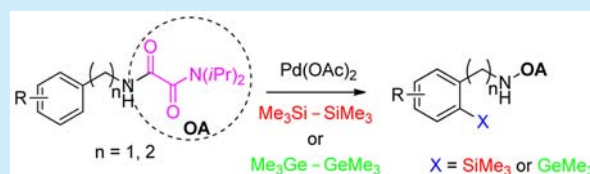


Palladium-Catalyzed Oxalyl Amide Directed Silylation and Germanylation of Amine Derivatives

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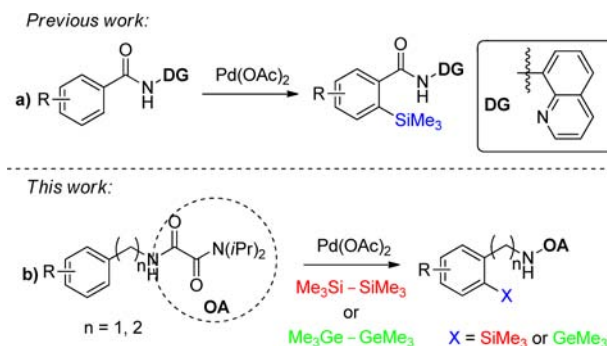
Supporting Information

ABSTRACT: Palladium-catalyzed direct *ortho*-silylation of oxalyl amide-protected phenylmethanamine and phenethylamine with commercially available disilanes is reported. Germanylation products were also produced under the same reaction conditions. This protocol tolerated oxalyl amide-protected aliphatic amines, which gave γ -C–H silylation products.



C–Si bond formation involving transition-metal-catalyzed C–H activation is of great importance in terms of atom and step economy. Organosilicon compounds possess unique physical and chemical properties that make them indispensable for application in organic synthesis and in material science.¹ The incorporation of silicon groups into drug candidates has been done recently in a growing number of relevant studies in medicinal chemistry.^{2–6} Therefore, considerable efforts have been made for the development of new methodology involving transition-metal-catalyzed silylation reactions during the last decades. Among these methods, catalytic silylation with hydrosilanes and hexamethyldisilane via C–H bond activation have been achieved. For example, Ir have been used in the catalytic silylation of aromatic, vinylic, and aliphatic C–H bonds.⁷ Hartwig also reported a Pt-catalyzed dehydrogenative coupling of hydrosilanes with aryl and aliphatic methyl C–H bonds.⁸ In 2011, the Sc-catalyzed *ortho*-silylation of alkoxy-substituted benzene derivatives was disclosed by Hou.⁹ Other catalysts such as Ru and Rh were also used in the direct silylation reactions.^{10,11} Despite the efficiency of direct C–H bond silylation reactions, there is still room for the development of catalytic silylation to expand the substrates which bearing various functional groups. As far as we know, using the directing group to control the regioselectivity of C–H silylation via palladium for the primary amine derivatives is rarely reported. In 2014, Kuninobu and Kanai reported the Pd-catalyzed silylation of carboxylic acid derivatives aided by the quinolyamidebidentate directing group (Scheme 1a).¹² From the significant progress in Pd-catalyzed, directing group promoted C–H borylation using diboron reagent (B_2pin_2),¹³ we determined whether we could use disilanes instead of diboron reagent species to develop a similar catalytic cycle as a new avenue for intermolecular C–H silylation. Herein, we report an example of Pd(II)-catalyzed intermolecular silylation of C(sp²)-H bonds in oxalyl amide-

Scheme 1. Palladium-Catalyzed Silylation and Germanylation of Amine Derivatives



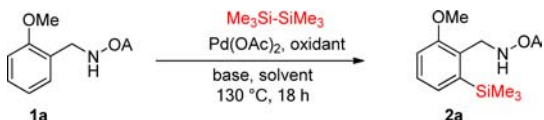
protected benzylamine and phenylethylamine to install an organosilicon moiety at the γ - and δ -positions.

Notably, the C(sp³)-H bonds in aliphatic amine derivatives could also be directly silylated at γ - and δ -positions under the new catalytic cycle.

We recently developed palladium-catalyzed direct alkenylation and arylation of amine derivatives through C–H activation aided by an oxalyl amide directing group.¹⁴ We found that oxalyl amide is a highly efficient agent that aids activation of a diverse range of amine C–H bonds via five, six, or even seven metal cyclic intermediates. It may be subsequently treated with various electrophiles to give the target products. We therefore decided to investigate C–H silylation using benzylamine substrate **1a**. We found that C–H silylation of **1a** with 3 equiv of hexamethyldisilane occurred in the presence of 5 mol % of Pd(OAc)₂ and 2.0 equiv of K₂CO₃ in 1,4-dioxane stirred at 130 °C for 18 h to give the desired silylation product **2a** in 2% yield (Table 1, entry 1).

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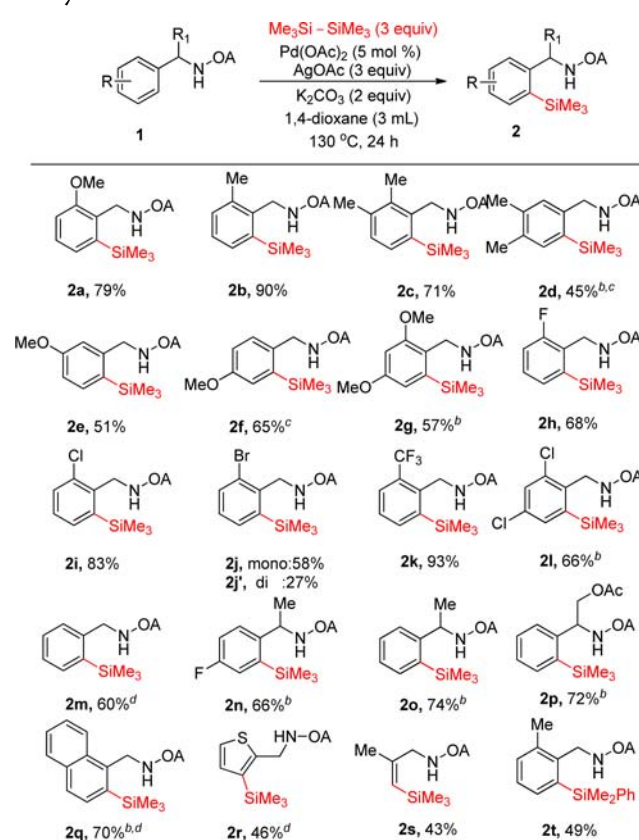
Table 1. Optimization Studies^a


entry	oxidant	base	solvent	yield of 2a (%)
1	none	K ₂ CO ₃	1,4-dioxane	2
2 ^b	AgCO ₃	K ₂ CO ₃	1,4-dioxane	10
3	AgO	K ₂ CO ₃	1,4-dioxane	9
4	AgOAc	K ₂ CO ₃	1,4-dioxane	84
5 ^b	K ₂ S ₂ O ₈	K ₂ CO ₃	1,4-dioxane	3
6	AgOAc	K ₂ CO ₃	DCE	39
7	AgOAc	K ₂ CO ₃	toluene	83
8	AgOAc	K ₂ CO ₃	DMF	4
9	AgOAc	K ₂ CO ₃	NMP	0
10	AgOAc	K ₂ CO ₃	<i>tert</i> -amyl-OH	0
11	AgOAc	none	1,4-dioxane	80
12	AgOAc	Na ₂ CO ₃	1,4-dioxane	72
13	AgOAc	KHCO ₃	1,4-dioxane	77
14	AgOAc	K ₂ HPO ₄	1,4-dioxane	79
15	AgOAc	K ₃ PO ₄	1,4-dioxane	67
16 ^c	AgOAc	K ₂ CO ₃	1,4-dioxane	0

^aReaction conditions: **1a** (0.1 mmol), Si₂Me₆ (0.3 mmol), Pd(OAc)₂ (5 mmol %), oxidant (0.3 mmol), base (0.2 mmol), solvent (1.5 mL), 130 °C, 18 h. ^bOxidant (0.2 mmol). ^cNo palladium catalyst. Yield was based on GC using tridecane as the internal standard.

Extensive screening of oxidants, bases, and solvents showed that the use of AgOAc as oxidant, K₂CO₃ as base, and 1,4-dioxane as solvent provided **2a** in 84% yield (Table 1, entry 4). Poor yields were obtained with other oxidants (entries 2, 3, and 5). The solvent effect showed that 1,4-dioxane was the optimal solvent. Protic and aprotic polar solvents such as *tert*-amyl-OH, DMF, and NMP inhibited the reaction. The solvent toluene gave a slightly decreased yield of silylated product, whereas use of DCE as solvent drastically decreased the yield (entries 6–10). It is noteworthy that silylation in toluene gave a yield similar to that obtained with 1,4-dioxane (entry 7). Further optimization showed that K₂CO₃ increased the yield of the product. Without base or upon replacement of K₂CO₃ with other inorganic base, the yield of silylated products decreased (entries 11–15). Control experiments confirmed that no reaction happened without use of palladium catalyst, implicating the crucial role of Pd(OAc)₂ for the transformation (Table 1, entry 16).

We surveyed the substrate scope of the silylation reaction by using a variety of benzylamines and disilanes under the optimized reaction conditions. As shown in Scheme 2, all of the reactions proceeded well and gave the corresponding silylation products in moderate to good yields and with excellent γ -regioselectivity and selectivity for monosilylated products. Functional groups such as Me, MeO, F, Cl, Br, and CF₃ were tolerated. Substituents bearing electron-donating groups and electron-withdrawing groups at the *ortho* position gave silylation products in high yields (**2a,b,h–k**). In addition, different substituents at the *ortho*, *meta*, or *para* positions of the benzylamines were tolerated. Generally, the *ortho*-substituted benzylamines gave a higher silylation yield than did *meta*- or *para*-substituted substrates. The silylation product of Br-substituted benzylamine under standard conditions at 58% yield and disilylation product at 27% yield (**2j,j'**) were obtained. The α -substituted benzylamine derivatives (**2n–p**) also gave the corresponding silylation products in moderate to high yield.

Scheme 2. Palladium-Catalyzed C(sp²)-H Silylation of Benzylamines^a

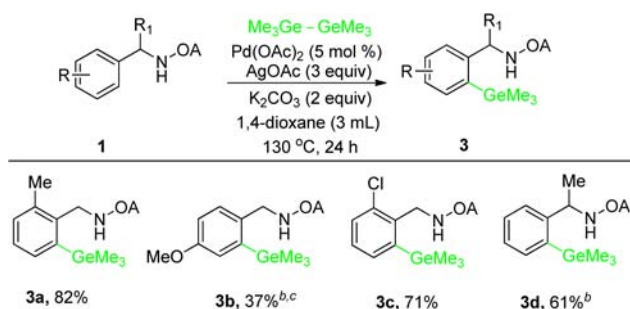
^aReaction conditions: **1** (0.2 mmol), Si₂Me₆ (0.6 mmol), Pd(OAc)₂ (5 mol %), AgOAc (0.6 mmol), K₂CO₃ (0.4 mmol), 1,4-dioxane (3 mL), 130 °C, 24 h, isolated yields. ^bPd(OAc)₂ (10 mol %). ^cToluene (1 mL). ^dToluene (3 mL).

Reaction of the substrates 1-naphthalenemethylamine and 2-thiophenemethylamine also proceeded well, providing silylation products (**2q,r**) in moderate to good yield. Notably, the challenging **2s** was also obtained in moderate yield with the same reaction conditions. Other silylation reagents such as phenyldimethylsilane gave silylation products in moderate yield (**2t**).

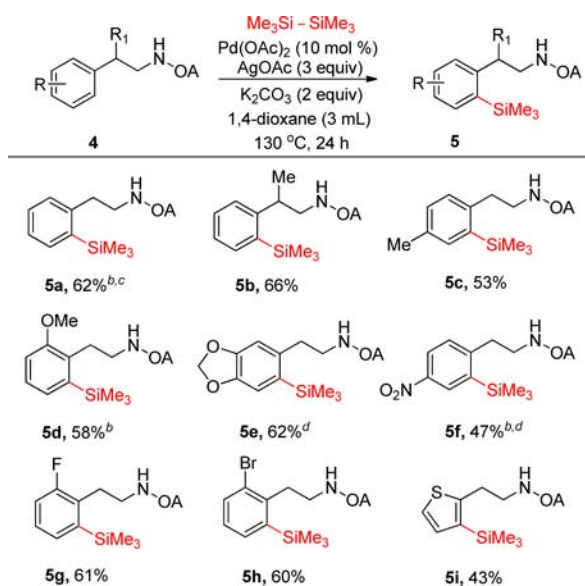
More importantly, germanylation of benzylamine derivatives also proceeded well under the optimized reaction conditions (Scheme 3), giving the germanylated product substituted (**3a–d**) at the γ -position of the benzylamines in moderate to good yield.

To gain a deep understanding of C–H silylation assisted by the oxalyl amide directing group, we treated oxalyl amide protected phenylethylamine **4** with hexamethyldisilane under the standard reaction conditions. Unexpectedly, products silylated at the δ -position of phenylethylamine and monosilylation products were obtained in moderate yield (Scheme 4). Substituents such as methoxyl, 3,4-dimethoxyl, nitro, F, and Br were tolerated (**5d–h**). In addition, reaction of the α -methyl substituent of the substrate phenylethylamine (**5b**) proceeded well to give the silylated product in moderate yield. Further exploration showed that heterocycloamines such as thiophene-2-ethylamine (**5i**) also gave the corresponding product silylated at the δ -position of the amine.

On the basis of the Pd-catalyzed C(sp²)-H silylation, we turned our attention to the more challenging C(sp³)-H bond.

Scheme 3. Palladium-Catalyzed C(sp²)-H Germanylation of Benzylamines^a

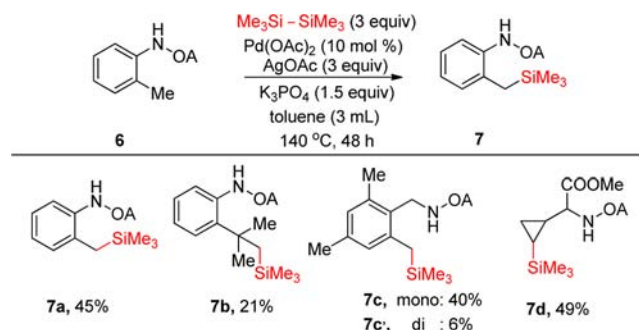
^aReaction conditions: **1** (0.2 mmol), Ge_2Me_6 (0.6 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %), AgOAc (0.6 mmol), K_2CO_3 (0.4 mmol), 1,4-dioxane (3 mL), 130 °C, 24 h, isolated yields. ^b $\text{Pd}(\text{OAc})_2$ (10 mol %). ^cToluene (1 mL).

Scheme 4. Palladium-Catalyzed C(sp²)-H Silylation of Phenylethylamine^a

^aReaction conditions: **4** (0.2 mmol), Si_2Me_6 (0.6 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), AgOAc (0.6 mmol), K_2CO_3 (0.4 mmol), 1,4-dioxane (3 mL), 130 °C, 24 h, isolated yields. ^bToluene (3 mL). ^c $\text{Pd}(\text{OAc})_2$ (5 mol %). ^d48 h.

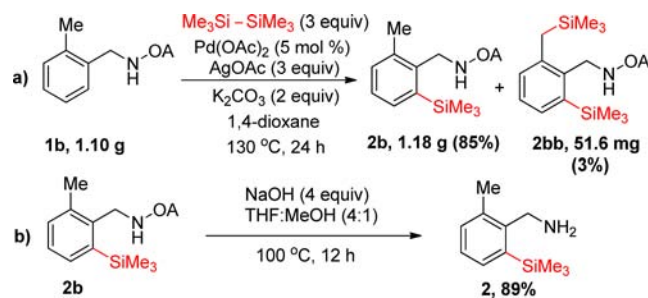
Under the modified reaction conditions, C(sp³)-H silylation products were obtained in moderate yield. As shown in Scheme 5, γ -silylation of the amines proceeded well. Silylation tolerated the cyclopropyl functional group and gave the corresponding cyclopropyl silylated product (7d). In addition, δ -silylation of *ortho*-substituted aniline was achieved (7b). It is noteworthy that with the use of the substrate 2,4,6-trimethylbenzylamine the corresponding δ -silylation product at 40% yield and a containment disilylation product at 6% were obtained (7c and 7c').

To demonstrate the utility of this method, a gram scale of the substrate **1b** was subjected to the standard reaction conditions. This gave the monosilylation product **2b** in 85% yield and a disilylation product **2bb** at 3%. The oxalyl amide could also be removed through 4 equiv of NaOH in THF/ CH_3OH = 4:1 and give the *ortho*-silylated free phenylmethanamine **2** in 89% yield (Scheme 6).

Scheme 5. Palladium-Catalyzed C(sp³)-H Silylation^a

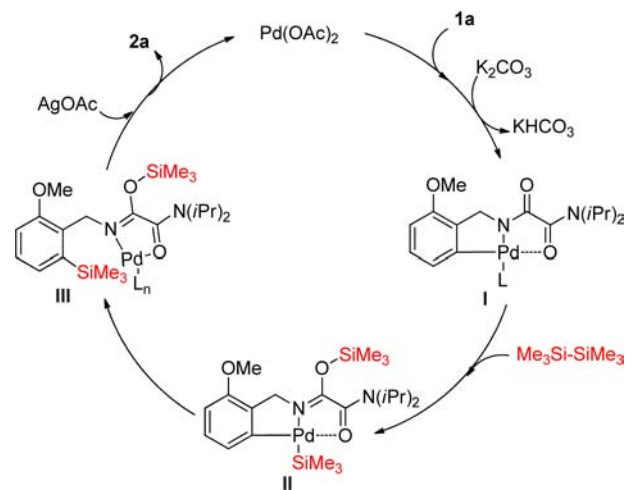
^aReaction conditions: **6** (0.2 mmol), Si_2Me_6 (0.6 mmol), $\text{Pd}(\text{OAc})_2$ (10 mol %), AgOAc (0.6 mmol), K_3PO_4 (0.3 mmol), toluene (3 mL), 140 °C, 48 h, isolated yields.

Scheme 6. Large-Scale Synthesis and Removal of Directing Group



Based on these results, we proposed the silylation mechanism (Scheme 7). Initially, the oxalyl amide directing group promoted

Scheme 7. Proposed Catalytic Cycle



C-H activation to form a five- or six-membered palladacycle that when treated with hexamethyldisilane underwent transmetalation followed by reductive elimination to give the desired silylation product, and the Pd(0) was reoxidized to Pd(II) by AgOAc to complete the catalytic cycle.

In conclusion, we have developed highly selective Pd^{II}-catalyzed direct silylation of benzylamine and phenylethylamine derivatives with the aid of an oxalyl amide directing group at the γ - and δ -positions. The inexpensive silicon source hexamethyldisilane could be used efficiently, and AgOAc was found to be the

best oxidant. Direct C(sp²)-H germanylation and C(sp³)-H silylation of oxalyl amide-protected benzylamine derivatives by modifying the reaction conditions produced moderate to good yield with tolerance for a broad range of functional groups. Oxalyl amide could be removed under mild conditions to afford silylated free amines. Detailed mechanistic studies and application of this method in the total synthesis of natural products are being studied in our laboratory.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01393.

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Notes

The authors declare no competing financial interest.

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