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Palladium-Catalyzed Direct C−H Silylation and Germanylation of Benzamides and Carboxamides

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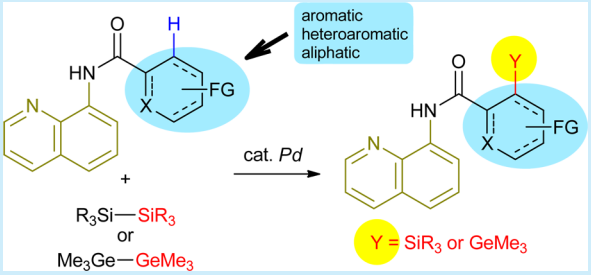
Supporting Information

ABSTRACT: A palladium-catalyzed regioselective activation of C(sp^2)−H and C(sp^3)−H bonds of benzamides and carboxamides, followed by coupling with disilanes to afford organosilanes in moderate to high yields, with the aid of 8-aminoquinoline as a directing group, is reported. Catalytic C(sp^2)−H germanylation of benzamides also proceeds under the same palladium catalysis. The reaction tolerates a wide variety of functional groups and is scalable without yield reduction. The bidentate directing group is readily removed and recovered by the reaction with a hydrazine, with concominant generation of an acyl hydrazide.



Organosilicon compounds are valuable synthetic intermediates in a variety of organic reactions[1] and have various potential uses in materials science.[2] In addition, recently there have been a growing number of interesting reports in the literature on the application of organosilicon compounds as therapeutically relevant molecules such as amsilarotene, sila-dimetracrine, a sila-analogue of tetrahydroisoquinoline, silaproline, and TMS-alanine in medicinal chemistry (Figure 1).[3]

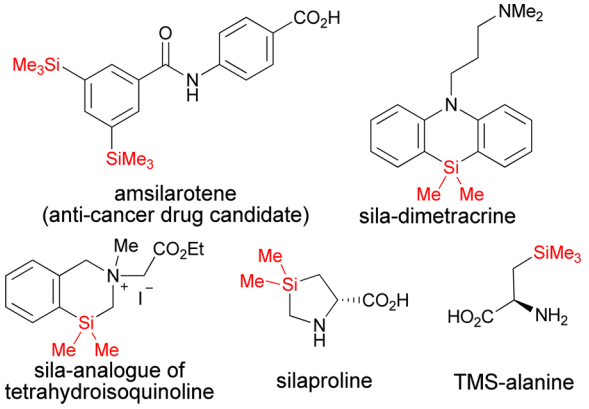


Figure 1. Examples of silicon-containing molecules of medicinal interests.

Consequently, development of new methods for efficient strategic installation of silyl groups into organic compounds is of significant importance in organic chemistry. Compared to the conventional methods for silylation reactions, synthesis of organosilanes through direct C−H bond functionalization is attractive from the viewpoints of atom economy, efficiency, and environmental benignity.[4] Several innovative contributions have been made in this field which allow for silylation of aromatic,[5] vinylic,[6] allylic,[7] and aliphatic[8] C−H bonds using transition metals such as Sc, Ru, Rh, Ir, and Pt as catalysts. Despite their extensive uses in a variety of organic reactions, palladium catalysts have not been used for the direct silylation of unactivated C(sp^3)−H bonds.

Inspired by recent works on the use of a quinolylamide bidentate directing group[9] to facilitate catalytic functionalizations of C−H bonds, we have developed a palladium-catalyzed direct silylation reaction of nonacidic C−H bonds of benzamide and carboxamide derivatives. Our strategy was successfully extended to germanylation of benzamides. Moreover, the bidentate directing group was readily removed and recovered by the reaction with a hydrazine, with concomitant generation of an acyl hydrazide.

Our initial optimization focused on the effects of oxidants to the silylation reaction of *N*-(8-quinolinyl)benzamide (**1a**, 0.200 mmol) with hexamethyldisilane (**2a**, 1.00 mmol) in the presence of $Pd(OAc)_2$ (10 mol %) in 1,4-dioxane (1.0 mL) as a solvent at 130 °C for 24 h (Table 1). Although only a trace amount of product **3aa** was observed by GC-MS without an oxidant (entry 1), the desired product was obtained in 53% yield when 1,4-benzoquinone was used (entry 2). Further screening revealed that silver oxidants are superior (entries 3−10), and the yield of the desired product increased to 70% GC yield when Ag_2CO_3 was employed (entry 6). In order to further improve the yield, we turned our attention to additives (entries 11−16) and found that the use of calcium sulfate improved the yield to 70% (75% GC yield) after isolation using flash column chromatography on silica gel (entry 14).[10] Although 20% of starting material **1a** was

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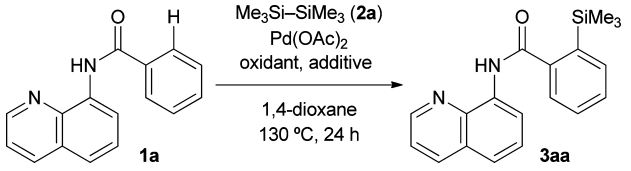
Table 1. Optimization Studies[a]



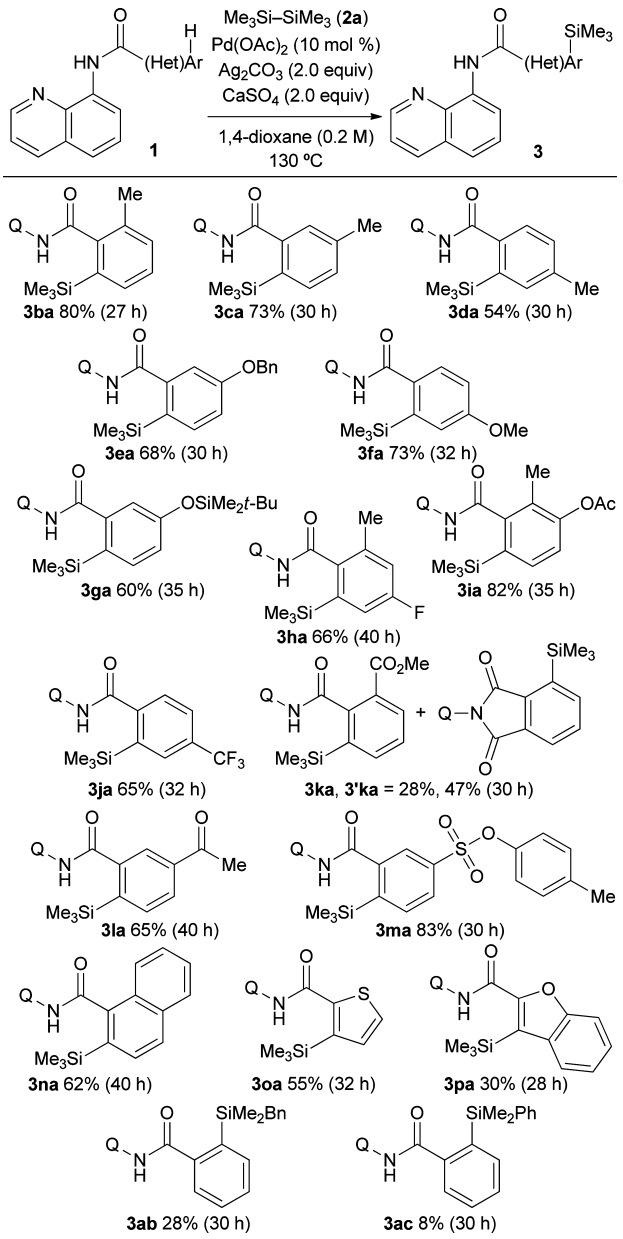
entry	oxidant	additive	yield of **3aa** (%)[b]
1	none	–	2
2	1,4-benzoquinone	–	53
3	AgOAc	–	63
4	AgOTf	–	9
5	Ag_2O	–	42
6	Ag_2CO_3	–	70
7	Ag_3PO_4	–	46
8	$CuCO_3$	–	2
9	$Cu(OAc)_2$	–	57
10	$Na_2S_2O_8$	–	1
11	Ag_2CO_3	MS 3A[c]	68
12	Ag_2CO_3	MS 4A[c]	71
13	Ag_2CO_3	MS 5A[c]	8
14	Ag_2CO_3	$CaSO_4$	75 (70)[d]
15	Ag_2CO_3	$MgSO_4$	40
16	Ag_2CO_3	Na_2SO_4	25
17[e]	Ag_2CO_3	$CaSO_4$	43

[a]Reaction conditions: **1a** (0.200 mmol), **2a** (1.00 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (0.400 mmol), additive (0.400 mmol), 1,4-dioxane (1.0 mL), 130 °C, 24 h. [b]Determined by GC-MS using undecane as an internal standard. [c]60 mg. [d]Isolated yield. [e]150 °C.

recovered in this case, further efforts to increase the yield were not successful. Increasing the temperature to 150 °C resulted in a lower yield of **3aa** (entry 17).

With the optimized conditions in hand, the scope of the reaction with benzamides was examined using hexamethyldisilane (**2a**) as the silylation partner (Scheme 1). Overall, the desired silylated products were successfully obtained from a wide range of substrates in moderate to high yields (up to 83%) with excellent *ortho*-regioselectivity and selectivity for monosilylated products (>95%). Under the optimized conditions, 2-, 3-, and 4-methyl-substituted *N*-(8-quinolinyl)benzamides gave the desired aryl silanes **3ba**, **3ca**, and **3da** in 80%, 73%, and 54% yields, respectively. Although these substrates have benzylic C–H bonds with smaller bond dissociation energies than aromatic C(sp^2)–H bonds, their silylation proceeded exclusively at the aromatic C–H bond.[8a] Various functional groups on the phenyl ring of benzamides were tolerable in this reaction, including benzyloxy (**3ea**), methoxy (**3fa**), and silyloxy (**3ga**) groups. Electron-withdrawing groups such as fluoro (**3ha**), acetoxy (**3ia**), trifluoromethyl (**3ja**), methoxycarbonyl (**3ka**), acetyl (**3la**), and sulfonyl (**3ma**) groups were also tolerated. In the case of 2-methoxycarbonyl substituent-containing **1k**, in situ intramolecular nucleophilic attack of the nitrogen atom in the amide moiety to the methoxycarbonyl group and elimination of methanol resulted in formation of phthalimide **3k′a**. 1-Naphthalene carboxamide was regioselectively silylated at the 2-position in 62% yield (**3na**). The value of this method was further demonstrated by the successful silylation of heterocycles such as thiophene (**3oa**) and benzofuran (**3pa**), albeit in moderate yields. Next, we sought to investigate the scope of the organosilicon sources. Compared to **2a**, $(Me_2BnSi)_2$ (**2b**) and $(Me_2PhSi)_2$ (**2c**) were less reactive, affording **3ab** and **3ac**,

Scheme 1. Palladium-Catalyzed C(sp^2)–H Silylation of Various Benzamides (1) with Disilanes (2)[a]



[a]Reaction conditions: benzamide (0.200 mmol), **2a** (1.00 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.400 mmol), $CaSO_4$ (0.400 mmol), 1,4-dioxane (1.0 mL), 130 °C. Het(Ar) = heteroaryl or aryl group, Q = 8-quinolinyl.

respectively. No desired product was observed when $(ClMe_2Si)_2$, $HSiMe_3$, and $HSiEt_3$ were used as organosilicon sources. Despite the low yield, the formation of **3ab** using this method is noteworthy because it can be used in Fleming–Tamao oxidation.[5j]

Although we have not yet investigated the mechanism of this silylation reaction in detail, we propose a catalytic cycle initiated by activation of the *ortho*-C–H bond of a benzamide by $Pd(OAc)_2$ to form intermediate A (Scheme 2). The following σ bond metathesis between intermediate A and disilane **2a** and *N*-to-*O* silicon migration will generate intermediate **B**. Subsequent C–Si reductive elimination would afford Pd(0) species and intermediate **C**, which provides the desired product **3aa** after

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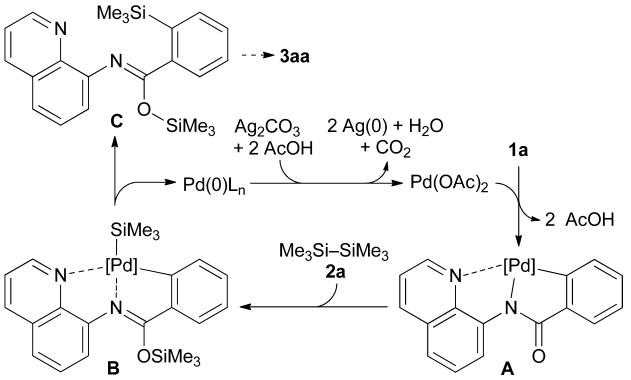
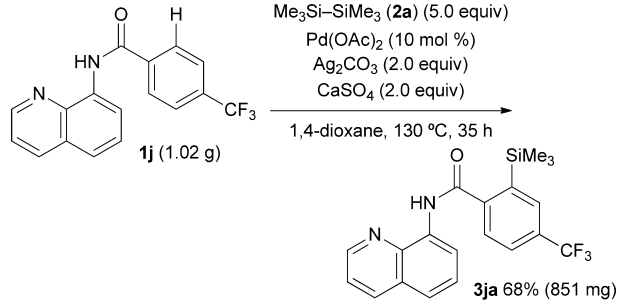
Scheme 2. A Plausible Mechanism for the Palladium-Catalyzed C−H Silylation



hydrolysis. Oxidation of the Pd(0) species by Ag_2CO_3 regenerates $Pd(OAc)_2$. Calcium sulfate possibly traps H_2O generated by the reaction of the Pd(0) species with Ag_2CO_3 and AcOH. An alternative mechanism involving transmetalation[11] also could be conceivable.[12]

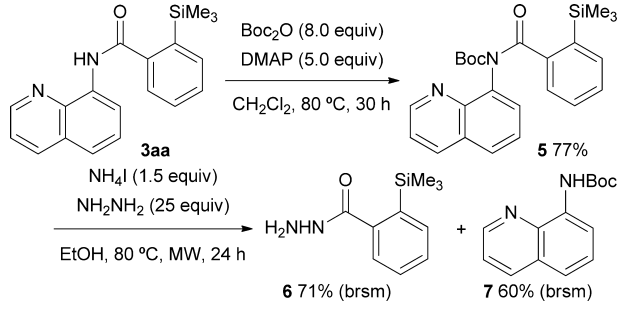
In order to demonstrate the efficiency and practicality of this catalytic process, we conducted the reaction on a gram scale using 1.02 g of **1j** (3.23 mmol) with **2a** (Scheme 3), which provided **3ja** in 68% yield (851 mg).

Scheme 3. Gram-Scale Silylation of 1j with 2a



The 8-quinolinylamino group in **3aa** can be readily removed and recovered in good yield as shown in Scheme 4. Activation of

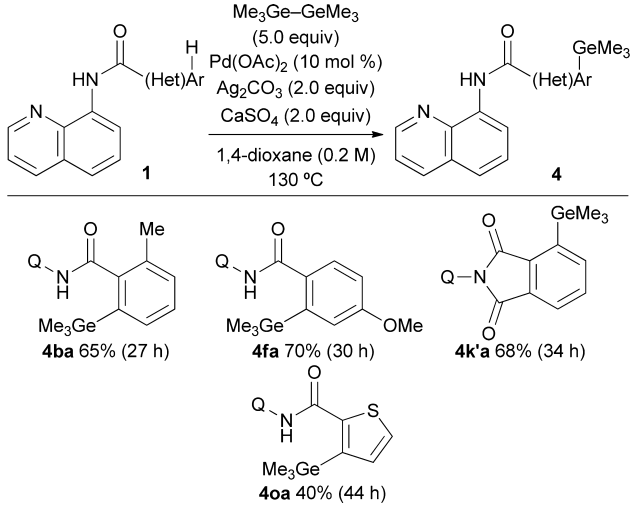
Scheme 4. Directing Group Removal: Synthesis of Acyl Hydrazide



the secondary amide moiety of **3aa** with a Boc group,[9j] followed by the reaction with hydrazine monohydrate under microwave irradiation, afforded *N*-acyl hydrazide **6** and Boc-protected quinolylamine **7** in 71% and 60% (based on the recovered starting material of 40%) yield, respectively.[13]

The present silylation strategy can be effectively extended to germanylation of benzamides (Scheme 5). Thus, under the same

Scheme 5. Palladium-Catalyzed C(sp²)−H Germanylation of Benzamides with Hexamethyldigermane[a]



[a]Reaction conditions: benzamide (0.200 mmol), Me_6Ge_2 (1.0 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.400 mmol), $CaSO_4$ (0.400 mmol), 1,4-dioxane (1.0 mL), 130 °C. (Het)Ar = heteroaryl or aryl group, Q = 8-quinolinyl.

palladium catalysis conditions, germanylated compounds **4ba**, **4fa**, **4k′a**, and **4oa** were obtained in moderate to high yield. To the best of our knowledge, this is the first example of transition-metal-catalyzed germanylation of C−H bonds to provide arylgermanes, which have been demonstrated to be useful synthetic intermediates.[14]

In contrast to transition-metal-catalyzed C(sp²)−H silylation reactions, C(sp³)−H silylation reactions are rare.[8] To this end, we examined whether the present silylation is applicable to aliphatic C(sp³)−H bonds. Initial application of the reaction conditions to **1q** with hexamethyldisilane (**2a**) gave less than 10% of the desired product **3qa**. After further optimization, we found that the use of *N*,*N*-dimethylformamide (DMF) as an additive resulted in an increase in reaction yield to 35% (Scheme 6).[15] Disilylated product **3′qa** was also formed in 5% yield. Under the same conditions, silylation of **1r** and **1s** also proceeded. Although the yield is moderate, this study presents the first example of intermolecular C(sp³)−H silylation at the internal positions of alkyl chains. The unreacted starting materials could be recovered quantitatively.

In summary, we have demonstrated a palladium-catalyzed regioselective activation of C(sp²)−H and C(sp³)−H bonds of benzamides and carboxamides, followed by coupling with disilanes to afford organosilanes in moderate to high yields, with the aid of 8-aminoquinoline as a directing group. Catalytic germanylation also proceeded smoothly under the same reaction conditions. The reaction tolerated a wide variety of functional groups and was scalable without yield reduction. Moreover, the bidentate directing group was readily removed and recovered by the reaction with a hydrazine, with concomitant generation of an acyl hydrazide. This study gives the first example of transition-metal-catalyzed germanylation of C(sp²)−H bonds and intermolecular C(sp³)−H silylation at the internal positions of alkyl chains. Further C(sp³)−H bond functionalizations based on detailed mechanistic studies are in progress in our laboratory.

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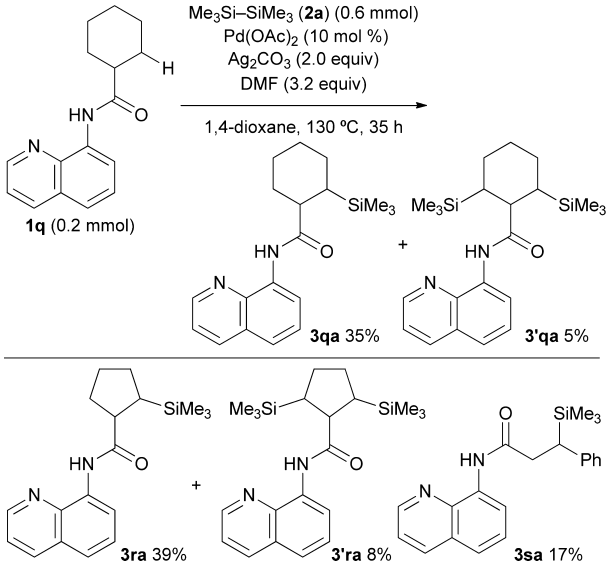
Scheme 6. Preliminary Extension to C(sp^3)–H Silylation of Carboxamides with Hexamethyldisilane (2a)



■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data for silylation and germanylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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(15) At present, the role of DMF in improving the reaction yield is unclear.