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Iridium-Catalyzed Regioselective Silylation of Aromatic and Benzylic C–H Bonds Directed by a Secondary Amine**

*Qian Li, Matthias Driess, and John F. Hartwig**

Abstract: *Reported herein is an iridium-catalyzed, regioselective silylation of the aromatic C–H bonds of benzylamines and the benzylic C–H bonds of 2,N-dialkylanilines. In this process, (hydrido)silyl amines, generated in situ by dehydrogenative coupling of benzylamine or aniline with diethylsilane, undergo selective silylation at the C–H bond γ to the amino group. The products of this silylation are suitable for subsequent oxidation, halogenation, and cross-coupling reactions to deliver benzylamine and arylamine derivatives.*

The direct silylation of C–H bonds catalyzed by transition-metal complexes provides a straightforward method to synthesize organosilanes.[1] The organosilane products are valuable synthetic intermediates,[2,3] which can be converted into useful compounds through a number of transformations, such as halogenation, oxidation, and Hiyama coupling.[4] Thus, a catalytic silylation of C–H bonds,[5–7] coupled with subsequent transformations of organosilanes, creates a convenient strategy to convert C–H bonds into common functional groups.

In recent years, a variety of directing groups have been used to control the regioselectivity of C–H bond silylation.[8,9] For example, imine,[8a,e] oxazoline,[8c,i] pyridine,[8d,f,i,j,9a,b] pyrazole,[8d,g] and tertiary amine[8d] functionalities have been used as directing groups for the silylation of aromatic and benzylic C–H bonds with trialkylsilanes. However, these directing groups are usually undesired in the final product, and multiple chemical transformations are needed to install and remove them. In addition, these reactions usually generate a mixture of mono- and disilylated products from substrates containing two C–H bonds that are available for silylation. Furthermore, the silylation of a C–H bond with trialkylsilanes produces tetraorganosilanes, which are less suitable for subsequent oxidation and cross-coupling reactions than analogous products containing a silicon–heteroatom bond. Therefore, the identification of directing groups that circumvent these issues would significantly increase the synthetic utility of the C–H silylation reaction.

Recently, we reported a hydroxy-directed silylation of aromatic[6d] and aliphatic[10] C–H bonds by generation of diethyl(hydrido)silyl ethers in situ. These reactions generate oxasilolanes, which can undergo oxidation and cross-coupling reactions to give diols and biphenyl products. Based on these studies, we reasoned that a secondary amine might serve as a directing group for the silylation of aromatic and aliphatic C–H bonds. An amine-directed silylation would generate azasilolanes in which the nitrogen atom on the silicon would activate the organosilane products towards further transformation.

However, several challenges face the translation of the silylation reactions directed by an alcohol to a silylation reaction directed by an amine. For example, the strong binding ability of a basic nitrogen atom might inhibit the catalytic activity of the transition-metal catalyst. In addition, the N–Si bond is significantly weaker and more sensitive to Brønsted acids than an O–Si bond.[11] Therefore, the Si–N linkage might not be stable to the conditions of the silylation reaction.

Herein we demonstrate that the complex formed from [{Ir(OMe)(cod)}$_2$] and 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen) catalyzes the regioselective silylation of the aromatic C–H bonds in benzylamines and the primary and secondary benzylic C–H bonds of 2,*N*-alkylanilines. In these reactions, disilylation processes do not occur because the C–H functionalization step is intramolecular. The silylation product obtained can undergo further functionalizations, such as oxidation, halogenation, and cross-coupling reactions.

To identify an active catalyst for the silylation of secondary amines, we first studied the reaction of *N*-methylbenzylamine (**1a**). The dehydrogenative coupling of **1a** with diethylsilane catalyzed by 0.5 mol% [{Ir(OMe)(cod)}$_2$] furnished the (hydrido)silyl amine **2a** in 78% yield at room temperature in THF after 20 hours (see Table 1). When the reaction was conducted under neat conditions, **2a** was formed quantitatively after 20 hours. With **2a** in hand, we studied the dehydrogenative silylation step (Table 1). In the presence of an iridium catalyst and 4,4′-di-*tert*-butylbipyridine as ligand, the intramolecular cyclization at 80 °C occurred to give the azasilolane product **3a** in 88% yield (entry 4). The electronic properties of the ligands had a strong influence on the yield. When 4,7-dichlorophenanthroline was used as a ligand, a lower yield (19%) of **3a** was obtained (entry 1). In contrast, when the more strongly electron-donating Me_4Phen was used, full conversion of **2a** was observed, thus affording the product in high yield (95%, entry 3).

[*] Dr. Q. Li, Prof. Dr. J. F. Hartwig
Department of Chemistry, University of California
Berkeley, CA 94720 (USA)
E-mail: jhartwig@berkeley.edu
Dr. Q. Li, Prof. Dr. M. Driess
Technische Universität Berlin, Institut für Chemie
Metallorganische Chemie und Anorganische Materialien, Sekr. C2
Strasse des 17. Juni 135, 10623 Berlin (Germany)

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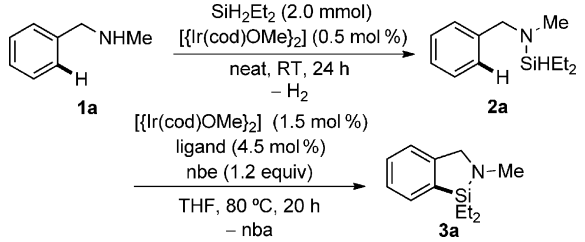
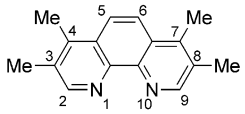
Table 1: Effect of the ligand on the silylation of benzylic silylamines.[a]

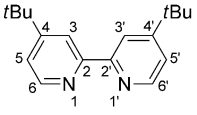


Entry	Ligand	Yield [%][b]
1	4,7-dichloro-1,10-phenanthroline	19
2	1,10-phenanthroline	87
3	3,4,7,8-tetramethyl-1,10-phenanthroline	95
4	4,7-di-*tert*-butyl-2,2′-bipyridine	88

[a] Reaction conditions: **1a** (1.0 mmol), SiH_2Et_2 (2.0 mmol), [{Ir(cod)-OMe}$_2$] (0.5 mol%), neat, RT, 24 h; evaporation of excess silane, [{Ir(cod)OMe}$_2$] (1.5 mol%), Me_4phen (4.5 mol%), nbe (1.2 equiv), THF, 80°C, 20 h. [b] Yield determined by GC using isododecane as an internal standard. cod = 1,5-cyclooctadiene, nbe = norbornene, nba = norbornane, THF = tetrahydrofuran.



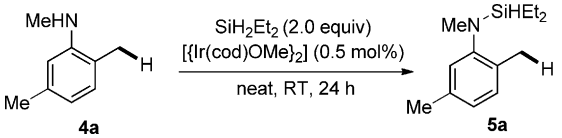
3,4,7,8-tetramethyl-1,10-phenanthroline



4,7-di-*tert*-butyl-2,2'-bipyridine

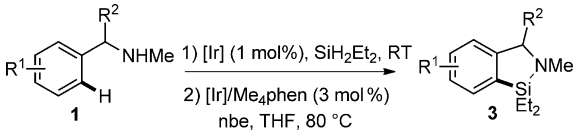
Having identified an efficient catalyst for the silylation of benzylamine, we studied the scope of this reaction (Table 2). Benzylamines containing a substituent at the *ortho* or *para* position underwent the silylation in good yields (**3b**,**c**). The reaction of benzyl silylamines bearing a *meta* substituent occurred with high regioselectivity for the more sterically accessible C–H bond. For example, silylation of benzylamines substituted in the *meta*-position with methyl, chloro, bromo, and methoxy substituents proceeded in high yields with greater than 20:1 regioselectivity (**3d**–**g**). The reaction of the 3-fluoro derivative was less regioselective, presumably because of the smaller size of fluorine relative to the other substituents (**3h**). The reaction of benzylamine containing a methyl group at the position α to the nitrogen atom also proceeded to completion (**3i**); however, a higher catalyst loading and temperature were required. This result contrasts with the silylation of benzyl alcohols,[6d] for which secondary alcohols were more reactive than primary alcohols.[12]

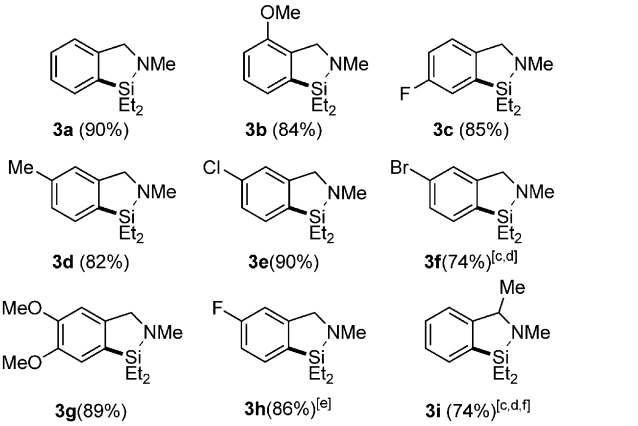
The high activity of the iridium catalyst for the amine-directed silylation of aromatic C–H bonds suggested the potential of the process to occur at sp^3 C–H bonds. The dehydrogenative coupling of 2,5-dimethyl-*N*-methylaniline (**4a**) with diethylsilane catalyzed by 0.5 mol% [{Ir(OMe)-(cod)}$_2$] produced the (hydrido)silyl aniline **5a** [Eq. (1)]. However, the same reaction conditions that we used for the silylation of benzylamines did not provide significant amounts of product from the silylation of the benzylic C–H bond of the arylamine.



(1)

Table 2: Silylation of benzylmethylamine.[a,b]





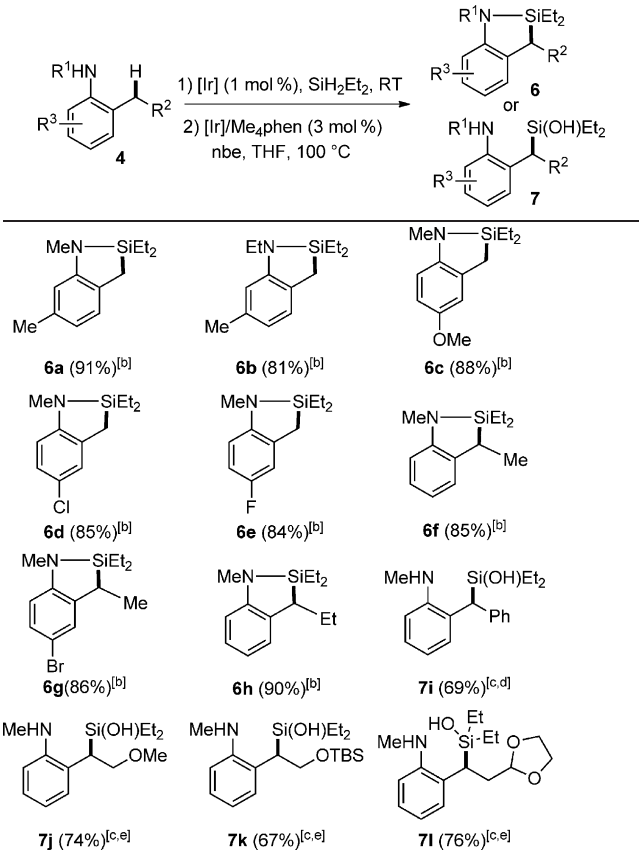
[a] Reaction conditions: **1** (1.0 mmol), SiH_2Et_2 (2.0 mmol), [{Ir(cod)-OMe}$_2$] (0.5 mol%), neat, RT, 24 h; evaporation of excess silane, [{Ir(cod)OMe}$_2$] (1.5 mol%), Me_4phen (4.5 mol%), nbe (1.2 equiv), THF, 80°C, 20 h. [b] Yield of product isolated from bulb-to-bulb distillation. [c] [{Ir(cod)OMe}$_2$] (2.5 mol%), Me_4phen (7.5 mol%). [d] There is a small amount of an inseparable impurity in the product. These impurities can be separated after oxidation. [e] Obtained as an inseparable mixture of constitutional isomers in a 1.0:1.7 ratio, as determined by ^{1}H NMR spectroscopy. [f] 100°C, 40 h.

Yet, a simple increase of the reaction temperature to 100°C led to complete consumption of the starting material and high yield of the cyclization product **6a**, as shown in Table 3. This silylation of the benzylic C–H bonds is not sensitive to the electronic properties of substituents on the arene. The silylation of 2-methylanilines bearing electron-donating groups occurred in yields similar to those of the silylation of 2-methylanilines bearing electron-withdrawing groups (**6b**–**e**).

The amine-directed silylation of benzylic C–H bonds also occurred at secondary benzylic C–H bonds. As a result of the steric hindrance, the reactivity of secondary C–H bonds is typically lower than that of primary C–H bonds when an organometallic intermediate is generated, and the examples of the high-yielding silylation of secondary C–H bonds are rare.[6h,9c,e,11c] Nevertheless, the amine-directed silylation of secondary benzylic C–H bonds occurred in good to excellent yields (**6f**–**h** and **7i**–**l**, Table 3). In some cases, longer reaction times (**7i**) or higher temperatures (**7j**–**l**) were required (Table 3). The reaction tolerated various functional groups on the alkyl chain, including bromide, methoxy, siloxy, and acetal groups (**6f**–**h**, **7i**–**l**). The silylation products were isolated by either bulb-to-bulb distillation or column chromatography on silica gel. When the silylation product was purified by column chromatography, the azasilolane ring opened to afford the corresponding silanol (**7i**–**l**),[13] which was suitable for further transformations (see below).

For these C–H bond functionalizations to be synthetically valuable, reaction conditions to transform the silylation

Table 3: Silylation of *N*,2-alkylanilines.[a]

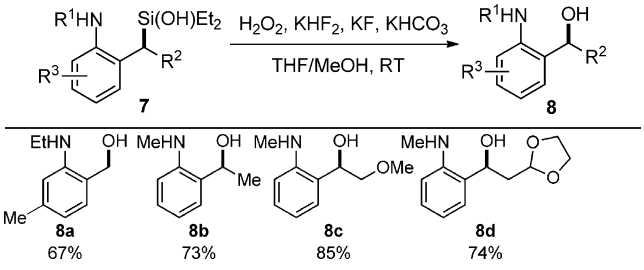


[a] Reaction conditions: **4** (1.0 mmol), SiH_2Et_2 (2.0 mmol), [{Ir(cod)-OMe}$_2$] (0.5 mol%), neat, RT, 24 h; evaporation of excess silane, then [{Ir(cod)OMe}$_2$] (1.5 mol%), Me_4phen (4.5 mol%), nbe (1.2 equiv), THF, 100°C, 20 h. [b] Yield of isolated product from bulb-to-bulb distillation. [c] Yield of product isolated from column chromatography on silica gel. [d] 100°C, 40 h. [e] 120°C, 30 h.

products must be developed. To do so, we subjected the products of the amine-directed C–H bond silylation to Fleming–Tamao oxidation conditions. The oxidation of both the primary and secondary benzylic silanols with hydrogen peroxide proceeded under mild reaction conditions to generate the benzyl alcohols **8a–d** in high yields (Table 4).[14] Under these mild reaction conditions, the free amino group was not oxidized. This strategy provides a method for the regioselective hydroxylation of primary and secondary benzylic C–H bonds directed by an unprotected amine.

Oxidation of the Si–C bonds in the products from the silylation of aromatic C–H bonds was more challenging because benzylamines are more susceptible to oxidation than are anilines. Direct oxidation of these azasilolanes under various reaction conditions afforded the phenol products in low yield (< 20%) because of the competing oxidation of the amino group. Therefore, we sought to protect the amine before oxidizing the silane. Exposure of the silylation product **3** to air for 2 hours provided the ring-opened product, which was then acylated to form the amide **9** (Table 5). Subsequent oxidation of **9** afforded the phenol product **10** in good yield. The sequence of amine protection and oxidation occurred in

Table 4: Oxidation of the silanol products to the corresponding amino-alcohols.[a,b]

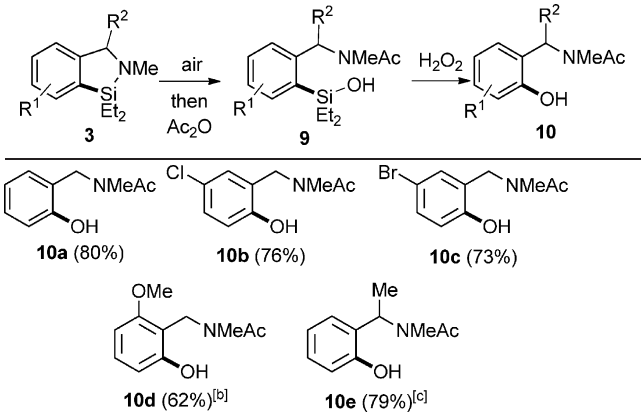


[a] Reaction conditions: 30% H_2O_2 (8.0 equiv), KHF_2 (8.0 equiv), KF (2.0 equiv), $KHCO_3$ (8.0 equiv), THF/MeOH (v/v = 1:1), RT, 16 h. [b] Yield of product isolated from column chromatography on silica gel.

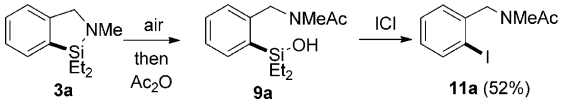
good yield with various azasilolanes, containing substituents on the arene or position α to nitrogen atom, to give the products **10a–e**. In addition to oxidation, **9** underwent halogenation. Treatment of **9a** with iodine monochloride gave the *ortho*-iodination product **11a** in 52% yield, as shown in Scheme 1. Thus, silylation and subsequent derivatization provides methods for the synthesis of *ortho*-hydroxylated and halogenated benzylamines.

Finally, we evaluated the potential of the azasilolanes or derivatives of them to undergo cross-coupling. Direct Hiyama cross-coupling of **3** or **9** with aryl halides under various reaction conditions did not provide the biaryl product. However, biaryl products were obtained by an alternative route: conversion of the phenol, which was derived from the

Table 5: Oxidation of the azasilolanes to the corresponding amino-phenols.[a]

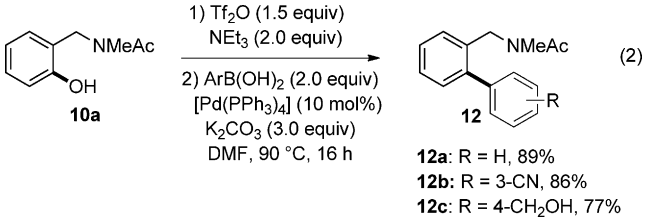


[a] Reaction conditions: air, THF, RT, 2 h, then Ac_2O (1.2 equiv), NEt_3 (1.5 equiv), DMAP (1.0 mol%), CH_2Cl_2, RT, 2 h; removal of volatiles, 30% H_2O_2 (8.0 equiv), KHF_2 (8.0 equiv), KF (2.0 equiv), $KHCO_3$ (8.0 equiv), THF/MeOH (v:v = 1:1), RT, 16 h. Yield of isolated products are reported. [b] 8 h. [c] 30% H_2O_2 (16 equiv).



Scheme 1. Iodination of **3a**. Reaction conditions: air, THF, RT, 2 h; then Ac_2O (1.2 equiv), NEt_3 (1.5 equiv), DMAP (2 mol%), CH_2Cl_2, RT, 2 h; removal of volatiles, ICl (2.0 equiv), CH_2Cl_2, RT, 12 h.

oxidation of the silanol, into the trifluoromethylsulfonate of **10a**, followed by reaction of this product with arylboronic acids under Suzuki–Miyaura coupling conditions furnished the biaryl compounds **12a–c** in 77–89% yield [Eq. (2); DMF = *N*,*N*,-dimethylformamide, Tf = trifluoromethanesulfonyl.



(2)

In summary, we have developed an iridium-catalyzed silylation of the *ortho*-aryl C–H bonds of benzylamines and the benzylic C–H bonds of 2,*N*-alkylanilines. The secondary amino group directs the iridium-catalyzed C–H bond activation by generation of diethyl(hydrido)silyl amines in situ and subsequent dehydrogenative cyclization. The silylation products contain a silicon–heteroatom bond, and this Si–X bond allows subsequent transformations, such as oxidation, and maintains the ability of the Si–C bonds to undergo halogenation. Further studies to expand the substrate scope and gain insight into the reaction mechanism are currently in progress.

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Keywords: arenes · C–H activation · iridium · oxidation · silane

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[12] For details about the differences in reactivities between α-substituted bezylic amine and α-substituted benzylic alcohol, and the differences in reactivities between α-substituted benzylic amine and α-unsubstituted benzylic amine, see the Supporting Information.
[13] Because the boiling points of the azasilolane products from **4i–l** are higher than those of the products from **4a–h**, purification of the products by the bulb-to-bulb distillation at higher temperature resulted in inseparable byproducts. Therefore, we used column chromatography on silica gel to purify the azasilolanes **6i–l**. These products undergo ring opening on silica gel to give the corresponding silanols **7i–l** as the isolated products.
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