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# Ruthenium-Catalyzed Site-Selective Intramolecular Silylation of Primary C−H Bonds for Synthesis of Sila-Heterocycles

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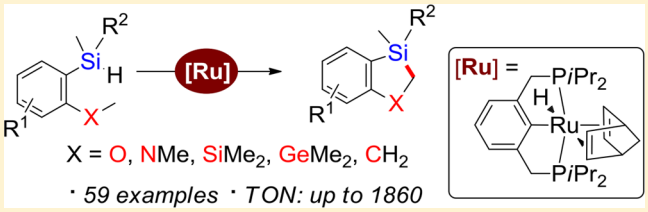
Supporting Information

**ABSTRACT:** Incorporating the silicon element into bioactive organic molecules has received increasing attention in medicinal chemistry. Moreover, organosilanes are valuable synthetic intermediates for fine chemicals and materials. Transition metal-catalyzed C−H silylation has become an important strategy for C−Si bond formations. However, despite the great advances in aromatic C($sp^2$)−H bond silylations, catalytic methods for aliphatic C($sp^3$)−H bond silylations are relatively rare. Here we report a pincer ruthenium catalyst for intramolecular silylations of various primary C($sp^3$)−H bonds adjacent to heteroatoms (O, N, Si, Ge), including the first intramolecular silylations of C−H bonds $\alpha$ to O, N, and Ge. This method provides a general, synthetically efficient approach to novel classes of Si-containing five-membered [1,3]-sila-heterocycles, including oxasilolanes, azasilolanes, disila-heterocycles, and germasilolane. The trend in the reactivity of five classes of C($sp^3$)−H bonds toward the Ru-catalyzed silylation is elucidated. Mechanistic studies indicate that the rate-determining step is the C−H bond cleavage involving a ruthenium silyl complex as the key intermediate, while a $\eta^2$-silene ruthenium hydride species is determined to be an off-cycle intermediate.




## INTRODUCTION

[1,3]-Sila-heterocycles that contain two heteroatoms in the same cycle, with one of them being a Si-atom, are not naturally occurring. Seminal works of Tacke and colleagues showed that the carbon-to-silicon switch in bioactive heterocycles could lead to sila-congeners with significantly altered properties, partly due to the different covalent radius and electronegativity of silicon from carbon.[1] Among the notable examples, [1,3]-sila-heterocycles bearing a stable tetraorgano-substituted silicon center, such as sila-rhubafuran,[2] tetrahydrosilaisoquinoline,[3] *N*-Boc-(*R*)-silaproline,[4] and disila-compound,[5] exhibit improved biological and/or physicochemical properties relative to their parent carbon compounds (Figure 1). Such attractive features, in combination with the lack of element-associated toxicity of silicon, have motivated extensive research on development of new organosilicon compounds for drug and odorant design. However, for several decades, the exploration into this field has been rather limited, largely because of the lack of synthetic efficient methods to introduce the silicon atom into heterocycles. For example, the existing methods for the synthesis of [1,3]-sila-dihydrobenzofurans[6] and [1,3]-sila-indolines[7] utilize highly reactive pyrophoric reagents (Na or PhLi) and commercially unavailable organosilicon reagents.

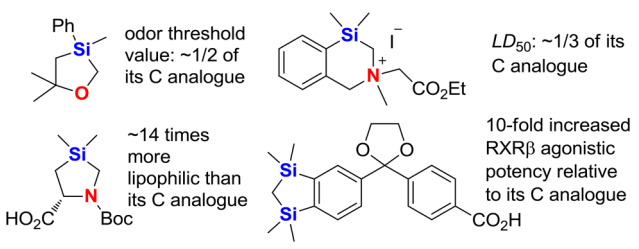



**Figure 1.** Examples of C/Si switch in drugs or fragrance leading to improved biological or physical properties.

These methods suffer from unsatisfactory yields, poor functional-group tolerance, and formation of waste inorganic salts. Transition metal-catalyzed dehydrogenative silylation of C−H bonds has emerged as a powerful tool for C−Si bond formations,[8−10] and the intramolecular reaction offers a useful route to the synthesis of Si-containing heterocycles. The past two decades have witnessed significant progress in the intramolecular silylations of aromatic C−H bonds.[11] By contrast, methods for the intramolecular silylation of aliphatic C−H bonds are scarce. In 2005, Hartwig reported the first example of intramolecular C($sp^3$)−H silylation: a platinum complex catalyzes the silylation of one *n*-butyl group of tri(*n*-butyl)silane at 200 °C (Figure 2a).[11a] The same transformation was achieved using a rhodium catalyst, forming a five-membered silolane at 180 °C.[12] In 2014, Gevorgyan disclosed a more general, Ir-catalyzed silylation of primary C−H bonds of silanes bearing a picoline group on Si as the directing group, furnishing five-membered silolanes at 140 °C.[13] Takai found that a Rh complex of diphosphine ligand is effective for the silylation of primary C−H bonds in the *ortho*-alkyl chains.[14] By

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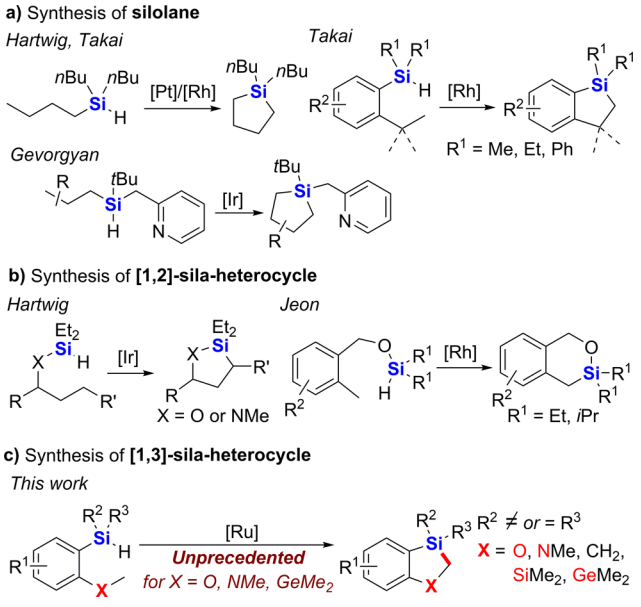



**Figure 2.** Catalytic methods for intramolecular silylation of C($sp^3$)–H bonds.

generating a silyl ether or silyl amine through in situ silylation of a hydroxyl or amino group, Hartwig developed Ir-catalyzed silylations of primary and secondary $\gamma$ C($sp^3$)–H bonds, producing [1,2]-sila-heterocycles.[11d,15] Jeon employed the same strategy for the Rh-catalyzed silylation of benzylic primary C–H bonds (Figure 2b).[11s]

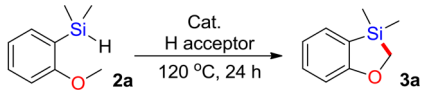
To date, catalytic methods of intramolecular silylation of C($sp^3$)–H bonds have been established for the preparation of silolanes and [1,2]-sila-heterocycles, however, the synthesis of [1,3]-sila-heterocycles via intramolecular silylation of C($sp^3$)–H bonds $\alpha$ to heteroatoms is extremely rare. Very recently, Takai and Murai reported the only example of intramolecular silylation of C($sp^3$)–H bonds $\alpha$ to heteroatom (Si): an Ir catalyst of $Me_4$Phen ($Me_4$Phen = 3,4,7,8-tetramethyl-1,10-phenanthrene) effects the intramolecular silylation of C($sp^3$)–H bonds $\alpha$ to the Si atom.[16] Unfortunately, attempted silylations of C($sp^3$)–H bonds $\alpha$ to O and N atoms to form [1,3]-oxasilolanes and [1,3]-azasilolanes were unsuccessful.

Driven by our interest in developing discrete organometallic catalysts for C($sp^3$)–H bond functionalizations, recently we synthesized new pincer Ir and Ru catalysts for alkane dehydrogenations,[17] and developed the first regioselective alkane silylations to form linear alkylsilanes using an iridium–iron-catalyzed dehydrogenation–isomerization–hydrosilylation.[18] Here we show that a pincer ruthenium complex is highly efficient for intramolecular silylations of various primary C–H bonds, allowing the synthesis of [1,3]-oxasilolanes, [1,3]-azasilolanes, [1,3]-disila-heterocycles, and [1,3]-germasilolane. The method enables facile construction of tetraorganosilicons bearing four different substituents at the Si-atom using simple, readily accessible starting materials (Figure 2c).

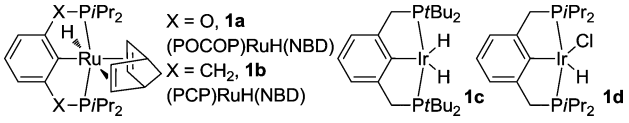
## RESULTS AND DISCUSSION

**Catalyst Evaluation.** Our studies commenced with the evaluation of catalysts for the intramolecular C($sp^3$)–H silylation using (*o*-OMe-aryl)dimethylsilane **2a** as the substrate. The results are summarized in Table 1. With *cis*-cyclooctene

**Table 1. Catalyst Evaluation for the Intramolecular Silylation of (2-Methoxyphenyl)dimethylsilane 2a**[a]




| entry | cat. (mol %) | solvent | H acceptor | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** [2.5] | none | COE | 96 |
| 2 | **1b** [2.5] | none | COE | 99 |
| 3 | **1b** [2.5] | THF | COE | 94 |
| 4 | **1b** [2.5] | toluene | COE | 96 |
| 5 | **1b** [2.5] | hexane | COE | 99 |
| 6 | **1c** [2.5] | none | COE | <5 |
| 7[c] | **1d** [2.5] | toluene | COE | 94 |
| 8[d] | ($Me_4$Phen)Ir [4] | THF | NBE | 23 |
| 9[e] | (Segphos)Rh [3] | dioxane | TBE | 31 |
| 10 | $Ru_3(CO)_{12}$ [2.5] | none | COE | 0 |
| 11 | (cod)Ru(2-methylallyl)$_2$ [2.5] | none | COE | 0 |
| 12 | [$RuCl_2$(*p*-cymene)]$_2$ [2.5] | none | COE | 0 |
| 13 | **1b** [0.1] | none | COE | 96 |
| 14[f] | **1b** [5] | none | COE | 90 |




[a]Reaction conditions: **2a** (0.2–4.0 mmol), hydrogen acceptor (1 equiv), and solvent (0.2 mL, unless otherwise noted). [b]Yields were determined by $^1$H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [c]The precatalyst was activated with NaO*t*Bu (3.75 mol %). [d]Using the same conditions utilized by Hartwig for the silylation of (hydrido)silyl ethers:[15b] [Ir(cod)OMe]$_2$ (2 mol %), $Me_4$Phen (4.8 mol %) in THF (0.75 mL); Substitution of COE with NBE gave 23% **3a**. [e]Using the same conditions utilized by Takai for the silylation of (*o*-Et-aryl)dimethylsilanes:[14] [Rh(cod)Cl]$_2$ (1.5 mol %), Segphos (4.5 mol %) in 1,4-dioxane (0.25 mL); Substitution of COE with TBE gave 47% **3a**. [f]At 80 °C for 48 h.



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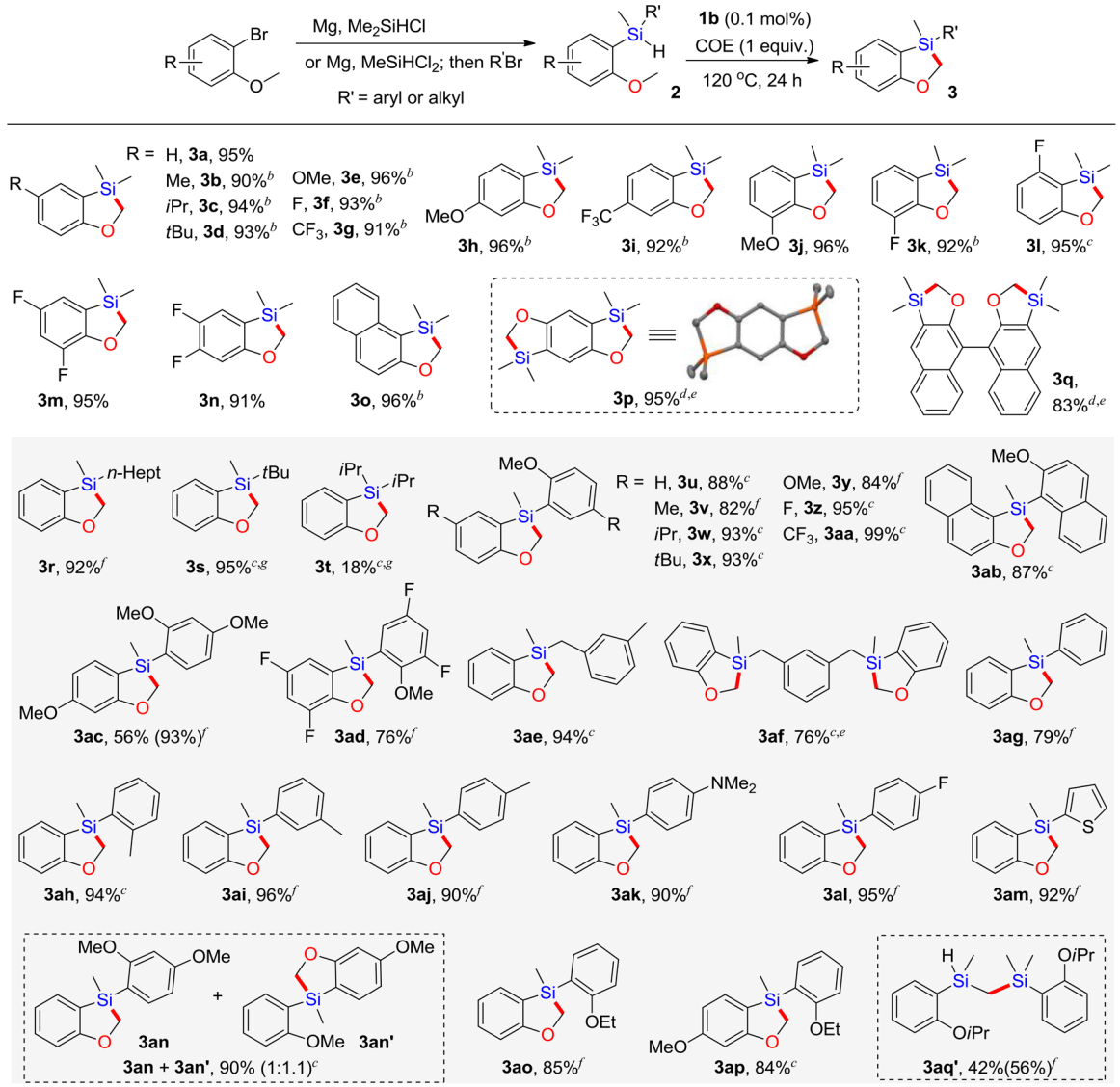
**Table 2. Substrate Scope of Ru-Catalyzed Intramolecular Silylation of C(sp$^3$)−H Bonds $\alpha$ to O-Atom**[a]




[a]Conditions: **2** (0.2−0.5 mmol), COE (1 equiv), **1b** (0.1 mol %) at 120 °C for 24 h. Yields shown are of isolated products. Values in the parentheses are NMR yields. [b]48 h. [c]**1b** (2.5 mol %). [d]**1b** (0.5 mol %). [e]COE (2 equiv). [f]**1b** (1 mol %). [g]At 150 °C for 60 h.

(COE, 1 equiv) as the hydrogen acceptor, the reaction of **2a** under neat conditions using (POCOP)RuH(NBD) (**1a**, POCOP = bis(phosphinite)-based pincer ligand, NBD = norbornadiene)[17d] as the precatalyst (2.5 mol %) previously developed in this group, generated [1,3]-sila-dihydrobenzofuran (**3a**) in 96% yield after 24 h at 120 °C (entry 1). The bis(phosphine)-based (PCP)RuH(NBD) (**1b**) was even more effective than **1a**, giving a quantitative yield of **3a** under the same conditions (entry 2). The generation of the silylation product is accompanied by a concomitant, complete conversion of COE to cyclooctane (COA). A screening of several hydrogen acceptor indicated that COE was the optimal choice (see the Supporting Information, SI). The catalysis with **1b** also occurred efficiently in organic media, such as THF, toluene, and hexane (entries 3−5, 94−99%). The related pincer Ir catalysts were also studied for the silylation. While the *t*Bu-substituted (PCP)Ir precatalyst **1c** was ineffective for this reaction (entry 6), the run with the *i*Pr-substituted variant **1d** gave the cyclization product in 94% yield (entry 7). An Ir catalyst[15b] of $Me_4$Phen and a Rh catalyst[14] of SEGPHOS (SEGPHOS = (*R*)-(−)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole), which proved highly efficient for the intramolecular C(sp$^3$)−H silylation of (hydrido)silyl ethers and (*o*-Et-aryl)dimethylsilanes, respectively, gave **3a** in low-to-moderate yields (entries 8 and 9). Other common Ru(0) and Ru(II) precatalysts, such as $Ru_3(CO)_{12}$, (cod)Ru(2-methylallyl)$_2$, and [$RuCl_2$(*p*-cymene)]$_2$, are inactive for the silylation (entries 10−12). The superior catalytic activity of the pincer Ru complexes is partly attributed to their high thermal stability.[19] The loading of the precatalyst **1b** could be reduced to 0.1 mol % without influencing the conversation significantly (entry 13).[20] Performing the reaction at 80 °C with **1b** gave the desired product in high yield, although a 5 mol % catalyst loading and a longer reaction time (48 h) was required (entry 14).

**Substrate Scope.** Having identified an effective precatalyst, **1b**, for the intramolecular C(sp$^3$)−H silylation, we examined the scope of this method (Tables 2, 3, and 4). Note that the starting materials, *o*-OMe-arylsilanes, *o*-$NMe_2$-arylsilanes, and *o*-$SiMe_3$-arylsilanes, can be readily prepared by one-step arylation



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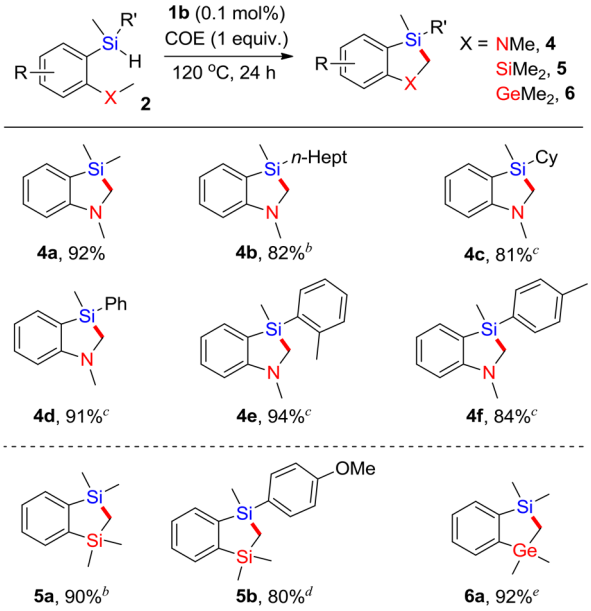
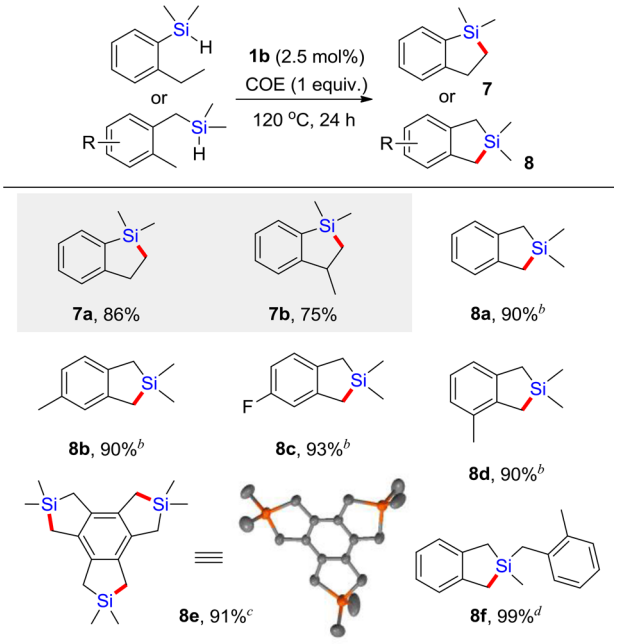
**Table 3. Substrate Scope of Ru-Catalyzed Intramolecular Silylation of C(sp$^3$)−H Bonds $\alpha$ to N-, Si-, or Ge-Atom**[a]




[a]Conditions: **2** (0.2−0.5 mmol), COE (1 equiv), **1b** (0.1 mol %) at 120 °C for 24 h. Yields shown are of isolated products. [b]**1b** (1 mol %). [c]**1b** (2.5 mol %). [d]**1b** (5 mol %). [e]**1b** (10 mol %). The substrate is synthesized from the reaction of (2-(dimethylsilyl)phenyl)lithium with chlorotrimethylgermane.

**Table 4. Substrate Scope of Ru-Catalyzed Intramolecular Silylation of C(sp$^3$)−H Bonds $\alpha$ to C-Atom**[a]




[a]Conditions: **2** (0.2−0.5 mmol), COE (1 equiv), **1b** (2.5 mol %) at 120 °C for 24 h. Yields shown are of isolated products. [b]At 80 °C. [c]COE (3 equiv). [d]**1b** (1 mol %).

of $R_2ClSiH$ (R = Me or *i*Pr), or one-pot, two-step arylation and arylation/alkylation of $MeCl_2SiH$ with the corresponding Grignard reagents. Most of the silylation reactions were carried out under neat conditions at 120 °C with low catalyst loadings (0.1−2.5 mol %), resulting in high isolated yields (>90%) regardless of the heteroatom adjacent to the C(sp$^3$)−H bond. The sila-heterocyclic products obtained in this study are moisture- and air-stable, and can be purified by flash chromotography and stored on the bench for several months without decomposition.

**Silylation of C(sp$^3$)−H Bonds $\alpha$ to O Atom.** (*o*-OMe-aryl)dimethylsilanes bearing electron-donating and -withdrawing groups in all positions of the aryl rings underwent the intramolecular silylation smoothly (**3b**−**3l**) (Table 2). Difluoro-substituted substrates were converted into the desired cyclization products **3m** and **3n** in 95% and 91% yield, respectively. In the presence of 2 equiv of COE, the reaction of **2p** resulted in double cyclizations to form the disilabenzodifuran derivative **3p** selectively. The product was characterized by X-ray diffraction analysis, which revealed a coplanar three-ring structure. Similarly, the disilylation product **3q** with a binaphthyl backbone was obtained in 83% isolated yield, along with 10% of the monosilylation product.

The substituents at the Si-atom have a large effect on the reactivity of the silylation. The reaction of (*n*-heptyl)-methylsilane **2r** proceeded smoothly under the standard conditions. Introducing a bulky *t*Bu group led to a less reactive substrate **2s**, although the desired product **3s** could be formed in high yield (95%) at elevated temperature (150 °C). However, under the same conditions, the substrate with two *i*Pr groups at Si afforded **3t** in only 18% yield. Clearly increasing the size of the substituents at Si reduces the catalytic efficiency of the silylation.

A wide range of diaryl methylsilanes are suitable substrates for the Ru-catalyzed silylation. Compounds containing two identical aryl groups underwent desymmetric silylations of C(sp$^3$)−H bonds. Regardless of the substituents in the aryl rings, all substrates provided the corresponding cyclization products in high yields (**3u**−**3ad**). In addition, the silylations of a series of tertiary silanes containing two different aryl substituents and one Me substituent at Si, were explored. A variety of functionalities, including ether (**3an**−**3ap**), amine (**3ak**), fluoro (**3al**), and thienyl (**3am**) groups, were found to be compatible with the reaction conditions. The disilylation product **3af** was obtained in 76% yield using 2.5 mol % of **1b** and 2 equiv of COE. The reaction of **2an** containing two *ortho*-OMe groups in different aryl rings resulted in the formation of a mixture of **3an** (43%) and **3an′** (47%).

This system is selective for the silylation of primary over secondary C(sp$^3$)−H bond $\alpha$ to O atom, as demonstrated by the site-selective silylation of *ortho*-OMe in one aryl ring, while the *ortho*-OEt group in the other ring remained intact (**3ao** and **3ap**). A tertiary C(sp$^3$)−H $\alpha$ to O is hardly active for the silylation. Attempted cyclization of **2aq** containing an *ortho*-O*i*Pr gave a trace amount of the cyclization product, but a 42% yield of a carbosilane dimer **3aq′** resulting from the intermolecular silylation of one Me substituent at Si from another molecule.[21]

**Silylation of C(sp$^3$)−H Bonds $\alpha$ to N-, Si-, and Ge-Atom.** The catalytic silylation was successfully extended to C−H bonds $\alpha$ to N-, Si-, and even Ge-atom (Table 3). A range of (*o*-$NMe_2$-aryl)methylsilanes with various alkyl or aryl substituents at Si formed the corresponding sila-methylindolines **4a**−**4f** in high isolated yields. Furthermore, the Ru-catalyzed intramolecular silylation of C−H bonds $\alpha$ to Si afforded [1,3]-disila-heterocycles **5a** and **5b** in 90% and 80% yield, respectively. To our satisfaction, an unprecedented [1,3]-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germasilolane **6a** was obtained in high yield by the silylation of C−H bond $\alpha$ to Ge, albeit with a high catalyst loading.

**Silylation of C($sp^3$)−H Bonds $\alpha$ C Atom.** The pincer Ru catalyst is also effective for the silylation of primary C−H with no heteroatom attached (Table 4). For example, the Me groups of *ortho*-Et and -*i*Pr moiety were silylated to form Si-containing heterocycles **7a** and **7b** in high yields. In addition, the silylation of primary benzylic C−H bonds could occur to form five-membered silolanes under relatively mild conditions. Treatment of dimethyl(2-methylbenzyl)silanes with 1 equiv of COE and **1b** (1 mol %) at 80 °C produced silolanes **8a**−**8d** in useful yields. A unique trisilylation product **8e** was obtained when 3 equiv of COE was used. The coplanar four-ring structure was unambiguously determined by X-ray crystallographic analysis.

**Large-Scale Synthesis and Synthetic Utility of [1,3]-Oxasilolanes.** The catalytic silylation process is scalable as shown by the isolation of 7.6 g of **3a** (93% yield) from a 50 mmol scale reaction using a minimum amount of the Ru catalyst (0.05 mol % **1b**), corresponding to a turnover number (TON) of 1860 (Figure 3a).

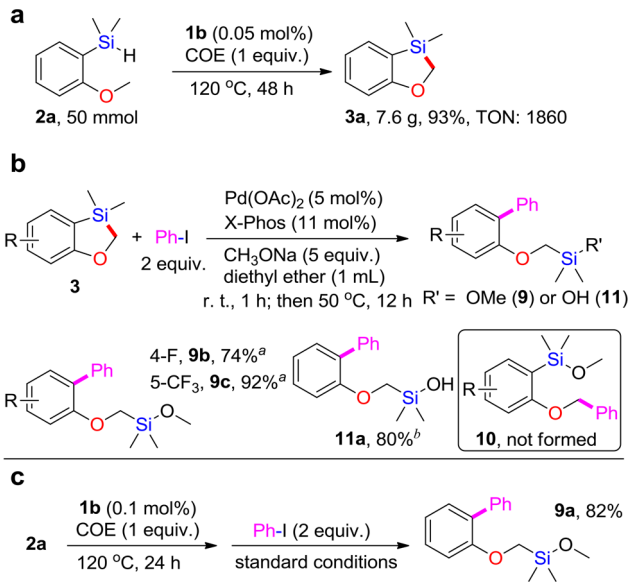


**Figure 3.** Lage-scale synthesis of [1,3]-sila-dihydrobenzofuran and synthetic utility of [1,3]-oxasilolanes. (a) Gram-scale synthesis of **3a**. (b) Pd-catalyzed Hiyama-Denmark cross-coupling of 3 with Ph-I. [a]Product isolated by distillation. [b]Product isolated by silica gel chromatography. (c) One-pot, two-step Ru-catalyzed silylation and Pd-catalyzed Hiyama-Denmark cross-couplings.

To demonstrate the synthetic utility of the silylation products, Pd-catalyzed Hiyama cross-coupling of [1,3]-oxasilolane **3** with PhI was investigated (Figure 3b). A combination of $Pd(OAc)_2$ with various phosphine ligands, in the presence of NaOMe (5 equiv), was effective for the coupling of **3a** and PhI. Unfortunately, most reactions gave a mixture of C($sp^2$)−C($sp^2$) (**9a**) and C($sp^3$)−C($sp^2$) (**10a**) coupling products with the former as the major product (see the SI, for product distributions). Delightfully, the use of X-Phos (5 mol %) as the ligand proved to be highly selective for the C($sp^2$)−C($sp^2$) coupling. The reactions of **3** and PhI in diethyl ether at 50 °C for 12 h afforded biaryl products in high yields. Depending on the purification procedures, either the products with a silyl ether (**9b**, **9c**) or silanol moiety (**11a**) could be isolated (Figure 3b).

Given the high conversions and low catalyst loadings of the silylation reaction, we envisioned that the crude silylation silylated product could be suitable to the subsequent cross-coupling with PhI in one pot without purification. Indeed, [1,3]-sila-dihydrobenzofuran **3a**, derived in situ from the Ru-catalyzed silylation of **2a**, underwent Pd-catalyzed cross-coupling with PhI to produce **9a** in 82% yield (Figure 3c).

**Reactivity of Different Types of Primary C−H Bonds.** To our knowledge, while a number of examples of functionalizations of C−H bonds $\alpha$ to heteroatoms are known, a comprehensive examination of the reactivity and selectivity of such C−H bonds toward transition metal-mediated functionalization has not been conducted. The examples presented in Tables 2−4 demonstrate the ability of the Ru complex **1b** to catalyze the intramolecular silylation of various types of primary C−H bonds, including C−H bonds $\alpha$ to heteroatom (O, N, Si, Ge), benzylic C−H bonds, and C−H bonds of the *ortho*-Et group. To assess the relative reactivity of these primary C−H bonds, we designed six substrates bearing two different types of primary C−H bonds on two aryl rings for intramolecular competition studies (Figure 4).

The C−H bond $\alpha$ to N appeared to be more reactive than that $\alpha$ to O as shown by the selective silylation of the *ortho*-$NMe_2$ (**12b**, 90%) versus the *ortho*-OMe group (**12a**, 3%) (eq 1). Given that the $NCH_2$−H and $OCH_2$−H bonds have similar strength with bond dissociation energies (BDE) of being ca.

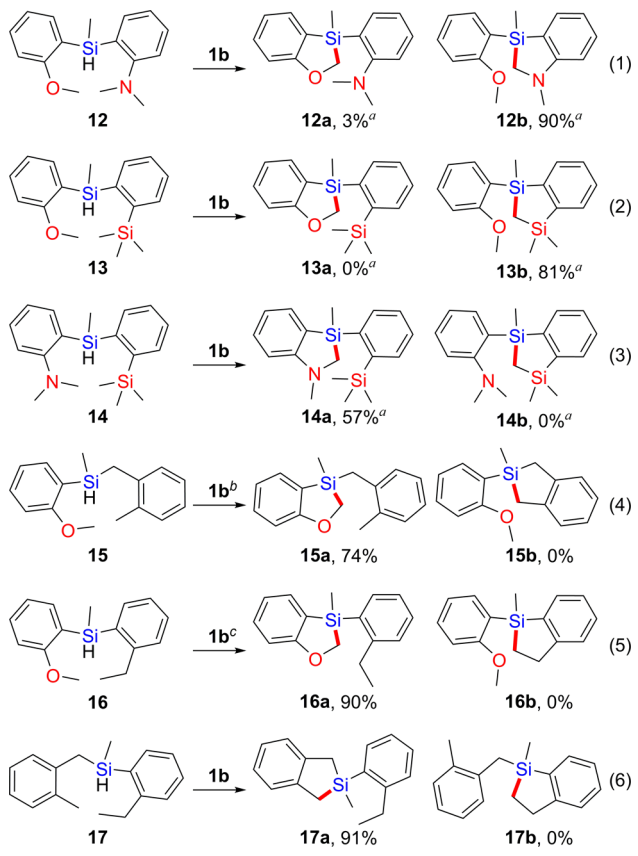


**Figure 4.** Intramolecular competitive silylation of different types of primary C−H bonds. Reaction conditions: **1b** (5 mol %), COE (1 equiv), at 120 °C for 24 h. Yields shown are of isolated products (unless otherwise noted). [a]Yields were determined by $^1H$ NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [b]**1b** (1 mol %). [c]**1b** (2.5 mol %).



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91.7 and 92 kcal/mol, respectively,[22] the high site-selectivity for the silylation of $NCH_2$–H is of significance. Even more intriguingly, the C–H of *ortho*-$SiMe_3$ was silylated exclusively (**13b**, 81%) in the presence of the C–H of *ortho*-OMe, despite the fact that the former has much higher BDE than the latter (98 vs 92 kcal/mol) (eq 2).[22a] By contrast, the competition between the *ortho*-$SiMe_3$ and *ortho*-$NMe_2$ groups in **14** resulted in the site-selective silylation of the latter (**14a**, 57%) (eq 3). The benzylic C–H has lower BDE than the C–H bond $\alpha$ to O (90 vs 92 kcal/mol),[22b] but the latter was effectively silylated while the benzylic C–H bond remained intact (eq 4). As expected, the reaction of the substrate containing the *ortho*-OMe and *ortho*-Et groups revealed a specific site-selectivity for the former (eq 5). Finally, in the presence of both of the benzylic C–H and C–H bond of *ortho*-Et, the silylation occurred exclusively at the position of the former (**17**, 91%) (eq 6).

The data gained above establish a reactivity order for the Ru-catalyzed silylation of primary C–H bonds that enables the formation of Si-containing "five-membered" heterocycles: $ArN(Me)CH_2$–H > $ArSi(Me)_2CH_2$–H > $ArOCH_2$–H > $ArCH_2$–H > $ArCH_2CH_2$–H. The trend cannot be strictly correlated with the BDE of the primary C–H bonds, implying that there are both electronic and steric contributions to the energetics of C–H activations. A Ru(II) silyl complex was determined to be a key intermediate prior to the rate-limiting C–H activation step (see below). The corresponding structure bearing the $SiMe_3$ group probably has the mostly favorable geometry optimized for the C–H interaction with the Ru center, while the complex with the $NMe_2$ group is expected to have a greater steric attraction than that with the OMe group. With a flexible $CH_2$ linker between Si and the aryl ring bearing an *ortho*-Me group in **15**, the unhindered rotations around the C($sp^3$)–Si and C($sp^3$)–C($sp^2$) bonds makes the access of the benzylic C–H bond to the metal center less likely than the C–H bond of *ortho*-OMe located in the other aryl ring.

**Mechanistic Analysis.** To provide insights into the mechanism of this silylation reaction, deuterium-labeling experiments were carried out (Figure 5). The deuterated substrate **2d**-$d_3$ containing an *ortho*-$OCD_3$ group was submitted to the standard catalytic conditions. NMR analysis of the isolated product (**3d**-$d_2$, 92% yield) revealed 10% D incorporation (0.58 D) in two methyl groups bonded to Si and 97% D content in the methene unit, as well as 1% D content in the 2-position of the aryl ring (eq 7).

To probe the possibility of intermolecular H/D scrambling, a 1:1:2 mixture of **2d**-$d_3$, **2i**, and COE was submitted to the catalytic reaction (eq 8, Figure 5). NMR analysis of two isolated silylation products revealed 8% D incorporation (0.48 D) in the $SiMe_2$ group of **3d**-$d_2$ and ~1% D incorporation (0.08 D) in the $SiMe_2$ group of **3i**-$d_x$. Note that there is 8% and 1% D content in the 2- and 5- positions of the aryl ring in **3i**-$d_x$, while D was barely observed in the methene unit of this molecule.

To assess whether the intermolecular D/H exchange observed in eq 8 involves the Si–H group, the Ru-catalyzed silylation of **2d**-$d_3$ was performed with one equiv of $PhSiMe_3$, in place of **2i** (eq 9, Figure 5). Heating the solution at 120 °C for 24 h resulted in 12% D incorporation (0.71 D) in the $SiMe_2$ group of **3d**-$d_2$. Notably, intermolecular D/H scrambling did not occur with the $SiMe_3$ group of $PhSiMe_3$. The resulting cyclooctane (COA) contained 0.35 D. Small amounts of deuterium were also present in the aryl rings of **3d**-$d_2$ and $PhSiMe_3$. These results, together with the phenomena of D

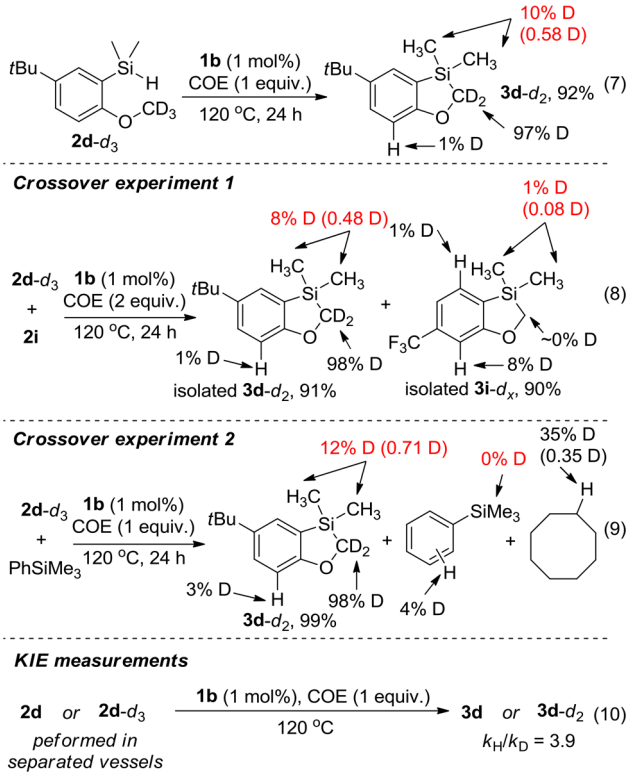


**Figure 5.** Deuterium-labeling experiments and KIE measurements.

incorporations into the aryl rings observed in **3d**-$d_2$ and **3i**-$d_x$ (cf. eqs 7 and 8), strongly suggest that an Ru(II) hydride (**A**) and deuteride (**A**-*d*) species were present in the system, and the H/D scramblings occurred through the exchange between the aromatic C–H and the Ru–D of **A**-*d*.

Provided the lack of D incorporation in the $SiMe_3$ groups of $PhSiMe_3$ (cf. eq 9), the H/D scramblings involving the $SiMe_2$ groups of **3d**-$d_2$ and **3i**-$d_x$ most likely occurred via a Ru(II) silyl intermediate (**D**), rather than the interaction of the $SiMe_2$ group with the Ru–D of **A**-*d*. A plausible H/D exchange pathway is depicted in Figure 6. A Ru(II) silyl complex (*t*Bu)-**D**-$d_3$ derived from the *t*Bu-substituted deuterated substrate **2d**-$d_3$, undergoes $\beta$-H elimination of the silyl methyl to form a $\eta^2$-silene Ru(II) hydride (*t*Bu)-**F**-$d_3$. H/D exchange between the Ru–H bond and the C–D bond of *ortho*-$OCD_3$ via a $\sigma$-bond metathesis mechanism would generate the $\eta^2$-silene Ru(II) deuteride (*t*Bu)-**F**-$d_3'$. The reinsertion of silene then gives the intramolecular H/D scrambling product (*t*Bu)-**D**-$d_3'$. For the intermolecular H/D crossover reaction, the silene ligand exchange between (*t*Bu)-**F**-$d_3'$ and ($CF_3$)-**F** gives (*t*Bu)-**F**-$d_2'$ and ($CF_3$)-**F**-*d*′. The latter undergoes the silene insertion into the Ru–D bond, resulting in the D incorporation into the silyl methyl groups of ($CF_3$)-**D**-*d*′. The rate of silene insertion occurring within (*t*Bu)-**D**-$d_3'$ would be expected to be greater than the rate of silene exchange, accounting for the much higher D incorporation in the $SiMe_2$ group of **3d**-$d_2$ compared to that in **3i**-$d_x$. Note that similar ruthenium silene complexes have been reported by Tilley/Rheingold[23] and Berry.[24]

Finally, measuring the initial rates of the silylations (<20% conversion) of nondeuterated (**2d**) and deuterated (**2d**-$d_3$) substrates in separated vessels revealed a primary kinetic isotope effect (KIE value: 3.9) (eq 10, Figure 5), indicating that the C($sp^3$)–H cleavage is the rate-determining step.



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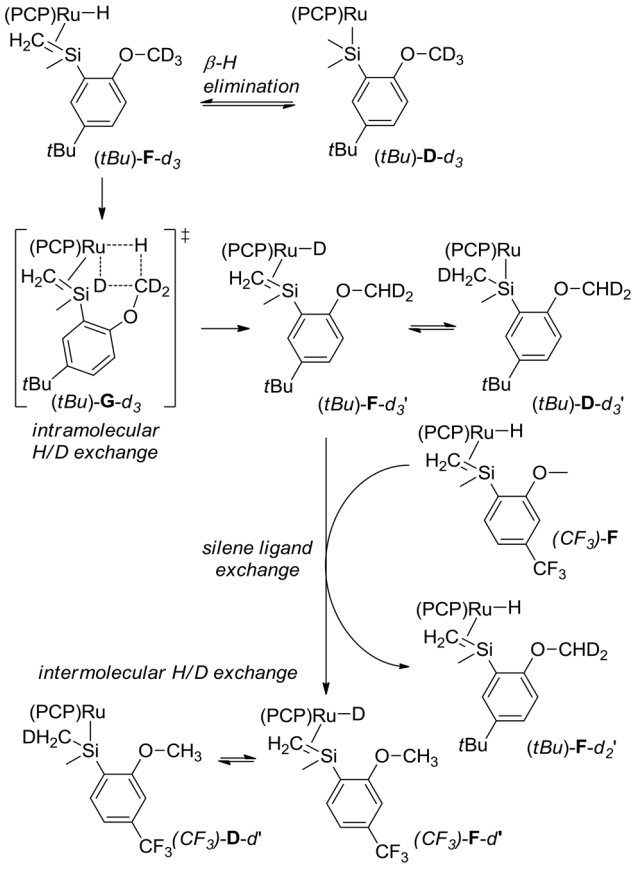


**Figure 6.** Proposed pathways for the intramolecular and intermolecular H/D scrambling.

A proposed working mechanism consistent with the experimental observations is shown in Figure 7. Considering

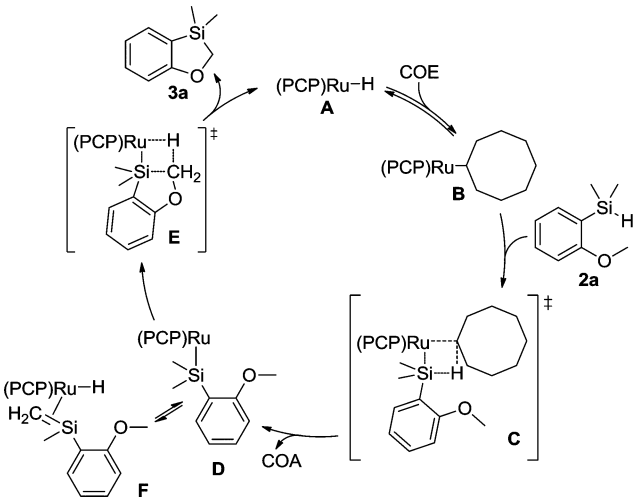


**Figure 7.** Proposed reaction mechanism for the intramolecular C(sp$^3$)–H silylation.

the reluctance of Ru(II) complexes toward two-electron oxidation,[25] the Ru-mediated activations of Si–H and C–H bonds most likely proceed through a $\sigma$-bond metathesis mechanism. The D incorporations observed in the aryl rings and COA provide evidence in support of the existence of the pincer Ru(II) hydride intermediate **A** during the catalysis. Migratory insertion of the hydrogen acceptor, COE, into the Ru–H bond forms a Ru(II) cyclooctyl **B**. The intermolecular $\sigma$-bond metathesis between the Ru–C bond of **B** and the Si–H bond of **2a** affords the Ru(II) silyl intermediate **D** and COA. The C–H bond activation via the intramolecular $\sigma$-bond metathesis, which was found to be the rate-determining step, would form the silylation product **3a** and regenerate **A**. The $\eta^2$-silene Ru(II) hydride **F** is a probable off-cycle intermediate on the basis of the facile H/D scramblings observed for the $SiMe_2$ group. In addition, the formation of the carbosilane dimer **3aq**′ in the reaction **2aq** (vide supra) fully accounts for the occurrence of the silene Ru(II) hydride species (see the proposed pathway for carbosilane dimer formation in the SI).[21]

## CONCLUSIONS

In summary, we demonstrate a highly efficient pincer ruthenium catalyst for C(sp$^3$)–H silylation to form novel [1,3]-sila-heterocycle classes, encompassing unprecedented catalytic intramolecular silylation of C–H bonds $\alpha$ to O, N, and Ge. This process can be scaled on a commercial synthesis module using a catalyst loading as low as 0.05 mol %. We also report a protocol for one-pot, two-step Ru-catalyzed silylation and Pd-catalyzed Hiyama-coupling of [1,3]-oxasilolane with aryl iodide. The Ru-mediated cleavage of C(sp$^3$)–H bond is determined to be the rate-determining step, and the reactivity order of various types of C(sp$^3$)–H bonds is established. This silylation method is applicable to the construction of a variety of tetraorganosilicons containing four nonidentical substituents, and further studies on catalyst development for the synthesis of optically active tetraorganosilicons are ongoing in this laboratory.

## EXPERIMENTAL SECTION

**Materials and Methods.** All manipulations were carried out in an argon-filled glovebox or under an atmosphere of dry argon using standard Schlenk techniques, unless otherwise stated. *n*-Hexane was purified by distillation over $CaH_2$. Toluene, diethyl ether, and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl prior to use. NMR spectra were recorded on Agilent 400 MHz, Varian Mercury 400 MHz, and Agilent 600 MHz spectrometer. $^1$H NMR spectra were referenced to residual protio solvent peaks or tetramethylsilane signal (0 ppm), and $^{13}$C NMR spectra were referenced to the solvent resonance.

**General Procedure for Intramolecular C(sp$^3$)–H Silylations.** In an argon-filled glovebox, a 5 mL dried Schlenk tube was charged with the desired amount of Ru complex **1b**, hydrosilane, and *cis*-cyclooctene. The tube was sealed tightly with a Teflon plug and the mixture was stirred at 120 °C for 24 h. After the resulting reaction mixture was cooled to room temperature, mesitylene (0.5 equiv) was added as an internal standard and the NMR yield was determined by $^1$H NMR. The crude mixture was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1:150) or bulb-to-bulb distillation to obtain the silylation product.

**General Procedure for Hiyama-Denmark Cross-Coupling of [1,3]-Sila-dihydrobenzofuran Products.** In an argon-filled glovebox, a 5 mL dried Schlenk tube was charged with $Pd(OAc)_2$ (3.4 mg, 15 $\mu$mol, 5 mol %), X-phos (15.8 mg, 33 $\mu$mol, 11 mol %), NaOMe (81 mg, 1.5 mmol) and diethyl ether (1 mL). Then, siladihydrobenzofuran (0.3 mmol) and PhI (0.6 mmol) was added. The tube was sealed tightly with a Teflon plug under Ar atmosphere and the mixture was stirred at room temperature for 1 h, and heated at 50 °C for 12 h. Then the volatile materials were removed in vacuo. Mesitylene (0.5 equiv) was added as an internal standard and the yield was determined by $^1$H NMR, and the crude mixture was purified by flash column chromatography (silica gel, ethyl acetate/petroleum ether = 1:8) or bulb-to-bulb distillation.


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## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06798.

General experimental information; synthesis of substrates, ruthenium catayzed intramolecular C($sp^3$)−H silylations; crystal structures and crystallographic data for **3p** and **8e**; Hiyama-Denmark Coupling of [1,3]-sila-dihydrobenzofuran with PhI; mechanistic studies; additional references; and NMR spectra (PDF)

Crystallographic data for **3p** (CCDC 1544564) (CIF)

Crystallographic data for **8e** (CCDC 1544565) (CIF)

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### Notes

The authors declare no competing financial interest.

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