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COMMUNICATION

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Iridium-Catalyzed Intramolecular C-H Silylation of Siloxane-Tethered Arene and Hydrosilane: Facile and Catalytic Synthesis of Cyclic Siloxanes

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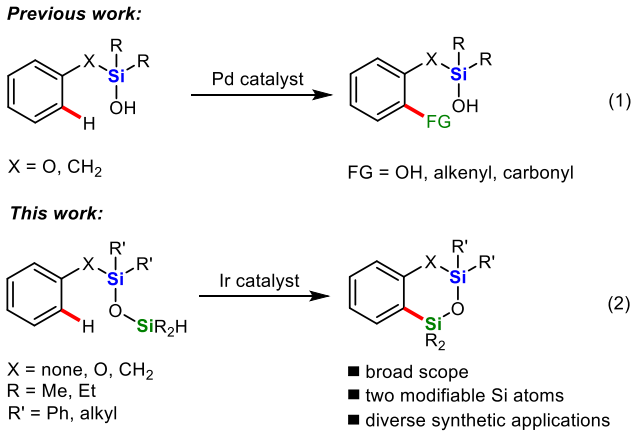
Abstract. Catalytic C-H silylation is an increasingly important topic in the field of organosilicon chemistry and homogenous catalysis as well as organic synthesis, but its synthesis and transformation is usually challenging and often incompatibility with some functional groups. In this manuscript, a new type of silanol-directed intramolecular dehydrogenative silylation under iridium catalysis has been developed. The described silylative cyclization had good functional group compatibility, providing a general and efficient route to unsymmetric cyclic siloxanes with multiple potentially modifiable silicon atoms in high site-selectivities. The resulting organosilicon compounds exhibited diverse synthetic applications owing to their unique structures.

Keywords: Homogeneous catalysis; silylation; iridium; cyclization; siloxane

Organosilicon compounds are extremely useful and have found widespread applications in the fields of organic synthesis,[1] silicon-based functional materials,[2] and biomedically relevant agents.[3] Thus accordingly, numerous synthetic methods to prepare organosilanes have been extensively developed, including nucleophilic substitution, cross-coupling, hydrosilylation, and others.[4] In addition, recent years have witnessed the development of transition metal-catalyzed direct silylation of inert C-H bonds. [5] The C-H silylation strategy is particularly attractive because this strategy avoids prefunctionalization of starting materials and shows excellent functional group tolerance. One of the principal challenges in silylation of C-H bonds is how to balance between reactivity and selectivity since C-H activation reactions generally require harsh reaction conditions, which might cause competing functionalization of undesired C-H sites in a complex molecule.[6] Although intermolecular regioselective silylation reactions have been reported in the past years, most successful cases are limited to heteroarenes, bulky arenes, or those with suitable directing groups.[5] An alternative approach is the intramolecular C-H silyaltion,[7] which has obvious advantages: (1) avoiding the use of excess silanes or arenes, (2) easy access to bifunctional products by further transformations, (3) creating the possibility to construct chiral organosilicon compounds with high stereoselectivities.[7h] Although these one-pot procedures allow the efficient dehydrogenative cyclization of *in situ* generated (hydrido)silyl ether, one major drawback associated with this strategy is the incompatibility with some functional groups sensitive to dihydrosilane under iridium or rhodium catalysis. Recently, organosilanol has been used as a robust, modifiable and/or removable directing group in catalytic regioselective functionalization of arenes through C-H activation (Scheme 1, equation 1).[8] However, no practical methods for the silanol-directed silylation reactions of inert C-H bonds with high levels of site-selectivity control exist, probably due to the inefficiency of silylation reactions of this type.

Despite the fundamental importance of organosilicon compounds, the application of the selective silylation of organosilanes to construct valuable silicon-based heterocycles containing multiple silicon atoms has not been reported. Moreover, no report concerning other heteroatoms except N and O atoms employed to facilitate the intramolecular cyclization process was documented. Inspired by the impressive C-H activation reactions, we envision that the intramolecular dehydrogenative silylation might be realized in a catalytic C-H activation manner if the silanol was used to tether the (hydrido)silyl group. To the best of our knowledge, so far, only few related examples have appeared, in which cyclic disilanes or hydrosilanes were used as

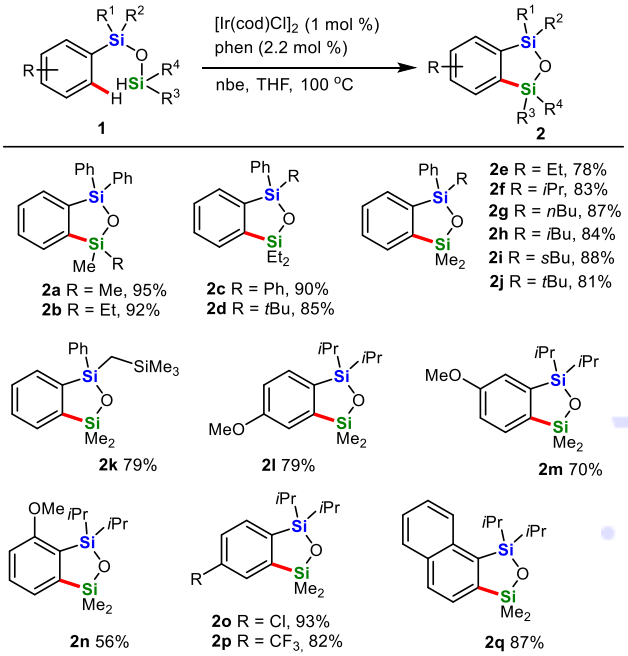
silylation reagents to introduce multiple silicon atoms into the target products.[9] And no report on further applications of silylation products existed, due to the difficulty to differentiate one silyl group from others. It would be highly desirable if each silicon atom in such multi-Si motifs has different reactivity and is suitable for further selective transformation, which will undoubtedly expand the scope of their synthetic applications.



Scheme 1. Silanol-directed arene C-H activation.

In this work, we wish to report a practical method to synthesize a variety of unsymmetric cyclic disiloxanes in good yields through the iridium-catalyzed dehydrogenative silylation of arene C-H bonds (Scheme 1, equation 2). The siloxane-tethered silane substrates were obtained easily by simple silylation of readily available aryl, benzyl, and phenoxysilanols and the following cyclization procedure displayed ample substrates scope. In addition, as expected, the resulting products showed vast application potential in a range of selective transformations, owing to the unique structures bearing two unequal and modifiable silicon atoms.

4,5-Benzo-2-oxo-1,3-disiloles serve as useful synthetic equivalents of benzynes to form polycyclic compounds with interesting photophysical properties. Previously, these compounds were prepared by oxidation reaction of 1,2-bissilylbenzene or Co-catalyzed [2+2+2] cycloaddition reaction of proper alkynes.[10] However, the two silicon atoms in most of them have the same substituents, which limited their further selective transformation. We initiated our studies aimed at developing a conceptually different pathway to this class of disiloxanes comprising two or more different silyl groups, which started from the organosilanols.



Scheme 2. Scope of substrates **1** from arylsilanols.

The substrates **1** (Scheme 2) were obtained by direct reactions of readily available silanols with the appropriate chlorosilanes. We evaluated the dehydrogenative silylations of **1a** to optimize the reaction conditions including metal salts, ligands, hydrogen acceptors, and temperatures (see Supporting Information). In general, varying the electronic properties of the substituents on the aromatic rings of the substrates had negligible effect on the cyclization process. As shown in Scheme 2, under the optimized conditions, the reactions of **1** decorated by various electron-donating (**1l**, **1m**, **1n**) and electron-withdrawing groups (**1o**, **1p**) proceeded smoothly to afford the corresponding disiloxanes in high yields. Substrates with *meta* and *para* substituents were transformed into the cyclized products in good to excellent yields, whereas those bearing substituents at *ortho* position on the arenes gave the desired products in slightly diminished yields. We observed the distinct effects of substituents at the two silicon atoms on cyclization reactions. Increasing the size of substituents on the (hydrido)silyl groups or decreasing the size of substitutents on the silicon atoms of silanol moieties lowered the yields of the products to some extent.[11] This trend can be elucidated since the Thorpe-Ingold effect in the linker can facilitate the cyclization and the steric hindrance at the end group will be detrimental for dehydrogenative silylation. The structure of **2a** was confirmed by X-ray crystallography.[12] Notably, the trimethylsilylmethyl group was also tolerated and the product **2k** with three silicon atoms was produced in 79% yield.

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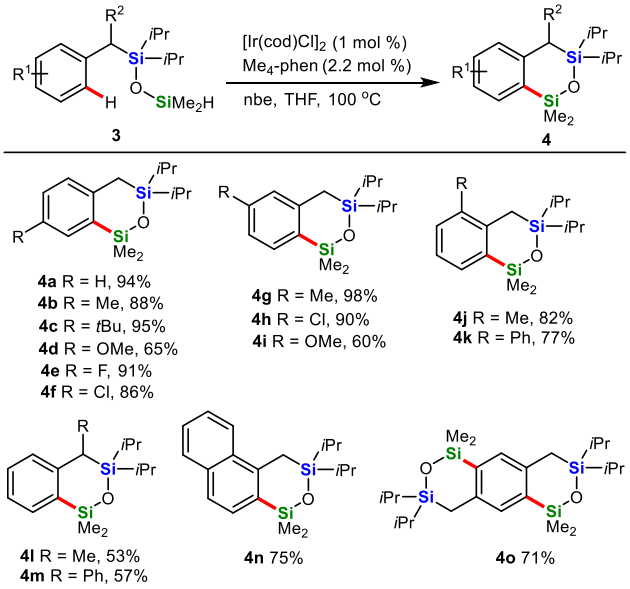
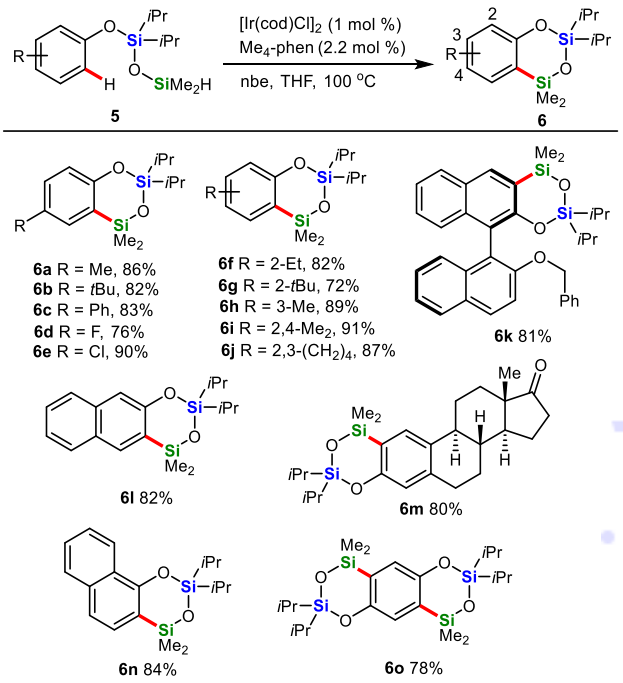


Scheme 3. Scope of substrates **3** from benzylsilanols.



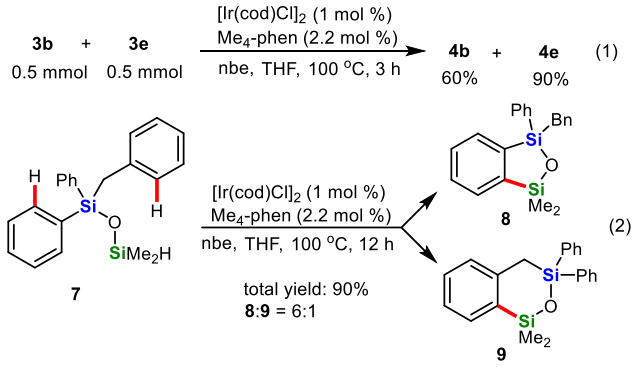
Scheme 4. Scope of substrates **5** from arenoxylsilanols.

The facile synthesis of five-membered cyclic disiloxanes under the present catalytic system encouraged us to turn our attention to construction of other cyclic variants in a similar way. We found that slight modification of standard conditions eliminated the obstacle to silanol-directed silylation of arene and allowed efficient synthesis of six-membered cyclic multi-Si molecules. To this end, **3a** was chose as a model substrate to enact this strategy (Scheme 3). Under similar conditions to those employed for silylation of **1**, the cyclized product **4a** was formed in moderate yield, with an incomplete conversion of starting material. To our delight, replacement of phen by the more strongly electron-donating Me_4-phen led to a full conversion, thus affording the product **4a** in 94% yield. Having identified the active catalyst for the dehydrogenative silylation of **3a**, we next surveyed the scope of this transformation using substrates bearing the hydrodimethylsilyl group. As illustrated in Scheme 3, substrates with an unsubstituted phenyl ring or containing an electron-rich or electron-deficient substituent on the arenes yielded the corresponding products in high yields. Remarkably, the silylation occurred exclusively at the sterically less hindered position (**4g**, **4h**, **4i**). Substitution at α carbon to the silicon atom in benzylsilyl moiety had considerable influence on the yields (**4l**, **4m**). Notably, the double functionalization was viable for substrate **3o** with two hydridosilyl groups *para* to each other, furnishing **4o** in 71% yield, a molecule with four silicon atoms, as confirmed by NMR analysis and X-ray single crystal structure.[12]

The dehydrogenative silylation reactions were not restricted to the substrates derived from aryl and benzyl silanols. Those resulting from phenoxylsilanols proved likewise applicable, yielding the cyclized products in a similar procedure (Scheme 4). It was found that the silylation reactions displayed broad substrate scope to include a variety of phenyl, naphthyl, and even more complex molecules. Firstly, the substrates underwent smooth intramolecular silylation reactions in spite of the electronic properties of substituents in aromatic rings. For example, the silylation reactions of substrates with *para* substituents delivered the desired products in good to excellent yields (**6a-6e**). In contrast to the report by Jeon and co-workers in which a specialized directing group was required to improve the overall yields,[7g] our catalytic silylation method tolerated well the bulky substituents at *ortho* position to hydroxyl group to provide the corresponding products in good yields (**6f**, **6g**, **6j**). The regioselectivity of the silylation reaction was mainly determined by the steric hindrance around the reactive sites. As expected, the silylation happened at *para* position to substituents for *meta*-substituted arenes (**6h**). Besides substituted phenols, naphthols were capable substrate precursors, giving the products in satisfactory yields with high levels of site-selectivity control (**6k**, **6l**, **6n**). The reaction of the chiral substrate **6k**, derived from the (*R*)-BINOL, gave the silylation product at 3' position without affecting the benzyl protecting group. Next, the application of our catalytic cyclization method to silylation of a more complex bioactive molecule was also examined. Compared with the Jeon's work, the selective C2-silylation of estrone was realized without extra protecting group manipulation. Finally,

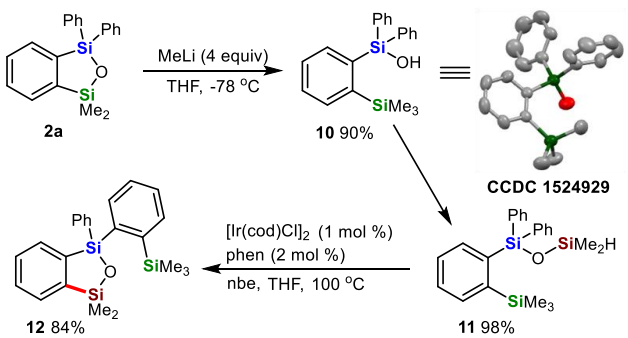
the double dehydrogenative cyclization of the substrate **5o** derived from hydroquinone was also achieved, producing **6o** in 78% yield.[12]

To gain insight into the silylation reactions, the parallel competitive cyclization of substrates **3b** and **3e** was conducted in one flask (Scheme 5, equation 1). Substrate **3e** bearing an electron-withdrawing fluorine atom proved to be more reactive than **3b**, indicating the nucleophilic nature of the generated silyl iridium species.[13] Further insight into this type of the reaction was obtained from the silylation of substrate **7** comprising two kind of available *ortho* C-H bonds in one molecule (Scheme 5, equation 2). The silylation occurred preferably at phenyl C-H bond over benzyl C-H bond, affording a mixture of regioisomers, in a 6:1 ratio of **8** to **9**.



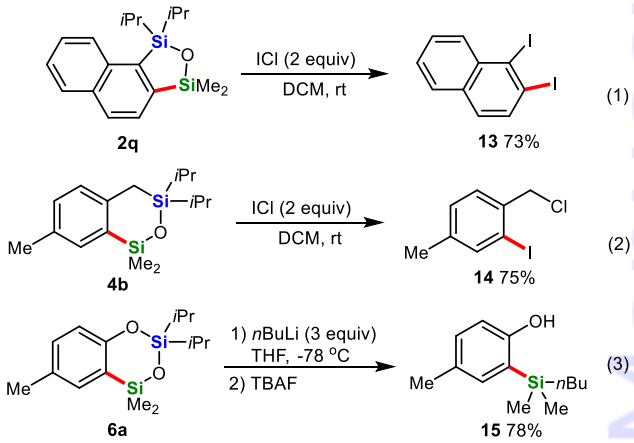
Scheme 5. Inter- and intramolecular competitive cyclization reactions.

The resulting silylation products are useful synthetic intermediates because both of the Si-C bonds and Si-O bonds are cleavable and/or modifiable, especially for the regio- and stereoselective transformations determined by the two unequal silyl groups. Starting from the commercially available triphenylsilanol, after two sequential silylative cyclization reactions, the product **12** containing three silicon atoms was obtained in good overall yield (Scheme 6). It was noteworthy that twice regioselective transformations occurred in the whole process, probably due to the steric hindrance exerted by the distinct silyl groups.



Scheme 6. Further transformation of **2a**.

The synthetic utilities of the developed silylation method were further highlighted by the selective transformations of Si-C and Si-O bonds in the products (Scheme 7). In the presence of ICl, **2q** and **4b** underwent smooth C-X bond formation reactions at C-Si sites. Interestingly, the aryl and benzyl Si-C bonds in **4a** were converted into C-I and C-Cl bonds, delivering the halide **13** that is difficult to access by other methods in one simple step. Considering the significance of phenolic motifs in pharmaceutically and biologically active compounds,[14] we further exploited a traceless directing group strategy for regioselective silylation of phenols. For **6a**, selective cleavage of Si-O bonds with BuLi followed by TBAF led to the formation of *ortho* silylated phenol, providing an alternative approach to this class of the compounds.[7g]



Scheme 7. Selective cleavage of Si-C and Si-O bonds.

In conclusion, we have developed a general method for siloxane-tethered arene *ortho*-silylation in which silanol formally serves as the directing group for iridium-catalyzed dehydrogenative silylation of arenes C-H bonds. This strategy features high efficiency, good functional group compatibility, and high regioselectivity, allowing the synthesis of a range of unsymmetric cyclic siloxanes containing two potentially modifiable silicon atoms from readily available aryl, benzyl, and phenoxysilanols, which is complementary to the impressive field of C-H activation reactions.[15] Furthermore, the resulting silylation products with the unique structures exhibited diverse synthetic applications. Further studies on the enantioselective silylation and the mechanism of this process are ongoing.

Experimental Section

Representative Procedure for the Synthesis of Disiloxane 2d:

$[Ir(cod)Cl]_2$ (6.7 mg, 1.0 mol%) and phen (3.9 mg, 2.2 mol%) were added to a flame-dried, nitrogen-purged

septum-capped vial .The mixture was dissolved in THF (3 mL), and **1d** (0.342 g, 1 mmol), nbe (0.113 g, 1.2 mmol) was added to the mixture. The septum on the vial was replaced by a screw cap with a Teflon liner under a N_2 atmosphere .The reaction mixture was stirred for 12 h at 100 °C. Flash silica gel column chromatography (hexane) purification of the residue gave the desired product **2d** as a colorless liquid.

Acknowledgements

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[12] Single crystals (**2a**, **4o**, **6o**, **10**) suitable for X-ray diffraction analysis were grown by slow vapor diffusion of *n*-hexane into each solution in DCM at room temperature. CCDC 1524935(2a), CCDC 1524921(**4o**), CCDC 1524930(**6o**) and CCDC 1524929(**10**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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