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Ring Expansion to 6−, 7− and 8−Membered Benzosilacycles through Strain−Release Silicon-based Cross-Coupling

Ying Qin, Jie-Lian Han, Cheng-Wei Ju, and Dongbing Zhao*[a]

Abstract: Silacycle synthesis is highly appealing due to their important applications in organic synthesis, medicinal chemistry as well as materials chemistry. However, sila-tetralins & sila-benzosuberanes are surprisingly under-represented to date due to the lack of general methodology to approach these compounds. Herein we successfully develop Pd-catalyzed strain−release silicon-based cross-coupling as an unprecedented ring expansion method, which constitutes one of the most general route for preparing diversified sila-tetralins & sila-benzosuberanes.

"Carbon/Silicon switch" has been regarded as an innovative strategy for the development of new materials, drugs and pesticides.[1] The structural units of tetralins & benzosuberanes at various oxidation levels are prevalent in numerous marketed drugs, and natural products (Figure 1a).[2] In light of this fact, investigations of sila-tetralins & sila-benzosuberanes are of great significance and in great demand. However, sila-tetralins & sila-benzosuberanes are surprisingly under-represented to date due to the lack of general methodology to approach these compounds (Figure 1a). The typical protocols to approach sila-tetralins & sila-benzosuberanes suffer several disadvantages such as the lack of flexibility, the need of hash conditions and multi-step synthesis.[3] Thus, it is highly desired for the development of the general and efficient strategy to directly constructing sila-tetralins & sila-benzosuberanes.

The palladium-catalyzed Hiyama-Denmark cross-coupling has developed over the past 30 years into an efficient and attractive carbon−carbon bond forming strategy (Figure 1b).[4] In general, the $-SiR_3$ group would convert to the corresponding silicon by-products as the wastes in thi cross-coupling. We wondered whether Hiyama-Denmark cross-coupling could be high-efficiently utilized as a ring expansion strategy enabling rapid construction of diverse silacycle skeletons even it has never been presented. It was revealed that the propensity of the 4− and 5−membered silacylces toward activation by a nucleophile as the pentacoordinate silicate is enhanced because of their inherent ring-strain-release Lewis acidity.[5] Its origins is the difference in coordination geometry between four-coordinate (tetrahedral) and five-coordinate (trigonal bipyramidal) silicon species (Figure 1c). Thus, the 4− and 5−membered silacylces appear to be more susceptible to transmetalation in organosilicon-based coupling reaction. This enhanced reactivity offers exciting possibilities for ring expansion via intramolecular Hiyama-Denmark cross-coupling by incorporation of aryl bromides and 4− or 5−membered silacycles into the same skeleton at the adjacent position. We envisioned that this pathway could be initiated if we could inhibit the problematic cross-coupling of aryl halides with O or N−nucleophiles during the reaction[6] by choice of proper nucleophile and catalytic system. Herein we describe the realization of ring expansion of 4− and 5−membered silacycles in the presence of alcohol by Pd-catalyzed strain−release silicon-based cross-coupling (Figure 1d). This method provides a modular means of assembling sila-tetralins & sila-benzosuberanes.

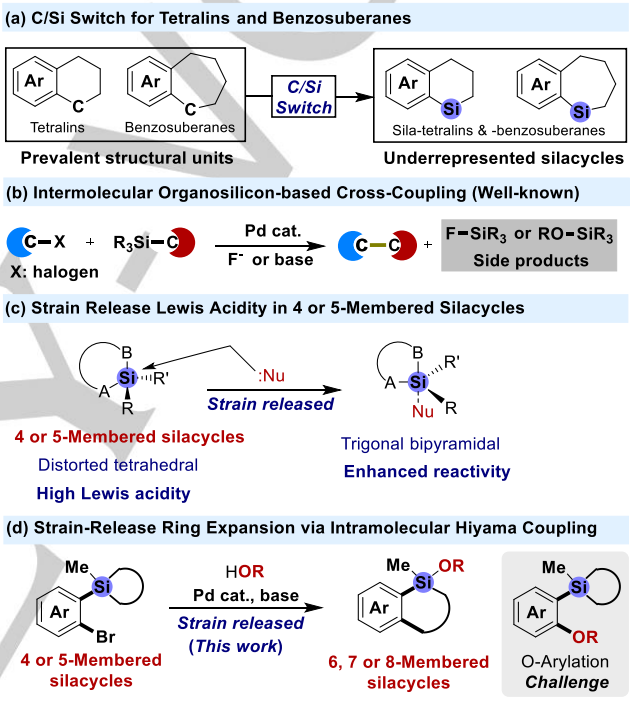

Figure 1. Research background and motivation for ring expansion of 4- and 5-membered silacycles via strain−release organosilicon-based cross-coupling.

Silacyclobutanes (SCBs) have been widely utilized as sila synthons in transition metal-catalyzed reactions due to its high ring strain and Lewis acidity.[7] Thus, the silacyclobutane derivative **1a** was subjected to Pd-catalytic conditions to try to develop an efficient approach to access sila-tetralin in our preliminary experiments. After extensive survey of the reaction parameters (more details, seeing SI), the palladium-catalyzed strain−release organosilicon-based cross-coupling smoothly occurred to yield sila-tetralin **2a** and the optimized conditions were identified to be: 5 mol % of $Pd(P^tBu_3)_2$, $TMSNEt_2$ (1.5 equiv), and ^{t}BuOH as the solvent and the nucleophile, wherein the desired product **2a** was afforded in 87% yield at 80 °C for 24 h. Next, we investigated the substrate scope and functional group tolerance (Figure 2). To our delight, whenever the 3-, 4-, 5- or 6-position of the phenyl ring bears electron-neutral, electron-rich or electron-withdrawing groups the reaction proceeded smoothly under the optimized conditions, with good to excellent yields (**2b−i**). Furthermore, the 3,6-, 4,5-, 5,6-, 4,6- and 5,6-disubstituted substrates also underwent the reaction

[a] Y. Qin, J. Han, C.-W. Ju, Prof. Dr. D. Zhao
State Key Laboratory and Institute of Elemento-Organic Chemistry
College of Chemistry, Nankai University
94 Weijin Road, Tianjin 300071 (China)
E-mail: dongbing.chem@nankai.edu.cn

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smoothly and the yields were comparable to those of the monosubstituted substrates (**2j–q**). Heteroaryl bromide bearing silacyclobutane group at adjacent position also provided the corresponding ring expansion product (**2r**). Additionally, we studied the influence of the nucleophile. We found that it did not significantly affect the reaction performance to switch of the ^{t}BuOH to different alcohols and phenols as the nucleophile and the solvent (**2s–w**). Introducing bromo and silacyclobutane group to 1-, and 8-position of naphthalenes individually, the intramolecular strain−release organosilicon-based cross-coupling reaction also works well, enabling access to the 7-membered silacycles **2x–y**. It is important to stress that this method was found to be compatible with a variety of important functional groups, including halogens, trifluoromethyl, cyano, and alkoxy substituents.

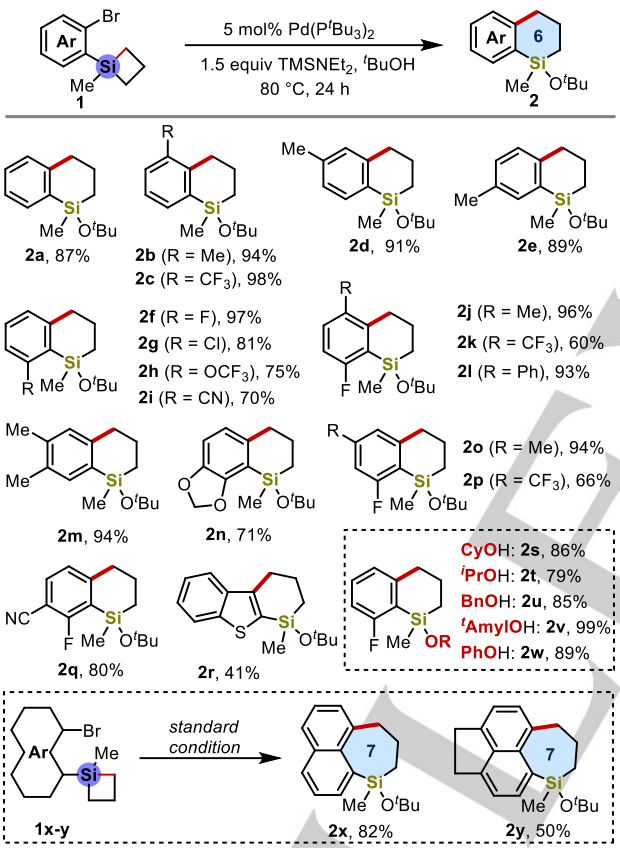


Figure 2. Substrate scope for ring expansion of silacyclobutane derivatives to access sila-tetralins. Values represent isolated yields.

To access sila-benzosuberanes, the intramolecular organosilicon-based cross-coupling reaction of aryl bromide bearing sila-cyclopentane at adjacent position (**3a**) was examined under the optimized condition. Unfortunately, only trace amounts of the desired silabenzosuberane were provided. After an extensive screening, we found that the reaction occurred smoothly in 91% yield (**4a**) by using the mixture of DMF/CyOH (1:1) as the solvent (CyOH as the nucleophile) at 150 °C for 24 h. We next examined the scope and functional group tolerance of sila-cyclopentanes **4** to approach diverse sila-benzosuberanes (Figure 3). Various sila-cyclopentanes bearing substituent at any position of phenyl ring with different electronic properties proceeded smoothly to afford the desired sila-benzosuberanes in satisfactory yields (**4b–l**). Again, our method could also be applied in ring expansion of multi-substituted substrates without any drop in yields (**4m–q**). Furthermore, we studied the influence of the nucleophile for this reaction. We found that both cyclohexylmethanol and phenol were competent nucleophiles, enabling access to silabenzosuberane derivatives (**4r–s**). Assembling of bromo- and sila-cyclopentane group to 1-, and 8-position of naphthalenes, the intramolecular strain−release organosilicon-based cross-coupling also works well to yield the 8-membered silacycles **4t**.

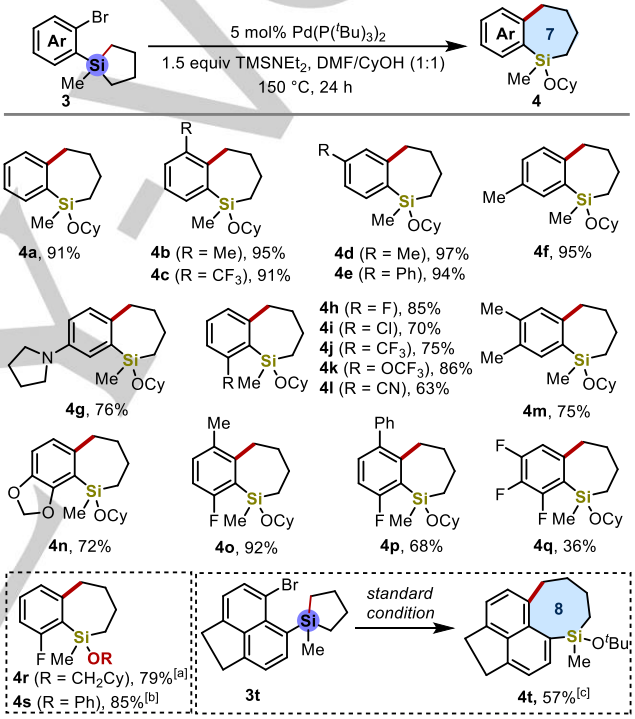


Figure 3. Substrate scope to access sila-benzosuberanes. Values represent isolated yields. [a] DMF/CyCH$_2$OH (1:1; 1 mL) as the solvent. [b] DMF/PhOH (1:1; 1 mL) as the solvent. [c] DMF/^{t}BuOH (1:1; 1 mL) as the solvent.

To demonstrate the synthetic utility of the silacycles obtained in our transformation, we first sought to conduct six additional transformations of the silicon center at our product **4h** to approach structurally diverse important building blocks (Figure 4, upper panel). Treatment of **4h** with 40% HF in THF/H_2O at room temperature for 1 h led to the cleavage of −OCy group at room temperature to yield product **5a** in 85% yield.[8] We prove that the −OCy group of the sila-benzosuberane **4h** can be easily cleaved and replaced by alkyl group to afford product **5b** (79% yield) by treatment with organolithium reagent.[9] Moreover, **4h** can also be easily hydrolyzed with ^{t}BuOOH/SeO_2 in DCM to give the corresponding silanol **5c** in 98% yield.[10] The structure of **5c** was clearly confirmed by single-crystal X-ray diffraction. Additionally, the Si–O bond of the product **4h** can be reduced by

$LiAlH_4$ to afford the cyclic hydrosilane **5d** (76% yield),[11] which can be further utilized as the synthetic intermediate in hydrosilylation.[12] In addition to reduction, we could also submit compound **4h** to the modified Tamao's oxidation condition to produce 2-hydroxyarylbutanol **5e** in 80% yield.[13] This strategy provides a general method for the preparation of 2-hydroxyarylbutanol skeletons, which have been widely utilized as the synthetic intermediates to approach numerous bioactive molecules.[14] Bisiodination via ring opening reaction of compound **4h** by treatment of NIS/AgF also smoothly proceeded to give 1-iodo-2-(4-iodobutyl)benzene **5f** in 56% yield,[15] which was synthesized in six steps.[16]

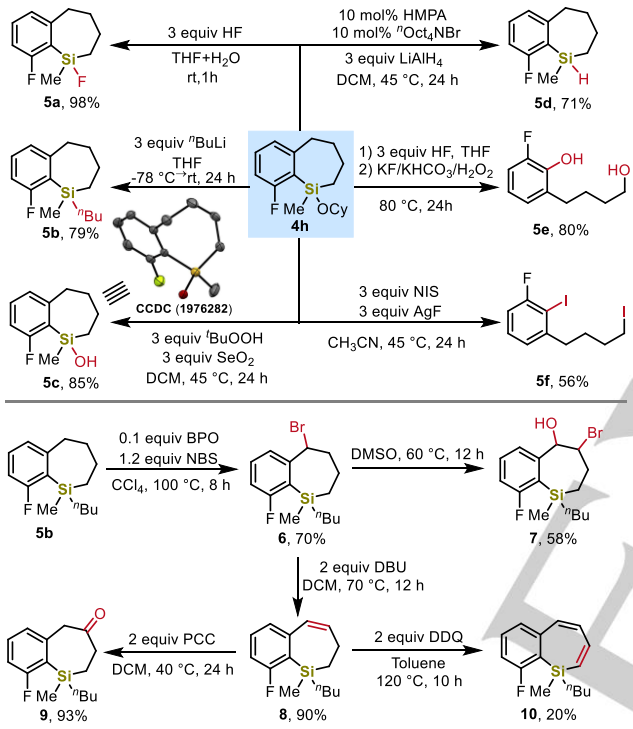
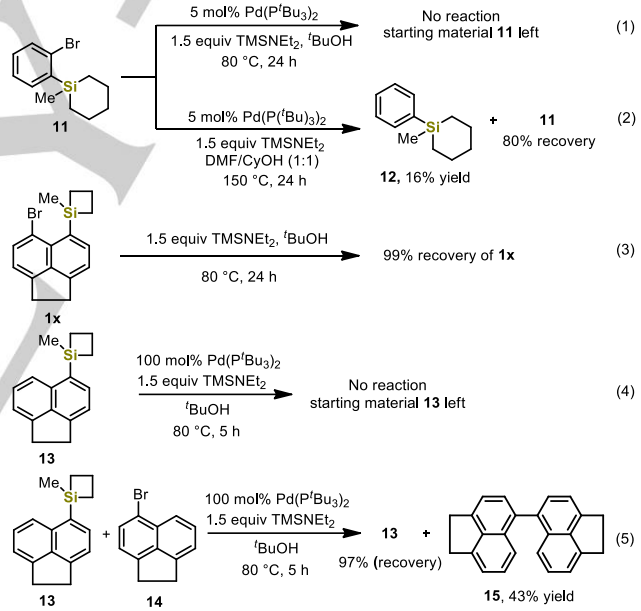


Figure 4. Synthetic applications of sila-benzosuberane **4h**.

Furthermore, we wondered if the carbocycle of our products could also been further functionalized resulting structurally diverse sila-tetralins or sila-benzosuberanes at various oxidation levels. Herein, we for the first time show that bromination at the 5-position of sila-benzosuberane **5b** occurred smoothly to yield the product **6** in 70% yield,[17] which could serve as a useful building block for further transformations (Figure 4, lower panel). Compound **6** could smoothly undergo oxidation in the presence of DMSO to yield brominated sila-benzosuberanol **7** with 58% yield.[18] Furthermore, the bromo group of **6** can be easily eliminated in the presence of DBU to form the unsaturated sila-benzosuberene **8**. The sila-benzosuberene **8** could be further oxidized either by PCC or DDQ to produce the corresponding sila-benzosuberone **9** or the conjugated system **10**.

We then carried out a series of control experiments to elucidate the mechanism. First, we found that no ring expansion took place by employment of silacyclohexane **11** as the substrate under conditions identical with ring expansion of 4-, or 5-membered silacycles (Eq. 1-2). The results indicate that the high ring strain of silacycles is indispensable in this intramolecular Pd-catalyzed organosilicon-based cross-coupling. Second, we submitted silacyclobutane **1x** to the standard condition in the absence of Pd^0 catalyst (Eq. 3). No reaction took place. This result indicates that our starting material doesn't form free pentacoordinate-silicon intermediate in ^{t}BuOH. Concerted formation of pentacoordinate-silicon species and transmetalation might be more preferred. Third, 100% of the starting material has been recovered if we exposed 1-methyl-1-(naphthalenyl)siletane **13** to the standard condition in the presence of stoichiometric $Pd(P^tBu_3)_2$ (Eq. 4). The result is consistent with a scenario in which silacyclobutane is inactive until it undergoes intramolecular transmetalation. Furthermore, the competition experiment between silacyclobutane **13** and aryl bromide **14** also elucidates that oxidative addition of C−Br bond is much faster than insertion of C−Si bond and the reaction started from the oxidative addition of C−Br bond because the dimerization of **14** smoothly happened to yield compound **15** in the presence of stoichiometric $Pd(P^tBu_3)_2$ (Eq. 5).



On the basis of literatures and our control experiments,[19] we propose a catalytic cycle that initiates with oxidation addition of Pd^0 to C–Br bond of **1** or **3** to form Pd^{II} intermediate **A**, which is followed by intramolecular transmetalation, thus affording the intermediate **B** (Figure 5, Path A). Complex **C** further undergoes an intermolecular etherification in the presence of ROH and base to deliver the intermediate **C** bearing a Si–OR bond, followed by reductive elimination to form the product **2** or **4** and regenerate the Pd^0 catalyst. Notably, an alternative pathway involving a Br/OR exchange of the Pd^{II} intermediate **A** in the presence of base and HOR to afford the Ar−Pd^{II}−OR species **B'** and subsequently concerted σ-bond metathesis between Pd^{II}−OR bond and C(sp^3)–Si bond to reach intermediate **C** was also possible (Figure 5, Path B).

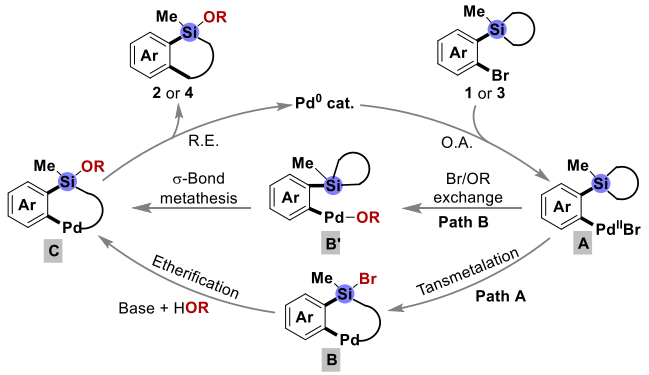


Figure 5. Proposed catalytic cycle.

In summary, we have described a mechanistically unique ring expansion process of 4− and 5−membered silacylces. With the aid of an alcohol, diversified 6−, 7− and 8−membered silacycles, along with wide range of functional group tolerance were synthesized. In fact, our study constitutes one of the most efficient and general route for preparing sila-tetralins & sila-(benzo)suberanes, which would trigger the development of new drug-like candidates due to the importance of the structural units of tetralins & benzosuberanes in medicinal chemistry and natural products.

Acknowledgements

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Keywords:

Organosilicon compounds • Silacycles • Ring expansion • Hiyama coupling • Strained ring

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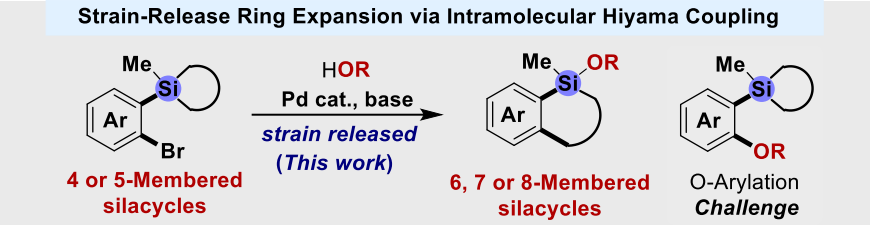

Ring Expansion via Hiyama-Denmark Coupling: Herein, the first intramolecular strain−release organosilicon-based cross-coupling proceeds smoothly by treatment of palladium catalyst, which constitutes the most efficient and general route for preparing diverse sila-tetralins & sila-(benzo)suberanes.

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