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Palladium-catalyzed synthesis of benzosilacyclobutenes *via* position-selective C(sp^3)–H arylation†

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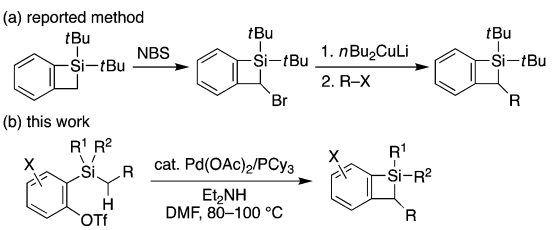
A palladium-catalyzed synthesis of benzosilacyclobutenes has been developed *via* position-selective C(sp^3)–H bond activation, including those having substituents at the methylene carbon on the 4-membered silacycle. The obtained products could be engaged in the palladium- or nickel-catalyzed ring-expansion reactions to give compounds possessing 6-membered silacycles.

4-Membered silacycles, silacyclobutanes and related compounds, belong to a synthetically useful class of compounds and a variety of transformations have been developed based on their ring strain and Lewis acidity.[1,2] Among them, arene-fused derivatives, benzosilacyclobutenes and their analogs, have been actively utilized as synthetic intermediates of more complex organosilanes,[3] but their available preparation methods are very limited. In fact, other than a recent report by Petit and coworkers where they utilized a niobium-catalyzed [2+2+2] cycloaddition,[4] most of the reported compounds are prepared from 2-bromobenzyl halides and dichlorosilanes using more than a stoichiometric amount of magnesium metal.[1,5] In addition, the synthesis of benzosilacyclobutenes having substituents at the methylene carbon on the 4-membered ring has been even less explored and essentially limited to bromination–metalation–nucleophilic substitution of pre-formed unsubstituted benzosilacyclobutenes (Scheme 1a).[5b,6]

As a new synthetic strategy of the 4-membered carbo- or heterocycles, the reactions involving a transition-metal-catalyzed intramolecular C–H bond activation can be a powerful alternative to the conventional approaches, and several effective methods have been reported to date for the synthesis of benzocyclobutenes and their analogs.[7,8] However, most of them rely on the activation of methyl C–H bonds, and only a few reports have been made on the 4-membered ring formations through the activation of methylene C–H bonds.[7d–f] In this context, herein we describe the development of a palladium-catalyzed 4-membered ring-forming intramolecular C(sp^3)–H bond arylation of 2-(alkylsilyl)aryl triflates,[8a–d] enabling the synthesis of substituted benzosilacyclobutenes at the methylene carbon of the silacycle (Scheme 1b).

Initially, we conducted a reaction of 2-naphthyl triflate **1a** having butyldicyclohexylsilyl group at 1-position in the presence of a catalytic amount of $Pd(OAc)_2/PPh_3$ with Et_2NH as the base in DMF at 80 °C. Under these conditions, desired naphthosilacyclobutene **2a** was obtained in a moderate yield of 40% along with some uncyclized butenyldicyclohexyl(1-naphthyl) silanes (Table 1, entry 1). The change of ligand to PCy_3 led to a significant improvement to give compound **2a** in 74% yield (entry 2), while the use of bulkier P(*t*Bu)$_3$ led to a decrease of the reaction efficiency (entry 3). On the other hand, no desired product **2a** was observed by using binap as the ligand (entry 4), and the ferrocene-based bisphosphine ligands such as dppf and dtbpf were found to be similarly ineffective as P(*t*Bu)$_3$ (entries 5 and 6).[9]

Under the conditions in Table 1, entry 2, several alkyl groups were installed at the alkyl carbon on the silacycle of compounds **2** by changing the R group of substrates **1** (Scheme 2). For example, in addition to propyl group, naphthosilacyclobutenes having isobutyl group or alkyl groups containing aryl, silyloxy,



Scheme 1 (a) Conventional and (b) new synthesis of benzosilacyclobutenes having substituents at the carbon on the 4-membered ring.

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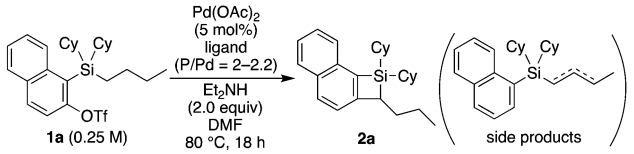
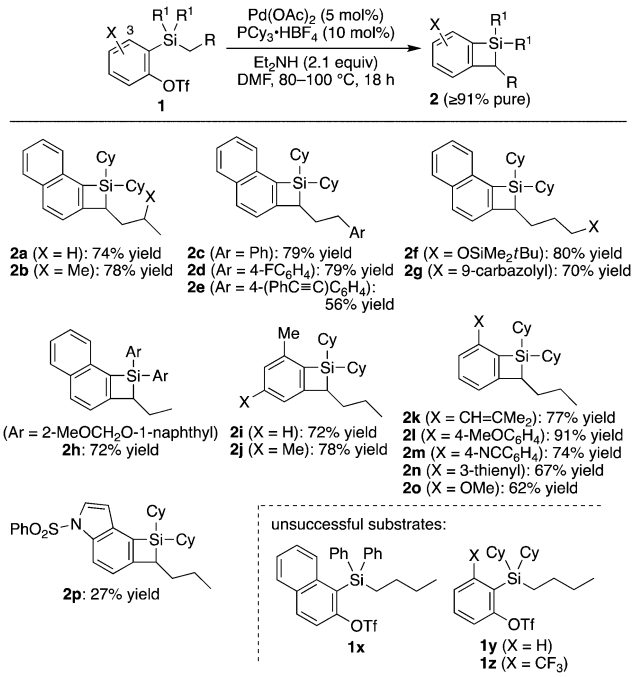
Table 1 Palladium-catalyzed reaction of **1a** to give **2a**: Ligand effect



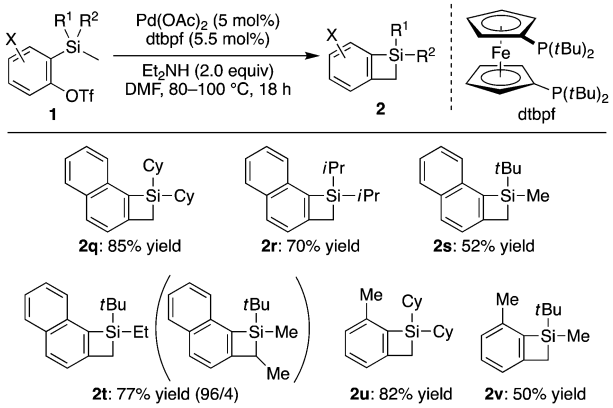
Entry	Ligand	Yield of **2a**[a] (%)	Yield of side products[a] (%)
1	PPh_3	40	8
2	**PCy_3**[b]	**74**	**2**
3	$P(tBu)_3$[b]	21	3
4	binap[c]	0	0
5	dppf[d]	27	2
6	dtbpf[e]	16	4

[a] Determined by ^1H NMR against internal standard. [b] $PR_3{\cdot}HBF_4/Et_2NH$ was used. [c] 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. [d] 1,1′-Bis(diphenylphosphino)ferrocene. [e] 1,1′-Bis(di-*tert*-butylphosphino)ferrocene.



Scheme 2 Palladium-catalyzed synthesis of **2** from **1** with R ≠ H.

and carbozolyl groups could be obtained in reasonably high yields (**2b–2g**). Regarding the 'spectator' groups on silicon, sterically demanding aryl groups could also be employed instead of cyclohexyl group as shown for the synthesis of compound **2h**, but simple phenyl group was more reactive toward C–H bond activation over an alkyl group for substrate **1x** to give the corresponding benzonaphthosilole preferentially instead of the desired naphthosilacyclobutene (data not shown).[10] In addition to naphthosilacyclobutenes, substituted benzosilacyclobutenes could also be synthesized by using phenyl triflate derivatives in the present catalysis. Thus, although 3-unsubstituted aryl triflates such as **1y** did not undergo this reaction, various 3-substituted substrates **1** could be employed to give corresponding benzosilacyclobutenes **2** in moderate to

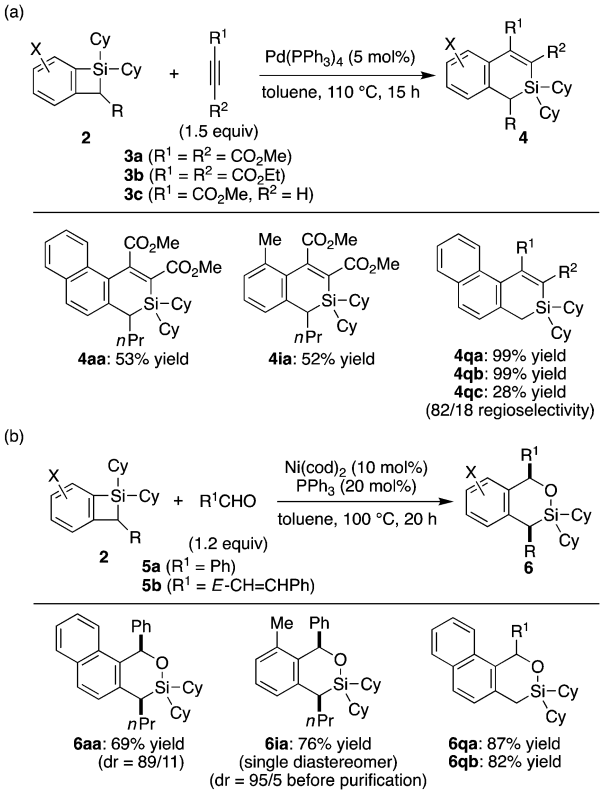


Scheme 3 Palladium-catalyzed synthesis of **2** from **1** with Si–Me.

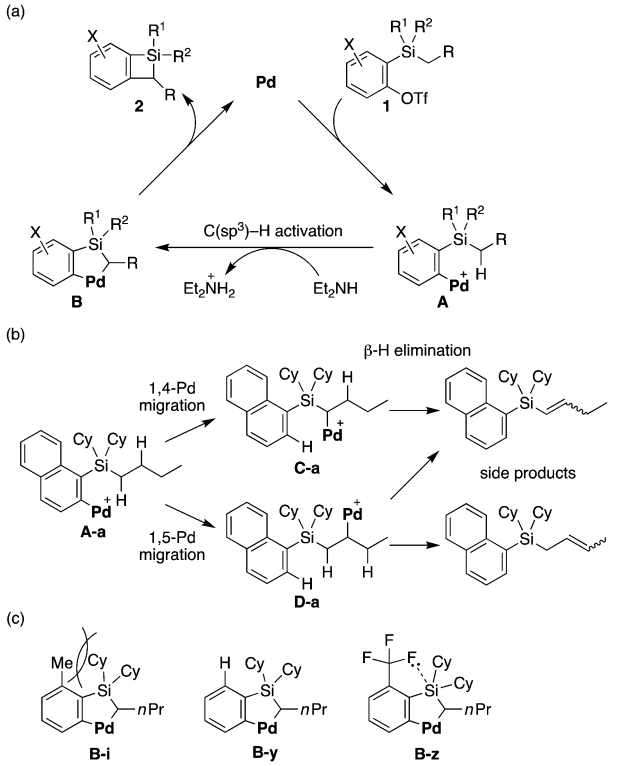
high yields (**2i–2o**). 4-Silyl-5-indolyl triflate **1p** could also be converted to product **2p** albeit with lower efficiency, but substrate **1z** having trifluoromethyl group at 3-position was not applicable. The structures of **2g** and **2p** were unambiguously confirmed by X-ray crystallographic analysis.[11]

The present catalysis was further extended to the synthesis of compounds **2** with no substituents at the carbon on the 4-membered ring by employing substrates having methyl group on silicon. Although the use of PCy_3 as the ligand gave almost no desired product **2q** for the reaction of 2-naphthyl triflate **1q** having dicyclohexyl(methyl)silyl group at 1-position, a high yield of 85% was realized by employing dtbpf, a ferrocene-based bulky bisphosphine ligand (Scheme 3). Under these conditions, the product yields were found to be higher for substrates having bulkier substituents on silicon, and a gradual decrease in the yield was observed by changing the substituents from dicyclohexyl (**2q**) to diisopropyl (**2r**) and to (*tert*-butyl) (methyl) (**2s**). It is worth noting that a C–H bond of methyl group was selectively activated over a methylene C–H bond or a methyl C–H bond of ethyl group on silicon as demonstrated for the synthesis of **2t**. In addition to naphthosilacyclobutenes, benzosilacyclobutenes **2u** and **2v** could also be synthesized with similar tendency.

With a series of naphtho- and benzosilacyclobutenes in hand, we briefly examined their reactivity by applying them to some reported transformations. For example, the reaction of naphthosilacyclobutene **2a** with dimethyl acetylenedicarboxylate (**3a**) in the presence of $Pd(PPh_3)_4$ (5 mol%) proceeded *via* selective C(aryl)–Si bond cleavage to give ring-expanded naphthosilacyclohexadiene **4aa** in 53% yield (Scheme 4a).[3b] A similar result was obtained with benzosilacyclobutene **2i** to give benzosilacyclohexadiene **4ia** in 52% yield. On the other hand, compound **2q** having no substituent at the alkyl carbon on the 4-membered ring showed a higher reactivity to give product **4qa** in a nearly quantitative yield. The reaction of **2q** with diethyl acetylenedicarboxylate (**3b**) also gave **4qb** in a high yield, but the use of methyl propiolate (**3c**) resulted in a lower yield of **4qc** as expected from the literature precedent.[3b] Furthermore, these could be employed in a nickel-catalyzed ring-expansion reaction with aldehydes as well.[3e,i] The reaction of **2a** or **2i** with



Scheme 4 Ring-expansion of **2** with (a) alkynes and (b) aldehydes.

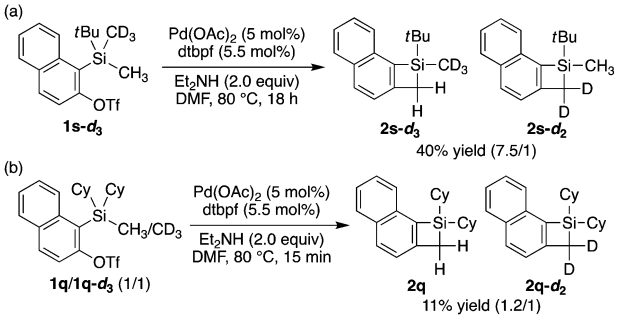


Scheme 5 (a) A proposed catalytic cycle for the synthesis of **2** from **1**, (b) proposed pathways toward alkene side products from **1a**, and (c) substituent effect on the formation and reactivity of intermediate **B**.

benzaldehyde (**5a**) proceeded with relatively high diastereoselectivity (89/11–95/5) to give corresponding dihydronaphtho- or dihydrobenzooxasiline **6aa** or **6ia** through the cleavage of a C(aryl)–Si bond (Scheme 4b). The relative configuration of the major diastereomer was determined to be *cis* by X-ray crystallographic analysis for both **6aa** and **6ia**.[11] A higher yield of 87% was achieved for the reaction of unsubstituted **2q** to give ring-expanded product **6qa**. *E*-Cinnamaldehyde (**5b**) could also be used for the reaction of **2q** to give compound **6qb** in 82% yield.

A proposed catalytic cycle of the present catalysis toward benzosilacyclobutenes is illustrated in Scheme 5a. Oxidative addition of aryl triflate of **1** to palladium(0) gives arylpalladium species **A**. This then undergoes C–H bond activation of the alkyl carbon adjacent to silicon to give 5-membered palladacycle **B**.[12] Carbon–carbon bond-forming reductive elimination leads to the formation of product **2** along with regeneration of palladium(0) species. As shown in Table 1, side products for the reaction of **1a** are butenyldicyclohexyl(1-naphthyl)silanes, and the formation of these compounds can be explained by the pathways shown in Scheme 5b. Instead of reductive elimination from intermediate **B**, 1,4- or 1,5-palladium migration from **A-a** gives alkylpalladium species **C-a** or **D-a**,[13] and subsequent β-hydrogen elimination would lead to the observed side products.

To gain insights into the reaction mechanism of the present catalysis, we conducted some control experiments. When the reaction of **1s-d$_3$** having *tert*-butyl(methyl)(methyl-d_3)silyl group was conducted under the conditions in Scheme 3, C–H bond activated product **2s-d$_3$** and C–D bond activated product **2s-d$_2$** were obtained in the ratio of 7.5/1 (Scheme 6a). We also carried out a competition between **1q** and **1q-d$_3$** to determine their relative reactivity, and found that C–H bond activated product **2q** and C–D bond activated product **2q-d$_2$** were obtained in the ratio of 1.2/1 at an early stage of the reaction (Scheme 6b). These results indicate that the C–H(D) bond activation step (**A** → **B** in Scheme 5a) is not the turnover-limiting step and occurs after the irreversible oxidative addition step.[14] Although we have not been able to determine the turnover-limiting step by kinetic experiments due to the existence of an induction period at the beginning of the reaction, 4-membered ring-forming reductive elimination step could be the turnover-limiting step, considering that this step generates a significant



Scheme 6 (a) Intramolecular and (b) intermolecular KIE experiments.

ring strain.[7d,f] It is also worth noting that the substituent effects observed in Scheme 2 could be explained by the difficulty of the 4-membered ring formation. As illustrated in Scheme 5c, the methyl group at 3-position of **1i** would facilitate the reductive elimination from intermediate **B-i** to reduce the steric repulsion between the methyl group and the silyl group. On the other hand, 3-unsubstituted **1y** does not have this effect in intermediate **B-y**. Along this line, the lack of reactivity of **1z** having trifluoromethyl group at 3-position might be due to the favorable interaction between the fluorine atoms and the silicon atom, which could retard the formation and/or subsequent reductive elimination of palladacycle **B-z**. Furthermore, the decrease of the product yield by reducing the steric bulk of the silicon substituents in Scheme 3 is also consistent with these explanations.

In summary, we developed a palladium-catalyzed synthesis of benzosilacyclobutenes from 2-(alkylsilyl)aryl triflates *via* position-selective C(sp^3)–H bond activation. Although the applicable substrates need to meet the steric requirement, various benzosilacyclobutenes could be synthesized including those substituted at the methylene carbon on the 4-membered silacycle. The obtained products could be employed in the palladium- or nickel-catalyzed ring-expansion reactions to give benzosilacyclohexadienes or dihydrobenzooxasilines possessing 6-membered silacycles. Future studies will be directed toward further expansion of this process for the synthesis of various functional organosilicon compounds.

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Conflicts of interest

There are no conflicts to declare.

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