

# Palladium-Catalyzed (4 + 4) Annulation of Silacyclobutanes and 2-lodobiarenes to Eight-Membered Silacycles via C–H and C–Si Bond Activation

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**S** ilicon is the second most abundant element in the Earth's crust.<sup>1</sup> Compared with carbon, the silicon atom has a larger covalent radius, less electronegativity, and extra 3d orbitals. These distinct properties make organosilicon compounds widely applicable in organic synthesis,<sup>2</sup> pharmaceuticals,<sup>3</sup> agrochemistry,<sup>4</sup> and material sciences.<sup>5</sup> Notably, the intriguing strategy of sila-substitution in medicinal chemistry to replace the parent carbon is continuously developing to seek less toxic, more stable, and lipophilic drugs.<sup>6</sup>

Because of the high ring strain and Lewis acidity of the silicon, silacyclobutanes as synthons to access organosilicon compounds have been extensively studied in the past few decades.<sup>8</sup> The tendency of releasing the strain energy makes the silacyclobutanes (siletanes) applicable to annulations via transition-metal catalysis (Scheme 1a). Major efforts have been spent on the development of (4 + 2) annulation reactions between alkynes and silacyclobutanes (Scheme 1b),<sup>9a-i</sup> since the seminal example reported by Sakurai and Imai in 1975.<sup>9a</sup> Recently, an enantioselective annulation with cyclopropenes was achieved by the Xu group.<sup>9j</sup> Using cyclopropylideneacetates and cyclopropenones as the annulation partners, (4 + 3)annulations with silacyclobutanes were successfully realized by the groups of Saito<sup>10a</sup> and Zhao,<sup>10b</sup> respectively (Scheme 1c). Direct aromatic C-H activation/silvlation of silacyclobutanes catalyzed by rhodium for the synthesis of siloles was also established by the He group (Scheme 1d).<sup>11</sup>

Despite the growing utility of silacyclobutanes as highly enabling reagents to access silacycles, their application in the construction of eight-membered silacycles is underdeveloped due to the kinetic and thermodynamic penalties during ring formation processes.<sup>12</sup> Additionally, dimerization of silacyclobutanes under transition-metal catalysis would also be problematic.<sup>13</sup> Hence, the development of efficient synthetic methods of eight-membered silacycles from readily available materials is highly appealing. Notably, the Oshima group utilized the oxygen affinity of silicon to realize palladiumcatalyzed (4 + 4) annulation of silacyclobutanes with enones leading to eight-membered cyclic silyl enolates (Scheme 1e).<sup>14a</sup> Formal annulations upon cleavage and exchange of C-C and C-Si  $\sigma$ -bonds were remarkably demonstrated by Murakami et al.<sup>14b,c</sup> In 2018, an inspirational report by Zhang and co-workers<sup>15a</sup> detailed a palladium-catalyzed disilylation of iodobiarenes through a five-membered palladacycle I, which formed by oxidative addition of aryl halides and subsequent activation of the neighboring C–H bond (Scheme 1f). On the basis of this finding and the studies toward the reactivity of palladacycle I in the literature,<sup>15b-d</sup> we envisaged that such palladium species would undergo a formal (4 + 4) annulation through ring-opening/cross coupling with silacyclobutanes. Herein, we report a palladium-catalyzed annulation of 2-halo biarenes and silacyclobutanes to directly assemble eightmembered silacycles (Scheme 1g). In comparison with the strained small rings (e.g., cyclobutanones, cyclopropenones) employed previously, biaryl halides used as an annulation partner are conveniently accessible.

Initially, 4,4'-difluoro-2-iodo-1,1'-biphenyl 1a and 1,1diphenylsiletane 2a were selected as model substrates for condition optimization (see Tables S1–S5 in Supporting Information for details). The reaction in DMF with  $Pd(OAc)_2$ 

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12<sup>d</sup>

DMF

KOAc

1:1.2



# Scheme 1. (a-g) Works on Annulation of Silacyclobutanes

(5 mol %) and  $K_2CO_3$  (2 equiv) at 100 °C provided the desired product 3a in 34% yield (entry 1, Table 1). The use of aprotic polar solvents (entries 1-2, Table 1) is crucial for the reaction, and poor reactivity was observed in nonpolar solvents such as toluene and THF (entries 3-4). The screening of bases identified that KOAc significantly improved the yield (entries 5-7), possibly because of its vital role in the process of concerted metalation deprotonation (CMD).<sup>16</sup> When we modified the molar ratio of 1a versus 2a as 1:1.2, the yield was slightly increased to 74% (entry 9). Raising the temperature to 120 °C also improved the yield (entry 10). Replacement of  $Pd(OAc)_2$  with other palladium sources resulted in lower reactivity (entry 11 and Table S5). To our delight, the yield (78%) was maintained by lowering  $Pd(OAc)_2$  loading from 5 mol % to 2.5 mol % (entries 10 vs 12). Therefore, the optimal conditions were identified: using 2.5 mol % of  $Pd(OAc)_2$  as the catalyst, KOAc as the base, and DMF as the solvent to perform the reaction at 120 °C.

With the optimized conditions in hand, we next investigated the scope of substrates (Table 2). The reactions with chloroand trifluoromethyl substituted 2-iodobiaryl substrates delivered the corresponding products 3b and 3c in excellent yields. Meanwhile, biaryl substrates with electron-neutral and electron-rich substituents gave the corresponding silacycles (3d-3f) in 71–94% yields. In addition, the annulation of 3',5dimethyl-substituted 2-iodobiphenyl 1g delivered product 3g in 90% yield. However, 2',6-dimethyl-substituted substrate 1h failed to give any desired product under the standard conditions, probably because the formation of the correspond-

/acscatalysis						Letter
Table 1. Optimization of Reaction Conditions						
F F	., + □	ີ <sup>∙Si</sup> ∼Ph − Ph	Pd(OA base (2 temp	Ac) <sub>2</sub> (5 mol %) equiv), solvent erature, 12 h		+ + F
1a		2a			3a	4
entry <sup>a</sup>	solvent	base	1a : 2a	temperature (°C)	yield of <b>3a</b> (%) <sup>b</sup>	yield of <b>4</b> (%) <sup>b</sup>
1	DMF	K <sub>2</sub> CO <sub>3</sub>	1 : 1.5	100	34	29
2	DMA	$K_2CO_3$	1 : 1.5	100	9	16
3	toluene	K <sub>2</sub> CO <sub>3</sub>	1 : 1.5	100	N.D.	8
4	THF	K <sub>2</sub> CO <sub>3</sub>	1 : 1.5	100	N.D.	28
5	DMF	K <sub>3</sub> PO <sub>4</sub>	1 : 1.5	100	9	9
6	DMF	KOAc	1 : 1.5	100	64 (60)	12
7	DMF	CsOAc	1 : 1.5	100	17	32
8	DMF	KOAc	1:1	100	52	8
9	DMF	KOAc	1 : 1.2	100	74 (74)	4
10	DMF	KOAc	1 : 1.2	120	82 (80)	5
11°	DMF	KOAc	1 : 1.2	120	56	11

<sup>a</sup>Reactions conducted with 0.1 mmol of 1a, 0.12–0.15 mmol of 2a in 1 mL of solvent for 12 h. <sup>b</sup>Determined by <sup>19</sup>F NMR of the crude product using 2-fluoropyridine as an internal standard and isolated yield included in the parentheses. <sup>c</sup>With CpPd( $\pi$ -allyl) as the catalyst. <sup>'d</sup>With 2.5 mol % Pd(OAc)<sub>2</sub>. N.D. = not detected. Blue text indicates optimal conditions.

120

80 (78)

ing five-membered palladacycle species is conformationally unfavorable. Next, the silacyclobutanes with different substituents were elucidated. The biaryl (2b, 2c)-substituted silacyclobutanes were found to be appropriate substrates and delivered the corresponding products (3i, 3j) in 87% and 81% yields, respectively. The reactions of the dialkyl (2d, 2e)substituted silacyclobutanes gave products 3k and 3l in moderate yields. In comparison, the reactions with 1,1dialkvlsilacyclobutane showed lower yields than that with 1,1-diarylsilacyclobutane, and deiodination of the biarene substrate was observed. The annulation of 4,4'-dicarboxylatesubstituted 2-iodobiphenyl 1i and silacyclobutane 2c resulted in the formation of product (3m) in 83% yield. Silacyclobutane 2f bearing two different exocyclic substituents was also feasible to the reaction, albeit poor diastereoselectivity was observed (3n, 78% yield, 1.2:1 dr). It should be mentioned that the annulation of 1a with 1,1-dimethylsilolane under the standard conditions failed to deliver the desired nine-membered silacycle. Instead, dimerization and deiodination of 1a were obtained (see Scheme S1 in Supporting Information for details). Notably, the reaction on a 3.5 mmol scale provided 1.09 g of the desired product 3a in 76% yield, which highlighted the robustness of this chemistry.

Next, the regioselectivity of the reaction using unsymmetric substrates was explored (Table 3). Interestingly, substrate 1j, with an electron-withdrawing (3'-CO2Me) substituent provided silacycle 30 (58%) in high regioselectivity together with **3p** (3%) as a minor product. An electron-donating group, 3'-OMe-substituted substrate (1k) was converted into the annulation products with silacycle 3r as the major one (3q/

### Table 2. Substrate Scope<sup>a</sup>



<sup>*a*</sup>Reactions conducted with 0.1 mmol of 1, 0.12 mmol of 2, 2.5 mol % of  $Pd(OAc)_2$  and 0.2 mmol of KOAc in 1 mL of DMF for 12 h at 120 °C. <sup>*b*</sup>0.2 mmol scale. <sup>*c*</sup>With 45% of starting material 1h and 45% of deiodination product isolated (see Scheme S1 in Supporting Information).

3r = 1:4.7). Moreover, the reaction with 11 bearing a 3'-Me substituent gave a mixture of products 3s and 3t in 86% total yield with the formation of 3t slightly favored (3s/3t = 1:1.3). Finally, the compatibility of the reaction to heteroaryl substrates was evaluated. Both pyrrole- and thiophene-substituted aryl iodides (1m and 1n) were feasible substrates delivering the products in good yields, and a C2'- and C4'-silylation mixture were obtained for the reaction with 1n.

Table 3. Selectivity of Unsymmetric Substrates<sup>4</sup>



<sup>*a*</sup>Reactions conducted with 0.2 mmol of 1, 0.24 mmol of 2a, 2.5 mol % of Pd(OAc)<sub>2</sub>, and 0.4 mmol of KOAc in 2 mL of DMF for 12 h at 120 °C. <sup>*b*</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture.

According to the above results, it is concluded that the annulation process tends to form silacycles with silicon attached on the electron-rich aromatics. This regioselective trend is in consistent with previous report.<sup>10,14b,c</sup>

A series of experiments were carried out to get insights into the mechanism of this unprecedented reaction. Subjecting 4ester-substituted biphenyl iodide 10 to the reaction conditions offered similar results with 1j (Table 3) in terms of yields and regioselectivities (Scheme 2a), which suggests the involvement of a common five-membered palladacycle I. To further confirm this, a bipyridine-coordinated palladacycle 5 was prepared according to the literature.<sup>17</sup> A stoichiometric reaction of complex 5 and silacyclobutane 2a delivered the corresponding product 3e in 86% yield (Scheme 2b). With the palladacycle 5 as a catalyst (2.5 mol %), the reaction of 2-iodobiphenyl 1e and silacyclobutane 2a generated eight-membered silacycles 3e in 71% yield (Scheme 2c). These results provided convincing evidence of the palladacycle intermediacy. Previously mechanistic studies toward a related chemistry, namely, palladiumcatalyzed annulation of 2-iodobiphenyls and CH<sub>2</sub>Br<sub>2</sub> for the



### Scheme 2. (a-d) Mechanistic Investigations

synthesis of fluorenes, by Zhang et al.<sup>15d</sup> revealed that the ratedetermining step is the oxidative addition of 2-iodobiphenyl with Pd(0) to generate Pd(II) species. They also found that the second slowest step is the concerted metalation deprotonation (CMD) to form the five-membered palladacycle I as evidenced by an intramolecular competition experiment. Accordingly, an intramolecular competition reaction with a 2'deuterated substrate (1e-*d*) was carried out (Scheme 2d), and a similar kinetic isotope effect was observed.

On the basis of above investigation and previous reports,<sup>15,18</sup> a plausible mechanism is depicted in Scheme 3. Oxidative addition of 2-iodobiphenyl 1 and Pd<sup>(0)</sup> generates Pd<sup>(II)</sup> species II. Subsequently, five-membered palladacycle I is formed via a concerted metalation deprotonation (CMD) mechanism.<sup>17b</sup> Then, oxidative insertion of palladacycle I into silacyclobutane 2 delivers spiro Pd<sup>(IV)</sup> species III. Upon the reductive elimination sequence of the Pd-Si bond and Pd-C bond, two possible nine-membered palladacycles IV and IV' are formed correspondingly. Because of the formation of the C-Si bond can significantly relieve the steric congestion of the palladium center, the corresponding reductive elimination to IV is likely favorable.<sup>18c</sup> Finally, the eight-membered silacycle 3 is produced through reductive elimination of IV or IV' with the release of  $Pd^{(0)}$  to continue the catalytic cycle. However, a direct  $\sigma$ -bond metathesis between silacyclobutane 2 and palladacycle I cannot be excluded at this stage (path 2).<sup>15b</sup>

In conclusion, we have developed an efficient approach for the synthesis of eight-membered silacycles from 2-iodobiaryls and silacyclobutanes. With 2.5 mol % of  $Pd(OAc)_2$  as the catalyst, the reaction performed smoothly in good yields. Mechanistic investigations indicate the involvement of a fivemembered palladacycle species. This methodology offers new insights into silacyclobutanes transformation and provides a

# Scheme 3. Proposed Mechanism



straightforward approach to medium-sized silacycles from readily available starting materials.

### ASSOCIATED CONTENT

# **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c00975.

Experimental details, characterization, and spectra of new compounds (PDF)

# Crystallographic data of 3o (CCDC 2018282) (CIF)

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#### Notes

The authors declare no competing financial interest.

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