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Catalytic Generation of Rhodium Silylenoid for Alkene−Alkyne−Silylene [2 + 2 + 1] Cycloaddition

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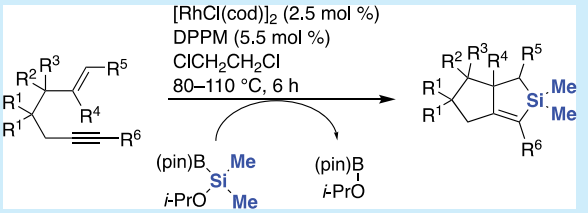
Supporting Information

ABSTRACT: An alkene−alkyne−silylene [2 + 2 + 1] cycloaddition takes place in the rhodium-catalyzed reaction of 1,6-enynes with borylsilanes bearing an alkoxy group on the silicon atoms, which react as synthetic equivalents of silylene. The reaction proceeds efficiently in 1,2-dichloroethane at 80−110 °C in the presence of a rhodium catalyst bearing bis(diphenylphosphino)methane (DPPM) as a ligand to afford 1-silacyclopent-2-enes in good to high yields.



Bioisosterism utilizing silicon, a technique used for improving the medicinal effects of bioactive organic compounds by replacing the functional group with a silicon-containing group, has received increasing attention in the drug discovery field.[1,2] Of particular interest in the screening of silicon-based bioisosteres is silicon-containing carbo- and heterocyclic skeletons. Examples of the skeletons that have been investigated in drug discovery are shown in Figure 1. 4-

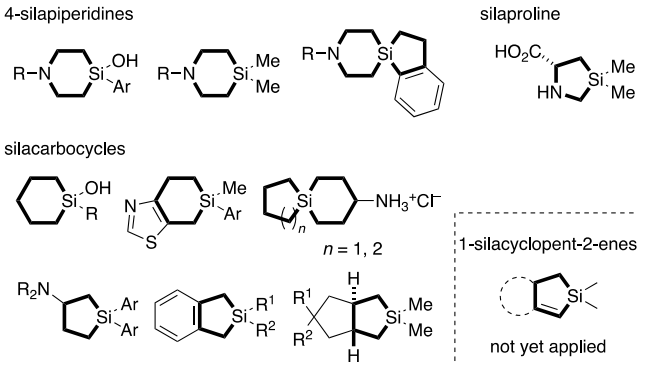


Figure 1. Examples of silicon-containing cyclic skeletons investigated in drug discovery.

Silapiperidines have been examined as bioisosteres of the piperidine and morpholine moieties in haloperidol, loperamide, and other compounds.[3] Silaproline has been studied as a surrogate of proline in the development of bioactive peptides.[4] Silacarbocycles have been tested as analogues of the parent carbocyclic compounds such as venlafaxine and atipamezole.[5] These examples suggest that a variety of silicon-containing cyclic skeletons may contribute to improving the medicinal effects of bioactive compounds. Hence, the development of efficient methods to construct untouched silicon-containing cyclic skeletons, including 1-silacyclopent-2-enes (Figure 1), is highly attractive and could accelerate the development of silicon-containing drugs.

Transition-metal-catalyzed [2 + 2 + 1] cycloaddition involving silylene as the one-atom-component is an attractive method for the construction of silicon-containing five-membered rings. Alkyne−alkyne−silylene [2 + 2 + 1] cycloaddition is well established as an efficient route to silacyclopentadienes (siloles).[6] However, to date, limited success has been achieved with alkene−alkyne−silylene [2 + 2 + 1] cycloaddition to afford 1-silacyclopent-2-enes.[7−9] This is in sharp contrast to the great success of the analogous three-component cyclization, the Pauson−Khand reaction.[10]

We have reported on palladium-catalyzed alkyne−alkyne−silylene [2 + 2 + 1] cycloaddition to afford silacyclopentadienes, where borylsilanes bearing a dialkylamino group on the silicon atoms react as the synthetic equivalent of silylenes.[11a] This palladium catalyst system was applied to 1,3-diene−silylene [4 + 1] cycloaddition[11b] and 2-alkenylindole−silylene [4 + 1] cycloaddition.[11c] However, all our attempts at achieving alkene−alkyne−silylene [2 + 2 + 1] cycloaddition on the basis of palladium catalysis failed. We therefore changed our strategy to the use of other transition metal catalysts. Here, we describe a rhodium-catalyzed alkene−alkyne−silylene [2 + 2 + 1] cycloaddition. The new rhodium catalysis using a borylsilane is applicable to the conversion of a wide range of 1,6- and 1,7-enynes to bicyclic 1-silacyclopent-2-enes.[7,8]

Diethyl malonate-derived 1,6-enyne **1a** was reacted with (pin)B−Si(NEt_2)Me_2 (**2**, 1.0 equiv)[12] in 1,2-dichloroethane at 80 °C in the presence of $[RhCl(cod)]_2$ (2.5 mol %) and a phosphorus ligand (5.5 mol %) (Table 1). When the reaction was carried out with DPPB as a ligand, 1-silacyclopent-2-ene **4a** and aminoboronate **5** were formed, albeit in low yields (5% and 20% yields, respectively), indicating that a rhodium catalyst could promote the [2 + 2 + 1] cycloaddition of **4a** with silylene formed from **2** (entry 1). It is interesting to note that the catalyst efficiency was significantly improved by the use of

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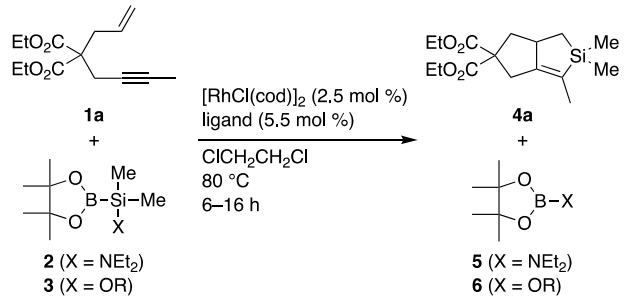
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Reaction Conditions[a]



entry	borylsilane	ligand	time (h)	yield (%) 4a[b]	yield (%) 5 or 6[c]
1	**2** (X = NEt_2)	DPPB[d]	16	5	20 (**5**)
2	**2**	DPPP[e]	16	48	86 (**5**)
3	**2**	DPPE[f]	16	38	89 (**5**)
4	**2**	DPPM[g]	16	82	>99 (**5**)
5	**2**	$PMePh_2$[h]	16	11	22 (**5**)
6	**2**	–	16	10	33 (**5**)
7	**3a** (X = OMe)	DPPM	6	79	86 (**6a**)
8	**3b** (X = OEt)	DPPM	6	80	97 (**6b**)
9	**3c** (X = O*i*-Pr)	DPPM	6	83 (83)[i]	94 (**6c**)
10	**3d** (X = O*t*-Bu)	DPPM	6	83	91 (**6d**)

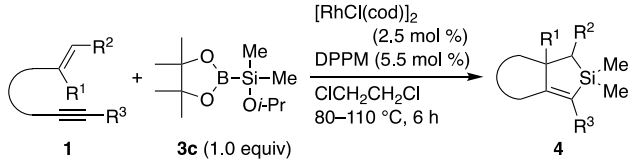
[a]**1a** (0.10 mmol), **2** (0.10 mmol), $[RhCl(cod)]_2$ (2.5 mol %), ligand (5.5 mol %), and $ClCH_2CH_2Cl$ (0.1 mL) were stirred at 80 °C for 6 h. [b]Determined by GC. [c]Determined by ^1H NMR. [d]$Ph_2P(CH_2)_4PPh_2$. [e]$Ph_2P(CH_2)_3PPh_2$. [f]$Ph_2P(CH_2)_2PPh_2$. [g]$Ph_2PCH_2PPh_2$. [h]10 mol %. [i]Isolated yield in the 0.30 mmol scale reaction.

bidentate phosphines with smaller bite angles (entries 2–4). In the reaction with DPPP or DPPE, **5** was formed in high yields (86–89%) and the yields of **4a** were improved to 38–48% (entries 2 and 3). A rhodium catalyst bearing DPPM showed the highest catalyst efficiency: **2** was fully converted to **5** and the reaction afforded **4a** in 82% yield (entry 4). The reaction with $PMePh_2$, or in the absence of phosphorus ligand, resulted in low catalyst efficiency (entries 5 and 6), indicating that bidentate coordination of DPPM is essential for high catalyst efficiency. As mentioned above, the Pd/$PMePh_2$ catalyst system that we reported previously[11] was not effective and no formation of **4a** took place.

It is interesting to note that the Rh/DPPM-catalyzed [2 + 2 + 1] cycloaddition of **1a** took place efficiently with alkoxy-substituted (pin)B–Si(OR)Me_2 (**3**),[12] which to date have not been used as silylene sources under the conditions for the palladium-catalyzed reaction.[11] **3a** (R = Me), **3b** (R = Et), **3c** (R = *i*-Pr), and **3d** (R = *t*-Bu) showed comparable reactivity. Reactions afforded **4a** in 79–83% yields and alkoxyboranes **6a–d** were formed (entries 7–10). Since the reactions of **3** were faster than **2** (see Supporting Information for detailed comparison), we determined **3c** to be the preferred silylene source in the reaction of **1**.

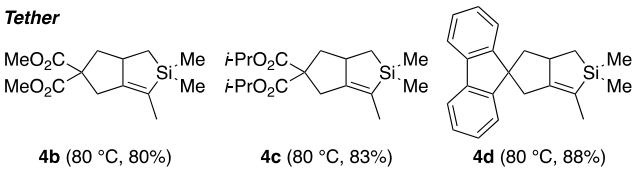
The Rh/DPPM-catalyzed [2 + 2 + 1] cycloaddition using **3c** as a silylene source was subjected to various enynes (Scheme 1). Dimethyl and diisopropyl malonate derivatives **1b** and **1c** reacted efficiently at 80 °C to afford the corresponding 1-silacyclopent-2-enes **4b** and **4c** in 80% and 83% yields, respectively. Highly efficient ring formation took place to afford **4d** in the reaction of 9*H*-fluorene-derived **1d**, probably due to the rigid fluorene backbone. Pentane-2,4-dione derivative **1e** afforded **4e** in 80% yield, where the electrophilic carbonyl and the acidic α-hydrogen of the methyl ketone did

Scheme 1. Synthesis of 1-Silacyclopent-2-enes through Rhodium-Catalyzed [2 + 2 + 1] Cycloaddition[a]

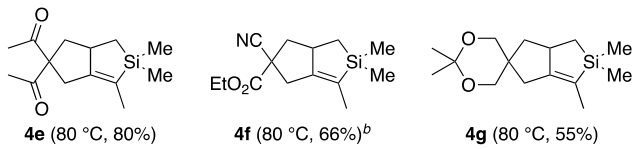


product (temp, isolated yield)

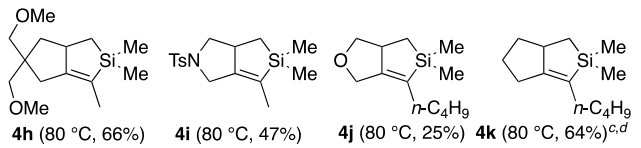
Tether



4b (80 °C, 80%) **4c** (80 °C, 83%) **4d** (80 °C, 88%)

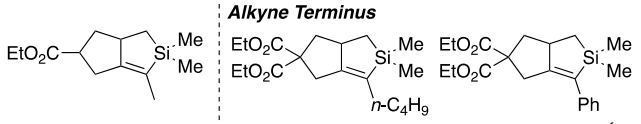


4e (80 °C, 80%) **4f** (80 °C, 66%)[b] **4g** (80 °C, 55%)

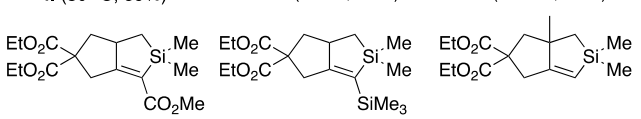


4h (80 °C, 66%) **4i** (80 °C, 47%) **4j** (80 °C, 25%) **4k** (80 °C, 64%)[c,d]

Alkyne Terminus

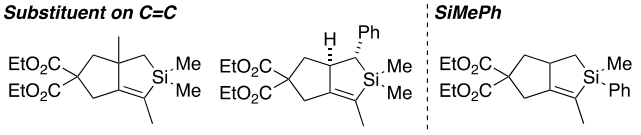


4l (80 °C, 59%)[e] **4m** (80 °C, 80%) **4n** (110 °C, 78%)[f]



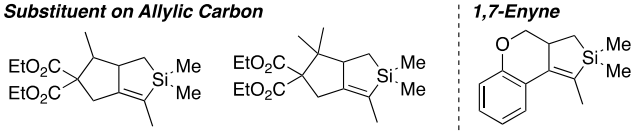
4o (110 °C, 62%)[c] **4p** (110 °C, 45%)[g] **4q** (110 °C, 54%)[c,h]

Substituent on C=C



4r (110 °C, 59%)[g] **4s** (110 °C, 68%)[g] **4t** (80 °C, 43%)[c,i,j]

Substituent on Allylic Carbon



4u (110 °C, 57%)[k] **4v** (110 °C, 74%) **4w** (80 °C, 42%)

SiMePh

1,7-Enyne

[a]**1** (0.30 mmol), **3c** (0.30 mmol), $[RhCl(cod)]_2$ (2.5 mol %), ligand (5.5 mol %), and $ClCH_2CH_2Cl$ (0.3 mL) were stirred at 80 or 110 °C for 6 h. [b]dr 1.5:1. [c]Reaction was carried out for 12 h. [d]Obtained as a mixture with a structural isomer (3%). [e]dr 2:1. [f]**3c** (1.2 equiv) was used. [g]Reaction was carried out for 18 h with **3c** (1.2 equiv). [h]DPPP was used instead of DPPM. [i](pin)B–Si(NEt_2)MePh (**7**) was used instead of **3c**. [j]dr 2.4:1. [k]dr 1:1.

not affect the reaction. Cyano and acetal groups were tolerated, and **4f** and **4g** were obtained by the [2 + 2 + 1] cycloaddition. Substrates having more flexible tether moieties were also acceptable: **1i**, **1k**, and **1l** afforded the corresponding products **4i**, **4k**, and **4l** in 47–64% yields.[13] Although allyl propargyl ether **1j** was consumed prior to **3c**, and therefore the yield was low, **4j** was also synthesized.

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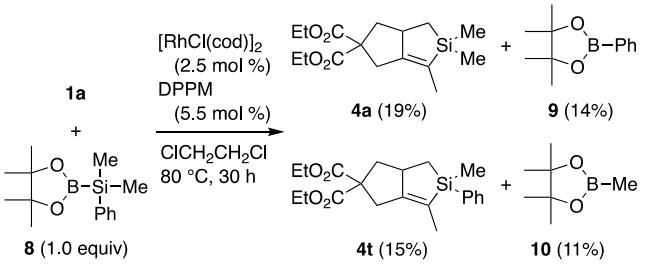
Org. Lett. XXXX, XXX, XXX–XXX

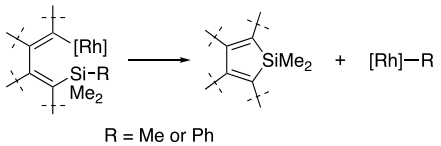
Substrate **1m** bearing a *n*-butyl group on the alkyne terminus underwent the [2 + 2 + 1] cycloaddition at 80 °C to afford **4m** in 80% yield. On the other hand, elevation of the reaction temperature (110 °C) was required for the conversion of phenyl-, methoxycarbonyl-, and trimethylsilyl-substituted **1n–p** to **4n–p**. It should be noted that when DPPP was used as a ligand, terminal alkyne **1q** also underwent the [2 + 2 + 1] cycloaddition to afford **4q**. The [2 + 2 + 1] cycloaddition was applicable to 1,6-enynes **1r–s** bearing substituents on the double bond and **1u–v** bearing methyl groups on the allylic positions, to afford **4r–s** and **4u–v** in 57–74% yields.[14] In addition to dimethylsilylene, the methylphenylsilylene moiety was introduced to form **4t**, when the reaction was carried out with (pin)B–Si(NEt_2)MePh (**7**).[15] It should also be noted that 1,7-enyne **1w** also underwent the [2 + 2 + 1] cycloaddition to afford **4w**, albeit in moderate yield.

The reaction of **1a** with (pin)B–$SiMe_2$Ph (**8**) having no heteroatom functional group on the silicon atom provided mechanistic information (Scheme 2). In the presence of Rh/DPPM catalyst, **1a** underwent the [2 + 2 + 1] cycloaddition even with **8**, to afford **4a** and **4t** in 19% and 15% yields, respectively. The ring formation took place with release of phenyl or methyl groups through Si–C bond cleavage. Ph–B(pin) (**9**) and Me–B(pin) (**10**) were also formed and present in the reaction mixture. Some reports describe the rhodium-catalyzed formation of five-membered silacarbocycles through substitution of the methyl or phenyl groups on silicon,[6e,h,16,17] where an elementary step shown in Scheme 3 is suggested. The formation of **4a** and **4t** indicates the existence of this elementary step in the present rhodium-catalyzed [2 + 2 + 1] cycloaddition.

Scheme 2. A Mechanistic Investigation

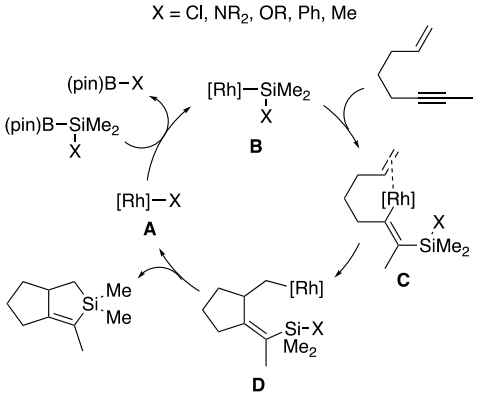


Scheme 3. An Elementary Step Suggested in the Literature for Rhodium-Mediated Cyclization through Substitution of the Methyl or Phenyl Groups on Silicon[6e,h,16]



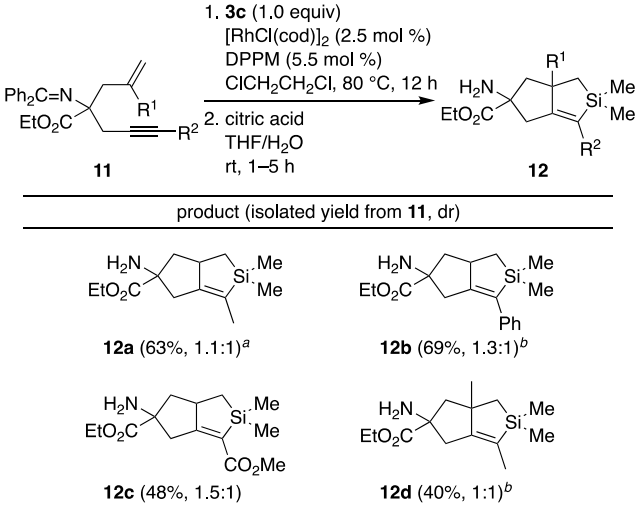
A proposed reaction mechanism is shown in Scheme 4. Transmetalation between [Rh]–X (**A**, X = Cl, NR_2, OR, Ph, or Me) and the borylsilane takes place to afford a rhodium silylenoid **B**.[18] Insertion of the C–C triple bond of 1,6-enyne into the Rh–Si bond of **B** proceeds in a regioselective manner to form alkenylrhodium **C**. Subsequent insertion of the C–C double bond into the Rh–C bond of **C** takes place to form alkylrhodium **D**. A silicon-containing five-membered ring is then formed through either nucleophilic substitution on the silicon center or σ-bond metathesis between Rh–C and Si–X bonds, accompanied by the reformation of **A**.

Scheme 4. Possible Mechanism



Silicon-containing amino acids have received much attention for their application in bioactive peptides.[2,4] The Rh/DPPM-catalyzed [2 + 2 + 1] cycloaddition was applied to the synthesis of a new class of silicon-containing amino acid derivatives (Scheme 5). The [2 + 2 + 1] cycloaddition of α-amino acid-derived 1,6-enynes **11a–d** with **3c** took place efficiently at 80–110 °C to afford the corresponding 1-silacyclopent-2-enes (dr ca. 1:1). The products were treated with aqueous citric acid in THF, and the aminoesters **12a–d** were obtained. The diastereomers of **12a** were separable by silica gel column chromatography; i.e., both diastereomers were readily accessible by the [2 + 2 + 1] cycloaddition. Because the starting compound **11** was readily prepared through two or three steps from *N*-(diphenylmethylene)-glycine ethyl ester, this method is practical for the synthesis of a variety of silicon-containing α-aminoesters.

Scheme 5. Application to Synthesis of Novel Silicon-Containing Amino Acid Derivatives



[a]The diastereomers were completely separable by silica gel column chromatography. [b]At 110 °C with **3c** (1.2 equiv) for the first step.

In conclusion, we established an efficient route to 1-silacyclopent-2-enes through Rh/DPPM-catalyzed alkene–alkyne–silylene [2 + 2 + 1] cycloaddition, where borylsilanes bearing an alkoxy group on the silicon atoms participated in

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the reaction as synthetic equivalents of silylene. A mechanism involving rhodium silylenoid is proposed based on the fact that the [2 + 2 + 1] cycloaddition proceeded even with the borylsilanes having no heteroatom functional group on the silicon atom.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00326.

Experimental procedures, characterization data of compounds, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX

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(14) An additional reaction example of a substrate derived from (*E*)-non-2-en-7-yne is described in the Supporting Information.

(15) **7** was prepared by the reaction of Li−Si(NEt_2)MePh with (pin)B−O*i*-Pr (see Supporting Information). Considering the ease of preparation, we used this amino(boryl)silane instead of the corresponding alkoxy(boryl)silane.

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Org. Lett. XXXX, XXX, XXX−XXX