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Palladium-Catalyzed Seven-Membered Silacycle Construction: 1,7-Enyne Hydroxycyclization To Give a Benzosilepine Skeleton

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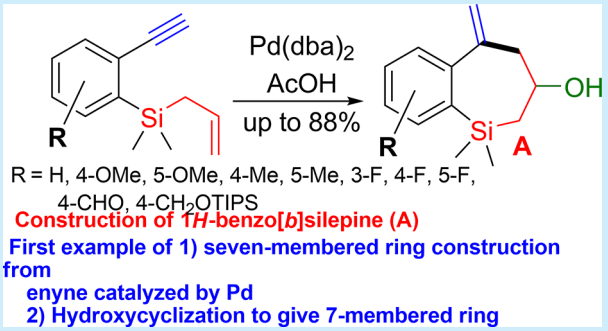
Supporting Information

ABSTRACT: A palladium-catalyzed hydroxycyclization reaction of 1,7-enynes to afford seven-membered silacycles (1*H*-benzo[*b*]-silepine skeletons) is developed. This is the first example of both seven-membered ring construction from enynes using a palladium catalyst and hydroxycyclization of enynes to give seven-membered silacycles.



Silicon is different from carbon in several crucial ways, including covalent radius and electronegativity. Therefore, silicon gives special reactivity to compounds through their beta effect, such as in Hosomi−Sakurai reactions.[1] Moreover, when a carbon atom is replaced with a silicon atom (a C−Si switch), the chemical and physicochemical properties of the organic compound are often dramatically changed.[2] The C−Si switch has been widely studied[3] since the pioneering work of Barcza on silasteroids,[4] with the strategy now applied intensively in the development of new pharmaceutical,[5] luminescent,[6] and odorant[7] compounds. Furthermore, completely new silicon-containing compounds, for which synthesis of the carbon analogues is difficult or impossible, are expected to have interesting properties. Therefore, investigation of the reactivity of silicon-containing compounds and the development of synthetic methods for silacyclic compounds remain important frontiers in synthetic chemistry.

Although a variety of methods have been developed for the preparation of five- or six-membered silacycles in the past decade, preparative methods for seven-membered silacycles remain relatively unexplored.

In the synthesis of seven-membered silacycles, formation of the C−Si bonds often relies on nucleophilic attack on a chlorosilane.[8] The construction of seven-membered silacycles by isomerization through [3.2.0] ring-opening using flash vacuum pyrolysis (FVP),[9] radical cyclization,[10] isomerization via silacyclobutane ring-opening,[11] olefin metathesis using Grubbs first catalyst,[12] and intramolecular hydrosilylation[13] has also been reported (see Supporting Information, Scheme S1). However, these conventional methods, except FVP, afford the corresponding seven-membered silacycles in low to moderate yields. Therefore, the functions and importance of seven-membered silacycles remain undefined[14] due to a lack of synthetic methodology, despite heteroatom-containing seven-membered rings, such as 1*H*-benzo[*b*]azepine, having important roles in medicinal chemistry.[15] Accordingly, the development of novel construction methods for seven-membered silacycles is demanded.

The transition metal-catalyzed cyclization of enynes is a powerful method for accessing cyclic structures from acyclic precursors with substantially less molecular complexity.[16] Consequently, there are several reports of the cyclization of 1,7-enynes to afford seven-membered rings, such as using Au as a π-acid catalyst[17] and via Mo-catalyzed enyne metathesis.[18] Other examples include an Ru-catalyzed 1,6-enyne cycloisomerization,[19] Pt-catalyzed 1,6-enyne cycloisomerization,[20] Au-catalyzed 1,8-enyne cycloisomerization,[21] and Rh-catalyzed allene−allene/allene−ene cycloisomerization.[22] However, seven-membered ring construction is difficult and remains unexplored because of ring strain in the product and metal-containing ring transition state. Moreover, hydroxycyclization, a cycloisomerization involving the introduction of a hydroxyl functional group, is less studied. Examples of the hydroxycyclization of 1,7-enynes to afford six-membered rings have been reported using Au(I)[23] and Hg(II)[24] as catalysts.

Herein, we report the hydroxycyclization of enyne compounds containing alkyne and allylsilane units, catalyzed by $Pd(dba)_2$ and AcOH, to afford seven-membered silacycles. The preparation of seven-membered cyclic compounds via Pd-catalyzed enyne cycloisomerization or hydroxycyclization have not been reported previously. This cyclization reaction can be performed with the introduction of a hydroxyl group at the 3-position in the silacycle products.

We prepared allyl(2-ethynylphenyl)dimethylsilane (**1a**) and subjected it to a variety of reaction conditions, including different

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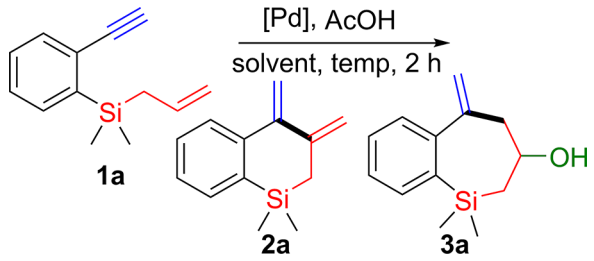
solvents and temperatures (Table 1). We treated **1a** with $Pd_2(dba)_3$ and AcOH, which are common cycloisomerization conditions, to afford both cycloisomerization product **2a** and hydroxycyclization product **3a** in 32% and 27% yields, respectively (run 1). When the amount of AcOH was increased, the yield of **3a** was increased to 51% (run 2). When the reaction mixture was diluted to 0.01 M solution, 62% of **3a** was obtained (run 3). However, when phosphine ligand was used, hydroxycyclization product **3a** was not obtained, and cycloisomerization product **2a** was afforded in 24% or 72% yields, respectively (runs 4 and 5). We changed the palladium catalyst to $Pd(dba)_2$ from $Pd_2(dba)_3$,[25] and solvent screening was performed (runs 6–9). Low polarity solvents, such as toluene and heptane, gave good results. The yield was increased when we added molecular sieves 3A[26] to the reaction system and ran the reaction at 95 °C (runs 10 and 11). When the amount of $Pd(dba)_2$ catalyst was reduced, the yield of **3a** slightly increased (runs 12 and 13). In contrast, when the amount of AcOH was reduced, the yield of **3a** decreased (runs 14–16).

Table 1. Optimization of Hydroxycyclization of 1a to 3a



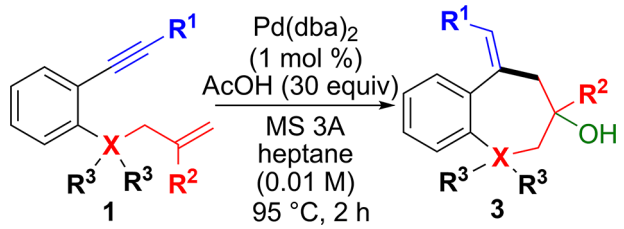
run	[Pd] (mol %)	AcOH (equiv)	solvent (mol/L)	temp (°C)	yields[d] (%) 1a[e]	2a	3a
1	$Pd_2(dba)_3$ (5)	2	PhMe (0.05)	60	0	32	27
2	$Pd_2(dba)_3$ (5)	30	PhMe (0.05)	60	0	16	51
3	$Pd_2(dba)_3$ (5)	30	PhMe (0.01)	60	0	20	62
4[a]	$Pd_2(dba)_3$ (5)	30	PhMe (0.01)	60	48	24	0
5[b]	$Pd_2(dba)_3$ (5)	30	PhMe (0.01)	60	0	72	0
6	$Pd(dba)_2$ (10)	30	PhMe (0.01)	60	0	11	67
7	$Pd(dba)_2$ (10)	30	AcOEt (0.01)	60	60	trace	16
8	$Pd(dba)_2$ (10)	30	THF (0.01)	60	82	trace	trace
9	$Pd(dba)_2$ (10)	30	nC_7H_{16} (0.01)	60	0	8	77
10	$Pd(dba)_2$ (10)	30	nC_7H_{16} (0.01)	95	0	8	77
11[c]	$Pd(dba)_2$ (10)	30	nC_7H_{16} (0.01)	95	0	9	83
12[c]	$Pd(dba)_2$ (2)	30	nC_7H_{16} (0.01)	95	0	6	85
13[c]	$Pd(dba)_2$ (1)	30	nC_7H_{16} (0.01)	95	0	6	88
14[c]	$Pd(dba)_2$ (1)	10	nC_7H_{16} (0.01)	95	0	11	73
15[c]	$Pd(dba)_2$ (1)	2	nC_7H_{16} (0.01)	95	11	6	66
16[c]	$Pd(dba)_2$ (1)	1	nC_7H_{16} (0.01)	95	39	7	24

[a]Ph_3P (20 mol %) was added. [b]$(o\text{-tolyl})_3P$ (20 mol %) was added. [c]MS 3A was added. [d]Isolated yield. [e]Recovered **1a**.

We then tested other metal hydride catalysts,[27] namely, $RuHCl(CO)(PPh_3)_3$, $RuH_2(CO)(PPh_3)_3$, and Grubbs second catalyst-trimethyl(vinyloxy)silane,[28] instead of $Pd(dba)_2$-AcOH. However, these control experiments showed no conversion of **1a** to **2a** or **3a**. We also applied π-acid catalysts to this cyclization, including Au,[23,29] Hg,[24] Ru,[30] Pd,[31] and Pt,[32] but none afforded hydroxycyclization product **3a** (see Supprting Information, Table S1).

The effects of substituents on the alkyne and allyl silane moieties were then investigated. Methyl- or trimethylsilyl-substituted alkyne compounds **1b** and **1c** were converted to the corresponding hydroxycyclization products in trace yields or showed no reaction (Table 2). Carbon analogue **1d** and nitrogen analogue **1e** did not react under these conditions, probably due to the lack of the β-effect provided by the silicon atom in **1a** in this seven-membered ring cyclization. Using substrates **1f**, which have substituents on the allylsilane moiety, the expected hydroxycyclization compound was obtained in low yields. Compounds **1g**, which have a diphenyl-substituted silicon atom, were converted to **3g** in 60% yield probably due to Thorpe–Ingold effect.[33]

Table 2. Effect of Substituents on Alkyne, Allyl Silane, and Silicon Atom Moieties



entry	substrate	R^1	R^2	XR^3	yield of **3** (%)
1	**1b**	Me	H	$SiMe_2$	trace
2	**1c**	TMS	H	$SiMe_2$	N.R.
3	**1d**	H	H	CMe_2	N.R.
4	**1e**	H	H	NTs	N.R.
5	**1f**	H	Me	$SiMe_2$	22
6	**1g**	H	H	$SiPh_2$	60

The effects of substituents on the benzene ring were also investigated to determine the scope, limitations, and mechanism of this hydroxycyclization. Substrates **1** were subjected to the reaction conditions employed in Table 1, run 13. Compounds with electron-donating substituents at the 4- or 5-position, **1i**, **1j**, **1p**, and **1q**, were converted to hydroxycyclization products **3i**, **3j**, **3p**, **3q**, and **3s** in moderate to good yields (Table 3). However, allyl silane with a methoxy group at the 3-position, **1h**, showed no reaction. In contrast, allyl silane with a fluoride substituent at the 3-position, **1l**, afforded **3l** in 35% yield. Therefore, a small substituent at the 3-position is favorable in this reaction. Compounds **1k** and **1o**, with substituents at the 6-position, showed no reaction. In the compounds substituted with electron-withdrawing group, **3l**–**3n** and **3r**, low yields were observed. These results indicate that electron-withdrawing groups weakened coordination between the alkyne and metal. Sharp contrasts were observed between 1,2,3-trisubstituted (**1h** and **1l**) and 1,2,6-trisubstituted substrates (**1k** and **1o**), although both had substituents at the ortho-positions relative to the 2-alkyne and 1-allylsilane groups, respectively. The 5-methoxy-substituted

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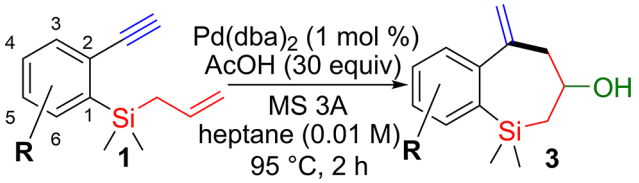
Table 3. Effect of Benzene Ring Substituents



entry	substrate	R	isolated yield (%) of **3**
1	**1a**	H	88 (59)[a]
2	**1h**	3-OMe	0 (0)[a]
3	**1i**	4-OMe	47 (58)[a]
4	**1j**	5-OMe	72
5	**1k**	6-OMe	0 (0)[a]
6	**1l**	3-F	35 (54)[a]
7	**1m**	4-F	39 (57)[a]
8	**1n**	5-F	12 (56)[a]
9	**1o**	6-F	0 (0)[a]
10	**1p**	4-Me	73
11	**1q**	5-Me	69
12	**1r**	4-CHO	trace (40)[a]
13	**1s**	4-$CH_2OSiiPr_3$	69

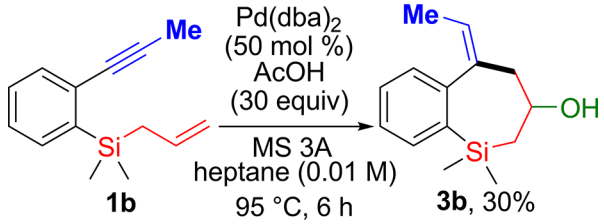
[a] *p*-Xylene was used as a solvent, and the reaction mixture was refluxed for 2 h.

compound **1j** gave a 72% yield of **3j**. In contrast, 5-fluoride-substituted compound **1n** gave **3n** in only 12% yield. These results demonstrated that the electronic effect of substituents at the para-position relative to the 2-alkyne was remarkable (**1j**, **1n**). These results suggested that some palladium species reacted with the alkyne moiety faster than the allyl silane moiety on **1** in this hydroxycyclization.

We also tested another condition to improve the yield of low reactivity compounds in this reaction. When **1i**, **1l**, **1m**, and **1n** were reacted in refluxing *p*-xylene, corresponding products **3i**, **3l**, **3m**, and **3n** were obtained in moderate yields. In contrast, **3h**, **3k**, and **3o** were also not obtained under these conditions.

Finally, the following experiment was conducted in order to better understand the reaction mechanism (Scheme 1). To

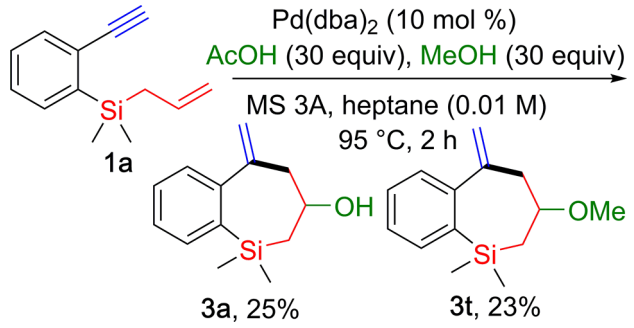
Scheme 1. Hydroxycyclization of Methyl-Substituted Alkyne 1b



assess the reaction of the alkyne and palladium catalyst, **1b** was treated with excess $Pd(dba)_2$; **3b** was obtained diastereoselectively in 30% yield. The stereochemistry of the olefin in **3b** was confirmed by nuclear Overhauser effect (NOE) experiments. In cases where the metal species operates as a π-acid catalyst, alkyne substituents were found to be positioned in a *trans*-alkene configuration after hydroxycyclization.[30,31c,32a,b] Therefore, hydrometalation of the palladium hydride species appears to occur via a *syn*-addition to the alkyne under these Pd-AcOH hydroxycyclization conditions.

The Wacker reaction is generally conducted using a palladium(II) catalyst with H_2O as an oxidant. When MeOH was added to the present reaction system, hydroxycyclization product **3a** and methoxycyclization product **3t** were obtained in 25% and 23% yields, respectively (Scheme 2). Furthermore,

Scheme 2. Hydroxycyclization in the Presence of Alcohol



when the amount of AcOH was increased, the yield of **3** increased (Table 1, runs 14–16). These results suggested that this hydroxycyclization occurred through nucleophilic addition to the allyl silane.

Based on the above experimental results and discussions, the reaction can be considered to involve a Wacker oxidation-type process[34] and nucleophilic attack taking place at the silicon β-position after hydrometalation. In an ordinary Wacker-type oxidation, a ketone is obtained after the introduction of oxygen atoms, β-elimination, and tautomerization. However, a hydroxyl compound was obtained in this hydroxycyclization, probably because the expected reductive elimination was faster than β-elimination.[35] The proposed reaction mechanism is summarized in Supporting Information, Scheme S2.

In conclusion, we have developed a palladium-catalyzed hydroxycyclization of allylsilane-alkynes to give benzosilepines. This is the first example of palladium-catalyzed seven-membered ring construction from enynes and hydroxycyclization to afford a seven-membered ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00271.

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

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Notes

The authors declare no competing financial interest.

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(25) (a) There is a possibility that the Pd species forms a dinuclear complex, but the mononuclear species has different activity and selectivity from the dinuclear complex. In general, both $Pd_2(dba)_3$ and $Pd(dba)_2$ are believed to be equivalent Pd(0) species. (b) The purity of the commercially available $Pd_2(dba)_3$ complexes is reported in the range 64−92%. See: Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302−2309.
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(35) An alternative route is a concerted process. Because **2** is obtained by a 6-exo-trig cyclization, **3** can be obtained by a 7-endo-trig cyclization. Both cyclizations are acceptable in the Baldwin's rule.

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