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3-Silaazetidine: An Unexplored yet Versatile Organosilane Species for Ring Expansion toward Silaazacycles

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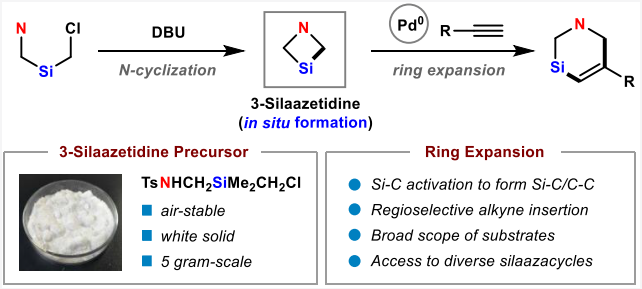
ABSTRACT: Small-ring silacycles are important organosilane species in main-group chemistry and have found numerous applications in organic synthesis. 3-Silaazetidine, a unique small silacycle bearing silicon and nitrogen atoms, has not been adequately explored due to the lack of a general synthetic scheme and its sensitivity to air. Here, we describe that 3-silaazetidine can be easily prepared *in situ* from diverse air-stable precursors ($RSO_2NHCH_2SiR^1{}_2CH_2Cl$). 3-Silaazetidine shows excellent functional group tolerance in a palladium-catalyzed ring expansion reaction with terminal alkynes, giving 3-silatetrahydropyridines and diverse silaazacycle derivatives, which are promising ring frameworks for the discovery of Si-containing functional molecules.



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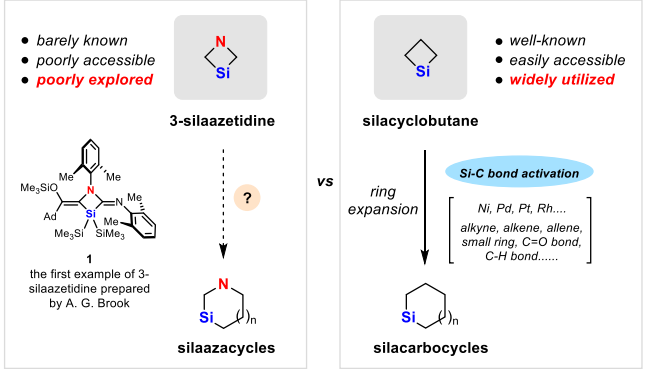
1. INTRODUCTION

Since Kipping's pioneering synthesis of octaphenylcyclotetrasilane,[1] strained three- or four-membered silacycles[2−5] have remained some of the most active research areas for chemists over the past 100 years. These small-ring silacycles have been extensively studied in main-group chemistry and have found numerous applications in organic synthesis. However, silaazetidines, including 2-silaazetidine[6−17] and 3-silaazetidine, bearing both Si and N atoms are some of the exceptions (Scheme 1, left). The synthesis, particularly for 3-silaazetidine, is extremely challenging and only a very few analogues[18−21] have been prepared. The challenge is evident from the important breakthrough in the formation of the first 3-silaazetidine example, **1**, achieved by Brook and co-workers.[18] They used silene and isocyanide derivatives, which had to be heavily substituted with bulky groups and were not readily accessible, to generate air-sensitive **1** by insertion of isocyanide into the Si−N bond of an initially formed silaaziridine. The lack of general synthetic pathways and the sensitivity to air mean that the reactivity and synthetic utility of 3-silaazetidine have been poorly explored in organic chemistry. This circumstance is in sharp contrast to its well-known carbon counterpart, silacyclobutane (Scheme 1, right).[4,22] Silacyclobutane can be readily prepared with wide structural diversity and is stable in air when it bears a tetraorganosilane. This species has been emerging as a valuable organosilane synthon for the preparation of silacarbocycles via ring expansion with a variety of reaction partners, which include alkynes,[23−32] alkenes,[26] allenes,[24] small rings,[33−38] C═O bonds,[39−45] C−H bonds,[46−49] and others.[50−53] The endocyclic Si−C bond activation[54−70] catalyzed by Ni-, Pd-, Pt-, or Rh-centered transition metals leads to the formation of a new Si−C bond, providing ring-expanded silacarbocycles with five-, six-, seven-, and eight-membered-ring structures.

Our group has focused on the synthesis of 3-silaazetidine derivatives due to their potential in the synthesis of

Scheme 1. Comparison of 3-Silaazetidine and Its Carbon Analogue Silacyclobutane



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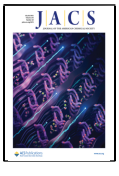

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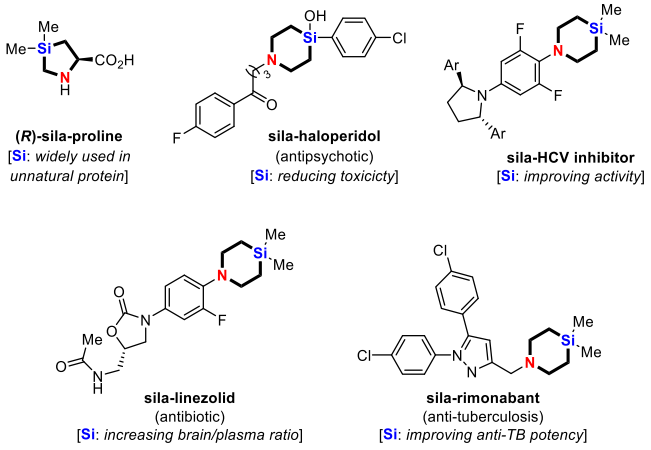
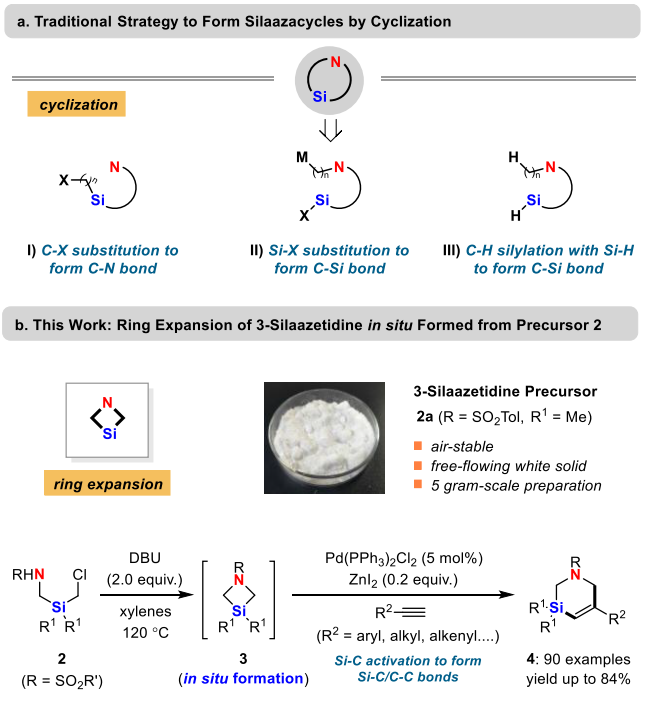
silaazacycles. Given that N-containing heterocycles are essential core frameworks in numerous pharmaceuticals and functional materials, silaazacycles are emerging as a particularly promising bioisostere for the development of Si-containing drugs[71−77] and advanced materials[78] (Scheme 2). In some

Scheme 2. Selected Examples of Bioactive Molecules Containing Silaazacycles



cases of medical applications, the unique characteristics of silicon have caused the silicon-containing bioactive compounds to have greater cell penetration,[79] greater bioactivity,[80] and lower toxicity[81] in comparison to the corresponding carbon analogues. In this regard, the development of efficient pathways for the construction of silaazacycles is of growing interest. Traditional methods toward silaazacycles utilize either C−X (X = halide) substitution with nitrogen to form a C−N bond (Scheme 3a-I),[74,82−86] or Si−X (X = halide) substitution with organolithium to form a C−Si bond (Scheme 3a-II).[87−93] Insertion of a nitrile into silacyclopropene also provided a novel entry into silaazacyclopentadiene and silaazacyclohexadiene.[94] In addition to the above methods, a great breakthrough achieved recently in the field of C−H silylation with hydrosilanes enabled the synthesis of silaazacycles under much milder conditions with a wider scope of substrates (Scheme 3a-III). The representative strategies include cross-dehydrogenative heteroaromatic C(sp^2)−H silylation catalyzed by an earth-abundant alkali-metal species (*t*-BuOK)[95] and C(sp^3)−H silylation catalyzed by Ir[96] or Ru catalysts[97] or by a transition-metal-free catalysis using $B(C_6F_5)_3$.[98,99] Despite this elegant progress, synthesis efforts have been limited primarily to the cyclization of chainlike precursors, indicating the need for new strategies for the construction of diverse silaazacycles from readily accessible precursors.

Scheme 3. Traditional Strategy to Form Silaazacycles by Cyclization (a) and Ring Expansion of 3-Silaazetidine to Form Silaazacycles (b; This Work)

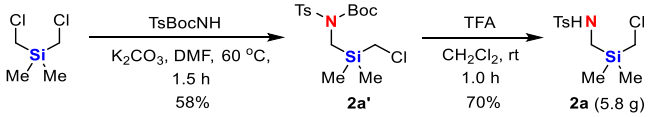


In the present study, we envisioned that 3-silaazetidine could serve as a general substrate for the synthesis of silaazacycles via a distinct ring expansion pathway (Scheme 3b). As a starting point, we prepared the structurally diverse 3-silaazetidine precursors **2** ($RSO_2NHCH_2SiR^1{}_2CH_2Cl$). The representative analogue **2a** was a stable white solid that was readily prepared in two steps on a 5 g scale using commercially available reagents. Upon reaction with DBU, precursors **2** gave 3-silaazetidine derivatives **3** via an intramolecular N-substitution. Although the derivatives **3** could not be isolated, they were stable *in situ*, effectively addressing the poor accessibility of 3-silaazetidine. A palladium-catalyzed ring-expansion reaction of **3** via endocyclic Si−C bond activation was then performed with terminal alkynes to facilitate the formation of new Si−C and C−C bonds. The reaction gives rise to 3-silatetrahydropyridines **4**, which were finally used to prepare diverse silaazacycles. Herein we report the details of this study.

2. RESULTS AND DISCUSSION

2.1. Synthesis of 3-Silaazetidine Precursor 2a. The 3-silaazetidine precursor **2a** was synthesized from commercially available $Me_2Si(CH_2Cl)_2$ and TsBocNH by the two-step procedure shown in Scheme 4. K_2CO_3-promoted mono-N-

Scheme 4. Synthesis of 3-Silaazetidine precursor 2a



substitution of $Me_2Si(CH_2Cl)_2$ with TsBocNH in DMF at 60 °C for 1.5 h gave rise to **2a′** in 58% yield. The potentially competitive bi-N-substitution was not observed due to the increased "neopentyl effect"[100] in **2a′** sterically prohibiting the second N-substitution. The subsequent Boc deprotection of **2a′** under acidic conditions afforded 3-silaazetidine precursor **2a** as an air-stable white solid in 70% yield on a 5 g scale.

2.2. Screening of Reaction Conditions. The reaction of **2a** and 1-phenylethyne using $Pd(PPh_3)_4$ as a catalyst, DBU as a base, and 4 Å molecular sieves as an additive in DMF at 80 °C afforded 3-silatetrahydropyridine **4a** and disiloxane **5a**, suggesting the formation of 3-silaazetidine **3a**. However, the ring-expanded product **4a** was obtained in only 11% yield (Table 1, entry 1), implying that most of the **3a** did not react with 1-phenylethyne. Instead, the ring opened hydrolytically during workup, giving the corresponding silanol, which in turn

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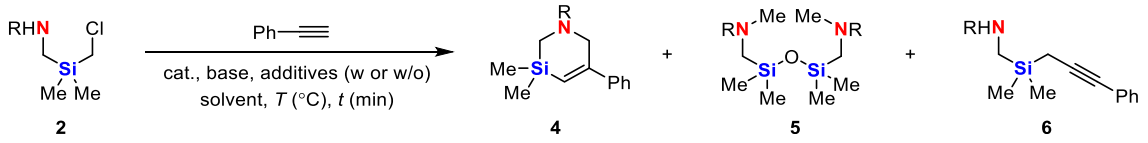
Table 1. Screening of Reaction Conditions[a]



entry	2	cat. (5 mol %)	base[c] (equiv)	solvent (M)	T (°C)	t (min)	additive	4 (%)	5 (%)	6 (%)
1	**2a** (R = SO_2Tol)	$Pd(PPh_3)_4$	DBU (1.2)	DMF (0.1)	80	180	4 Å MS	11	56	-
2	**2a** (R = SO_2Tol)	$Pd(PPh_3)_4$	DBU (1.2)	toluene (0.1)	80	180	4 Å MS	44	12	-
3	**2a** (R = SO_2Tol)	$Pd(PPh_3)_4$	DABCO (1.2)	toluene (0.1)	80	180	4 Å MS	-	-	-
4	**2a** (R = SO_2Tol)	$Pd(PPh_3)_4$	TMG (1.2)	toluene (0.1)	80	180	4 Å MS	-	-	-
5	**2a** (R = SO_2Tol)	$Pd(PPh_3)_2Cl_2$	DBU (1.2)	toluene (0.1)	80	180	4 Å MS	43	23	-
6	**2a** (R = SO_2Tol)	$Pd(PPh_3)_2Cl_2$	DBU (2.0)	xylenes (0.4)	120	10	-	60	9	10
7	**2a** (R = SO_2Tol)	$Pd(PPh_3)_2Cl_2$	DBU (2.0)	xylenes (0.4)	120	10	ZnI_2	72 (68[b])	-	-
8	**2b** (R = SO_2t-Bu)	$Pd(PPh_3)_2Cl_2$	DBU (2.0)	xylenes (0.4)	120	10	ZnI_2	44	-	-
9	**2c** (R = SO_2Me)	$Pd(PPh_3)_2Cl_2$	DBU (2.0)	xylenes (0.4)	120	10	ZnI_2	44	-	-
10	**2d** (R = COC_6H_4-p-CF_3)	$Pd(PPh_3)_2Cl_2$	DBU (2.0)	xylenes (0.4)	120	10	ZnI_2	-	-	23

[a]Conditions for entries 1−5: **2** (0.1 mmol), 1-phenylethyne (0.12 mmol), cat. (5 mol %), 4 Å MS (40 mg), solvent (1.0 mL). Conditions for entries 6−10: **2** (0.2 mmol), 1-phenylethyne (0.24 mmol), cat. (0.05 mol %), ZnI_2 (0.04 mmol) except for entry 6, solvent (0.5 mL). See Tables S-1−S-3 in the Supporting Information for details. [b]3 g scale after recrystallization. [c]Abbreviations: DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TMG, 1,1,3,3-tetramethylguanidine.

dimerized to disiloxane **5a** in 56% yield. In contrast, the formation of **4a** (44%) was significantly favored in nonpolar toluene, while the generation of the undesired byproduct **5a** was significantly inhibited (12%; entry 2). Among the tested bases, DBU was the most effective, as the less basic DABCO was ineffective for N−H deprotonation (entry 3), while the stronger base TMG promoted the decomposition of **3a** (entry 4). Screening of Pt-, Ni-, or Rh-centered catalysts as well as other Pd catalysts revealed that $Pd(PPh_3)_2Cl_2$ was as effective as $Pd(PPh_3)_4$ (entry 5). However, the overall formation efficiency of 3-silaazetidine **3a** was higher with $Pd(PPh_3)_2Cl_2$ than with $Pd(PPh_3)_4$ (67% vs 56%), identifying $Pd(PPh_3)_2Cl_2$ as the optimal reaction catalyst.

Furthermore, with an increase in the temperature from 80 to 120 °C, the concentration of **2a** to 0.4 M, and the loading of DBU to 2.0 equiv, while the solvent was also changed to xylenes, favored the ring expansion of **3a**, giving **4a** in 60% yield (Table 1, entry 6). The additive 4 Å MS, which was used for absorption of water in the reaction at 80 °C (entries 1−5), was no longer needed at 120 °C due to the much faster ring expansion of **3a** toward **4a**. However, the new byproduct **6a** was also formed in 10% yield, resulting from the nucleophilic substitution of the 1-phenylethyne anion with **2a**. In order to inhibit this side reaction, various Lewis acids were tested to reduce the nucleophilicity of 1-phenylethyne. ZnI_2 proved to be the most effective,[101] affording **4a** in 72% yield and completely eliminating the formation of **5a** and **6a** (entry 7). Under these optimized conditions, **4a** could also be prepared on a 3 g scale with a comparably high yield of 68% (entry 7). A series of N-substituents were also tested to examine their effect on the formation efficiency of **4**. Similar to the case for **2a**, sulfonamide precursors **2b**,**c** gave compounds **4b**,**c**, respectively, in 44% yield (entries 8 and 9). In contrast, **2d** bearing the less electron-withdrawing p-CF_3-C_6H_4CO group could not be deprotonated, affording only **6d** in 23% yield (entry 10).

2.3. Scope of Alkynes. The scope of alkynes was examined using the 3-silaazetidine precursor **2a** (Table 2). Aryl alkynes bearing a phenyl ring substituted with various electron-donating or electron-withdrawing groups gave 3-silatetrahydropyridines **4e−x** in generally good yields. The higher yield of the 4-Me-C_6H_4-substituted analogue **4g** (75%) in comparison to that of 2-Me-C_6H_4-substituted **4e** (59%) suggested that the *ortho* substitution sterically hindered the alkyne insertion. A primary amine and a secondary amide were also tolerated, yielding **4n**,**o** in respective yields of 38% and 57%. However, aryl bromide, a typical moiety used in Pd-catalyzed cross-coupling reactions, interfered with our process, giving **4t** in only 12% yield. The formation of **4aa** indicated the potential utility of the approach in developing ferrocene-type ligands. Alkynes substituted with heterocycles bearing one or more N, O, or S heteroatoms served as good substrates for **4ab−am**. The basic N-heterocycle moiety in the substrates did not interfere with the basic function of DBU.

Functionalized alkyl alkynes, including those derived from propargyl alcohol or thiol (**4an−aw**), were also well tolerated, except for **4aq** containing a free hydroxyl group. The yield differences among **4an−ap** indicated a certain steric bias against alkynes. Extensive examination of a wide range of propargyl amines and amides indicated that free secondary or tertiary amines (**4ax−az** and **4ba−bf**), either in chainlike substrates or in ring structures with three or five to seven members, can function well in this approach without affecting the chirality of the functional groups (**4ay**). Good applicability was also observed for secondary and tertiary propargyl amides and lactams (**4bg−bp**), while rings with three to eight members or spirocyclic rings were well tolerated. Analogues **4bq−bu** bearing a diene moiety from the corresponding enynes were also successfully synthesized in good yields. However, the reaction failed to give **4bv** from the corresponding diyne, in which both terminal and internal alkynes were inactive under these conditions. An inefficiency was also observed for ring expansion with 1-phenyl-1-propyne, indicating that the reaction was unsuitable for more sterically demanding internal alkynes. Although methyl propiolate proved to be a more challenging substrate in comparison to inactivated alkynes, because the aza-Michael addition significantly interfered with the ring expansion, the analogue **4bw** was successfully prepared in 32% yield using 5 mol % of $PdCp(\eta^3\text{-}C_3H_5)$ as the catalyst and 10 mol % of PPh_3 as the ligand by forming the intermediate **3a** prior to the alkyne

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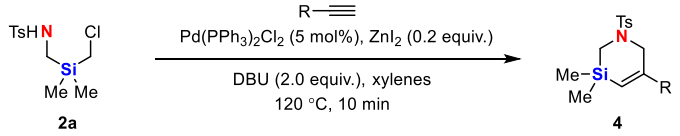
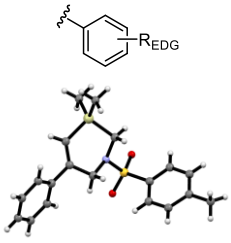
Table 2. Scope of Alkynes[a]

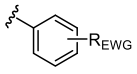


Aryl

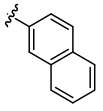


4a (CCDC 2074774)

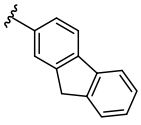
4a: 72% (R = H)
4e: 59% (R = 2-Me)
4f: 61% (R = 3-Me)
4g: 75% (R = 4-Me)
4h: 63% (R = 4-*t*-Bu)
4i: 72% (R = 4-$SiMe_3$)
4j: 50% (R = 4-Ph)
4k: 72% (R = 4-OMe)
4l: 82% (R = 3,4-OMe)
4m: 51% (R = 3,4-OCH_2O-)
4n: 38% (R = 3-NH_2)
4o: 57% (R = 4-NHAc)



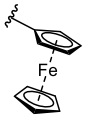
4p: 65% (R = 2-Cl)
4q: 57% (R = 3-Cl)
4r: 72% (R = 4-Cl)
4s: 58% (R = 3-F)
4t: 12% (R = 4-Br)
4u: 59% (R = 4-CF_3)
4v: 39% (R = 4-CN)
4w: 61% (R = 4-COPh)
4x: 62% (R = 4-CO_2Me)



4y: 68%

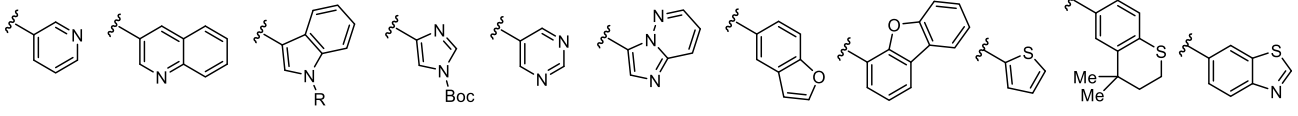


4z: 66%



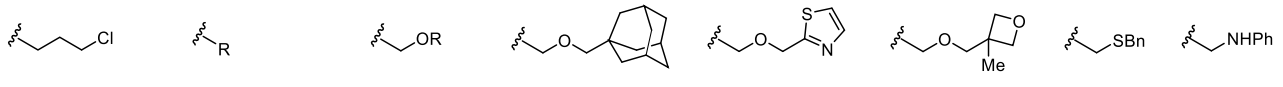
4aa: 54%

Heterocycle

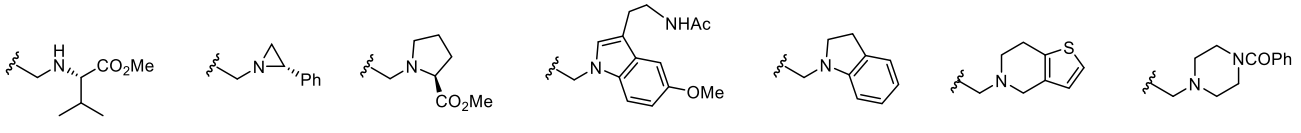


4ab: 53% **4ac**: 71% **4ad**: 67% (R = Me) **4af**: 47% **4ag**: 58% **4ah**: 37% **4ai**: 67% **4aj**: 63% **4ak**: 61% **4al**: 66% **4am**: 76%
4ae: 42% (R = Boc)

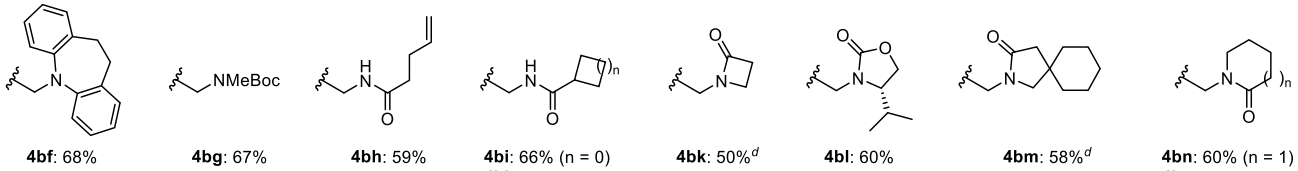
Alkyl



4an: 53% **4ao**: 37% (R = Cy)[b] **4aq**: N.D. (R = H)[f] **4at**: 80% **4au**: 61% **4av**: 68% **4aw**: 41% **4ax**: 74%
4ap: N.D. (R = *t*-Bu)[f] **4ar**: 72% (R = $SiEt_3$)
4as: 68% (R = Bn)

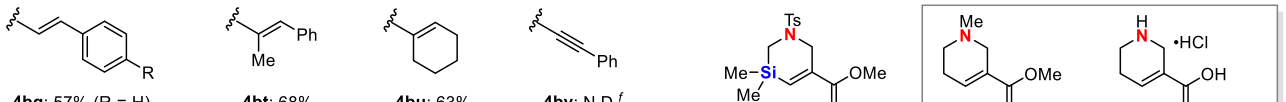


4ay: 48% **4az**: 75% **4ba**: 66% **4bb**: 66%[c] **4bc**: 56% **4bd**: 75% **4be**: 45%



4bf: 68% **4bg**: 67% **4bh**: 59% **4bi**: 66% (n = 0) **4bk**: 50%[d] **4bl**: 60% **4bm**: 58%[d] **4bn**: 60% (n = 1)
4bj: 73% (n = 1) **4bo**: 56% (n = 2)
4bp: 70% (n = 3)

Alkenyl



4bq: 57% (R = H) **4bt**: 68% **4bu**: 63% **4bv**: N.D.[f]
4br: 68% (R = OMe)
4bs: 61% (R = F)

Electron-withdrawing Group

4bw: 32%[e]

arecoline **guvacine hydrochloride**

https://doi.org/10.1021/jacs.1c04667
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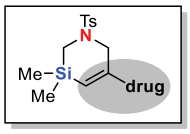
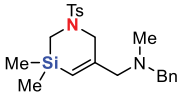
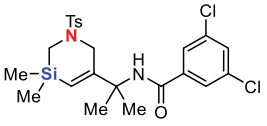
Table 2. continued

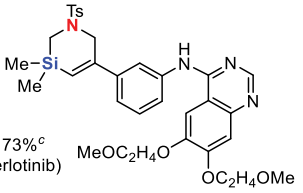




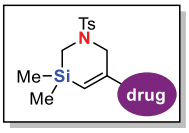
4bx: 60%
(from pargyline)

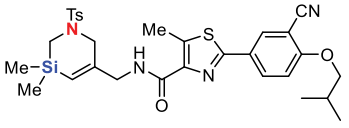


4by: 61%
(from propyzamide)

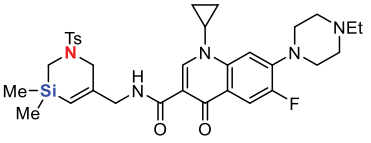


4bz: 73%[c]
(from erlotinib)

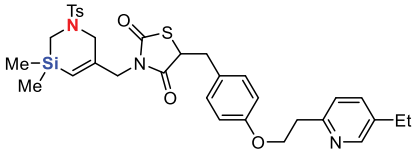




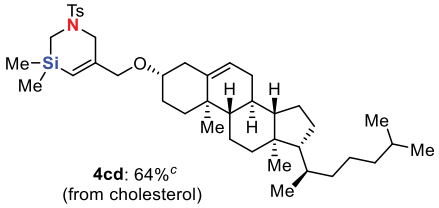
4ca: 57%[c]
(from febuxostat)



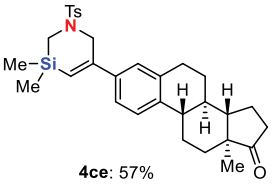
4cb: 84%[c]
(from enrofloxacin)



4cc: 70%[c]
(from pioglitazone)



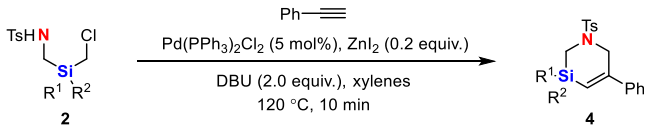
4cd: 64%[c]
(from cholesterol)

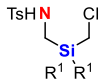
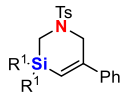
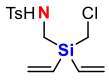
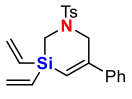
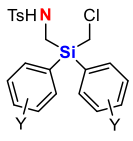
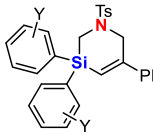


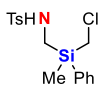
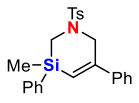
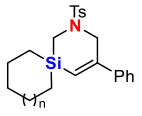
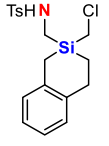
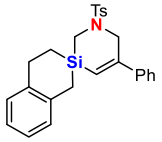
4ce: 57%
(from estrone)

[a]General optimized reaction conditions: **2a** (0.2 mmol), alkynes (0.24 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), DBU (0.4 mmol), ZnI_2 (0.04 mmol), xylenes (0.5 mL), 120 °C, 10 min. Abbreviations: DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene. [b]Alkyne (5.0 equiv). [c]**2a** (2.0 equiv). [d]Alkyne (2.0 equiv). [e]5 mol % of $PdCp(\eta^3\text{-}C_3H_5)$ and 10 mol % of PPh_3; **3a** was formed prior to the alkyne addition. [f]Disiloxane **5a** was observed as the predominant product.

Table 3. Scope of 3-Silaazetidine Precursors 2[a]



Entry	2		4		Yield (%)
1		**2e** (R^1 = Et)		**4cf**	61
2		**2f** (R^1 = *n*-Bu)		**4cg**	60
3		**2g** (R^1 = *i*-Pr)		**4ch**	51
4		**2h** (R^1 = *c*-C_5H_9)		**4ci**	50
5		**2i**		**4cj**	N.D.
6		**2j** (Y = H)		**4ck**	65
7		**2k** (Y = 3-OMe)		**4cl**	77
8		**2l** (Y = 4-F)		**4cm**	58

Entry	2		4		Yield (%)
9		**2m**		**4cn**	77
10		**2n** (n = 0)		**4co**	45
11		**2o** (n = 1)		**4cp**	63
12		**2p**		**4cq**	56

[a]General optimized reaction conditions: **2** (0.2 mmol), 1-phenylethyne (0.24 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), DBU (0.4 mmol), ZnI_2 (0.04 mmol), xylenes (0.5 mL), 120 °C, 10 min.

addition. Of note, **4bw** is a silicon analogue of the natural alkaloids arecoline (GABA transporter inhibitor) and guvacine hydrochloride (agonist at both muscarinic and nicotinic acetylcholine receptors), indicating its potential in the development of silicon-containing molecules possessing bioactivity relevant to central nervous system targets.

The applicability of our approach was further demonstrated by the late-stage functionalization (LSF)[102] of drug molecules bearing a terminal alkyne (pargyline, propyzamide, erlotinib)

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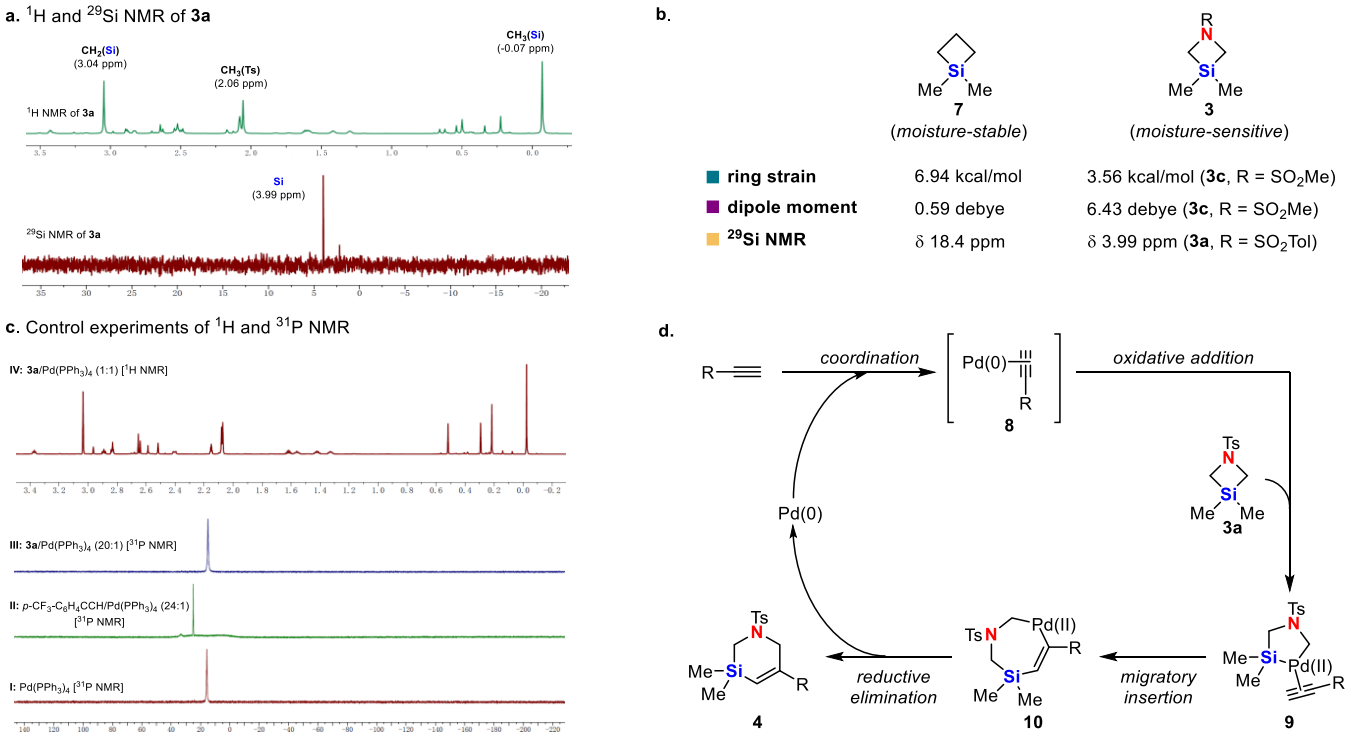

Figure 1. Elucidation of the ring expansion mechanism. (a) ^{1}H and ^{29}Si NMR spectra of **3a**. (b) Ring strain, dipole moment, and ^{29}Si NMR chemical shifts of silacyclobutane **7** and 3-silaazetidines **3c** and **3a**. (c) ^{31}P NMR spectra of $Pd(PPh_3)_4$ (I), CF_3-*p*-$C_6H_4C{\equiv}CH/Pd(PPh_3)_4$ (24:1) (II), **3a**/$Pd(PPh_3)_4$ (20:1) (III) and the ^{1}H NMR spectrum of **3a**/$Pd(PPh_3)_4$ (1:1) (IV) monitored at 90 °C. All experiments were carried out in toluene-d_8. (d) Proposed catalytic mechanism for the ring expansion of **3a** toward 3-silatetrahydropyridines **4**.

or of drug derivatives readily obtained via condensation with propargyl amine (febuxostat, enrofloxacin) by N- or O-propargylation (pioglitazone, cholesterol) and by cross-coupling with alkyne (estrone) (Table 2). The 3-silatetrahydropyridine moiety was efficiently installed (**4bx−bz** and **4ca−ce**), while various functionalities were well tolerated, such as heterocycles (**4bz,ca,cb,ce**), a ketone (**4ce**), a nitrile (**4ca**), or a potentially sensitive *α,β*-unsaturated keto amide (**4cb**). This indicates the potential of the approach in drug discovery and other applications.

2.4. Scope of 3-Silaazetidine Precursor 2. The scope of the 3-silaazetidine precursors **2** was examined using 1-phenylethyne as the model alkyne (Table 3). Disubstitution of the Si atom with Et or *n*-Bu or the bulkier *i*-Pr or cyclopentyl groups (**2e−h**) did not affect the reaction efficiency and afforded **4cf−ci** in 50−61% yield (entries 1−4), which were slightly lower than that of **4a**. However, the divinyl-substituted analogue **2i** decomposed quickly and **4cj** was not isolated (entry 5). In contrast, mono- or disubstitution of the Si atom with an aryl moiety (**2j−m**) led to the formation of the corresponding 3-silatetrahydropyridines **4ck−cn** in good yields (entries 6−9). Furthermore, 3-silaazetidine precursors **2n−p** bearing a silacycle enabled the synthesis of the respective analogs **4co−cq**, where Si served as the ring junction (entries 10−12).

2.5. Mechanism. *In situ* ^{1}H and ^{29}Si NMR spectroscopic studies of **3a** were performed by mixing **2a** and 1.0 equiv of DBU in toluene-d_8 at 120 °C for 10 min. A peak at 3.04 ppm corresponding to the symmetrical CH_2 in **3a** was observed in the ^{1}H NMR spectrum (Figure 1a), while the ^{29}Si chemical shift of the Si atom in **3a** was detected at 3.99 ppm (Figure 1a). Although the spectroscopic data confirmed the formation of **3a**,[103] this intermediate could not be isolated by chromatography or crystallization due to its high sensitivity to moisture, which led to rapid hydrolytic ring opening, giving disiloxane **5a**. In order to identify the origin of this instability, particularly given the higher moisture stability of silacyclobutane, we calculated the ring strain[104−107] and dipole moment of 3-silaazetidine **3c** and silacyclobutane **7**.[108] Interestingly, **3c** had a lower ring strain energy than **7** (3.56 vs 6.94 kcal/mol), while its dipole moment (6.43 D) was 10 times that of **7** (0.59 D) (Figure 1b). These results suggest that the high moisture sensitivity of **3** is probably due not to ring strain but to the strong dipole moment, which increases the electrophilicity of the Si atom, facilitating its attack by H_2O. This idea was supported by ^{29}Si NMR data, where the peak of **3a** (3.99 ppm) was more upfield than that of **7** (18.4 ppm) (Figure 1b), consistent with Krapivin's observation that peaks move more upfield as the positive charge on the Si atom increases.[109]

To determine the first reaction step, we carried out a series of control NMR experiments (Figure 1c and Figures S1−S5 in the Supporting Information). The addition of CF_3-*p*-$C_6H_4C{\equiv}CH$ to $Pd(PPh_3)_4$[110] (Figure 1c-I) in a 24:1 molar ratio resulted in a distinct ^{31}P NMR spectrum (Figure 1c-II), in which a new peak at 25.0 ppm appeared, along with two broad peaks ranging from −8 to 35 ppm probably due to the rapid ligand exchange. These results imply that coordination of the palladium catalyst with the alkyne occurs, despite the fact that it is weaker than that with electron-deficient alkynes such as $MeO_2CC{\equiv}CCO_2Me$,[29,111] which is more effective for encouraging back-bonding from palladium. However, no new peak or notable change was observed in the ^{31}P NMR spectrum when **3a** was mixed with $Pd(PPh_3)_4$ in a 20:1 molar ratio (Figure 1c-III). The ^{1}H NMR spectrum of a mixture of

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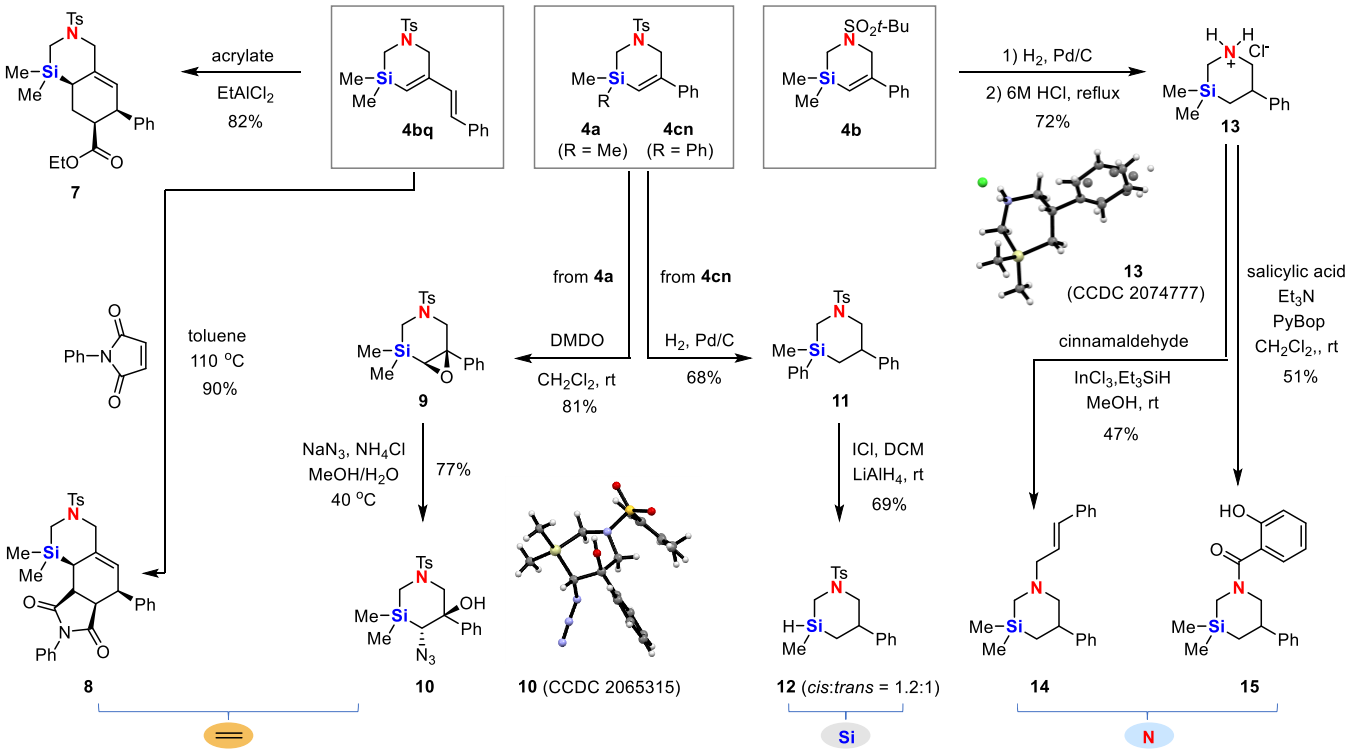
Scheme 5. Diverse Transformations of 3-Silatetrahydropyridines 4



3a and $Pd(PPh_3)_4$ in a 1:1 molar ratio also remained unchanged even at 90 °C, in contrast to that of **3a** (Figure 1c-IV). These results suggest that $Pd(PPh_3)_4$ on its own does not interact with **3a**.

On the basis of the above observations, the reaction pathway triggered by the coordination of Pd(0) with alkyne[111,112] seems more reasonable for our case and is consistent with previous experimental[29] and theoretical studies (Figure 1d).[113,114] The resulting intermediate **8** might adopt an L-shaped π complex according to the Dewar−Chatt model. While we cannot completely rule out the possibility that **8** undergoes transmetalation via σ-bond metathesis with **3a** to give Pd-silacycloheptene **10**, we more prefer the pathway in which **8** adds oxidatively to the endocyclic Si−C bond of 3-silaazetidine **3a**, leading to the five-membered palladium cycle **9**. A migratory insertion into the Pd−Si bond follows,[115] affording Pd-silacycloheptene **10** with the large phenyl group distal to the bulky silyl moiety. Reductive elimination of **10** ultimately generates 3-silatetrahydropyridine **4** and releases Pd(0) into the next catalytic cycle.

2.6. Diverse Transformations. The endocyclic alkene, silicon, and nitrogen moieties of selected 3-silatetrahydropyridines **4** were further functionalized to examine the applicability of the synthesized analogues to the preparation of silaazacyclic compounds (Scheme 5). **4bq** underwent an *endo*-type Diels−Alder reaction to give the sila-bicyclic analogue **7** in 82% yield in the presence of $EtAlCl_2$ or the sila-tricyclic analogue **8** in 90% yield upon heating. Epoxidation of **4a** with DMDO gave epoxysilane **9** in 81% yield, which underwent a regioselective epoxide ring opening reaction with NaN_3, affording the sila-azido alcohol **10** in 77% yield. In contrast, **4cn** was hydrogenated to afford 3-silapiperidine **11** in 68% yield. Subsequent removal of the phenyl substituent on Si using iodine monochloride, followed by reduction with $LiAlH_4$, furnished two isolable hydrosilane diastereomers **12** (*cis*:*trans* = 1.2:1) in 69% yield. Hydrogenation of **4b** and removal of the *t*-BuSO_2 group with 6 M aqueous HCl formed the salt **13**. Reductive amination of **13** with cinnamaldehyde afforded the 3-silapiperidine **14** bearing a tertiary amine in 47% yield. The nitrogen moiety in **13** also reacted with salicylic acid, giving the silaazacyclic analogue **15** in 51% yield.

3. CONCLUDING REMARKS

In summary, we have developed a range of air-stable 3-silaazetidine precursors ($RSO_2NHCH_2SiR^1{}_2CH_2Cl$). The representative precursor **2a** (R = Ts, R^1 = Me) was practically accessed in two steps on a 5 g scale using commercially available reagents. DBU-promoted N-cyclization of precursors enables the *in situ* synthesis of 3-silaazetidine analogues, effectively addressing the longstanding poor accessibility of 3-silaazetidine. A palladium-catalyzed ring expansion of 3-silaazetidine via endocyclic Si−C bond activation was achieved to give a wide range of 3-silatetrahydropyridines by forming new Si−C and C−C bonds with terminal alkynes. The resulting 3-silatetrahydropyridines could be further functionalized at the endocyclic alkene, silicon, and nitrogen moieties, confirming the applicability of the developed approach to the synthesis of silaazacyclic compounds. DFT calculations of ring strain and dipole moment for 3-silaazetidine and silacyclobutane suggest that the moisture sensitivity of 3-silaazetidine is due to its strong dipole moment. The mechanistic studies revealed that the coordination of Pd(0) with alkyne initiated the reaction and triggered the oxidative addition to the endocyclic Si−C bond of 3-silaazetidine.

Our synthetic method toward 3-silaazetidine shows good generality and clearly supports that this untapped small-ring silacycle can be readily prepared. We expect that this method would inspire more creative strategies that allow the synthesis of more diverse 3-silaazetidines. Our ring expansion reaction

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also showcased the first application of 3-silaazetidine in organic synthesis, highlighting that it could be used as a robust and versatile synthon and could find wide application in the synthesis of silaazacycles and other silicon-containing functional molecules. Further research will focus on the development of more structurally diverse 3-silaazetidine precursors, the application of 3-silaazetidine to other types of ring expansion, and the enantioselective construction of chiral silicon centers via asymmetric Si−C bond activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04667.

Experimental procedures, details of screening of ring expansion conditions, details of calculations, information about mechanistic studies, characterization data, crystallographic information, and spectra for all new compounds (PDF)

Accession Codes

CCDC 2065315, 2074774, and 2074777 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): Z.S., L.G., W.W., S.Z., L.L., and Y.H. have filed a provisional patent application (202110297658.3). All other authors declare no competing interests.

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