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Communication

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Catalytic Access to Bridged Sila-*N*-Heterocycles from Piperidines via Cascade sp^3 and sp^2 C–Si Bond Formation

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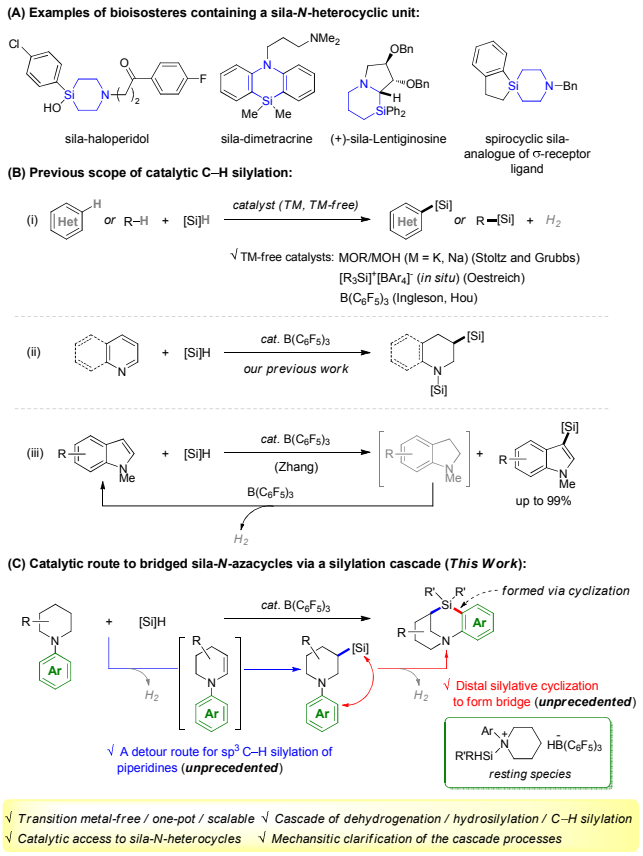
Supporting Information Placeholder

ABSTRACT: Described herein is the development of an unprecedented route to bridged sila-N-heterocycles via $B(C_6F_5)_3$-catalyzed cascade silylation of N-aryl piperidines with hydrosilanes. Mechanistic studies indicated that an outer-sphere ionic path is operative to involve three sequential catalytic steps having N-silyl piperidinium borohydride as a resting species: (i) dehydrogenation of the piperidine ring, (ii) β-selective hydrosilylation of a resultant enamine intermediate, and (iii) intramolecular dehydrogenative sp^2 C–H silylation.

*I*n medicinal chemistry, silicon-linked heterocycles are considered to be able to constitute an interesting carbon isostere of the corresponding bioactive molecules since silicon has unique physicochemical properties.[1] With the prevalence of N-heterocyclic units in numerous pharmacophores and alkaloids, the preparation of sila-N-heterocycles (azasilaheterocycles) as a potent bioisostere is of growing interest (Scheme 1A).[1d,2] In this regard, the development of a catalytic system enabling the construction of azasilaheterocycles from readily accessible compounds via a cyclization approach accompanied by new C–Si bond formation would be highly promising, but still challenging.[3]

Dehydrogenative silylation of organic compounds by the reaction with hydrosilanes is one of the most straightforward synthetic strategies to install a silyl group at the targeted C–H bonds.[4] While a number of transition metal complexes are shown to facilitate the dehydrogenative silylation of (hetero)arenes to form C–Si bonds,[5-6] more convenient "transition metal-free" catalytic procedures using alkaline metal alkoxides,[7] borate salts,[8] and $B(C_6F_5)_3$[9] have been documented [Scheme 1B(i)]. Our group also found that $B(C_6F_5)_3$ catalyst enables a dearomative hydrosilylation cascade of N-heteroarenes to afford reduced N-heterocycles bearing a sp^3 C–Si bond *beta* to nitrogen [Scheme 1B(ii)].[10-11] Being related to this dearomative reduction, $B(C_6F_5)_3$ has been recently demonstrated to catalyze dehydrogenation of saturated N-heterocycles to provide synthetically important N-heteroarenes.[12] Similarly, Zhang showed that $B(C_6F_5)_3$ catalyzes convergent disproportionation reaction of indoles with hydrosilanes, in which some portion of the *in situ* generated indolines are converted back to the parent indoles via dehydrogenation to eventually deliver C3-silylated indoles as the final product up to 99% yields [Scheme 1B(iii)].[13] Being aware of the catalytic versatility of $B(C_6F_5)_3$,[9-13] we envisaged a new transformation of N-aryl piperidines to polycyclic bridged sila-N-heterocycles

Scheme 1

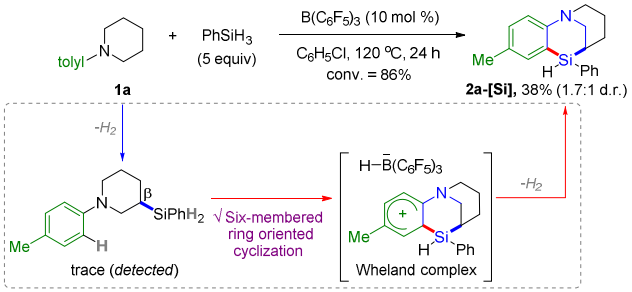


by inducing cascade processes which are all predicted to be catalytic in $B(C_6F_5)_3$: (i) dehydrogenation of N-aryl piperidines; (ii) β-selective hydrosilylation of the resultant enamine intermediates; and (iii) a unique remote silylative cyclization (Scheme 1C). Described herein is the experimental results on our working hypothesis that represent the first catalytic route to such bridged sila-N-heterocycles. The scope of substrates is presented along with mechanistic details.

At the outset of this study, we chose 1-tolylpiperidine **1a** as a model substrate and it was subjected to tentative thermal conditions with a $B(C_6F_5)_3$(cat.)/hydrosilane system (Scheme

2).[14] To our delight, the reaction furnished a tricyclic sila-amine product **2a-[Si]** in 38% yield (1.7:1 d.r.), while the presupposed β-silylated piperidine intermediate was detected in ~5% by ^{1}H NMR. This result implies that, as we envisioned, a

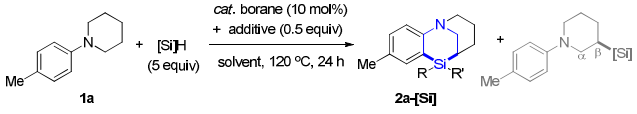
Scheme 2. $B(C_6F_5)_3$-Catalyzed Silylation Cascade of 1a



newly introduced silyl group undergoes an intramolecular dehydrogenative coupling with the N-tolyl C(sp^2)–H bond presumably via a Wheland complex.[15-16]

Encouraged by this promising observation, an optimization study for this transformation was next conducted (Table 1).[17] Reactions with $PhSiH_3$ were performed in various solvents: a reaction in C_6H_5Cl gave the corresponding tricyclic sila-amine **2a-[Si]** in 38% yield at 120 °C for 24 h in the presence of $B(C_6F_5)_3$(10 mol %), while reactions in other solvents or *neat* conditions afforded **2a-[Si]** in 7~21% yield (entries 1–4). The use of cyclohexene as a hydrogen acceptor did not improve the catalytic efficiency (entry 5).

Table 1. Optimization of Reaction Conditions[a]

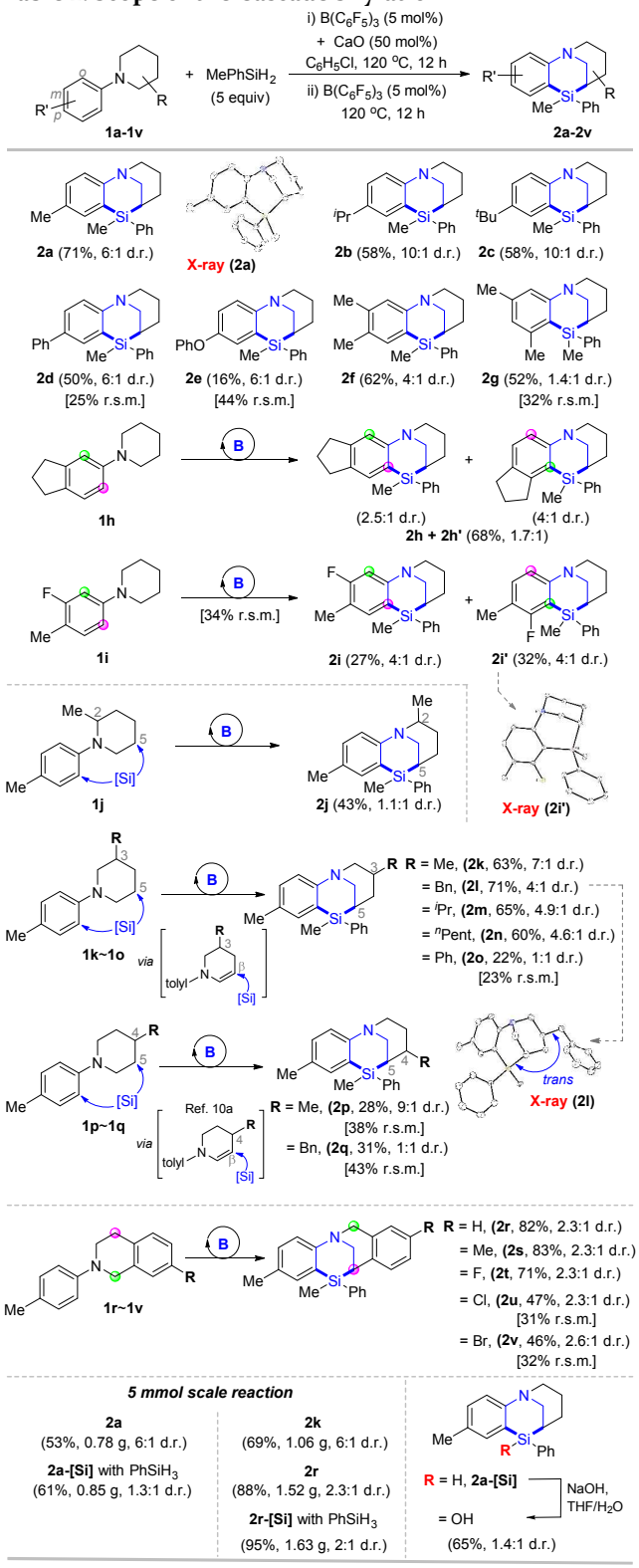


entry	solvent	silane	additive	**2a-[Si]**[b](d.r.) [**1a**][c]
1	C_6H_5Cl	$PhSiH_3$	-	38(1.7:1) [14]
2	toluene	$PhSiH_3$	-	18(1.1:1) [59]
3	1,2-DCE	$PhSiH_3$	-	7(1.2:1) [53]
4	neat	$PhSiH_3$	-	21(1.7:1) [18]
5	C_6H_5Cl	$PhSiH_3$	cyclo-hexene[d]	16(1.2:1) [67]
6	C_6H_5Cl	$PhSiH_3$	MgO	45(1.8:1) [11]
7	C_6H_5Cl	$PhSiH_3$	ZnO	43(1.5:1) [5]
8	C_6H_5Cl	$PhSiH_3$	CaO	47(1.2:1) [17]
9[e]	C_6H_5Cl	$PhSiH_3$	CaO	59(1.4:1) [<5]
10[e]	C_6H_5Cl	^{n}BuSiH$_3$	CaO	68(1.5:1) [<5]
11[e]	C_6H_5Cl	Et_2SiH_2	CaO	26 [50]
12[e]	C_6H_5Cl	Ph_2SiH_2	CaO	29 [43]
13[e]	C_6H_5Cl	$MePhSiH_2$	CaO	71 (**2a**, 6:1) [<5]
14[e]	C_6H_5Cl	Me_2PhSiH	CaO	22[f] [44]
15[g]	C_6H_5Cl	$PhSiH_3$	CaO	<1 [95]

[a]$B(C_6F_5)_3$ (10 mol%), **1a** (0.2 mmol), silane (5 equiv), and solvent (0.5 mL) at 120 °C for 24 h. [b]Isolated yields of **2a-[Si]**. [c]Recovered **1a**. [d]2 Equivalents were added. [e]$B(C_6F_5)_3$ was added in two portions (5+5) mol% over a (12+12) h period. [f]Isolated yield of β-silyl-piperidine. [g]Ph_3B (10 mol %) was used instead of $B(C_6F_5)_3$.

To improve the reaction efficiency, the use of metal oxide additives was considered with an assumption that they could work as a base to affect the presupposed ionic cascade transformation.[18] Gratifyingly, sub-stoichiometric amounts of MgO,

Table 2. Scope of the Cascade Silylation[a]



[a]$B(C_6F_5)_3$ (5+5) mol%, substrate (0.2 mmol), $MePhSiH_2$ (5 equiv) and C_6H_5Cl (0.5 mL) at 120 °C for (12+12) h in a reaction vial.

Yields and diastereomeric ratio of isolated products. The numbers (%) in brackets indicate the recovered starting materials (r.s.m.).

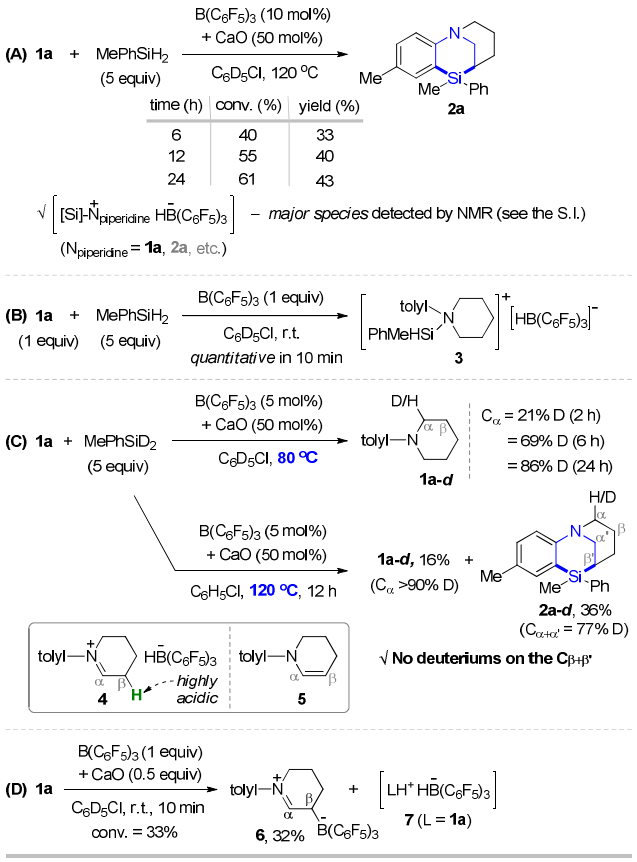
ZnO, or CaO additives (0.5 equiv) led to improved yield of **2a-[Si]** (entries 6–8 *vs*. entry 1) (also see the S.I. for details). Moreover, the addition of $B(C_6F_5)_3$ catalyst in *two portions of* (5+5) mol% over a period of (12+12) h was more effective in giving higher yield (entry 9). With this two-portion addition protocol, the scope of silanes was further explored: a reaction with $^nBuSiH_3$ furnished the desired product in 68% yield (1.5:1 d.r.), whereas the use of Et_2SiH_2 or Ph_2SiH_2 brought about lower yields of **2a-[Si]** (entries 10–12). Finally, a reaction with $MePhSiH_2$ provided the best yield of **2a** (71%) with good diastereoselectivity (6:1) (entry 13).[19] As predicted, a β-silylated piperidine was obtained albeit in moderate yield when a tertiary silane was applied (entry 14), again supporting our mechanistic consideration. Ph_3B was inactive under the standard conditions (entry 15).

With the optimal conditions in hand (Table 1, entry 13), substrate scope and scalability of this unprecedented transformation were investigated (Table 2). N-Aryl piperidines bearing an alkyl or phenyl group at the *para*-position of the aryl moiety reacted with $MePhSiH_2$ to provide the corresponding bridged sila-N-heterocycles in 50~71% yields with high diastereomeric ratios of 6:1~10:1 (**2a-2d**). The solid structure of **2a** was unambiguously confirmed by X-ray crystallographic analysis. A phenoxy substituent at the same position, however, gave inferior yield (**2e,** 16%, 6:1 d.r.). Substrates bearing a disubstituted N-aryl ring at the *meta*- and/or *para*-positions smoothly underwent the desired cyclization reactions (**2f-2i**, 52~68%, 1.4:1~4:1 d.r.). When *N*-indanyl piperidine (**1h**) was subjected to the optimal conditions, two regioisomeric *tetracyclic* products (**2h** and **2h'**) were obtained, slightly favoring a cyclization path at the sterically less demanding position. It needs to be mentioned that the present procedure readily offers a route to polycyclic products as in this case.

As another probe of substrate scope, variation at the piperidine moiety was next examined. When *N*-tolyl-(2-methyl)piperidine (**1j**) was subjected, a cyclized product **2j** was obtained bearing a new sp^3 C–Si bond at the sterically less demanding C-5 position rather than C-3. The same regiooutcome was observed with substrates having a C3-substituted piperidinyl unit. In these cases, a range of substrates were viable (**1k**–**1n**), whereas a reaction of 3-phenylpiperidinyl substrate (**1o**) was rather inefficient. The crystal structure of **2l** was obtained to exhibit a *trans* relationship between the Si–C5 and the prepositioned C3–Bn bonds, suggesting stereoselective hydrosilylation of a presupposed enamine intermediate. Cyclization of N-tolylpiperidines (**1p**–**1q**) possessing substituents at the C-4 position of a piperidine moiety were found to be less efficient albeit with varied diastereoselectivity.[20] Low product yields are attributable to steric congestion around the reacting C5 position during the sp^3 C–Si bond forming hydrosilylation process. A significant structural variation was tested by employing tetrahydroisoquinoline derivatives instead of piperidines. Pleasingly, they reacted all smoothly to afford the corresponding tetracyclic products in moderate to good yields (**2r-2v**).[21-22] The present borane catalysis was also operative even in gram scale as demonstrated for the formation of several multicyclic products (**2a**, **2a-[Si]**, **2k**, **2r**, **2r-[Si]**) in 5 mmol-scale runs. Considering the biological relevance (Scheme 1A) as well as synthetic utility of silanols,[1c,1g-h] we oxidized the Si–H bond of product **2a-[Si]** (R = H) to its silanol in good yield by treating NaOH in THF/H_2O.

To shed light on the pathway of the present silylative cyclization, a series of mechanistic experiments were performed (Scheme 3). Firstly, a reaction progress was monitored by NMR spectroscopy under the developed catalytic conditions (Scheme 3A). While the conversion of **1a** was 40% (6 h) and 61% (24 h) in reaction with $MePhSiH_2$, product yields of **2a** were 33% (6 h) and 43% (24 h), suggesting that the product-yielding pathway competes with certain side reaction(s). ^{19}F NMR of the crude reaction mixture exhibited one set of major signals assignable to *N*-silyl piperidinium borohydride, thus leading us to assume that piperidinium ion species having a borohydride $(C_6F_5)_3BH^-$ counter anion is in a resting state. Indeed, a stoichiometric treatment of **1a** with $B(C_6F_5)_3$ (1 equiv) and $MePhSiH_2$ (5 equiv) generated the supposed N-silyl piperidinium borohydride **3** in quantitative yield within 10 min at 25 °C (Scheme 3B).[13,23] A reaction of **1a** with deuterated silane $MePhSiD_2$ was monitored under the present catalyst system

Scheme 3. Mechanistic Studies

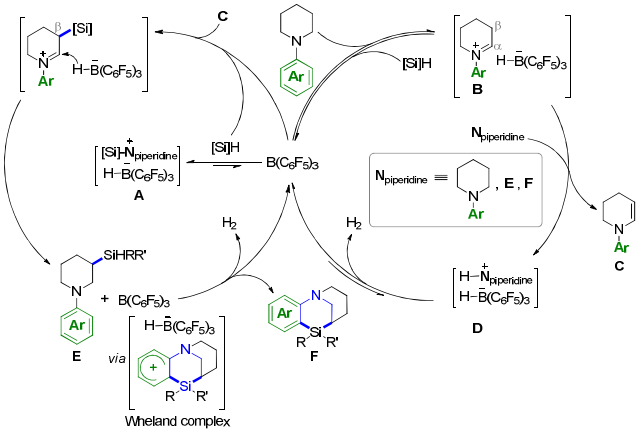


(Scheme 3C). While the cyclized product was not formed at 80 °C, only deuterium incorporation occurred at the α carbon of the piperidine ring (21% D in 2 h and 86% D in 24 h) along with the H/D exchange of $MePhSiD_2$. In contrast, deuterium was not incorporated at the β-carbon (C_β). Based on these observations, we propose that $B(C_6F_5)_3$ catalyzes the α-hydrogen abstraction of substrate **1a** to form an iminium borohydride **4**, and this process is reversible in the presence

of hydrosilane at 80 °C. Upon heating at 120 °C, **1a** smoothly underwent the cascade silylation to give **2a-*d*** in 36% yield over 12 h. Notably, the fact that both **2a-*d*** ($C_{\alpha+\alpha'}$ = 77% D) and recovered **1a-*d*** (C_{α} > 90% D) did not incorporate deuterium at the β-carbons, corroborates that the β-hydrogen cleavage of a putative iminium intermediate **4** is likely irreversible to give enamine **5**.

In an effort to observe an enamine **5** as a plausible intermediate, a stoichiometric reaction of **1a** with $B(C_6F_5)_3$ was attempted in the presence of CaO (0.5 equiv) (Scheme 3D). A zwitterion species **6**[24] consisted of iminium and borate was found to form in 32% yield in 10 min. Although enamine like **5** is not detected in this experiment, we assume that the formation of **6** supports our working hypothesis on the cascade event, wherein $B(C_6F_5)_3$ first mediates an α-hydrogen abstraction of **1a** to lead to iminium **4**, and then a relatively acidic C_{β}-H bond is deprotonated[13] presumably by the assistance of **1a** to afford enamine **5** along with protonated piperidinium borohydride **7**. Enamine **5** is proposed to rapidly interact with $B(C_6F_5)_3$ to give **6** *in the absence of hydrosilanes*,[24] while the presence of silane would induce the $B(C_6F_5)_3$-catalyzed hydrosilylation to furnish β-silylated piperidines as seen in the above experiments (Scheme 2 and Table 1: entry 13).

Scheme 4. Proposed Catalytic Pathway



Based on the above mechanistic observations and insightful precedents albeit being applied to different systems,[25] our mechanistic proposal is depicted in Scheme 4 on the present $B(C_6F_5)_3$-catalyzed cascade silylation of N-aryl piperidines. This borane catalysis involves a series of consecutive conversions to bridged sila-N-heterocycles: (i) formation of *N*-silyl piperidinium borohydride **A** as a resting species; (ii) reversible conversion of a substrate to its iminium **B**;[26,27] (iii) generation of an enamine intermediate **C**;[9c,10a,28] (iv) formation of β-silylated piperidine **E**;[10] and (v) intramolecular sp^2 C–H silylation of **E** to the final bridged cyclization product **F** via a Wheland complex.[15-16,29] Although the role of CaO additive in improving the reaction efficiency is not clearly understood at the present stage, we presume that it likely takes part in the deprotonation step as a base, thus forming **C** and **F**.[18]

In summary, we have developed an unprecedented silylation cascade of N-aryl piperidines to afford bridged sila-N-heterocycles via sequential formation of new sp^3 and sp^2 C–Si bonds. Mechanistic studies validate a series of stepwise transformations which are all catalyzed by $B(C_6F_5)_3$. This result represents a new synthetic route to azasilaheterocycles, potentially a carbon isostere of alkaloids and bioactive compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental details, characterization data, and copies of NMR spectra (PDF)
Crystallographic data for **2a**, **2i'**, and **2l** (CIF)

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Notes

The authors declare no competing financial interests.

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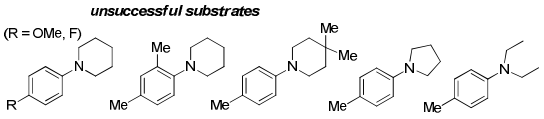
(19) Poor diastereoselectivity (1.1:1~1.8:1 d.r.) observed in the reactions with $PhSiH_3$ or $^nBuSiH_3$ are likely ascribed to the facile epimerization of liberated tricyclic product **2a**-[**Si**] by $B(C_6F_5)_3$: Kim, Y.; Chang, S. *Angew. Chem., Int. Ed.* **2015**, *55*, 218.
(20) As in the case of **2l**, the stereo-relationship between the Si–C_5 and C_4–alkyl bonds in the resulting sila-N-heterocycles is assumed to be *trans*, which results from the selective silylium ion transfer to the C_β of a presupposed enamine.[10a]
(21) Some of starting materials were recovered in a range of 23-50% after the catalytic reactions, while side products arising from reduction or hydrodehalogenation were not detected.
(22) N-Aryl amine substrates possessing sterically demanding and/or electronically biased substituents were not reactive under the standard conditions (see the S.I. for details).



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(24) ^{1}H and ^{13}C NMR of the reaction mixture showed characteristic signals at δ 8.3 and δ 187.5 which are assignable to the iminium α-proton and α-carbon of **6**, respectively, while a ^{11}B signal at δ -11.3 was assigned to the tetravalent borate anion center at the β-position (see the S.I.). For the *in situ* generation of a similar zwitterion species, see: Millot, N.; Santini, C. C.; Fenet, B.; Basset, J. M. *Eur. J. Inorg. Chem.* **2002**, 3328.
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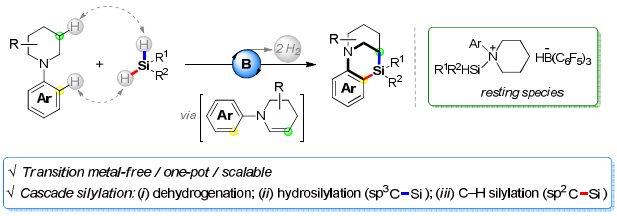
(29) It is assumed that the final step of sp^2 C–H silylation of **E** leading to **F** is turnover limiting.

TOC Graphic



√ *Transition metal-free / one-pot / scalable*

√ *Cascade silylation:* (*i*) dehydrogenation; (*ii*) hydrosilylation (sp^3C–Si); (*iii*) C–H silylation (sp^2C–Si)