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Selective Silylative Reduction of Pyridines Leading to Structurally Diverse Azacyclic Compounds with the Formation of sp^3 C−Si Bonds

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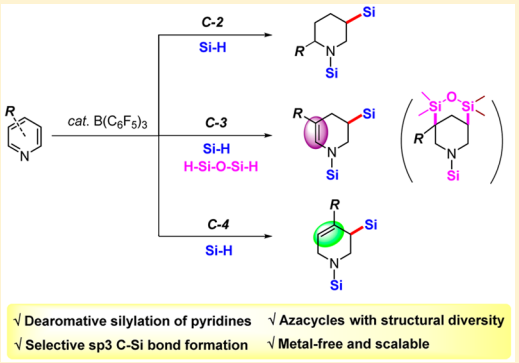
Supporting Information

ABSTRACT: Tris(pentafluorophenyl)borane-catalyzed silylative reduction of pyridines has been developed giving rise to the formation of sp^3 C−Si bonds selectively beta to the nitrogen atom of azacyclic products. Depending on the position and nature of pyridine substituents, structurally diverse azacycles are obtained with high selectivity under the borane catalysis. Mechanistic studies elucidated the sequence of hydrosilylation in this multiple reduction cascade: 1,2- or 1,4-hydrosilylation as an initial step depending on the substituent position, followed by selective hydrosilylation of enamine double bonds eventually affording β-silylated azacyclic compounds.



INTRODUCTION

Organosilicon compounds are widely utilized as an important building unit in synthetic, medicinal, polymer, and materials chemistry.[1] Hydrosilylation is one of the most straightforward methods to introduce the silyl group into organic molecules by reacting with unsaturated bonds.[1a−c] More recently, dehydrogenative silylation of unactivated C−H bonds has also drawn special attention as an alternative strategy to provide silylated alkanes and arenes.[2] While a range of transition metal complexes have long been employed as efficient catalysts for the (hydro)silylation of various functional groups, transition metal-free reductive silylation turned out to be a competent procedure in terms of cost and convenience.[3] In particular, $B(C_6F_5)_3$ and related Lewis acidic analogues are well documented to show remarkable catalytic performance for reductive (hydro)silylation of alkenes, (thio)carbonyls, imines, ethers, and alcohols.[4] Given such intrinsic catalytic activity of borane toward hydrosilylation of both C═C and C═N bonds, we recently developed the $B(C_6F_5)_3$-catalyzed silylative reduction of quinolines[5a] and α,β-unsaturated nitriles[5b,c] accompanied by the formation of sp^3 C−Si bonds selectively at the β-position relative to the nitrogen atom. The reaction of quinolines was found to proceed via a consecutive hydrosilylation at the C═N and C═C bonds to yield a variety of β-silylated tetrahydroquinoline compounds.

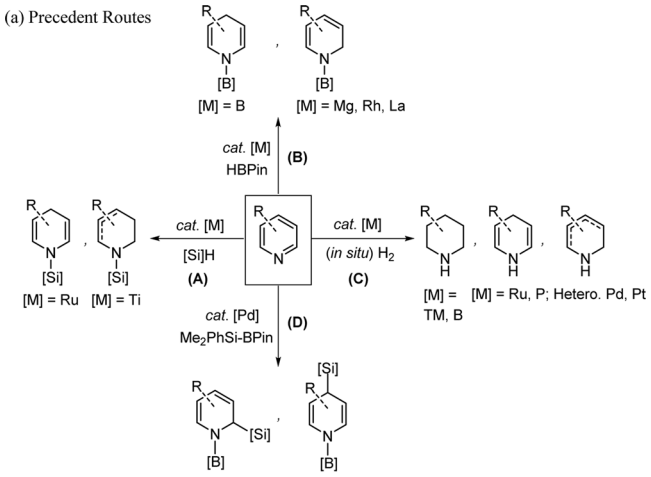
In a similar context, pyridines can be regarded as versatile precursors for the synthesis of piperidines or partially reduced azacyclic analogues, which are important skeletons found in biologically active natural and synthetic alkaloids.[6] However, in general, reduction of pyridines may cause a concern in regard to controlling regio- and/or chemoselectivity, thus nonselectively giving rise to various products such as 1,2- or 1,4-dihydropyridines, tetrahydropyridines, and fully saturated piperidines.[7] To address this selectivity issue, a handful of elegant catalytic procedures have been developed. Representatively, Oestreich and Nikonov research groups independently reported 1,4-hydrosilylation of pyridines using ruthenium catalysts to afford 1,4-dihydropyridines,[8a−c] while Harrod, Samuel, and co-workers presented a titanocene-based hydrosilylation−hydrogenation approach to convert substituted pyridines to *N*-silyldihydropyridines or *N*-silyltetrahydropyridines (Scheme 1a, method A).[8d,e] More recently, 1,2-selective hydrosilylation of pyridines catalyzed by a *N*,*N*-bidentate calcium complex was reported by Harder and co-workers.[8f]

Catalytic hydroboration of pyridines using HBPin as a reducing agent was recently demonstrated to be effective to selectively provide dihydropyridines: a Lewis acidic borane[9a] promotes hydroboration of pyridines in a 1,4-manner affording 1,4-dihydropyridines, while metal complexes based on Mg,[9b] Rh,[9c] and La[9d] catalyze 1,2-hydroboration to yield 1,2-dihydropyridines (Scheme 1a, method B). A range of efficient reduction procedures using H_2, referred to as (transfer)-hydrogenation, are known for the selective construction of 2-, 3-, or 4-substituted piperidines from pyridines.[10] In this context, transition metal mediated partial hydrogenation of pyridines was also explored, giving unsaturated azacyclic compounds (Scheme 1a, method C).[11] In addition, Suginome, Ohmura, and co-workers recently developed silaboration of pyridines catalyzed by a palladium complex, in which the Si−B bond is activated to insert into pyridines in a 1,2- or 1,4-fashion depending on the position of substituents, eventually affording

Received: August 31, 2015
Published: November 18, 2015

DOI: 10.1021/jacs.5b09209
J. Am. Chem. Soc. 2015, 137, 15176−15184

Scheme 1. Catalytic Reduction of Pyridines



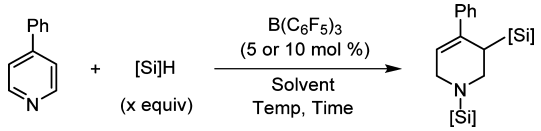
diverse dihydropyridines possessing a C(sp^3)−Si bond at the C-2 or C-4 position (Scheme 1a, method D).[12]

Despite such elegant methods for the pyridine reduction, there has been no report of transition metal free reduction of pyridines accompanied by the generation of new C(sp^3)−Si bonds with partial or complete dearomatization. Reported herein is the development of borane-catalyzed silylative reduction of pyridines giving rise to structurally diverse azacyclic compounds with the concomitant formation of sp^3 C−Si bonds beta to the nitrogen atom (Scheme 1b). Significantly, the position of pyridine substituents was found to critically guide the chemoselectivity in the hydrosilylative cascade conversions of pyridines, resulting in remarkable molecular diversity in the obtained azacycles. Mechanistic studies were also conducted to elucidate the sequence of hydrosilylation in this multiple reduction cascade: 1,2- or 1,4-hydrosilylation as an initial step depending on the substituent position and then selective hydrosilylation on the enamine double bonds, eventually giving *β*-silylated *N*-heterocycles as the final products.

RESULTS AND DISCUSSION

Based on our previous study of the borane-catalyzed silylative reduction of quinolines,[5a] we were curious if similar catalytic conditions [1−5 mol % $B(C_6F_5)_3$, 4−8 equiv of Et_2SiH_2 at 25−60 °C] could also be applicable to the selective reduction of pyridines, which are more challenging substrates. At the outset of this study, we were aware of several potential issues[10a] to cope with in the pyridine reduction which is largely differed from the reaction of quinolines as follows: (i) the resonance stabilization of pyridine is higher than that of the pyridine core in quinolines, thus probably requiring more forcing reaction conditions; (ii) there would exist more paths in the pyridine reaction leading to poor chemo- and/or regioselectivity; and (iii) stronger basicity of pyridines may bring about catalyst deactivation more easily than quinolines. With these issues in mind, our plan was to develop a borane-catalyzed hydrosilylation of readily accessible pyridines with satisfactory regio-, chemo-, and stereoselectivities.

Table 1. Optimization of Silylative Reduction of 4-Phenylpyridine[a]

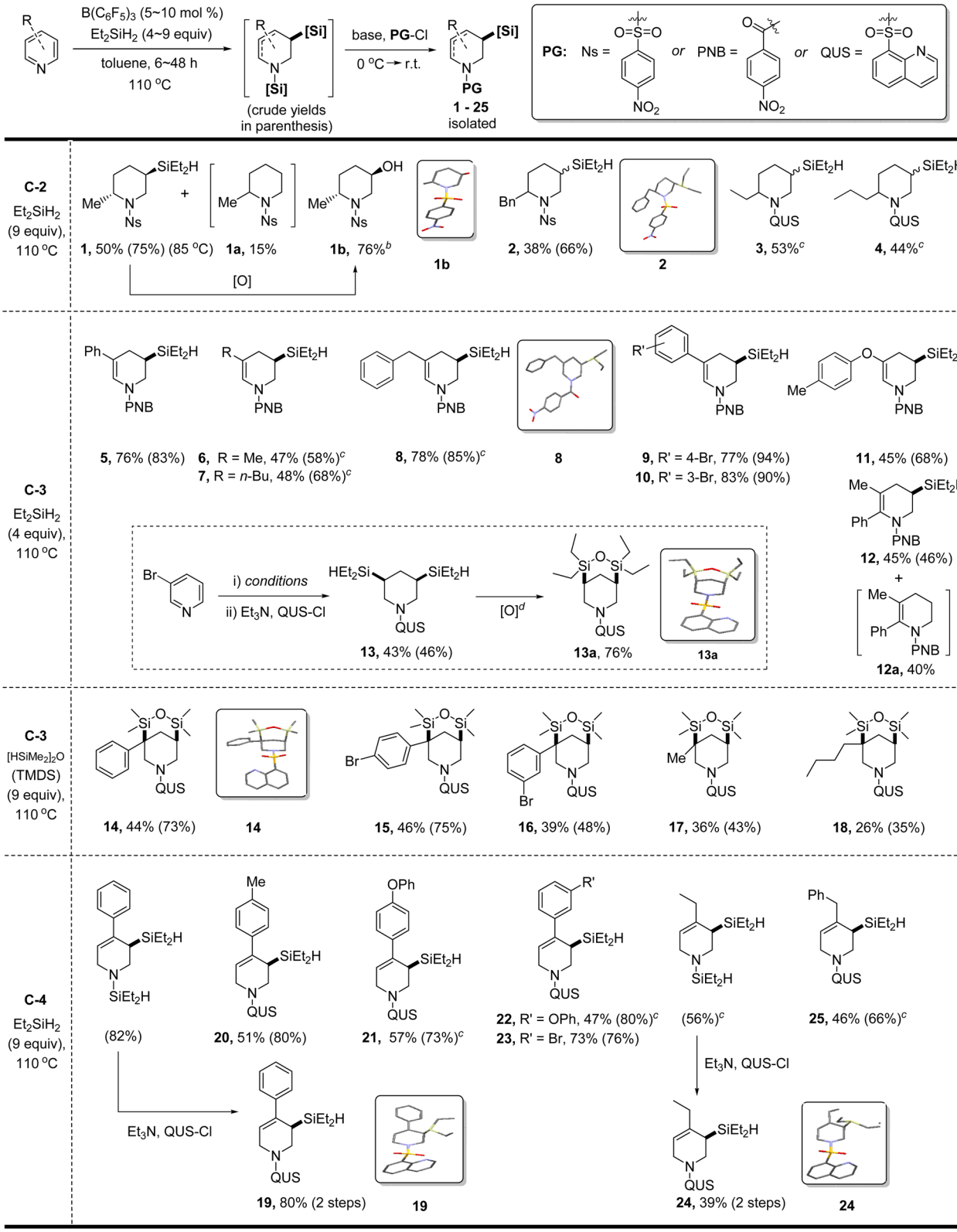


entry	silanes (equiv)	$B(C_6F_5)_3$ (mol %)	solvent	*T*, (°C)	time (h)	conv (%)[b]	yield (%)[b]
1	Et_2SiH_2 (4)	5	toluene-d_8	110	24	95	36
2	Et_2SiH_2 (4)	10	toluene-d_8	110	24	97	57
3	Et_2SiH_2 (6)	5	toluene-d_8	110	24	90	58
4	Et_2SiH_2 (9)	5	toluene-d_8	110	24	100	82
5[c]	Et_2SiH_2 (9)	5	toluene	110	24	93	78
6	Et_2SiH_2 (9)	5	toluene-d_8	110	6	30	15
7	Et_2SiH_2 (9)	5	toluene-d_8	80	24	5	<1
8	Et_2SiH_2 (9)	5	benzene-d_6	110	24	38	23
9	Et_2SiH_2 (9)	5	$CDCl_3$	110	36	85	65
10	Et_2SiH_2 (9)	5	chorobenzene-d_5	120	24	90	47
11	Et_2SiH_2 (9)	5	neat	110	24	72	40
12	Ph_2SiH_2 (9)	5	toluene-d_8	110	24	79	16
13	Me_2PhSiH (9)	5	toluene-d_8	110	24	50	23

[a]Carried out in a J-Young NMR tube on a 0.5 mmol scale (substrate) under Ar atmosphere. [b]Conversion and yields based on the ^1H NMR analysis (internal standard: mesitylene). [c]Performed in a reaction vial.

DOI: 10.1021/jacs.5b09209
J. Am. Chem. Soc. 2015, 137, 15176−15184

Table 2. Substrate Scope in the Silylative Reduction of Pyridines[a]



[a]Substrate (0.5 mmol), silane (4–9 equiv), and $B(C_6F_5)_3$ (5–10 mol %): isolated yields [numbers in parentheses are crude yields of the initially formed *N*-silyl products based on ^1H NMR analysis (internal standard: mesitylene or 1,1,2,2-tetrachloroethane)]. [b]Tamao's oxidation conditions.[13] [c]10 mol % of $B(C_6F_5)_3$. [d]Hydrolytic oxidation conditions using $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst.[16]

Optimization Study. We commenced our studies by examining a reaction of 4-phenylpyridine as the model substrate with Et_2SiH_2 as a silylative reducing agent to search for the optimal reaction conditions (Table 1, and see the Supporting Information for more details). Treatment of 4 equiv of silane in the presence of 5 mol % of $B(C_6F_5)_3$ catalyst resulted in 95%

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conversion at 110 °C in a NMR tube (toluene-d_8), providing 1,3-bis(diethylsilyl)-4-phenyl-1,2,3,6-tetrahydropyridine as a major product in 36% NMR yield after 24 h (entry 1). While increasing the catalyst loading (10 mol %) gave slightly improved yield of the desired product with similar conversion (entry 2), addition of higher equivalents of Et_2SiH_2 turned out to be more effective, leading to satisfactory product yield (entries 3, 4). An almost similar result was also obtained performed in a reaction vial under otherwise same conditions (entry 5).

On the other hand, alteration of key operating parameters (e.g., shortening reaction time or lowering temperatures) was also examined, but only resulting in significant decrease in yields (entries 6, 7). Solvents other than toluene were less effective in delivering the desired 1,3-bis-silyltetrahydropyridine (entries 8−10) although the conversion was maintained still high in $CDCl_3$ or chorobenzene-d_5, thus implying that the selectivity becomes poor upon this variation. A reaction under solvent-free conditions worked to some extent (entry 11). It was interesting to observe that the use of a bulkier silane (entry 12) or monohydrosilane (entry 13) gave inferior results in terms of conversion and selectivity.

With the optimal conditions in hand [5 mol % $B(C_6F_5)_3$, 9 equiv of Et_2SiH_2, toluene, 110 °C], we next investigated the scope of pyridine substrates bearing substituents at each position of C-2, C-3, and C-4 (Table 2). We were interested to see that a high degree of chemodivergence resulted depending on the *position* rather than the *type* of substituents. As a result, the present hydrosilylative reaction of readily available pyridines can provide azacyclic compounds with structural diversity, which are important building units in organic synthesis and medicinal chemistry.[6]

Reaction of 2-Substituted Pyridines. Borane-catalyzed hydrosilylation of pyridines bearing substituents at the C-2 position gave fully reduced piperidine products possessing a sp^3 C−Si bond at the C-5 position. For instance, when 2-methylpyridine was reacted with diethylsilane (9 equiv) at 85 °C in the presence of $B(C_6F_5)_3$ (5 mol %), a diastereomeric mixture of *anti*- and *syn*-2-methyl-1,5-bis(diethylsilyl)piperidine was formed in 75% crude yield determined by ^1H NMR. Since the purification of the 1,5-bis-silylpiperidine product failed due to its instability, we decided to convert the crude products to the corresponding *N*-sulfonylated derivatives *in situ* after the main catalytic reaction.

Thus, *N*-(4-nitrobenzenesulfonyl)-2-methylpiperidine (**1**) was isolated in 50% yield with high diastereoselectivity (*anti*/*syn*, > 95:5) in addition to a fully reduced piperidine having no C−Si moieties on the azacyclic ring (**1a**) as a byproduct (15%). The structure of the major isomer of **1** was confirmed by X-ray crystallographic analysis after converting the C-5 silyl moiety to a hydroxy group (**1b**) in good yield.[13]

In a similar manner, additional pyridine substrates having benzyl, ethyl, or propyl substituent at the C-2 position were subjected to standard conditions [5−10 mol % $B(C_6F_5)_3$, 9 equiv of Et_2SiH_2, 110 °C, 24−48 h] for the silylative reduction. The reaction of 2-benzylpyridine proceeded with good efficacy (66% crude yield) to give the desired product, 1,5-bis-(diethylsilyl)-2-benzylpiperidine as a diastereomeric mixture (*anti*/*syn*, 4:1) (**2**, 38% over 2 steps). 2-Ethyl- and 2-propylpyridines were also viable substrates to afford the corresponding 1,5-bis-silylpiperidines. The *N*-sulfonylation of the crude mixture gave a diastereomeric mixture of the desired products: **3** with 2:1 and **4** with 4:1 ratio (*anti*- to *syn*-isomers) in moderate isolated yields (**3**, 53% and **4**, 44% over two steps, respectively). It is noteworthy that the *anti*/*syn* selectivity in the reaction of 2-substituted pyridines seems to be changed depending on the type of those substituents although the altered diastereoselectivity is not clearly accounted for at the present stage.

Reaction of 3-Substituted Pyridines with Et_2SiH_2. Next, we investigated the reactivity pattern of C-3 substituted pyridines using Et_2SiH_2 as a reducing reagent. When optimized conditions were applied to these substrates (see the Supporting Information for more details), partially reduced cyclic 2,3-enamine compounds were obtained as major products with the formation of a C−Si bond at the C-5 position in moderate to high efficiency. Initially formed *N*-silylated enamine products were converted to the corresponding benzamides for the convenience of isolation. 3-Phenylpyridine was reacted smoothly with Et_2SiH_2 (4 equiv) under the optimal conditions (5 mol % of $B(C_6F_5)_3$ at 110 °C) to give the *N*-silylated product (83%), which was subsequently converted to its *N*-(4-nitro)benzoyl derivative (**5**) in 76% over two steps. The NMR analysis revealed that two isomers of **5** exist in a ratio of 3:1 at 23 °C and coalesce at *ca.* 60 °C (see the Supporting Information), suggesting restricted rotation of the C−N amide bond of **5** at room temperature.[14] The reaction efficiency of 3-alkylpyridines was satisfactory albeit with higher loading of the borane catalyst, affording reasonable yields (in 2 steps) of *N*-benzoylated products (**6**−**8**). The solid structure of compound **8** was representatively confirmed by X-ray crystallography in addition to NMR analysis.

Likewise, 3-(haloaryl)pyridines smoothly underwent the silylative reduction to produce the desired *N*-silyl products in excellent yields, which were subsequently isolated as the amide form (77% for **9** and 83% for **10** over 2 steps). Notably, the reaction of 3-(*p*-tolyloxy)pyridine with Et_2SiH_2 smoothly proceeded without cleavage of C−O bonds to provide the corresponding *β*-silylated tetrahydropyridine (**11**) in good yield. The newly generated enol ether moiety of **11** would be promising as a valuable synthetic precursor in synthetic chemistry as demonstrated in numerous places in the literature.[15]

Reactivity of 2,3-disubstituted pyridines was also examined under the standard conditions, revealing that the chemoselectivity was not maintained high in this case. For instance, 2-phenyl-3-methylpyridine was reacted to give a similar ratio of two products after *N*-benzolylation: a fully reduced tetrahydropyridine **12a** lacking a sp^3 C−Si bond and an expected C5-silylated compound **12**. Interestingly, a reaction of 3-bromopyridine afforded 1,3,5-tris(diethylsilyl)piperidine in 46% crude yield showing that *two* C−Si bonds were formed regioselectively while dehalogenation[10n] took place during this silylative reduction. After converting the crude product to its *N*-sulfonyl derivative (**13**, 43% over 2 steps), we conducted an oxidation on two silyl groups of **13** in an attempt to obtain their silanols for the convenience of isolation. Interestingly, using our previously reported hydrolytic catalytic procedure (H_2O oxidant with $[Ru(p\text{-cymene})Cl_2]_2$ catalyst at 25 °C),[16] a bicyclic siloxane compound (**13a**) was isolated in good yield, and its structure was confirmed by X-ray crystallographic analysis.

Reaction of 3-Substituted Pyridines with TMDS. The formation of the above unprecedented bicyclic structure of a disiloxane product (**13a**) led us to envision to synthesize those bicyclic derivatives by using disilane reactants directly. Indeed,

DOI: 10.1021/jacs.5b09209
J. Am. Chem. Soc. 2015, 137, 15176−15184

we were delighted to obtain this peculiar type of compound under newly optimized conditions using 1,1,3,3-tetramethyldisiloxane (TMDS) instead of Et_2SiH_2 (see the Supporting Information for more details). A range of pyridine substrates were reacted with TMDS to provide the corresponding bicyclic products having *O*-bridged double sp^3 C−Si bonds beta to the nitrogen atom in moderate to good yields (**14**−**18**).

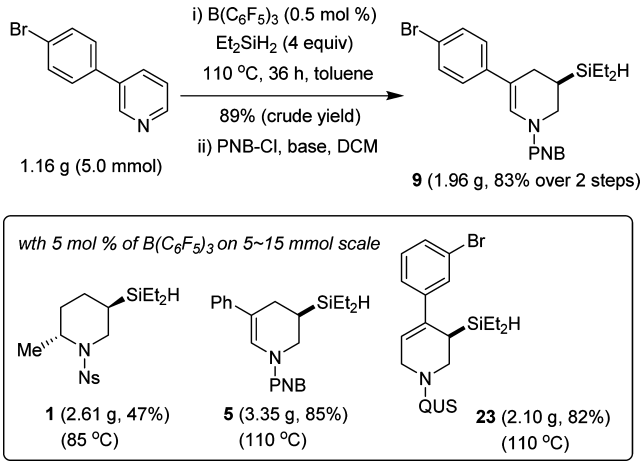
Representatively, a reaction of 3-phenylpyridine gave rise to a bicyclic azacycle in 73% crude yield, which was then transformed to an isolable *N*-sulfonamide product (**14**, 44% over 2 steps). The structure of this unique product **14** was characterized through NMR and X-ray crystallographic analysis. This result can be tentatively linked to a mechanistic consideration (*vide infra*) that *β*-selective intramolecular hydrosilylation[17] over a C═C bond of an enamide intermediate takes place as the final step to deliver an *N*-silyl azabicycle. 3-Arylpyridines bearing halides on the phenyl ring were readily hydrosilylated with similar efficiency to afford the corresponding bicyclic products as sulfonamide derivatives (**15**, **16**). Moreover, 3-alkylpyridines were also viable to form azabicyclic compounds in moderate yields under the newly optimized reductive conditions (**17**, **18**).

Reaction of 4-Substituted Pyridines. As the final type of substrate, we were curious if para-substituted pyridines display any interesting aspects in terms of reactivity and selectivity. Again, we were pleased to observe a unique chemoselectivity in this case affording *β*,*γ*-unsaturated azacyclic products in high yields. For instance, a reaction of 4-phenylpyridine with Et_2SiH_2 (9 equiv) was effective in the presence of $B(C_6F_5)_3$ (5 mol %) at 110 °C to furnish a (4-phenyl)-1,2,3,6-tetrahydropyridine having two silyl groups at the C-1 and C-5 positions in 82% crude yield, which was subsequently sulfonylated to give **19** (80% over 2 steps). The structure of compound **19** was identified by X-ray crystallographic analysis, unambiguously confirming the *β*,*γ*-position of an olefinic double bond. Similarly, 4-arylpyridines bearing various substituents at the phenyl moiety such as methyl, phenoxy, or halide groups also underwent the hydrosilylative reduction to produce the desired *β*,*γ*-unsaturated azacyclic compounds initially as an *N*-silyl form in good yields (73−80%). The crude reaction mixture was subjected to the *N*-sulfonylation conditions to furnish isolable *N*-sulfonamides (**20**−**23**, 47−73% over 2 steps).

Pyridine bearing an ethyl substituent at the para-position was also hydrosilylated albeit with higher loading of borane catalyst (10 mol %) to afford the corresponding unsaturated *N*-silyl compound in 56% crude yield that was isolated after *N*-sulfonylation (**24**, 39% yield over 2 steps, X-ray structure shown). 4-Benzylpyridine underwent the same reaction process to give **25** in reasonable yield. Since 3,4-disubstituted piperidine derivatives obtainable by the present procedure are substructures of a wide range of natural and synthetic alkaloids and/or pharmaceutical drugs with important biological activities,[18] our developed metal-free procedure providing a series of 4-substituted-3-silylated *β*,*γ*-unsaturated azacycles could be a promising synthetic methodology.

The presently developed transition metal free procedure was convenient, enabling gram-scale reactions to be performed (Scheme 2). When 3-(4-bromophenyl)pyridine (1.16 g, 5.0 mmol) was reacted with Et_2SiH_2 (4 equiv) in the presence of the borane catalyst as low as 0.5 mol %, the corresponding product **9** was obtained in high yield after *N*-benzoylation (1.96 g, 83% yield over 2 steps). Similarly, gram-scale reactions of 2-, 3-, or 4-substituted pyridines also worked selectively to afford

Scheme 2. Gram-Scale Reactions[a]



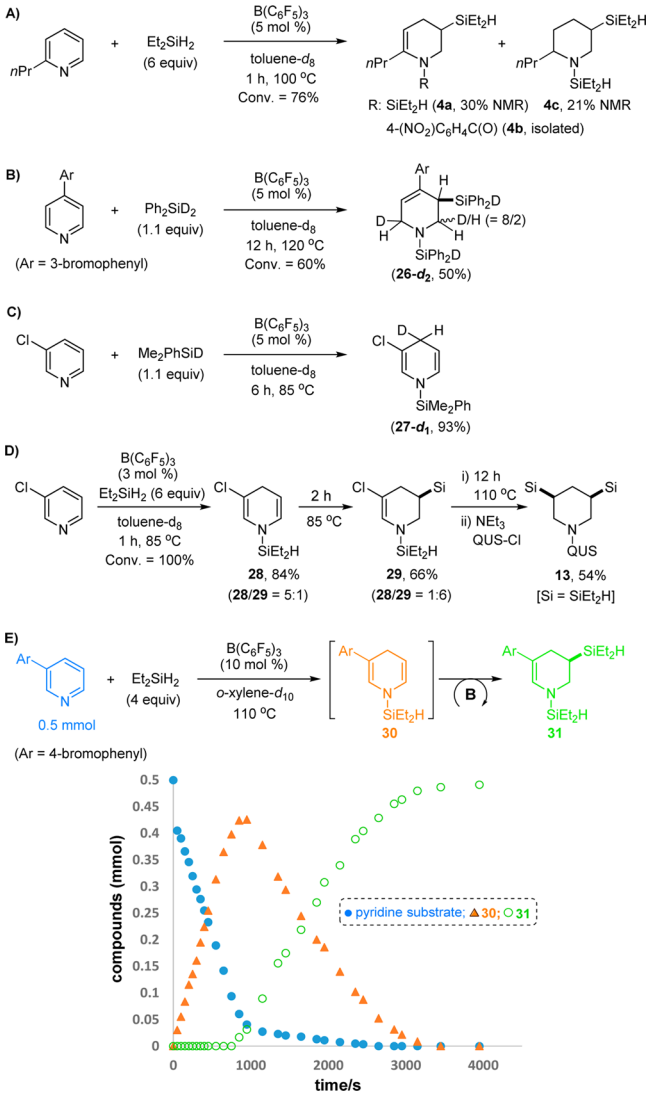
[a]Carried out in a reaction vial on a 5.0−15.0 mmol scale (substrate) under Ar atmosphere by using Et_2SiH_2 (4−9 equiv) and $B(C_6F_5)_3$ (0.5−5 mol %) at 85−110 °C for 24−36 h in toluene (1.5−4.5 mL). Isolated yields are calculated based on the amount of the employed pyridine starting materials.

the corresponding azacyclic products in good to excellent efficacy (**1**, **5**, and **23**, respectively).

Mechanistic Studies. In order to shed light on the mechanistic pathways, a series of experiments were conducted including deuterium-labeling, *in situ* generation of key intermediates, and NMR monitoring of the reaction (Scheme 3). A reaction of 2-propoylpyridine with 6 equiv of Et_2SiH_2 using 5 mol % of $B(C_6F_5)_3$ at 100 °C was monitored by NMR to reveal that 1,3-bis-silylated 1,2,3,4-tetrahydropyridine (**4a**) was observed to form in 1 h (30% NMR yield with 76% conversion), which was subsequently isolated as an amide form (**4b**) upon *N*-benzoylation (Scheme 3A). Moreover, under these milder conditions, a fully saturated product (**4c**) was also generated albeit in low yield. This result strongly suggests that the silylative reduction of 2-substituted pyridines involves an enamine intermediate such as **4a** that is eventually reduced to the desired piperidine products. Next, the initial reaction step was investigated in this hydrosilylation cascade by using a deuterated hydrosilane. When 1.1 equiv of Ph_2SiD_2 and dimethylphenylsilane-d_1 (Me_2PhSiD) were allowed to react with 4-(3-bromophenyl)pyridine and 3-chloropyridine, respectively, in the presence of 5 mol % of the borane, partially reduced 1,2,3,6-tetrahydropyridine[19] and 1,4-dihydropyridine (**26**-d_2 and **27**-d_1, respectively) were *in situ* generated in yields of 50% and 93%, respectively, with an *exclusive* incorporation of deuterium at the C-2 and C-4 positions, respectively (Scheme 3B,C). These results indicate that an initial step of hydrosilylation is not a single path but it is *highly regiodivergent* depending on the position of substituents on the pyridine ring. Subsequently, 3-chloropyridine was subjected to the conditions [3 mol % $B(C_6F_5)_3$ with 6 equiv of Et_2SiH_2 at 85 °C] to result in a mixture of 3-chloro-*N*-silyl-1,4-dihydropyridine (**28**) and an additionally hydrosilylated compound **29** with the ratio of **28**/**29** = 5:1 (100% conversion in 1 h). Heating this reaction mixture at 85 °C for additional 2 h allowed for a high conversion of **28** to **29** leading to a ratio of 1:6 = **28**/**29** (90% conversion of **28**), and the latter slowly underwent an exhaustive reduction at 110 °C accompanied by dehalogenation with the formation of another sp^3 C−Si bond at the *β*-position

DOI: 10.1021/jacs.5b09209
J. Am. Chem. Soc. 2015, 137, 15176−15184

Scheme 3. Preliminary Mechanistic Studies



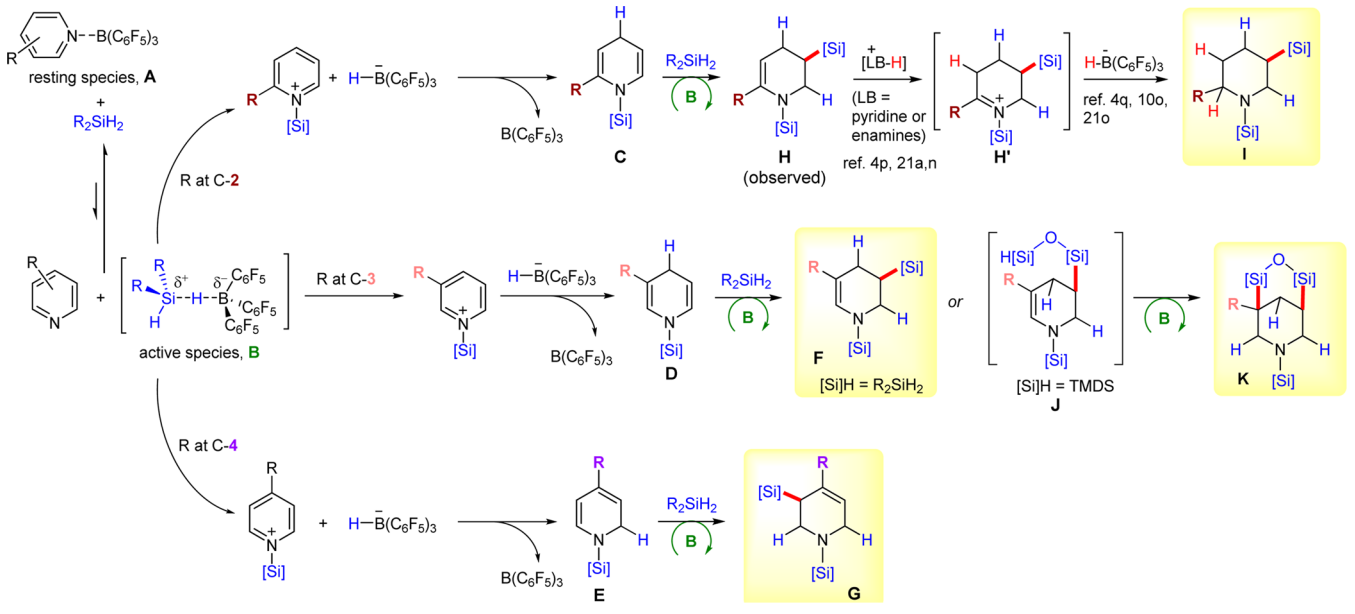
to eventually give a final product **13** upon the *N*-sulfonylation (combined 54% yield, Scheme 3D). The observed sequential conversion of 3-chloropyridine to the end product **13** clearly indicates that the silylative reduction of 3-substituted pyridines proceeds through 1,4-dihydropyridine and then β-silylated tetrahydropyridine intermediates.

The reaction progress was monitored by ^{1}H NMR spectroscopy in *o*-xylene-d_{10} in an attempt to understand the relative rate among the presupposed multiple steps (Scheme 3E). The conversion of 3-arylpyridine (blue circle) to a 1,4-addition adduct **30** (scarlet triangle) was observed to reach 95% in 18 min at 110 °C (10 mol % of borane catalyst). During the catalytic turnover, the initially formed dihydropyridine **30** was accumulated in the reaction mixture without being further converted to any compounds. The second transformation started to occur only after the pyridine substrate was completely consumed. Interestingly, this kinetic behavior of pyridines is quite similar to the case of the silylative reduction of quinolines[5a] or α,β-unsaturated nitriles,[5b] reported by us recently.

The subsequent hydrosilylation on a sterically more accessible C═C bond of an enamine intermediate **30** occurred at its peak concentration to deliver the final product, β-silylated tetrahydropyridines **31** (green empty circle) in quantitative yield within 35 min. The ^{1}H NMR analysis showed a constant concentration of a pyridine adduct with $B(C_6F_5)_3$ (~0.05 mmol, ~10 mol %)[5a,b,20] throughout the overall reaction steps, strongly suggesting that this is a resting species. It is noteworthy that the formation of 1,4-dihydropyridines from pyridines is faster than the conversion of the latter to the corresponding β-silylated tetrahydropyridines, whereas the formation of 1,4-addition products from quinolines was shown to be slower relative to the hydrosilylation of preformed 1,4-dihydroquinolines to give β-silylated tetrahydroquinolines.[5a]

Based on the above observations and precedents indicating stepwise process in the reduction of unsaturated compounds,[5,8a−c,21] we propose a mechanistic pathway of the present borane-catalyzed silylative reduction of pyridines (Scheme 4). The silylative reduction is believed to proceed via an ionic

Scheme 4. Proposed Mechanism of the $B(C_6F_5)_3$-Catalyzed Silylative Reduction of Pyridines



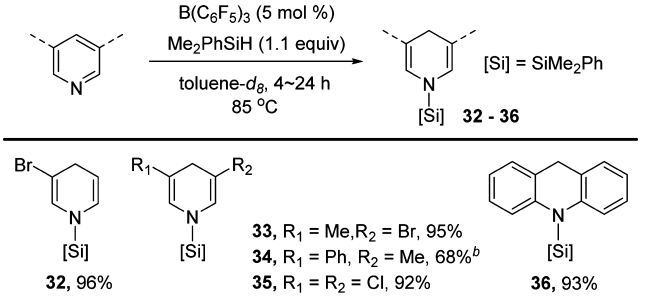
DOI: 10.1021/jacs.5b09209
J. Am. Chem. Soc. 2015, 137, 15176−15184

hydrosilylation pathway involving the transfer of silylium ion (R_3Si^+) to substrates, followed by hydride attack. $B(C_6F_5)_3$ initially forms a stable adduct with pyridines owing to their high basicity leading to **A**,[20] which is the resting species[5a,b] and it is in equilibrium with free pyridines and active species **B**[21e] in the presence of excess silane. The first step is assumed to be the transfer of a silylium ion from an active species **B** to pyridyl nitrogen atom to form a pyridinium ion,[21b] followed by hydride attack at the either C-2 or C-4 site depending on the position of pyridine substituents, yielding two types of dihydropyridines: 2- or 3-substitued pyridines lead to 1,4-dihydropyridines **C** and **D**,[8a−c,9a] while 4-substituted pyridines are reduced in a 1,2-manner to afford 1,2-dihydropyridines **E**.[8f,9b−d]

As the second step, a C=C bond of enamine moieties of the *in situ* generated dihydropyridines is selectively hydrosilylated by the action of an active species **B** at the sterically less demanding *β*-position to the nitrogen atom to liberate the final products **F** and **G** in cases of 3- and 4-substituted pyridines, respectively. When bis-siloxane (e.g., TMDS) was employed in the reaction with 3-substituted pyridines, an intermediate **J**, otherwise being ended as the final product, undergoes an additional hydrosilylation *intramolecularly* under the borane catalysis to give the *O*-bridged bicyclic aza compound **K** bearing double $C(sp^3)$−Si bonds at both C-3 and C-5 positions as the final product. We propose that the double bond in an intermediate **H** reacts with a proton source that is believed to be salts of pyridine[21n] and/or enamine intermediates,[4p,21a] bearing a borohydride counteranion. This proton transfer can lead to an iminium ion, **H′**, which is finally reduced to a *β*-silyl-substituted piperidine **I** via hydride transfer from borohydride at the C-2 position.[4q,10o,21o] Recently, the Oestreich group revealed a mechanistic aspect of the $B(C_6F_5)_3$-promoted hydrosilylation of imines in which an imine substrate undergoes deprotonation by the second imine substrate after the transfer of a silylium ion to the nitrogen atom by the action of $B(C_6F_5)_3$. This gives an enamine intermediate with the generation of an iminium salt bearing a borohydride anion as in our case. The iminium salt *in situ* generated was found to serve as both proton and hydride sources for the reduction of enamine intermediate to the corresponding amine products.[21a] Similarly, indoles were reported to undergo silylation followed by deprotonation with the second indole substrate at the C-3 position to form equimolar amounts of C-3 silylated indole and C-3 protonated iminium salt having a borohydride counteranion.[4p] Based on these published reports, although more comprehensive studies are needed to verify the origin of hydrogen that is required for the conversion of **H** to **I**, we propose that 1,4-dihydropyridine intermediate **C** can undergo dehydrogenative silylation[22] with the generation of salts of pyridine and/or enamines possessing a borohydride anion [LB-H·$(C_6F_5)_3$BH], with which iterative protonation and hydride transfer[23] take place at the C-3 of **H** and then at the C-2 of **H′**, respectively.

In the course of monitoring the reaction by ^{1}H NMR spectroscopy, a series of partially reduced dihydropyridines were found to form with exclusive 1,4-selectivity. Thus, this mechanistic observation led us to envisage selective hydrosilylation of pyridines, giving rise to synthetically valuable 1,4-dihydropyridines[24] by controlling the stoichiometry and sterics of hydrosilanes employed (Scheme 5). We were pleased to see that indeed, when 3-bromopyridine was treated with Me_2PhSiH (1.1 equiv) in the presence of $B(C_6F_5)_3$ catalyst (5 mol %), 1,4-addition product **32** could be formed in 96% yield. Likewise,

Scheme 5. 1,4-Hydrosilylation of Pyridines[a]



[a]Substrate (0.5 mmol), silane (1.1 equiv) and $B(C_6F_5)_3$ (5 mol %) at 85 °C for 4−24 h in a J-Young NMR tube: crude product yields were determined based on the ^{1}H NMR analysis (internal standard: mesitylene). [b]Reaction performed at 110 °C for 24 h.

3,5-disubstituted pyridine derivatives underwent the partial reduction process to furnish the corresponding 1,4-dihydropyridines in good to high yields (**33**−**35**). In a similar manner, acridine reacted smoothly with the silane to provide the desired 1,4-addition product (**36**) in high yield. Unfortunately, those products were too unstable to isolate by conventional silica column chromatography and, therefore, their formation was confirmed by the NMR analysis on the crude reaction mixture (see the Supporting Information for details).

CONCLUSIONS

We have developed a silylative reduction of pyridines accompanied by the concomitant formation of sp^3 C−Si bonds beta to the nitrogen atom of azacyclic products. This silylative reduction process is efficiently mediated by $B(C_6F_5)_3$ catalyst. Depending on the position and nature of pyridine substituents, structurally diverse azacyclic compounds could be obtained selectively. The present transition metal free silylative reduction is convenient to perform even on a large scale with broad scope without any precaution, for example, maintaining inert atmosphere and/or employing high purity of pyridine substrates. Mechanistic investigation revealed that the initial 1,2- or 1,4-hydrosilylation path is controlled by the position of substituents of pyridines. The subsequent hydrosilylation of the *in situ* generated dihydropyridine intermediates was found to be slow, generating a new $C(sp^3)$−Si bond. Formation of the structurally unique bicyclic disiloxane compounds was found to proceed via triple hydrosilylation of 3-substituted pyridines with TMDS involving an intramolecular hydrosilylation as a final and key step. The procedure developed in this study offers a simple but efficient and selective synthetic route to functionalized alkaloids starting from readily available pyridines, thus anticipating its wide applications in synthetic, medicinal, and materials chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09209.

Experimental procedures and characterization (PDF)
X-ray crystallographic data for **1b** (CIF)
X-ray crystallographic data for **2** (CIF)
X-ray crystallographic data for **8** (CIF)
X-ray crystallographic data for **13a** (CIF)
X-ray crystallographic data for **14** (CIF)

DOI: 10.1021/jacs.5b09209
J. Am. Chem. Soc. 2015, 137, 15176−15184

X-ray crystallographic data for **19** (CIF)
X-ray crystallographic data for **24** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is dedicated to Prof. Maurice Brookhart. We thank Jisu Jeong, Dr. Amit B. Pawar, Dr. Seewon Joung, and Jinseong Jeong for their valuable discussions. This research was supported by the Institute for Basic Science (IBS-R010-D1) in Korea.

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(22) In fact, we conducted a series of hydrosilylation reactions of 2-substituted pyridines with hydrosilanes (Et_2SiH_2 or Ph_2SiH_2) with $B(C_6F_5)_3$ catalyst under variable conditions in an effort to observe intermediates having an sp^2 C−Si bond that is believed to be formed via the dehydrogenative enamine silylation. Although some species showing peaks at about 100 ppm in ^{13}C NMR were found to form from the reaction mixture (see the Supporting Information for details) that can be assigned as the proposed olefinic carbons bearing a silyl group, more conclusive evidence is still required to support the reductive pathway from an intermediate **H** to **I** in regard to the origin proton sources.
(23) A hydride transfer from $HB(C_6F_5)_3$ to the postulated C2-carbocation of an intermediate **H**′ would favor an axial attack over equatorial approach on the basis of Felkin's model, thereby affording the *trans* product of **I** selectively, which well accounts for our observed high *trans*-selectivity (>20:1) of a product **1** (see Table 2): (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *9*, 2205.
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