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Communication

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Jianbo Zhang, and Sukbok Chang

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cine-Silylative Ring-Opening of α-Methyl Azacycles Enabled by the Silylium-Induced C–N Bond Cleavage

Jianbo Zhang[†,‡] and Sukbok Chang[*,†,‡]

[†]Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, South Korea
[‡]Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 34141, South Korea

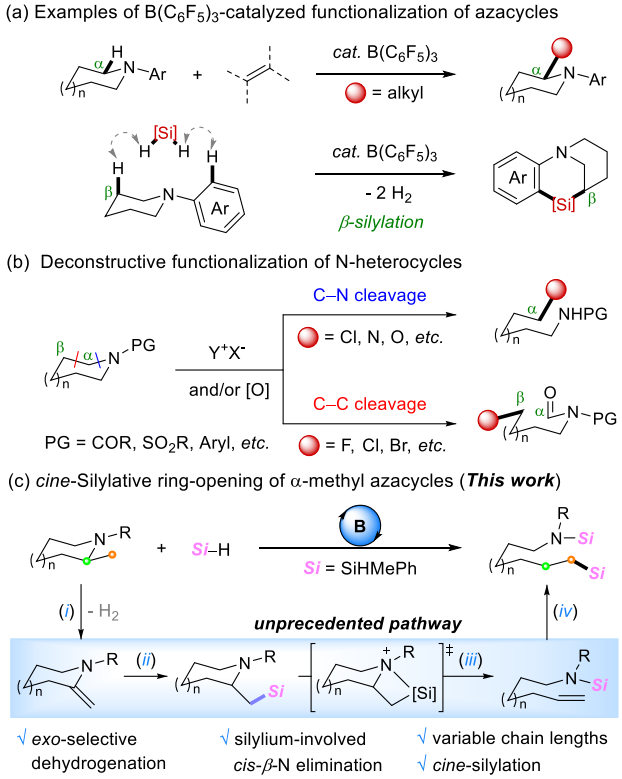
KEYWORDS: borane catalysis, azacycles, silylative C–N bond cleavage, β-silicon effect.

ABSTRACT: Described herein is the development of a borane-catalyzed *cine*-silylative ring-opening of α-methyl azacycles. This transformation involves four-step cascade processes: (i) *exo*-dehydrogenation of alicyclic amine, (ii) hydrosilylation of resultant enamine, (iii) silylium-induced *cis*-β-amino elimination to open the ring skeleton, and (iv) hydrosilylation of terminal olefin. The present borane catalysis also works efficiently for the C–N bond cleavage of acyclic tertiary amines. On the basis of experimental and computational studies, the silicon atom was elucidated to play a pivotal role in the β-amino elimination step.

N-Heterocyclic compounds are widely presented as a key component of numerous natural products, pharmaceuticals and materials.[1] Readily available saturated azacycles such as pyrrolidine and piperidine are versatile synthetic building units allowing an installation of functional groups into the cyclic skeletons (Scheme 1a).[2] In endeavors to achieve site-selective modifications of azacycles, transition metal catalysis has emerged as a powerful tool with the assistance of directing groups while the approaches based on organocatalyst are often limited in scope.[2a] Notably, tris(pentafluorophenyl)borane $B(C_6F_5)_3$ has been appreciated as a versatile catalyst toward various types of N-heterocycle transformations.[3-6] For instance, Wasa,[5a,5b] Paradies[5c] and Wang[5d] have independently reported borane-catalyzed α-alkylation of organoamines by trapping iminium intermediates with alkenes (Scheme 1a, top). Our group previously showed that $B(C_6F_5)_3$-catalyzed a cascade process of β-silylation of N-arylpiperidines via enamine intermediates (Scheme 1a, bottom).[6]

As a complementary strategy, the deconstructive functionalization of N-heterocycles has also drawn an increasing interest in recent years (Scheme 1b).[7,8] This approach provides acyclic amines tethered with remote functional groups. Despite the notable skeletal reorganization associated with the deconstructive transformation, it often suffers from unsatisfactory regioselectivity and poor functional group tolerance due to the oxidative reaction conditions.[7,8] While an *ipso*-functionalized ring-cleavage of N-heterocycles can be achieved by masking the nitrogen atom with suitable protecting groups, the deconstruction of alicyclic amines incorporating organic groups adjacent to the C–N bond (*cine*-substitution)[9] remains highly challenging. In this regard, Sarpong and coworkers recently disclosed a silver-mediated C–C bond cleavage of azacycles to install a halide group at the initial β-carbon to nitrogen (Scheme 1b).[8]

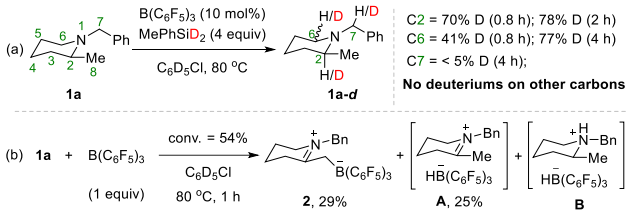
Scheme 1. Functionalizations of Azacyclic Compounds



Given that β-heteroatom elimination was comprehensively elaborated with transition metal complexes,[10] we conceived a $B(C_6F_5)_3$-catalyzed cascade process involving a *cine*-silylative ring-opening of α-methyl azacycles (Scheme 1c). A consecutive tandem process was envisaged operating: (i) *exo*-selective dehydrogenation of N-heterocycles; (ii) hydrosilylation of resultant enamines; (iii) silylium-induced *cis*-β-amino elimination leading to ring-cleavage; and (iv) β-

selective hydrosilylation of terminal alkenes. Described herein is an unprecedented silylative ring-opening of 2-methyl azacycles to access α,ω-aminosilanes that are tethered with variable carbon chains. The procedure was readily expanded to the C–N bond cleavage of acyclic tertiary amines.[11] On the basis of integrated experimental and computational studies, a silylium-involved β-amino elimination was clarified as the crucial step.

Scheme 2. *d*-Scrambling and Stoichiometric Experiments



At the beginning of this study, we attempted to validate our working hypothesis especially on the first step of $B(C_6F_5)_3$-promoted dehydrogenation of azacycles. A deuterium scrambling experiment was performed on *N*-benzyl-2-methylpiperidine (**1a**) given that it contained three types of α-C–H bonds (C2, C6 and C7) (Scheme 2a). When **1a** was subjected to the $MePhSiD_2$ and $B(C_6F_5)_3$ catalytic conditions, deuterium incorporation at the cyclic α-C–H bonds was observed to increase gradually over time at 80 °C. At the earlier stage, the C2–H was deuterated more favorably than C6–H although each incorporation reached a saturation after a prolonged time. In contrast, it was interesting that the benzylic α-carbon (C7) was not deuterated at 80 °C. When **1a** was treated with a stoichiometric amount of $B(C_6F_5)_3$, NMR analyses of the crude reaction mixture showed that a zwitterion species **2** was formed (29%) along with an iminium borohydride **A** (25%) at 80 °C (Scheme 2b).[6,12] These results suggested that the cyclic α-C2–H and C6–H bonds are more labile than the noncyclic C7–H bond under the borane catalysis.

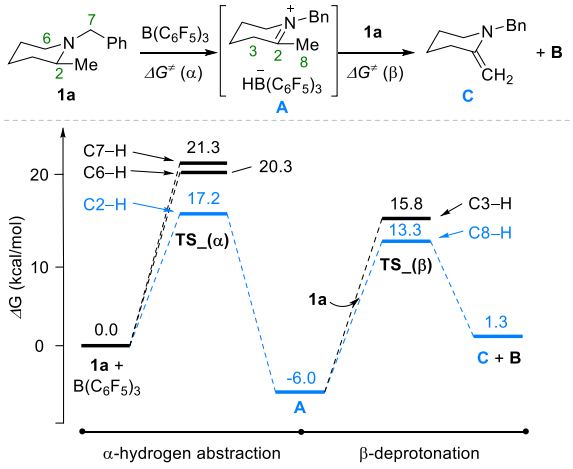
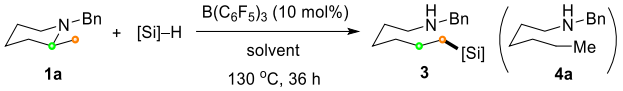


Figure 1. Dehydrogenation path of **1a** by the action of $B(C_6F_5)_3$

To ascertain the feasibility of the hypothesis theoretically, DFT calculations were briefly conducted (Figure 1). When the barrier for each dehydrogenation path was compared, an abstraction of tertiary α-C2–H bond was found to be more favorable by 3~4 kcal/mol over the other sterically less hindered C6–H and benzylic C7–H bonds, thus selectively generating ketiminium **A** bearing $(C_6F_5)_3BH^-$ counteranion. The subsequent β-deprotonation of **A** was computationally validated that a path leading to *exo*-enamine **C** is more feasible than a route to *endo*-enamine by 2.5 kcal/mol (see the Supporting Information for details).

Motivated by the above clues, we initiated an optimization study of a model reaction of **1a** with hydrosilanes and $B(C_6F_5)_3$ catalyst (Table 1). When $PhSiH_3$ (4.0 equiv) was employed in toluene, the reaction afforded a mixture of two ring-opened products: *N*-benzyl-6-(phenyl)silylhexylamine **3a** (16%) and a minor *N*-benzylhexylamine **4a** (6%, entry 1).[13] Yield of **3a** was improved up to 47% by performing the reaction in C_6H_5Cl for 36 h (entries 2–3). The reaction efficiency and selectivity were found to be dependent on the hydrosilanes employed. For instance, while the reaction became sluggish with Et_2SiH_2, no desired product was obtained with Me_2PhSiH (entries 4–5). The yield of 6-silylamine (**3a'**, 60%) was slightly increased when $MePhSiH_2$ was engaged (entry 6). While the reaction efficiency was decreased by lowing the temperature or reducing the catalyst loading (entries 7–8), reaction ran in higher concentration led to an increased ratio of **3a'**/**4a** (entries 9–10).

Table 1. Optimization of Reaction Conditions[a]



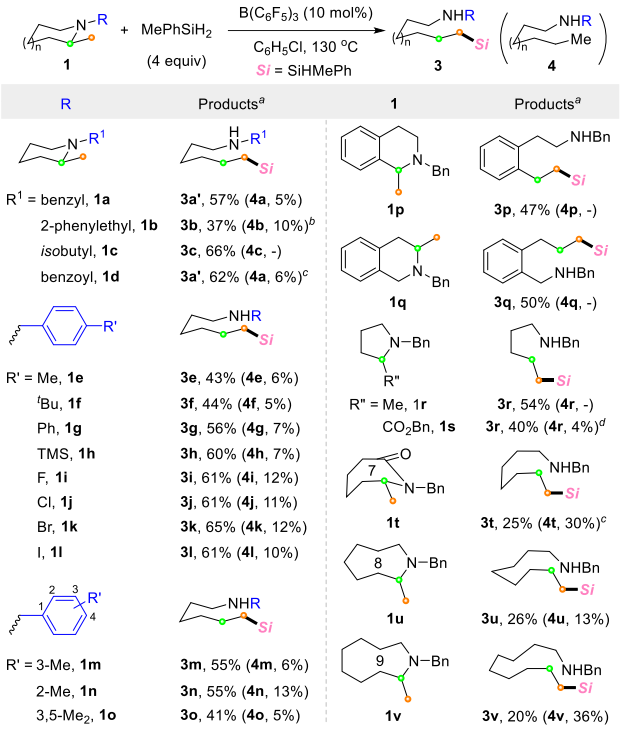
entry	silane	solvent (mL)	conv. (%)[b]	yield (%)[b]
1[c]	$PhSiH_3$	toluene (0.4)	57	16 (6)
2[c]	$PhSiH_3$	C_6H_5Cl (0.4)	80	35 (14)
3	$PhSiH_3$	C_6H_5Cl (0.4)	93	47 (19)
4	Me_2PhSiH	C_6H_5Cl (0.4)	25	< 5 (-)
5	Et_2SiH_2	C_6H_5Cl (0.4)	48	33 (9)
6	$MePhSiH_2$	C_6H_5Cl (0.4)	93	60 (14)
7[d]	$MePhSiH_2$	C_6H_5Cl (0.4)	29	< 5 (-)
8[e]	$MePhSiH_2$	C_6H_5Cl (0.4)	80	50 (17)
9	**$MePhSiH_2$**	**C_6H_5Cl (0.1)**	**99**	**65 (6)**
10	$MePhSiH_2$	C_6H_5Cl (1.0)	60	26 (10)

[a] $B(C_6F_5)_3$ (10 mol%), substrate **1a** (0.2 mmol), silane (4 equiv), and solvent at 130 °C for 36 h. [b] Conversion of **1a** and yields of **3** (**4a**) were determined by ^1H NMR analysis of the crude mixture. [c] For 24 h. [d] Performed at 110 °C. [e] $B(C_6F_5)_3$ (5 mol%) was added.

With the optimized conditions in hand, we surveyed the scope of azacyclic substrates (Table 2). Substituents on the nitrogen atom were first examined. 2-Methylpiperidines bearing N-alkyl groups were smoothly converted to the corresponding acyclic aminosilanes (**3a'**–**3c**, 37~66%). N-Carbonyl protected substrate **1d** was ring-opened with concomitant deoxygenation to give **3a'** in good yield. Next, variation of the N-benzyl group of 2-methylpiperidines was examined to find that alkyl, phenyl or silyl substituents at the *para*-position did not alter the reaction efficiency (**3e**–**3h**, 43~60%). Moreover, the *cine*-silylative ring-opening of substrates having halide substituents all took place smoothly to furnish the desired α,ω-silylamines (**3i**–**3l**, 61~65%) together with minor non-silylative compounds (**4i**–**4l**, 10~12%). N-Benzyl groups bearing *meta*- or *ortho*-

substituents were also viable for the current reaction (**3m**–**3o**, 41~55%). Tetrahydroisoquinoline derivatives (**1p**–**1q**) underwent the ring-opening process to afford 1,n-silylamine products in modest yields (**3p**–**3q**, 47~50%). This reaction was observed to be highly flexible to the ring size. 2-Methylpyrrolidine was readily applicable (**3r**, 54%), and proline derivative **1s** was ring-opened to afford **3r** in 40%. Interestingly, the reaction efficiency was slightly decreased upon increase of the ring size. When 7-methylcaprolactam (**1t**) was tested, carbonyl-reduced ring-cleavage product was obtained in moderate yield, and the present borane catalysis was also operative for the 8- and 9-membered azacycles (**1u**–**1v**).

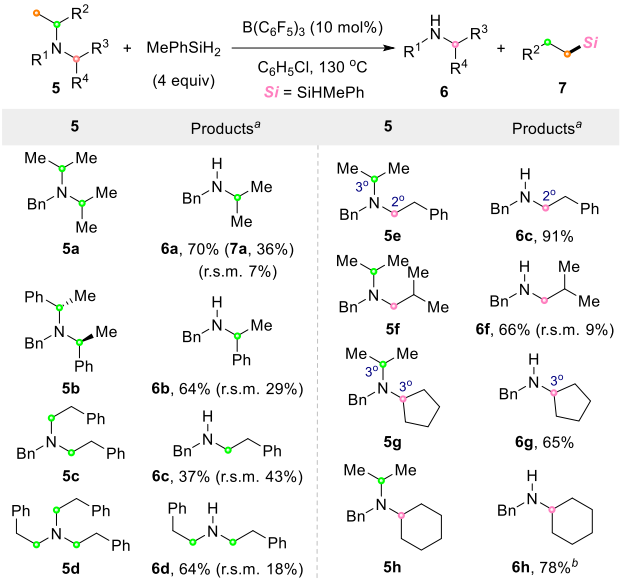
Table 2. Scope of the Silylative Ring-Opening of Azacycles[a]



[a]$B(C_6F_5)_3$ (10 mol%), substrate (0.4 mmol), $MePhSiH_2$ (4 equiv), and C_6H_5Cl (0.2 mL) at 130 °C for 36 h. Isolated yields. [b]Methyl(2-phenethyl)(phenyl)silane (11%) was obtained. [c]$MePhSiH_2$ (6 equiv) was added. [d]$MePhSiH_2$ (8 equiv) was added.

Next, we wondered whether this transformation would be applicable for the C–N bond cleavage of acyclic tertiary amines (Table 3). For tertiary amines possessing two identical α-methyl-containing substituents (**5a**–**5b**), the reaction furnished the secondary N-benzylamine products (**6a**–**6b**, 70~64%) along with alkylsilanes (e.g., **7a**), formed by a borane-catalyzed hydrosilylation of alkenes generated *in situ* from the C–N bond cleavage.[14] Significantly, this process took place efficiently also for the substrates lacking an α-methyl group (**5c**–**5d**, 37~64%). The protocol was highly selective for the activation of tertiary C–N bond as demonstrated by **5e** and **5f**, which have both α-secondary and tertiary carbon centers (**6c** and **6f**, 91%~66%). Interestingly, it also displayed a distinctive reactivity difference between cyclic and acyclic 3° carbon centers. For instance, substrates **5g** and **5h** were converted to N-benzylcycloalkylamines exclusively (**6g**–**6h**, 65~78%), suggesting that an acyclic tertiary C–N bond is more reactive than the corresponding cyclic counterpart. It is worth noting that the benzylic C–N bond having lower bond-dissociation energy (BDE) remained intact while aliphatic C–N bonds with higher BDEs reacted selectively under the present borane catalysis.[11b,15]

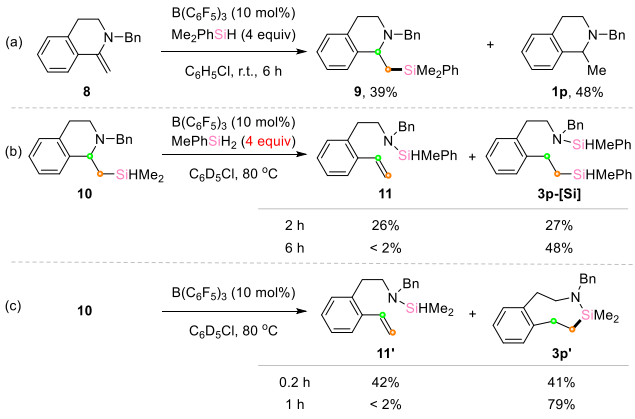
Table 3. Scope of the Silylative Deconstruction of Acyclic Tertiary Amines[a]



[a]$B(C_6F_5)_3$ (10 mol%), substrate (0.4 mmol), $MePhSiH_2$ (4 equiv), and C_6H_5Cl (0.2 mL) at 130 °C for 36 h. Isolated yield. [b]For 7 days. r.s.m. = recovery of starting material.

To shed light on the reaction pathway, a series of mechanistic experiments were carried out (Scheme 3). An independently prepared *exo*-enamine **8** underwent a $B(C_6F_5)_3$-catalyzed hydrosilylation to afford β-silylazacycle **9** (39%) with a reduced compound **1p** (48%, Scheme 3a).[14,16] In fact, the interconversion between the saturated amine and its enamine species was known to be in equilibrium under the borane catalysis.[6,17] Thereafter, when β-silylazacycle **10** was treated with $MePhSiH_2$ (4 equiv) and $B(C_6F_5)_3$ catalyst at 80 °C, an alkene intermediate **11** was observed at the early stage and then hydrosilylated to afford the final product **3p**-[**Si**] (Scheme 3b).

Scheme 3. Investigation of Reaction Intermediates



Notably, this ring-cleavage was observed to proceed even in the absence of $MePhSiH_2$ (Scheme 3c), indicating that the external hydrosilane is not required for the C–N bond cleavage. However, no reaction occurred in the absence of borane catalyst. These results strongly support our initial assumption that the ring-opening process is operative via a silylium-involved β-amino elimination (Scheme 1c).

In an effort to better understand the ring-cleavage process, density functional theory (DFT) studies were conducted (Figure 2). Given that the external hydrosilane does not incorporate in the C–N bond cleavage process (Scheme 3c), a borane-promoted intramolecular activation of β-silylazacycle **D** was considered. Indeed, a bicyclic silylammonium species **E** was accessible by the $B(C_6F_5)_3$ catalysis, and this process was estimated to be exergonic (**D** → **E**, ΔG = -8.9 kcal/mol).[18]

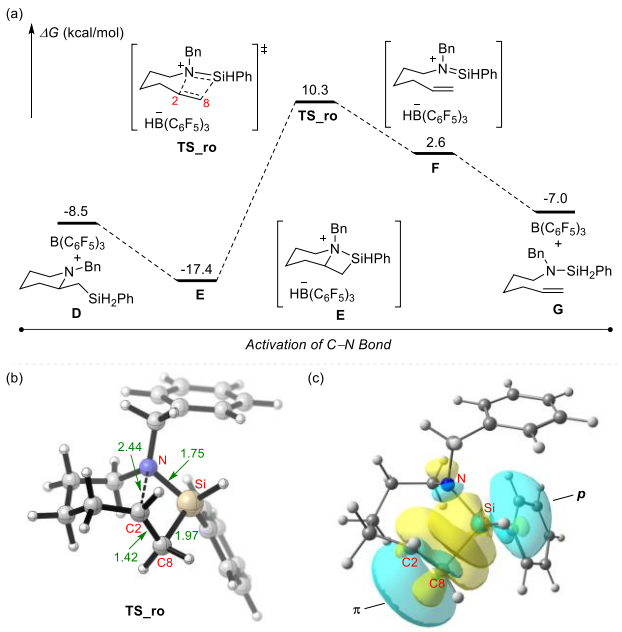
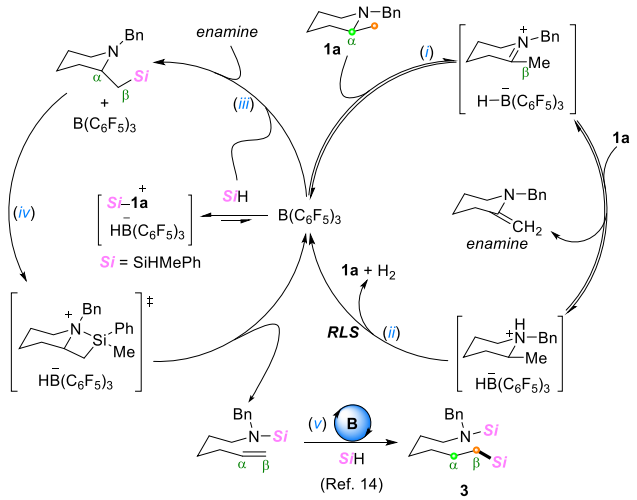


Figure 2. (a) Energy profile (kcal/mol) for the *cine*-silylative ring-opening of azacycles calculated at the level of M06-2X(SMD, chlorobenzene)/6-311++G(d,p)//M06-2X/6-31G(d,p) (403.15 K, 1.0 atm). (b) Computed model of **TS_ro**. (c) NBO analysis of **TS_ro**: overlap of π- and *p*-orbitals in three-dimensional orbital rendering. Bond distances in Å. Counteranion: $[HB(C_6F_5)_3]^-$.

Barrier for the subsequent ring-opening process traversing the transition state **TS_ro** was computed to be 27.7 kcal/mol leading to a silaniminium intermediate **F**, and then a hydride transfer from $(C_6F_5)_3BH^-$ to the N=Si double bond afforded N-silylaminoalkene **G**.[10,19] It was noteworthy that the transition state **TS_ro** displayed both C2–N bond (2.44 Å) and C8–Si bond (1.97 Å) greatly elongated, while C2–C8 (1.42 Å) and N–Si bond (1.75 Å) showed double bond characters (Figure 2b).[20] As illustrated in Figure 2c, a second-order perturbation natural bond orbital (NBO) analysis of **TS_ro** was executed to reveal that the relatively low activation barrier was attributed to a considerable stabilization of **TS_ro** by means of a significant π-donation from the π-C2–C8 bond to the proximal silicon *p*-orbital, also known as the β-silicon effect.[21]

According to the above experimental and computational rationale as well as the precedents,[3-6,10-12,14,17] a reaction pathway of the $B(C_6F_5)_3$-catalyzed *cine*-silylative ring-cleavage of α-methyl azacycles is depicted in Scheme 4. We propose that the overall transformation involves four-step cascade processes: (i) reversible *exo*-dehydrogenation of α-methylpiperidine **1a** to enamine via consecutive α-hydrogen abstraction and β-deprotonation;[5,6,12,17] (ii) rate-limiting liberation of H_2 from $[\mathbf{1a}\text{-}H^+][(C_6F_5)_3BH^-]$ salt ($\Delta G^{\neq}$ = 35.2 kcal/mol, see the Supporting Information for details);[3c,3d,6,17] (iii) hydrosilylation of enamine to form β-silylpiperidine;[4,6] (iv) ring-opening C–N bond cleavage enabled by *cis*-β-amino elimination of 2-silazetidinium intermediate leading to N-silylaminoalkene;[10,18] and (v) β-selective hydrosilylation of the olefin to give final product **3**.[14]

Scheme 4. Proposed Catalytic Pathway



In summary, we have developed an unprecedented borane-catalyzed *cine*-silylative ring-opening of α-methyl azacycles. The current $B(C_6F_5)_3$-catalyzed silylative transformation was found to operate for not only medium-sized azacycles but also acyclic tertiary amines. Experimental and computational studies revealed that the conversion constitutes a series of cascade processes promoted by borane catalysis, wherein the β-silicon effect plays an important role to facilitate the ring-opening C–N bond cleavage process.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* sbchang@kaist.ac.kr

Notes

The authors declare no competing financial interest.

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Table of Contexts (TOC)