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Boron-Catalyzed Silylative Reduction of Quinolines: Selective sp^3 C–Si Bond Formation

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Ⓢ *Supporting Information*

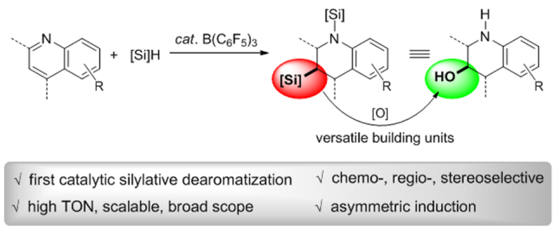
ABSTRACT: A silylative reduction of quinolines to synthetically versatile tetrahydroquinoline molecules involving the formation of a $C(sp^3)$–Si bond exclusively β to nitrogen is described. Triarylborane is a highly efficient catalyst (up to 1000 turnovers), and silanes serve as both a silyl source and a reducing reagent. The present procedure is convenient to perform even on a large scale with excellent stereoselectivity. Mechanistic studies revealed that the formation of a 1,4-addition adduct is rate-limiting while the subsequent $C(sp^3)$–Si bond-forming step from the 1,4-adduct is facile.

Chemical reduction of multiple bonds of readily available chemical feedstocks is one of the most fundamental transformations in organic chemistry.[1] In particular, the reductive transformation of N-heteroaromatics such as quinolines is of special interest since the reduced products (tetrahydroquinolines) are important building blocks as well as versatile intermediates in the synthesis of alkaloids, pharmaceuticals, and agrochemicals.[2] Although *stoichiometric* metal hydrides (including $NaBH_4$ and $LiAlH_4$) or reactive metals (e.g., Na) have been employed for the reduction of N-heteroaromatics, these methods suffer from lack of chemo- and regioselectivity, limited substrate scope, and generation of copious amounts of waste.[3] In this regard, hydrogen gas is undoubtedly one of the most straightforward and atom-efficient means to effect reduction, thereby leading to a number of catalytic hydrogenation procedures of aromatic N-heterocycles.[4] However, these processes are typically operated under high pressure (H_2) and/or at elevated temperature, giving rise to exhaustive reduction products. From a synthetic point of view, such a tendency toward complete reduction of N-heterocycles with H_2 limits opportunities for the construction of *functionalized* alkaloids.

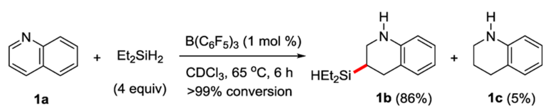
On the other hand, hydrosilanes have been used as a convenient and cheap alternative to H_2 in the metal-mediated reductive conversion of N-heteroaromatics, often leading to partially reduced products.[5] Recently, tris(pentafluorophenyl)borane [$B(C_6F_5)_3$] and related Lewis acid analogues have been shown to be viable catalysts for the hydrogenation[6] and hydrosilylation[7] of unsaturated compounds such as imines, olefins, and/or N-heteroaromatics. Being aware of the advantages of adopting metal-free protocols and also utilizing the excellent catalytic activity of $B(C_6F_5)_3$ in the hydrosilylation of imines, we envisaged that the silylative dearomatization of N-heterocycles accompanied by the generation of a $C(sp^3)$–Si bond in the reduced products would be plausible via consecutive hydrosilylations under Lewis acidic catalytic conditions.

Herein we report the development of a boron-catalyzed silylative reduction of quinolines (Scheme 1) in which the N-aromatic is converted to a piperidinyl unit with the incorporation of a $C(sp^3)$–Si bond exclusively β to the nitrogen atom. The process is highly diastereoselective in that the pre-existing substituents control the syn or anti relationship in a predictable manner. In this procedure, the silane plays a dual role as an incorporating silyl source as well as a reducing agent. Considering the fact that the C–Si bond is synthetically equivalent to a C–OH bond, our procedure creates a catalytic route to versatile synthetic building units of functionalized alkaloids. The present catalytic system is highly efficient, achieving turnover numbers (TONs) of up to ~1000, and is workable on a large scale.

Scheme 1. Catalytic Silylative Reduction of Quinolines



Inspired by recent reports of metal-catalyzed hydrosilylation of N-aromatic compounds,[5b,c] we initially chose Et_2SiH_2 as a reducing agent for the reductive hydrosilylation of quinoline (**1a**) using 0.01 equiv of $B(C_6F_5)_3$ as a catalyst in $CDCl_3$ (eq 1).



(1)

Monitoring of this reaction by ^1H NMR spectroscopy revealed that it proceeded smoothly to give quantitative conversion within 6 h at 65 °C, affording 1,3-bis-silylated tetrahydroquinoline as a major product; a minor product that does not bear a C–Si bond was also detected. The N-silylated species were readily converted

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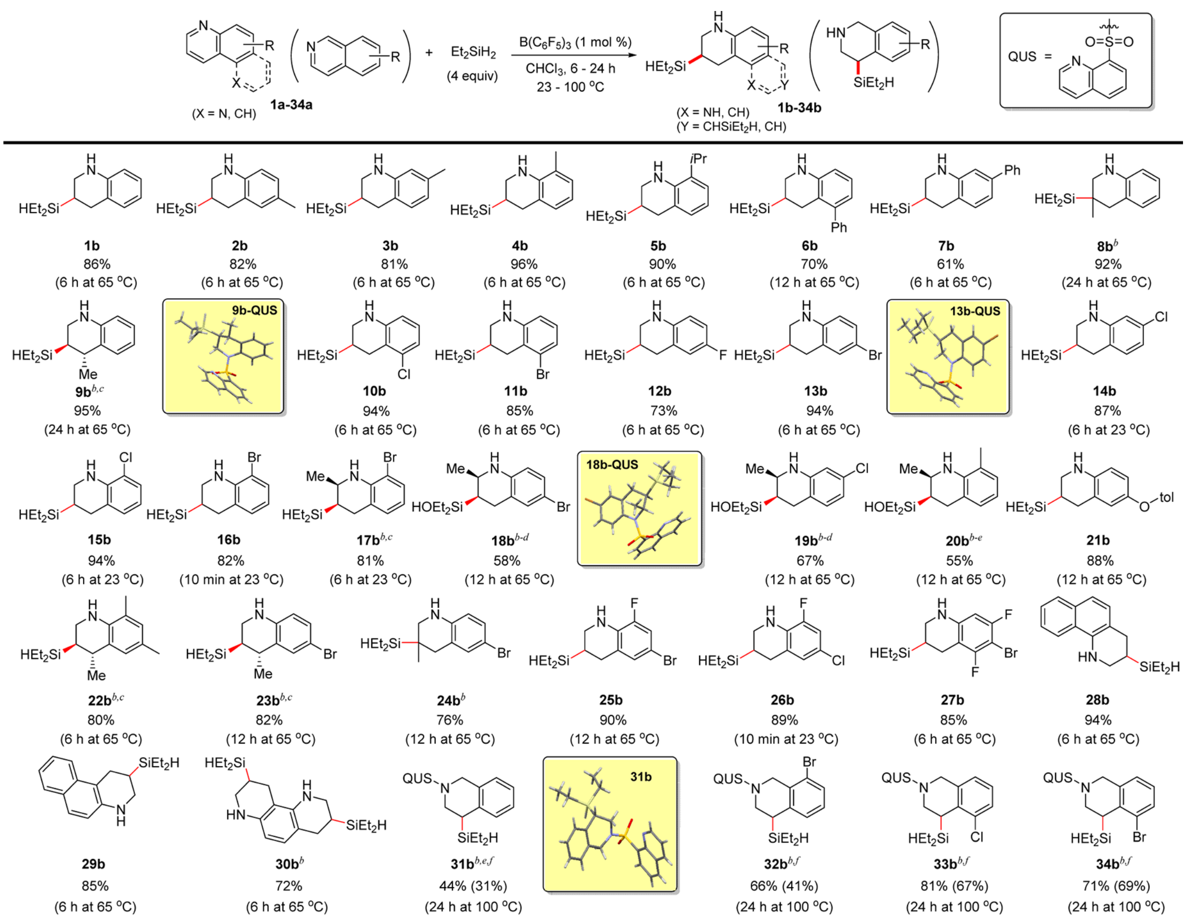
Table 1. Substrate Scope in the Silylative Reduction[a]



[a]Reactions were conducted on a 0.5 mmol scale (substrate) in $CHCl_3$ (0.5 mL), and yields are for isolated compounds unless otherwise stated. [b]8 equiv of Et_2SiH_2. [c]Obtained as a single diastereomer. [d]Isolated as the silanol after hydrolytic oxidation using $[Ru(p\text{-cymene})Cl_2]_2$ as a catalyst (ref 8). [e]5 mol % $B(C_6F_5)_3$ catalyst. [f]Crude yields of initially formed products and isolated yields of N-protected derivatives are shown in parentheses.

to the corresponding isolable N–H products **1b** and **1c** in 86% and 5% yield, respectively, upon silica gel chromatography.

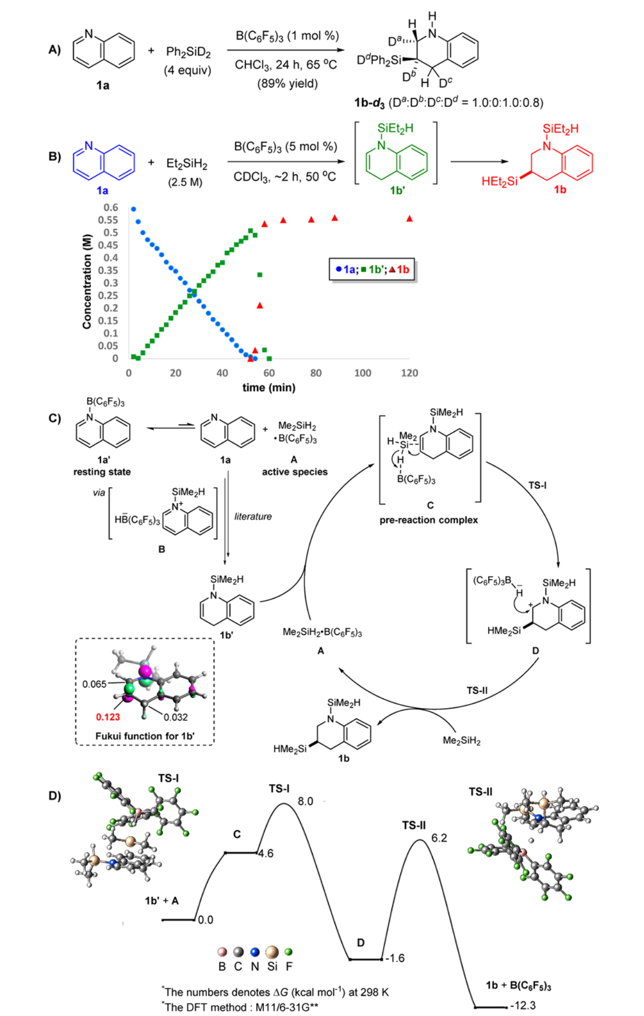
Encouraged by this finding of an unusual silylative reduction of quinoline, we next investigated the optimization of the reaction conditions (scope of silanes and effects of solvent) in the reaction of **1a** using 1 mol % $B(C_6F_5)_3$ at 65 °C [see the Supporting Information (SI)]. This revealed that the use of sterically analogous silanes such as Ph_2SiH_2, $MePhSiH_2$, and Me_2PhSiH also resulted in the formation of the silylated product in yields and selectivities comparable to those obtained from Et_2SiH_2. Along this line, the reactions with bulkier silanes such as $^tBu_2SiH_2$, Et_3SiH, and Ph_3SiH became sluggish, leading to **1b** in low yields under the same conditions. In addition, the reduction efficiency was moderate when 1,1,3,3-tetramethyldisiloxane (TMDS) was employed to afford **1b** in 78%, whereas polymethylhydrosiloxane (PMHS) did not give **1b**. Among various solvents screened, $CHCl_3$ was the most effective and thus was chosen for the subsequent studies, although the solvent effects were not substantial.

With the optimized conditions [1 mol % $B(C_6F_5)_3$, 4 equiv of Et_2SiH_2, $CHCl_3$, 65 °C, 6–12 h],[9] the reactivity scope of quinolines was explored (Table 1). Quinolines bearing a methyl group at C6, C7, or C8 underwent the reaction efficiently to give the silylated products (**2b–4b**) in high yields (81–96%). 8-Isopropylquinoline and 5- and 7-phenylquinoline were also viable under the optimal conditions, giving **5b**, **6b**, and **7b** in 90%, 70%, and 61% yield, respectively. 3-Methylquinoline was efficiently converted to the corresponding product **8b** with the formation of a *quaternary* $C(sp^3)$–Si bond. The reaction of 4-methylquinoline was highly selective, leading exclusively to the trans product **9b**;[10] longer reaction times (24 h) were required, however. We were pleased to observe that substrates bearing chloro, bromo, or fluoro groups at C5–C8 were selectively reduced to their corresponding products (**10b–16b**) in good to excellent yields. It was notable that the reductions of 7-chloro-, 8-chloro-, and 8-bromoquinoline (**14a–16a**) occurred with high efficiency, *even at room temperature,* in short reaction times (10 min for **16b**).

We next investigated quinolines having multiple substituents. 2-Methylquinolines bearing halides (**17a–19a**) or an additional methyl group (**20a**) were readily converted to the corresponding products (**17b–20b**) in moderate to good yields. The relative stereochemistry between the pre-existing methyl group and the newly generated silyl group was determined to be cis, which can be rationalized by an anti addition of Si–H to a double bond by virtue of the $B(C_6F_5)_3$ catalyst.[7c] A substrates having an aryloxy group at C6 (**21a**) was converted to the desired product (**21b**) in 88% yield without unwanted cleavage of the C_{aryl}–O bond, thus proving the tolerance of those building units. Moreover, quinolines multisubstituted at various positions were also facile for the silylative reduction, leading to the desired products **22b–27b** in good yields. We also explored the reactivity of polyaromatics and isoquinolines. Benzoquinolines were highly reactive, affording products **28b** and **29b** in excellent yields. As expected, both N-aromatic rings of 1,7-phenanthroline were reduced, leading to bis-silylated product **30b** in good yield.[11] Although isoquinoline reacted rather slowly to give a moderate yield of product **31b** under more forcing conditions, the silyl group was still installed at the position β to nitrogen. On the other hand, having halide substituents on isoquinolines increased the reactivity while maintaining high regioselectivity, giving moderate to good yields of N-sulfonylated products (**32b**−**34b**).

In order to gain insights into the reaction pathway, a series of mechanistic experiments were performed (Scheme 2). When the

Scheme 2. Preliminary Mechanistic Studies



reduction of **1a** was conducted with Ph_2SiD_2, the silylated product **1b-*d*₃** was obtained with complete incorporation of deuterium at C2 and C4 but without deuteration at C3 (Scheme 2A), indicating that a highly regioselective pathway is operative under the present reduction conditions. Similarly, when quinoline-d_7 was treated with Et_2SiH_2, the proton was incorporated only at C2 and C4 (see the SI).

Next, we monitored the reaction progress by ^{1}H NMR spectroscopy with two different initial concentrations of silane (Scheme 2B). Linear consumption of **1a** (blue circles) was observed at the lower initial concentration (0.9 M Et_2SiH_2) to afford the 1,4-addition adduct **1b′**, giving rise to about 50% conversion in 2 h with an initial rate (v_i) of 0.00248 M min^{-1} (see the SI). The same reaction at higher initial concentration (2.5 M Et_2SiH_2) displayed faster and quantitative formation of **1b′** (green squares) in 1 h (v_i = 0.01044 M min^{-1}), and then rapid consumption of the accumulated **1b′** furnished **1b** as the final product (red triangles) within 5 min (Scheme 2B). In addition, an adduct of **1a** with borane, $(C_9H_7N)B(C_6F_5)_3$ (**1a′**),[12] was clearly observed by NMR spectroscopy during the conversion of **1a** to **1b′**. As a result, this study led us to propose that (i) the final product **1b** is formed via a 1,4-addition adduct **1b′**; (ii) the formation of **1b′** from quinoline is the rate-limiting step; (iii) the formation of **1b′** is first-order-dependent on the silane concentration; (iv) the conversion of the 1,4-addition intermediate **1b′** to the final product **1b** begins almost at the peak concentration of **1b′**; and (v) a quinoline−borane adduct (**1a′**) is a resting species.

On the basis of the above observations, we propose the reaction pathway for the $B(C_6F_5)_3$-catalyzed silylative reduction of **1a** shown in Scheme 2C. In parallel, an energy profile for this catalysis was computed by carrying out density functional theory (DFT) calculations using Me_2SiH_2 as a model silane (Scheme 2D). The reaction is proposed to work largely via two stages: formation of the 1,4-addition adduct **1b′** (rate-limiting) and subsequent hydrosilylation. Initially, $B(C_6F_5)_3$ rapidly forms a stable adduct with **1a**, leading to **1a′** as a resting species. The 1,4-adduct formation takes place with the active species, the borane−silane complex $(C_6F_5)_3B{\cdot}H_2SiMe_2$ (**A**), by transfer of its silylium cation to **1a** to form quinolinium salt **B** possessing a borohydride anion, in which the hydride is then delivered to C4 of **B** to release 1,4-adduct **1b′**.[5b,c,6e,13,14] Interestingly, rapid buildup of the silylating reagent **A**[15] occurs only after nearly complete conversion of **1a** to **1b′**, and thus, completion of the first reduction is required before the second reduction cycle can be initiated. Most importantly, following quantitative conversion of **1a** to **1b′**, the C2−C3 π electrons (**1b′**) interact with the electron-deficient silicon of a boron-coordinated hydride to form prereaction complex **C**.[16] An electrophilic silyl group of **C** is then transferred selectively to C3, forming a new $C(sp^3)$−Si bond to give intermediate **D**[7b] via transition state **TS-I** involving a small barrier of 8.0 kcal mol^{-1} (calculated relative to **1b′** + **A**). The final product **1b** is eventually liberated by hydride attack at C2 of intermediate **D** with the regeneration of active species **A** via transition state **TS-II**. The energy barrier for this hydride transfer to cationic C2 of **D** was calculated to be 7.8 kcal mol^{-1}. Overall, the pathway furnishing the substitution into **1b** from **1b′** via two transition states **TS-I** and **TS-II** requires only ∼8.0 kcal mol^{-1} of free energy. Such low energy barriers are consistent with the kinetic behavior of a rapid conversion of **1b′** to **1b** (Scheme 2B).

Furthermore, we calculated the Fukui function $f^{\,-}$ of **1b′** (shown in the dotted rectangle at the left in Scheme 2C) in an attempt to rationalize the observed β-silylation (C3) selectivity.[17] This revealed that electron density at C3 of **1b′** is most viable for the external electrophile transfer (Me_2HSi^+) relative to those at other positions, thereby resulting in a $C(sp^3)$−Si bond β to the nitrogen atom (see the SI).

The synthetic utility of the present silylative reduction was also explored (Scheme 3). The reaction of benzoquinoline (**28a**) was performed successfully on a gram scale using 0.1 mol % $B(C_6F_5)_3$ to give a 95% yield of product **28b** (TON ≈ 1000), and subsequent N-benzylation and Tamao oxidation of **28b**[18] delivered *N*-benzyl-*β*-hydroxytetrahydrobenzo[*h*]quinoline (**36**) in high yield (Scheme 3A). Similarly, reactions of various quinoline derivatives (**1a**, **8a**, **9a**, and **10a**) worked well on a large scale, leading to the corresponding products **1b**, **8b** (quaternary

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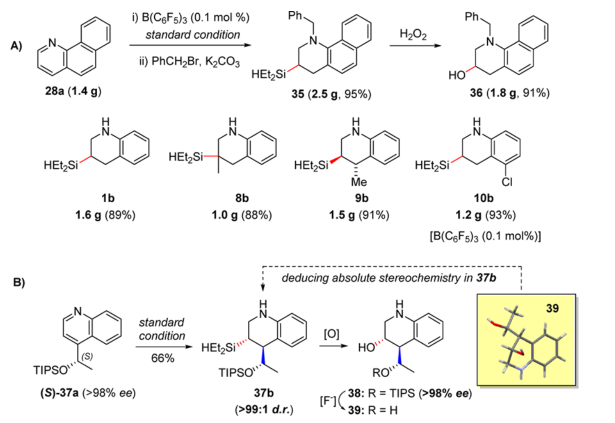
Scheme 3. Synthetic Applications



C−Si bond), **9b** (trans stereochemistry), and **10b** (TON ≈ 1000), all in high yields.

To examine a plausible asymmetric induction, the optically active quinoline (*S*)-**37a** was subjected to the silylative reduction. Pleasingly, a single diastereomeric product **37b** (>99% d.r.) was found to form with the concomitant generation of two new stereogenic centers (Scheme 3B), the stereochemistry of which was determined after conversion of **37b** to **39** (crystal structure is shown) in two steps via **38** (>98% ee).

In summary, we have developed a silylative reduction of quinolines catalyzed by $B(C_6F_5)_3$ in which a new $C(sp^3)$−Si bond is generated exclusively β to nitrogen. The reaction scope is broad, including quinolines, benzoquinolines, and isoquinolines, and the stereochemistry of the silylative reduction products was controlled by the position (C2 and C4) of substituents of the substrates. The rate-limiting step was found to be the formation of the initial 1,4-addition adduct, while the subsequent silylation is rather facile. This procedure is convenient and scalable, giving high turnover numbers (up to 1000). Asymmetric induction was also realized (>99% d.r.), offering a new route to functionalized alkaloids that can be used in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(9) Initial mixing of $B(C_6F_5)_3$ and Et_2SiH_2 in $CHCl_3$ followed by the addition of **1a** resulted in a higher yield of **1b** (86%) than when the silane was added last into a solution of $B(C_6F_5)_3$ and **1a** in $CHCl_3$ (79%) (see the SI). Thus, we applied the former protocol to the other substrates in this study unless otherwise specified.

(10) The resulting anti (trans) relationship between the two groups at C3 and C4 in **9b** is especially noteworthy in view of the fact that the $B(C_6F_5)_3$-catalyzed hydrosilylation of 1-methyl-1-cyclohexene resulted in the corresponding cis product (see ref 7c.).

(11) The relative stereochemistry of the two newly generated C−Si bonds was not determined.

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