Reduction

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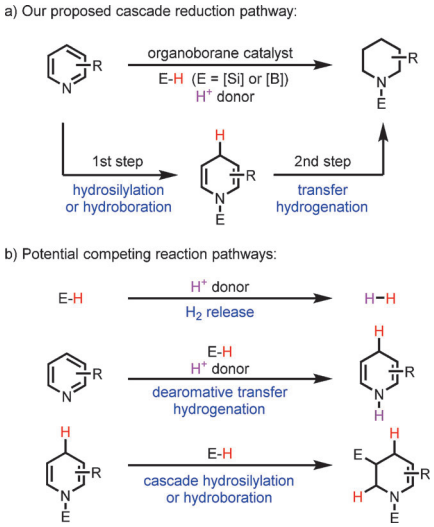
$B(C_6F_5)_3$-Catalyzed Cascade Reduction of Pyridines

*Zhi-Yun Liu, Zhi-Hui Wen, and Xiao-Chen Wang**

Abstract: *$B(C_6F_5)_3$ has been found to be an effective catalyst for reduction of pyridines and other electron-deficient N-heteroarenes with hydrosilanes (or hydroboranes) and amines as the reducing reagents. The success of this development hinges upon the realization of a cascade process of dearomative hydrosilylation (or hydroboration) and transfer hydrogenation. The broad functional-group tolerance (e.g. ketone, ester, unactivated olefins, nitro, nitrile, heterocycles, etc.) implies high practical utility.*

The catalytic reduction of pyridines is a research subject of significant interest to the synthetic community since the reduced products, including piperidines and partially reduced azacyclic compounds, are prevalent building blocks for the syntheses of many bioactive alkaloids and commercial drugs.[1] Extensive efforts have been made for the development of transition metal catalyzed hydrogenations of pyridines using various heterogeneous[2] and homogeneous[3] catalysts. However, harsh reaction conditions and the use of precious metals were often required for efficient catalytic turnover. These requirements have limited the substrate scope and the practical utility of these methods. In contrast, with the development of frustrated Lewis pair chemistry,[4] several studies of metal-free organoborane-catalyzed pyridine reductions have appeared in the literature over the past few years, including hydrogenations developed by the groups of Stephan,[5] Du,[6] and Crudden,[7] the 1,4-hydroboration developed by the group of Wang,[8] the cascade hydrosilylation developed by the group of Chang,[9] and the transfer hydrogenation developed by the group of Du.[10] Despite these advances, there are still drawbacks: 1) For hydrogenation and transfer-hydrogenation reactions,[5–7,10] the presence of bulky *ortho* substituents on the pyridine ring was necessary to circumvent the deactivation of catalysts by the coordination of the nitrogen atom; 2) Unsaturated functional groups such as alkenes, esters, ketones, nitriles, and nitro groups are rarely compatible because they were prone to reduction.

In a search for a general and operationally simple methodology, we envisioned that pyridine reduction might be alternatively achieved by an organoborane-catalyzed cascade process, consisting of either a dearomative 1,4-hydroboration[8] or hydrosilylation,[9,11] and subsequent transfer hydrogenation[10,12] of the enamine double bonds, by using either a hydroborane or a hydrosilane, and a proton donor, as reductants (Scheme 1 a). In this way, either the boryl or the silyl group would become a protecting group for the nitrogen atom, thereby effectively preventing its deactivation of catalysts. At the same time, a judicious choice of the hydrogen source with careful tuning of the reaction conditions might provide the desired chemoselectivity for reductions at the pyridine ring while preserving other reducible functional groups.



Scheme 1. Reduction of pyridines by a cascade process.

At the outset, we were aware that our proposed cascade reduction would face several key challenges (Scheme 1 b). First, instead of reacting with pyridines, hydroboranes and hydrosilanes might directly react with the proton donor to release H_2.[12c,d] Second, it was unclear whether the initial dearomative hydroboration or hydrosilylation would be faster than the competitive dearomative transfer hydrogenation. Should the latter reaction occur, the formed unprotected dihydropyridine would be a strong inhibitor for the catalyst in the absence of bulky *ortho* substituents.[10] Third, either a cascade hydroboration or hydrosilylation[9] might proceed to give the C-boryl- or C-silyl-substituted, respectively, heterocycles.

With these challenges in mind, we commenced our study with the *meta*-substituted pyridine **S1** as the model substrate and the commercially available $B(C_6F_5)_3$ as the catalyst to test various reaction conditions (Table 1). In the presence of 10 mol% $B(C_6F_5)_3$, treatment of **S1** with 9-BBN and Ph_2NH in toluene at 110 °C for 24 hours failed to give any product (entry 1). However, when HBcat was applied, the desired

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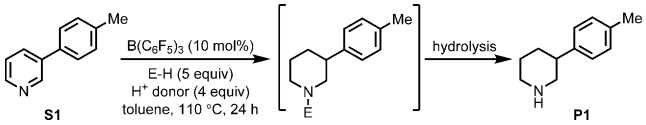
Table 1: Optimization of reaction conditions.[a]



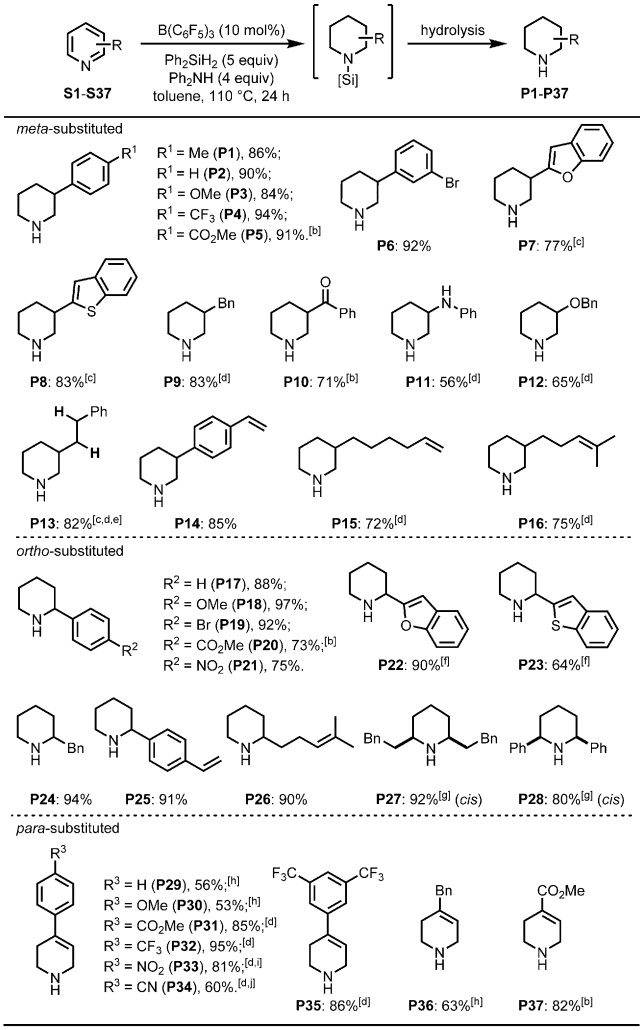
Entry	E-H	H^+ donor	Yield [%][b]
1	9-BBN	Ph_2NH	n.d.
2	HBcat	Ph_2NH	18
3	HBpin	Ph_2NH	84
4	Ph_3SiH	Ph_2NH	n.d.
5	Et_3SiH	Ph_2NH	n.d.
6	Et_2SiH_2	Ph_2NH	40
7	$PhMe_2SiH$	Ph_2NH	86
8	Ph_2SiH_2	Ph_2NH	89
9	Ph_2SiH_2	$PhNH_2$	28
10	Ph_2SiH_2	Ph(Me)NH	50
11	Ph_2SiH_2	Ph(*p*-$CF_3C_6H_4$)NH	n.d.
12	Ph_2SiH_2	*n*Pr_2NH	n.d.
13	Ph_2SiH_2	*i*Pr_2NH	80
14	Ph_2SiH_2	CF_3CH_2OH	n.d.
15	Ph_2SiH_2	*i*PrOH	n.d.
16	Ph_2SiH_2	H_2O	n.d.

[a] Unless otherwise specified, all reactions were performed in 0.25 mL toluene with 0.1 mmol **S1** under N_2. [b] Yields determined by NMR spectroscopy with *N*,*N*-dimethylaniline as the internal standard. n.d. = not detected.

transformation occurred, thus providing the piperidine **P1** in 18% yield after hydrolysis of the boryl group (entry 2). To our delight, use of HBpin greatly enhanced the reactivity, and the yield was increased to 84% (entry 3). Hydrosilanes were then examined. Although Ph_3SiH and Et_3SiH were unreactive (entries 4 and 5), Et_2SiH_2 was able to generate **P1** in 40% yield (entry 6). Remarkably, $PhMe_2SiH$ and Ph_2SiH_2 exhibited excellent reactivity, giving 86 and 89% yields, respectively (entries 7 and 8; for a detailed study of the reaction conditions, see the Supporting Information). Furthermore, subsequent experiments reveal that this reduction protocol is quite sensitive to both the steric effect and the acidity of the proton donor. Use of aniline, *N*-methylaniline, and the more acidic Ph(*p*-$CF_3C_6H_4$)NH was either less reactive or even inactive (entries 9–11). With dialkylamines, *n*Pr_2NH was not reactive (entry 12), but *i*Pr_2NH reacted well, thus generating **P1** in 80% yield (entry 13). Other proton donors such as trifluoroethanol, isopropyl alcohol, and water were unreactive (entries 14–16).

The scope of this cascade pyridine reduction was investigated using Ph_2SiH_2 and Ph_2NH as the reducing reagents (Table 2). With *meta*-aryl-substituted pyridines, the electron-donating and electron-withdrawing groups on the aryl ring were well tolerated, thus providing the piperidines **P1**–**P6** in high yields. For reactions with benzofuran- and benzothiophene-substituted pyridines, the electron-deficient pyridine ring was selectively reduced, thus generating the corresponding piperidines **P7** and **P8** in 77 and 83% yields, respectively. The protocol was also compatible with pyridines bearing benzyl (**S9**), benzoyl (**S10**), phenylamino (**S11**), and benzyloxy groups (**S12**) at the *meta*-position, thus giving the products **P9**–**P12** in moderate to high yields upon isolation.

Table 2: Scope with respect to the pyridines.[a]



[a] Unless otherwise specified, all reactions were performed with 0.2 mmol substrate in 0.5 mL toluene under N_2. Yields are those of the isolated products. [b] Used 5 mol% $B(C_6F_5)_3$. [c] Used 6 equiv Ph_2SiH_2 and 5 equiv Ph_2NH. [d] At 120°C. [e] The original olefin group underwent transfer hydrogenation (hydrogen atoms in bold) in **P13**. [f] Used 6 equiv Ph_2SiH_2 and 5 equiv $PhNH_2$. [g] Used 5 equiv Ph_2SiH_2 and 4 equiv $PhNH_2$. [h] At 130°C. [i] The HCl salt was obtained after the acidic workup. [j] Used 5 equiv HBpin and 4 equiv Ph_2NH.

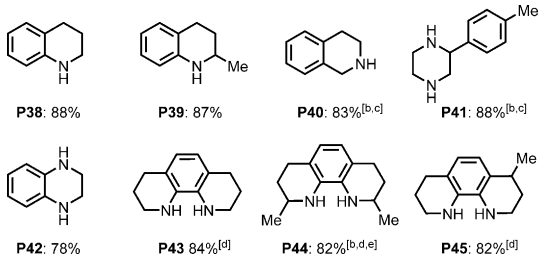
With *meta*-styrylpyridine (**S13**), transfer hydrogenation of the olefin unit occurred (**P13**). In contrast, the unactivated terminal and internal olefins, which are not directly attached to the pyridine ring, were retained in the products **P14**–**P16**. Remarkably, it is well documented that functional groups such as ketone, ester, alkoxy, trifluoromethyl, and olefin are reactive with hydrosilanes during catalysis with $B(C_6F_5)_3$,[13–16] but they remain intact in **P3**–**P5**, **P10**, **P12**, and **P14**–**P16**. We reason that, under the current reaction conditions, the initial pyridine hydrosilylation is more reactive than the hydrosilylation reactions with these functional groups. After the pyridine hydrosilylation, the borane-activated hydrosilane prefers to interact with Ph_2NH for transfer hydrogenation of the enamine intermediate[12a,c,17] rather than react with these functional groups.

Then, *ortho*-substituted pyridines (**S17**–**S28**) were surveyed (Table 2). Again, the tolerance of methoxy (**P18**), halo (**P19**), ester (**P20**), nitro (**P21**), heterocycles (**P22** and **P23**), and unactivated olefins (**P25** and **P26**) implies great potential for this methodology in applications in medicinal chemistry. The reactions with *ortho*-di-substituted pyridines selectively generated the *cis*-disubstituted products (**P27** and **P28**) in high yields. Notably, use of $PhNH_2$ instead of Ph_2NH as the proton donor provided better yields for some *ortho*-substituted pyridines (**S22**, **S23**, **S27**, and **S28**).

Interestingly, when we subjected the *para*-substituted pyridines (**S29**–**S37**) to these reaction conditions, one carbon–carbon double bond on the hetero-ring was retained (Table 2). Furthermore, their reactivities were found to be sensitive to the electronic properties of their substituents, and yields were higher for substrates bearing electron-withdrawing groups (**S31**–**S33**, **S35** and **S37**) than those with electron-donating groups (**S30** and **S36**). The nitrile group in **S34** was hydrosilylated under the standard reaction conditions,[18] but was retained (**P34**) by using HBpin in place of Ph_2SiH_2. Nevertheless, by harnessing the cascade reduction we obtain a series of diversely functionalized tetrahydropyridines which are difficult to synthesize by other methods.

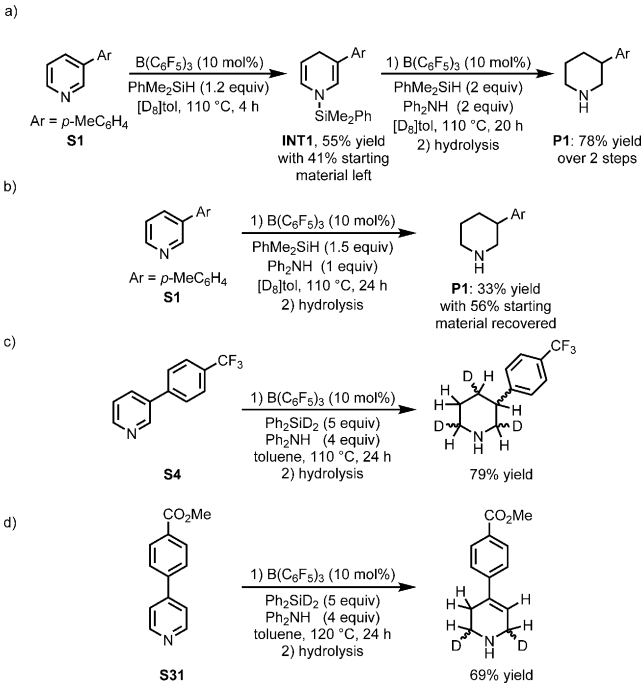
The reduction is also reactive with other electron-deficient N-heteroarenes (Table 3).[19] The reactions of quinolines (**S38** and **S39**), isoquinoline (**S40**), pyrazine (**S41**), quinoxaline (**S42**), and phenanthrolines (**S43**–**S45**) produced the reduced heterocycles in high yields. For these reductions, switching the proton donor to $PhNH_2$ generally provided better yields except for the reactions with isoquinoline (**S40**) and pyrazine (**S41**) where Ph_2NH was still optimal.

Table 3: Scope with respect to other N-heteroarenes.[a]



[a] Unless otherwise specified, all reactions were performed with 5 mol% $B(C_6F_5)_3$, 0.2 mmol substrate (**S38**–**S45**), 5 equiv of Ph_2SiH_2 and 4 equiv of $PhNH_2$ in 0.5 mL toluene at 110 °C for 24 h under N_2. Yields are those of the isolated products. [b] Used 10 mol% $B(C_6F_5)_3$. [c] Used 5 equiv Ph_2SiH_2 and 4 equiv Ph_2NH. [d] Used 6 equiv of Ph_2SiH_2 and 5 equiv of $PhNH_2$. [e] *cis*/*trans* = 1.7:1.

To study the reaction mechanism, we performed several experiments (Scheme 2). First, when **S1** was treated with 1.2 equivalents of $PhMe_2SiH$ in the presence of 10 mol% $B(C_6F_5)_3$ at 110 °C for 4 hours, the partially reduced N-silyl 1,4-dihydropyridine **INT1** was obtained in 55% yield together with 41% unreacted starting material as determined by NMR analysis of the reaction mixture (Scheme 2a). Treatment of this mixture with additional $PhMe_2SiH$, Ph_2NH, and fresh catalyst, led to the fully reduced product in 78% yield over



Scheme 2. Mechanistic studies.

two steps. In contrast, when we directly reacted **S1** with decreased loadings of $PhMe_2SiH$ and Ph_2NH, **INT1** was not observed in the reaction mixture. Instead, the fully reduced product **P1** was obtained in 33% yield after hydrolysis, together with 56% of the recovered starting material (Scheme 2b). These results prove that the reduction is initiated by dearomative hydrosilylation. However, once formed under the standard reaction conditions, the N-silyl 1,4-dihydropyridine intermediate (**INT1**) will undergo rapid transfer hydrogenation to give the final product.

The deuterium-labelled hydrosilane (Ph_2SiD_2) was used in the reaction with **S4** and **S31**. The deuterium was exclusively transferred to the C2-, C4-, and C6-positions in the heterocycles (Scheme 2c and d). These results confirm the hydrosilane as the sole hydride donor in both steps of dearomative hydrosilylation and transfer hydrogenation (for the overall reaction mechanism that is proposed based on previous studies,[9,12,13] see the Supporting Information). Moreover, it was the same as the observation made by Chang and co-workers in the study of the cascade hydrosilylation reaction,[9] the initial dearomative hydrosilylation step proceeds in a 1,2-addition fashion with *para*-substituted pyridines. The following transfer hydrogenation of the enamine double bond gives the tetrahydropyridine product.

In summary, we have developed a $B(C_6F_5)_3$-catalyzed metal-free pyridine reduction strategy by a cascade process of dearomative hydrosilylation (or hydroboration) and transfer hydrogenation. The broad functional-group tolerance provides easy access to an array of diversely functionalized piperidines and tetrahydropyridines which are valuable building blocks in synthesis. Its suitability for use in the reduction of other N-heteroarenes has also been demonstrated. Further studies utilizing this cascade reduction in synthesis are underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: boron · chemoselectivity · homogeneous catalysis · nitrogen heterocycles · reduction

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[17] At the end of each reaction, $Ph_2SiH\text{-}NPh_2$, resulting from both the transfer hydrogenation and the direct condensation between Ph_2SiH_2 and Ph_2NH, was also obtained. When we reacted Ph_2SiH_2 (1 equiv) with Ph_2NH (1 equiv) in the presence of 5 mol% $B(C_6F_5)_3$ in toluene at room temperature, a gas extrusion was observed, and after stirring for 3 h, $Ph_2SiH\text{-}NPh_2$ was obtained in high conversion (> 90%, NMR).

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Communications

Reduction

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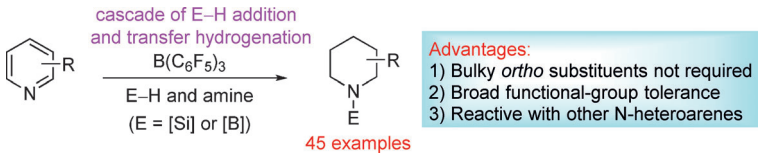

Reduction cascade: An operationally simple $B(C_6F_5)_3$-catalyzed pyridine reduction method has been developed. The reaction occurs by a cascade process of dearomative hydrosilylation (or hydroboration) and transfer hydrogenation. The reduction features very broad functional-group tolerance.