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Borenium-Catalyzed Reduction of Pyridines through the Combined Action of Hydrogen and Hydrosilane

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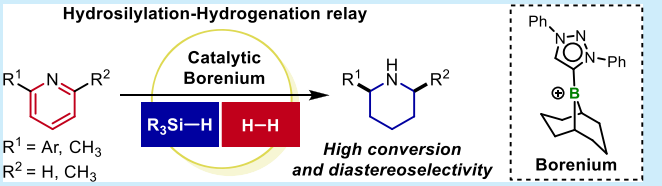
ABSTRACT: Mesoionic carbene-stabilized borenium ions efficiently reduce substituted pyridines to piperidines in the presence of a hydrosilane and a hydrogen atmosphere. Control experiments and deuterium labeling studies demonstrate reversible hydrosilylation of the pyridine, enabling full reduction of the N-heterocycle under milder conditions. The silane is a critical reaction component to prevent adduct formation between the piperidine product and the borenium catalyst.

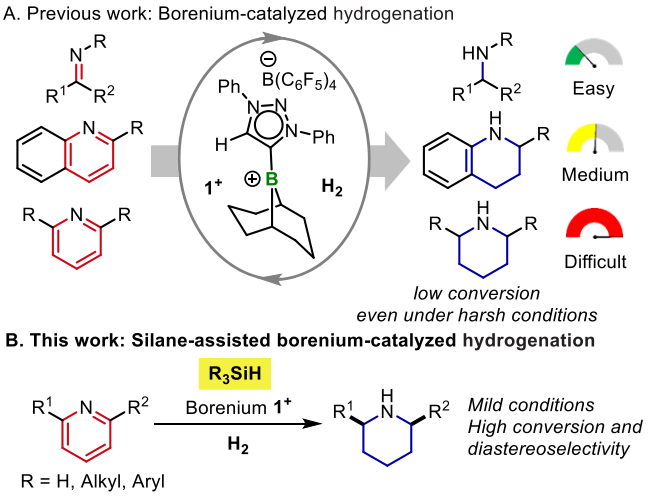


Nitrogen-containing heterocycles are key functional groups in pharmaceutical science, with 59% of drugs containing at least one N-heterocycle and piperidines being the most common ring structure.[1] Transition-metal-catalyzed hydrogenation of pyridines is a common route to piperidines,[2] but it may require pretreatment with acid or protecting groups and can result in metal contamination.[3] Hydroboration/hydrosilylation of pyridines and other heterocycles represents an alternative to direct hydrogenation and has been reported with frustrated Lewis pair (FLP) catalysts.[4,5]

Stephan reported the first example of the use of $B(C_6F_5)_3$ to hydrogenate quinoline[6] and other heterocycles, including lutidine as a single pyridyl example.[7,8] Chang's group reported the use of $B(C_6F_5)_3$ to catalyze the reductive hydrosilylation of quinolines with turnover numbers of up to 1000[9] and also described the hydrosilylation of pyridines in which different levels of reduction were observed depending on the substitution pattern of the pyridine.[10] Du described catalytic hydrogenation using a catalyst derived from the reaction of $HB(C_6F_5)_2$ and alkenes, which included a selected pyridine reduction.[11] Wang[12] reported a combined hydrosilylation/transfer hydrogenation in the hydrogenation of a wide variety of pyridines. Despite requiring excesses of both the silane and proton sources, the reaction is highly effective for the reduction of a variety of pyridines.

Our group and others have employed borenium ions in FLP-catalyzed hydrogenation reactions and organic transformations.[13−18] Borenium ions are isoelectronic with neutral boranes, but their full positive charge negates the need for multiple perfluorinated aromatic substituents. Recently, our group showed that borenium ions stabilized by electron-donating mesoionic carbenes (MICs) are effective reduction catalysts (Scheme 1A). Sterically encumbered imines were reduced at room temperature and H_2 at atmospheric pressure, and quinolines were also reduced at higher hydrogen pressures. Pyridines could be reduced but required more forcing conditions and reacted in poor to moderate yields. Inspired by the concept of using mixed reducing agents, we report the facile reduction of even monosubstituted pyridines with borenium ion $\mathbf{1}^+$ in combination with silanes and hydrogen, illustrating the important role of the silane in preventing catalyst decomposition.

Scheme 1. Borenium-Catalyzed Hydroboration of Imines and Pyridines



We began our studies with precatalyst **1-H** (eq 1), which was previously shown to be the optimal catalyst for imine

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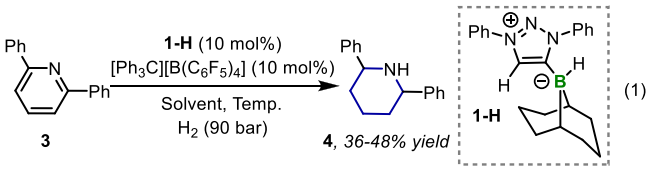
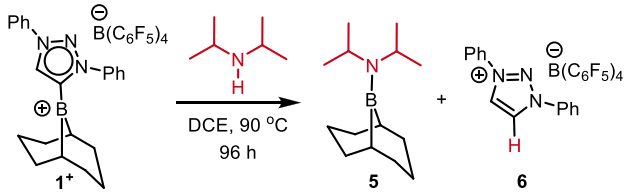


hydrogenation because of the electron-donating triazolylidene and the decreased steric hindrance provided by the presence of one C−H bond adjacent to the nascent borenium ion. In situ activation of this precatalyst is accomplished by hydride abstraction with $Ph_3C^+B(C_6F_5)_4^-$. The high reactivity of the borenium ion generated in this manner requires the use of solvents with low coordinating ability, such as 1,2-dichloroethane (DCE) or toluene (Table S1). With these preliminary activation parameters in hand, we investigated the hydrogenation of 2,6-diphenylpyridine (**3**), which is a bulky Lewis base known to form FLPs with Lewis acids such as $B(C_6F_5)_3$ (eq 1).[19]

Reaction of **3** with catalyst $\mathbf{1}^+$ under a high pressure of hydrogen gave the desired piperidine product **4** in 36−48% yield (see the Supporting Information for details). Increasing the temperature, catalyst loading, or reaction time did not significantly increase the yield of the product, suggesting issues with product inhibition or catalyst decomposition. To test this hypothesis, we treated $\mathbf{1}^+$ with $^iPr_2NH$ as a surrogate for the reaction product (Scheme 2A). Heating this mixture at 90 °C

Scheme 2. Borenium Ion Deactivation Pathway



for 4 days resulted in complete decomposition of $\mathbf{1}^+$. A broad singlet at 47.8 ppm in the ^{11}B NMR spectrum is assigned to amino borane **5**. A singlet at 8.95 ppm in the ^1H NMR spectrum of the crude reaction mixture indicates the presence of triazolium salt **6**. The presence of both **5** and **6** in the reaction mixture was confirmed by high-resolution mass spectrometry (HRMS).

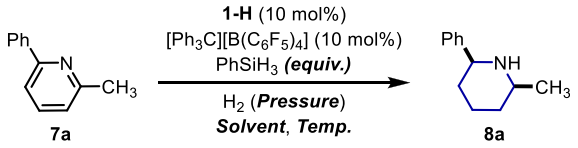
Although our group has not previously observed catalyst decomposition of this type, this reactivity is not unprecedented. Bourissou and co-workers reported C−B bond protonolysis in a phosphine-stabilized borenium ion in the presence of Ph_2NH.[20] A two-step mechanism was proposed, in which coordination of the amine to the boron center takes place, followed by boron−carbon bond scission.

To decrease the likelihood of amine-promoted catalyst decomposition, we examined a combined hydrosilylation and hydrogenation approach. We envisioned two possible beneficial effects of the silane. First, the weaker, more polarized Si−H bond might be more easily activated by the FLP, resulting in a milder process. Second, the silyl group would increase the steric bulk of the Lewis basic product, deterring adduct formation with the catalyst, facilitating catalyst turnover, and decreasing catalyst decomposition.

The concept of dearomatization/hydrogenation cascades has been explored with other catalysts and has been shown to be a useful tool for sensitive or difficult substrates, including the reduction of fluorinated pyridines with rhodium catalysts,[21] pyridines with titanium catalysts[22] and α,β-unsaturated ketones with a $B(C_6F_5)_3$/phosphine intermolecular FLP.[23]

In the event, introducing $PhSiH_3$ into the reaction mixture dramatically improved the reduction of 2-phenyl-6-methylpyridine (**7a**) (Table 1).[24] Adding 2 equiv of $PhSiH_3$ to the

Table 1. Optimization of the Reaction Conditions for 2,6-Disubstituted Pyridine 7a[a]



entry	equiv of silane	solvent	pressure (bar)	temp. (°C)	yield[b] (conv)
1	0	DCM	103	RT	33[c]
2	0	DCE	90	90	40 (41)
3	2.0	DCE	50	90	84 (100)
4	1.5	DCE	50	RT	52 (61)
5	1.1	PhMe	50	RT	52 (69)
6	1.5	PhMe	50	RT	67 (65)
7	1.5	PhMe	50	40	87 (96)

[a]All of the reactions were carried out on a 0.125 mmol scale of **7a** over 19 h. [b]Yields are based on ^1H NMR analysis in the presence of an internal standard. [c]Entry 1 was taken from ref 16.

reaction mixture resulted in complete conversion to piperidine **8a** in 84% yield and full conversion (entry 3), compared with only 40% yield without silane (entry 2), while decreasing the required dihydrogen pressure by almost half (90 bar vs 50 bar). Even at room temperature with a lower number of equivalents of silane (entry 6), we were able to achieve 67% yield at 50 bar H_2. Increasing the temperature to 40 °C gave our optimal conditions, resulting in 87% yield of the product with 96% conversion (entry 7).

With viable conditions in hand, we examined the scope of this transformation. Electron-neutral and electron-rich substrates were reduced in excellent yields (**7a**−**c**), but electron-deficient pyridines required elevated temperatures. Heating to 90 °C was sufficient for the reduction of trifluoromethylated substrate **7d** and chlorinated arylpyridine **7e**. It is important to note that for **7d** we did not observe hydrodefluorination, which has been observed with highly electrophilic silicon and aluminum cations.[25] π-Extended derivative **7f** was reduced without concomitant reduction of the naphthyl group. Less sterically demanding 2,6-lutidine (**7g**) was also reduced to give **8g** in 47% yield, and 50% of **7g** was recovered. Unfortunately, pyridine substrates containing very large substituents such as 2,4,6-triisopropylphenyl in **7h** or lacking steric protection around nitrogen as in **7i** are not amenable to reduction with the current protocol. In the case of **7h**, the starting material was recovered largely intact, with only trace protodebromination detected by ^1H NMR spectroscopy.

The reaction was found to be highly diastereoselective in all cases, giving the *cis*-2,6-arylmethylpiperidine products with typically greater than 97:3 selectivity (Scheme 3). DFT calculations by Li et al. indicated that this high degree of stereoselectivity is a result of a lower energy barrier for the final hydrogenation step as well as the stability of the final product, in which both the methyl and phenyl substituents occupy equatorial positions.[26]

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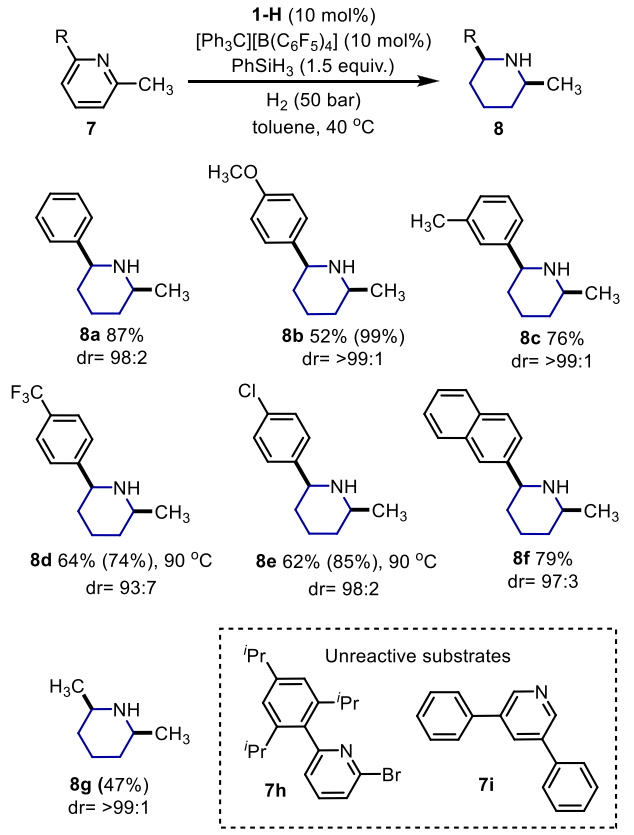
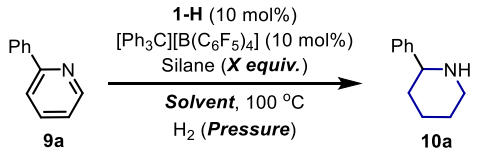
Scheme 3. Substrate Scope for 2,6-Disubstituted Pyridines[a]



[a]All of the reactions were carried out on a 0.125 mmol scale of **7** over 19 h (except the reaction with **7b**, which was run on a 0.25 mmol scale). Yields are of isolated products after purification, with ^{1}H NMR yields given in parentheses.

As a more stringent test of the reduction procedure, monosubstituted 2-arylpyridines were examined (Table 2). The diminished steric demands of 2-substituted pyridines do affect their reactivity, requiring a higher temperature (90 °C) and pressure (90 bar) to reduce these substrates. However, successful reduction was achieved under these conditions. More highly substituted silanes were employed to disrupt potential product/catalyst complexes. Thus, $PhMe_2SiH$ gave a better yield of 2-phenylpiperidine (**10a**) (Table 2, entry 6) compared with less-substituted $PhSiH_3$ or Ph_2SiH_2. Interestingly, Ph_3SiH showed no reactivity, indicating the importance of properly tuning the steric parameters of the silane (entry 7). The reduction of **9a** did not take place without $PhMe_2SiH$, showing the importance of the silane additive in 2-substituted pyridine reductions (entry 8).

Table 2. Optimization of the Reaction Conditions for Reduction of 2-Phenylpyridine[a]

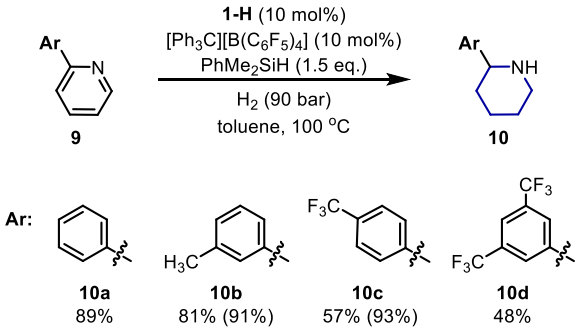


entry	silane	equiv of silane	solvent	pressure (bar)	yield[b] (conv.)
1[c]	$PhSiH_3$	1.1	DCE	47	NR
2	$PhSiH_3$	1.1	DCE	47	33 (44)
3	$PhSiH_3$	1.5	PhMe/DCE	90	64 (70)
4	$PhSiH_3$	1.5	PhMe	90	73 (68)
5	Ph_2SiH_2	1.5	PhMe	90	68 (75)
6	$PhMe_2SiH$	1.5	PhMe	90	85 (86)
7	Ph_3SiH	1.5	PhMe	90	NR
8	none	0	PhMe	90	NR

[a]All of the reactions were carried out on a 0.125 mmol scale of **7a** over 19 h at 100 °C. [b]^{1}H NMR yields obtained with an internal standard. NR = no reaction. [c]The reaction was conducted at room temperature.

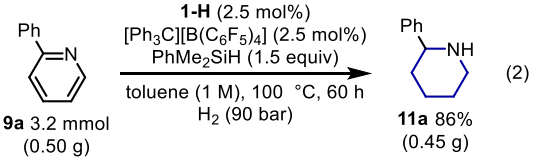
Under these optimized conditions, phenyl, *m*-tolyl, and *p*-trifluorotolyl-substituted 2-arylpyridines gave the desired products in excellent yields (Scheme 4).[27] The highly electron-deficient 3,5-bis(trifluoromethyl)-substituted pyridine **9d** gave the desired product **10d** in a moderate yield of 48%. Once again, our catalyst leaves the CF_3 functional group intact. Currently there is only one reported example of the hydrogenation of 2-arylpyridines by FLPs,[11] reflecting the difficulty in reducing these sterically unencumbered substrates, where strong binding of the product to the catalyst (Lewis acid or metal) has the potential to inhibit catalysis.

Scheme 4. Substrate Scope for 2-Substituted Pyridines[a]



[a]All of the reactions were carried out on a 0.125 mmol scale of **9** over 19 h. Isolated yields are reported, with yields obtained by crude ^{1}H NMR analysis with an internal standard shown in parentheses.

Finally, we demonstrated a half-gram-scale reduction of **9a** with 2.5 mol % **1-H** using less solvent than under the optimized conditions to give **11a** in 86% yield (eq 2).



To investigate the mechanism of this transformation, several control experiments were performed. To examine the potential involvement of silylium ion catalysis,[28] which would result from hydride abstraction from silane by Ph_3C^+, we carried out the reaction by mixing $PhMe_2SiH$ with 10 mol % $[Ph_3C][B(C_6F_5)_4]$ in toluene in the absence of borenium precatalyst **1-H** (Scheme 5A). Immediate decoloration of the solution occurred, suggesting successful hydride abstraction by Ph_3C^+ to form Ph_3CH and the silylium ion. Under our typical conditions, $[Ph_3C][B(C_6F_5)_4]$ is mixed with a slight excess of **1-H** before the addition of silane or pyridine to promote borenium formation over silylium formation. 2-Phenylpyridine

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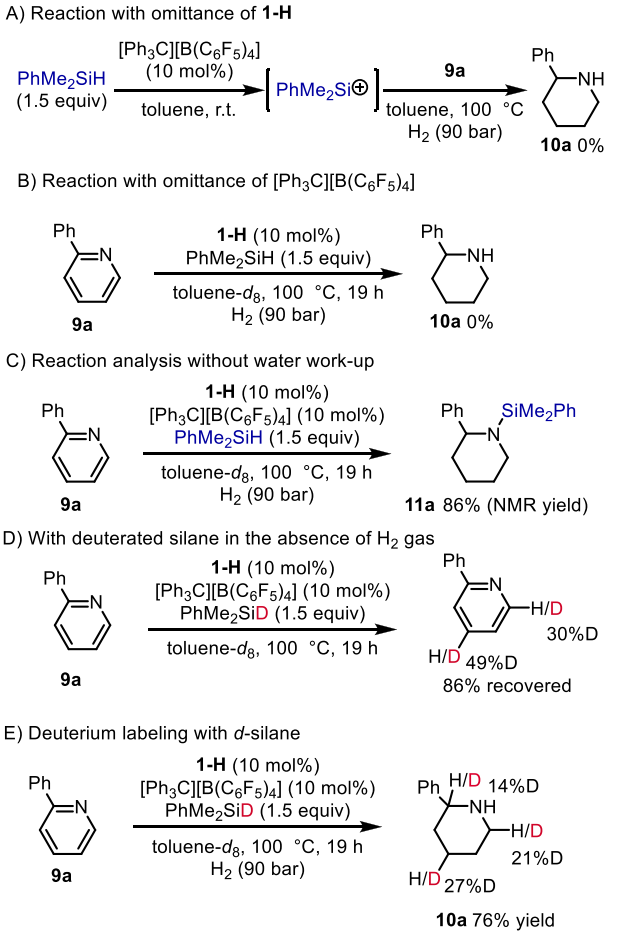
Scheme 5. Mechanistic Studies



(**9a**) was added to the mixture with silylium ion, which was then heated to 100 °C under H_2 gas at 90 bar. After 19 h, no reduced product **10a** was formed as determined by ^{1}H NMR analysis, providing strong evidence against silylium ion catalysis in this reaction.

Next, to confirm that the reduction is catalyzed by the borenium Lewis acid rather than the hydride sources, a reaction was undertaken without the addition of $[Ph_3C][B(C_6F_5)_4]$ (Scheme 5B). Here we observed no conversion to the piperidine product **10a**, once again affirming the necessity of $\mathbf{1}^+$ in the reduction process.

For more insight into the fate of the silane, we hydrogenated **9a** under the optimized conditions and analyzed the crude reaction mixture by ^{1}H and ^{13}C NMR spectroscopy before workup (Scheme 5C). As shown in Scheme 3C, *N*-silylated piperidine **11a** was obtained in 86% NMR yield, providing evidence for either hydrosilylation of the pyridine over the course of the reaction or a dehydrocoupling reaction with the penultimate N−H product.

Next, we carried out the reaction with $PhMe_2SiD$ in the presence of $\mathbf{1}^+$ without dihydrogen. After 19 h at 100 °C, no reduced product was observed by ^{1}H NMR analysis before the reaction workup. Upon the purification of the crude mixture, deuterium exchange at the 4- and 6-positions of the pyridine ring was confirmed by ^{1}H NMR spectroscopy. Under typical conditions (in the presence of dihydrogen), an 85% yield of product was observed (Table 2, entry 6). This suggests that hydrosilylation of the pyridine takes place to generate intermediate dihydropyridines but that full reduction of the ring is not possible without H_2 (Scheme 5D).[10] This result is aligned with observations made by Wang,[12] who showed that when 1.2 equiv of silane was used with $B(C_6F_5)_3$ as the catalyst, 1,4-hydrosilylation of a 3-substitued pyridine was observed. When dihydrogen was added to the $PhMe_2SiD$ reduction, the expected piperidine was observed with deuterium incorporated at the 2-, 4-, and 6-positions (Scheme 5E).

In conclusion, we have discovered that the presumed thermally stable triazolylidene-stabilized borenium ion $\mathbf{1}^+$ undergoes protolytic cleavage in the presence of bulky secondary amines at elevated temperatures. This decomposition pathway has consequences for the hydrogenation of pyridine substrates, in which only low yields for the hydrogenation of substituted pyridines were obtained in the presence of dihydrogen and $\mathbf{1}^+$. The addition of hydrosilane, a more soluble and stronger reducing agent, mitigates the deactivation of $\mathbf{1}^+$ with the production of a N−Si bond over a N−H bond. Furthermore, the *N*-silyl group deters Lewis acid−Lewis base adduct formation between the product and the Lewis acid catalyst, as the product piperidine is more basic than the starting pyridine, allowing the reaction to be performed at lower pressure and temperature while giving rise to substituted piperidines in good yields. Deuterium labeling experiments demonstrated the reversible reduction of pyridine by the hydrosilane at the *ortho* and *para* positions, providing insight into the mechanism of this transformation. The hydrosilane−dihydrogen tandem system may find important uses in other fields in which adduct formation with basic heteroatoms remain problematic.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01892.

Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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