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Reduction of Amine *N*-Oxides by Diboron Reagents

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Supporting Information

ABSTRACT: Facile reduction of alkylamino-, anilino-, and pyridyl-*N*-oxides can be achieved via the use of diboron reagents, predominantly bis(pinacolato)- and in some cases bis(catecholato)diboron [$(pinB)_2$ and $(catB)_2$, respectively]. Reductions occur upon simply mixing the amine *N*-oxide and the diboron reagent in a suitable solvent, at a suitable temperature. Extremely fast reductions of alkylamino- and anilino-*N*-oxides occur, whereas pyridyl-*N*-oxides undergo slower reduction. The reaction is tolerant of a variety of functionalities such as hydroxyl, thiol, and cyano groups, as well as halogens. Notably, a sensitive nucleoside *N*-oxide has also been reduced efficiently. The different rates with which alkylamino- and pyridyl-*N*-oxides are reduced has been used to perform stepwise reduction of the *N*,*N*′-dioxide of (*S*)-(−)-nicotine. Because it was observed that $(pinB)_2$ was unaffected by the water of hydration in amine oxides, the feasibility of using water as solvent was evaluated. These reactions also proceeded exceptionally well, giving high product yields. In constrast to the reactions with $(pinB)_2$, triethylborane reduced alkylamino-*N*-oxides, but pyridine *N*-oxide did not undergo efficient reduction even at elevated temperature. Finally, the mechanism of the reductive process by $(pinB)_2$ has been probed by ^1H and ^{11}B NMR.

INTRODUCTION

Amine *N*-oxides are frequently encountered in organic synthesis,[1] and often the chemical methodology calls for a reduction of the *N*-oxide to the amine. A variety of methods involving metals have been developed for the *N*-oxide to amine conversion.[2−21] There are fewer methods that do not rely on the use of metals, such as processes involving sulfurous acid,[22] SO_2,[23] sulfur monoxide,[24] trimethyl(ethyl)amine−SO_2 complex,[25] PCl_3,[26] PPh_3 at high temperatures,[27] di-*n*-propyl sulfoxylate,[28] CS_2,[29] bakers' yeast,[30] and alcohols and a base.[31]

Many of these methods for *N*-oxide to amine conversion are encumbered with functional group incompatibility problems, the need for high temperatures and/or sealed tube techniques, reagents that produce undesired side reactions, and difficult access to reagents and/or catalysts. Thus, a mild and simple method for the selective conversion of amine *N*-oxides to the corresponding amines continues to be synthetically desirable.

In the course of recent work, we had observed an unusual deoxygenation of O^6-(benzotriazolyl)inosine and 2′-deoxyinosine derivatives (a class of purine-benzotriazole ethers) upon exposure to bis(pinacolato)diboron [$(pinB)_2$] and Cs_2CO_3 (Scheme 1), and had proposed a plausible mechanism for the conversion.[32] The products from the deoxygenation reactions are C-6 benzotriazolyl purine nucleoside derivatives, which were isolated in good yields.[32] In this reaction, it appears that the oxygen atom attached to the benzotriazolyl moiety is transferred to $(pinB)_2$, which undergoes oxidation to $(pinB)_2O$.

$(PinB)_2$ and the corresponding catechol derivative [$(catB)_2$] have been briefly investigated for their abilities to reduce *N*-oxides of pyridine, 4-phenylpyridine, and 4-methylmorpholine. Although pyridine *N*-oxide was stated to be reduced in 90% yield by $(catB)_2$, no preparative use of these reagents has been reported to date.[33] Nevertheless, deoxygenation by diboron reagents is anticipated to be an exceptionally mild and selective process, with broad functional group compatibility. Both $(catB)_2$ and $(pinB)_2$ are commercially available. The latter is a comparatively less-expensive, stable compound, which requires no special handling protocols. These considerations led us to explore the use of diboron reagents for the reduction of amine *N*-oxides.

RESULTS AND DISCUSSION

The generally oxophilic nature of boron and the relatively stable B−O bond (∼120−130[34,35] kcal/mol) in comparison to the B−B bond (∼68 kcal/mol[35]), and the large favorable enthalpy associated with the formation of two B−O bonds (ΔH ca. 180 kcal/mol[33]), all bode well for the use of diboron reagents as reducing agents. Furthermore, trimethylamine *N*-oxide has been known for some time to be an effective oxidant for converting organoboranes to alcohols.[36−39] With these data, we conducted an NMR tube experiment, where 4-methylmorpholine *N*-oxide was exposed to a slight stoichiometric excess of $(pinB)_2$, in $CDCl_3$ at room temperature. No additional

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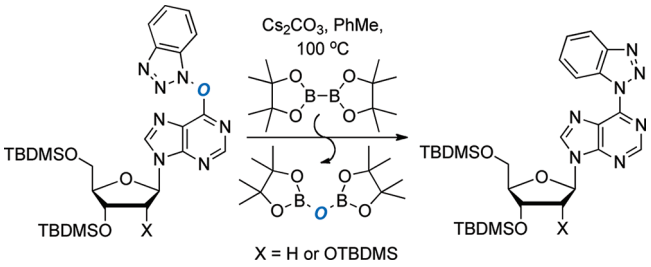
Scheme 1. Deoxygenation of O^6-(Benzotriazol-1-yl)inosine and 2′-Deoxyinosine Using $(pinB)_2$



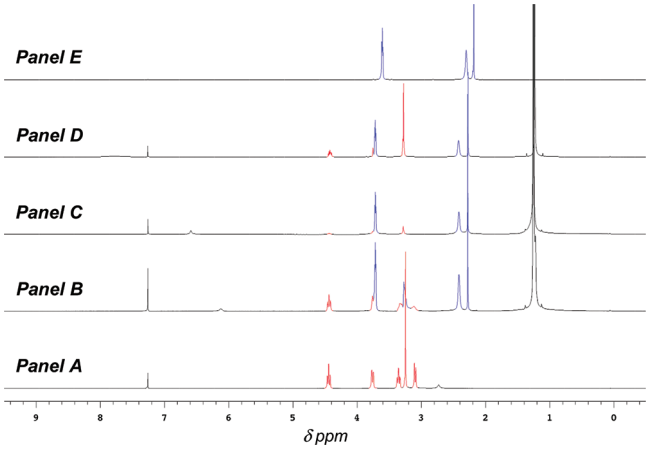


Figure 1. Evaluating the reduction of 4-methylmorpholine *N*-oxide with $(pinB)_2$ by NMR (at 500 MHz in $CDCl_3$). Panel A: spectrum of 4-methylmorpholine *N*-oxide prior to addition of $(pinB)_2$. Panel B: immediately after addition of 1.0 mol equiv $(pinB)_2$ (mixture was not shaken). Panel C: immediately after shaking the reaction mixture. Panel D: mixture of $(pinB)_2$ and 1.5 mol equiv of 4-methylmorpholine *N*-oxide. Panel E: spectrum of pure 4-methylmorpholine.

precautions were taken, such as the use of inert atmosphere or anhydrous conditions. On the basis of ^{1}H NMR evaluation, this reaction was extremely rapid (Figure 1) and *complete reduction took no more than 10 min at room temperature.* In C_6D_6 this reaction is reported to be complete within 1 h at 25 °C, leading to a 74% isolated yield of a morpholine·$(pinB)_2O$ adduct.[33] Contact of 4-methylmorpholine *N*-oxide with $(pinB)_2$ at room temperature, in the absence of solvent, led to an immediate, violent reaction with evolution of fumes.

We then queried whether the hybridization of the nitrogen atom made any difference on the course of the reaction. We chose to conduct the reduction with 4-methoxypyridine *N*-oxide hydrate because this compound was expected to be reasonably reactive based on the anticipated reaction mechanism (vide infra). Again, an experiment was conducted in an NMR tube using CD_3CN as solvent (based upon solubility of reagents and the fact that the reaction mixture could be heated, if necessary), and upon mixing 4-methoxypyridine *N*-oxide hydrate and $(pinB)_2$, a reaction was clearly evident. However, the reaction was much slower than that of 4-methylmorpholine *N*-oxide and reached completion within 20 h at room temperature. In comparison to 4-methylmorpholine *N*-oxide, a similar slower reduction of pyridine *N*-oxide by $(pinB)_2$ has been noted.[33] The exotherm associated with the deoxygenation of 4-methylmorpholine *N*-oxide and 4-methoxypyridine *N*-oxide was determined to be about 0.6 kcal/g by calorimetry.

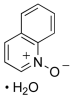
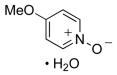
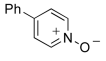
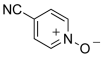
With the information gleaned from NMR studies, we turned our attention to the broader synthetic generality of the reductive process. We were aware that alkylamine *N*-oxides underwent rapid reactions, whereas pyridine *N*-oxides were slower to react. One other issue remained to be addressed: the formation of amine complexes with the boron-based byproduct, $(pinB)_2O$,[33] which we also observed. The formation of amine·$(pinB)_2O$ adducts has been attributed to the increased Lewis acidity at the boron center after oxidation of the B−B bond.[33] We reasoned that addition of a strongly coordinating alkyldiamine should liberate the desired amine from the complex, and we chose water-soluble ethylenediamine for the workup protocol. The results of the reduction procedure are presented in Table 1.

Some notable points emerge from the results in Table 1. *N*-Oxides or their hydrates can be reduced, and water does not seem to hamper this reaction by degradation of $(pinB)_2$ (entries 3 and 5). Reactions of some amine *N*-oxides were slow at room temperature, and heating accelerated the reduction. There does not appear to be an appreciable effect of solvent, and solubility of reactants as well as reaction temperature may be the only considerations for solvent selection (entries 4 and 11). Thiol and hydroxyl groups did not need any specific caution or protection (entries 8 and 9). Halogens are well tolerated, and steric crowding by two chlorine atoms does not deter the reduction (entries 10 and 11). Electron-deficient *p*-cyanopyridine *N*-oxide also underwent clean reduction (entry 12). The substituents in examples 10−12 could be incompatible with some other reduction methods. *N*-Oxides of *N*,*N*-diethylaniline, *N*-benzylpiperidine, and *N*-benzylmorpholine were all reduced rapidly (entries 13−15).

In the cases of pyridine, 2-picoline, 3-picoline, and 2,6-lutidine *N*-oxides, although reductions with $(pinB)_2$ proceeded smoothly, product volatility made their separation from pinacol-based byproducts somewhat more cumbersome. Use of bis(catecholato)diboron [$(catB)_2$] ameliorated the purification problems (entries 16−19). In our hands, reactions with $(catB)_2$ appeared slower as compared to $(pinB)_2$, and $(catB)_2$ seems to be moisture-sensitive. As an example, in CH_3CN, reduction of pyridine *N*-oxide with stoichiometric $(pinB)_2$ was complete within 10 h at 70 °C. On the other hand, even with 1.5 mol equiv of $(catB)_2$, a comparable reaction was incomplete at 24 h and a temperature of 120 °C was necessary. Nevertheless, reductions can be conducted with $(catB)_2$, and the steric bulk in 2,6-lutidine *N*-oxide was not an impediment. In prior work, a difference has been noted in the reactivities of $(pinB)_2$ and $(catB)_2$, but reduction of pyridine *N*-oxide with $(catB)_2$ was complete within 3 h at 25 °C, whereas reaction with $(pinB)_2$ required 6 h at 70 °C.[33]

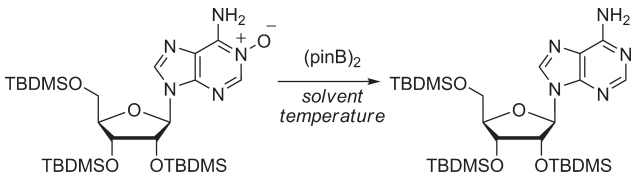
Next we wanted to test the deoxygenation of more complex substrates. Given our interest in nucleoside functionalization, we synthesized 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)adenosine *N*1-oxide (**1** in Scheme 2) using a known procedure.[40] This compound is significantly more fragile as compared to the substrates in Table 1. Exposure of a 0.08 M solution of trisilyl nucleoside **1** to $(pinB)_2$ in either CH_3CN at 70 °C, or in diglyme at 120 °C, led to clean reduction, and trisilyl adenosine **2** was isolated in 71% and 87% yield, respectively (Scheme 2).

Table 1. Generality of Amine *N*-Oxide Reduction with Diboron Reagents[a]

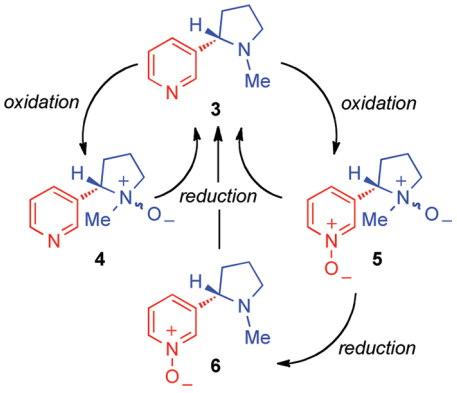
entry	amine *N*-oxide	solvent	conditions	yield[b]
Reductions using (pinB)$_2$:				
1		$CDCl_3$	rt, 5 min	Quant[c]
2		$CDCl_3$	rt, 5 min	Quant[c]
3		CH_3CN	70 °C, 8 h	76%
4		CH_3CN	70 °C, 21 h	64%[d]
		Diglyme	120 °C, 12 h	72%
5		CH_3CN	70 °C, 5 h	91%
6		CH_3CN	70 °C, 6 h	96%
7		CH_3CN	70 °C, 8 h	86%
8		Diglyme	120 °C, 10 h	67%
9		CH_3CN	70 °C, 8 h	82%
10		CH_3CN	70 °C, 8 h	84%
11		1,4-Dioxane	100 °C, 10 h	66%
		Diglyme	120 °C, 4 h	72%
12		CH_3CN	70 °C, 8 h	80%
13		CH_3CN	rt, 10 min	95%
14		CH_3CN	rt, 5 min	97%
15		CH_3CN	rt, 10 min	92%
Reductions using (catB)$_2$:[e]				
16		CH_3CN	120 °C, 12 h	78%
17		CH_3CN	120 °C, 12 h	79%
18		CH_3CN	120 °C, 12 h	88%
19		CH_3CN	120 °C, 24 h	65%

[a] Reactions were conducted at 1 M amine *N*-oxide concentration. [b] Where reported, yield is of isolated and purified product. [c] NMR tube experiment showed complete disappearance of the *N*-oxide resonance(s) and appearance of product resonance(s). Some chemical shift differences and/or signal broadening was observed, likely due to coordination of the amine to $(pinB)_2O$ in the reaction mixture (as reported in ref [33]). [d] Reaction was incomplete. [e] Bis(catecholato)diboron: $(catB)_2$.

Scheme 2. Reduction of 2′,3′,5′-Tri-*O*-(*tert*-butyldimethylsilyl)adenosine *N*1-Oxide Using $(pinB)_2$



Scheme 3. Reduction of Nicotine *N*-Oxides with $(pinB)_2$



(*S*)-(−)-Nicotine presents an interesting case study because it contains alkylamino and pyridyl nitrogen atoms. Both the *N*-oxide **4** and the *N*,*N*′-dioxide **5** were synthesized using known procedures.[41,42] These compounds gave us excellent models to test selective as well as comprehensive *N*-oxide reduction (Scheme 3). Reaction of nicotine *N*-oxide **4** with 1 mol equiv of $(pinB)_2$ gave nicotine (**3**) in 95% yield within 10 min, at room temperature. On the other hand, reduction of the *N*,*N*′-dioxide **5** with 1 mol equiv of $(pinB)_2$ led exclusively to *N*-oxide **6**[30,42] in 96% yield, within 10 min at room temperature. By contrast, reduction of **5** to **6** has previously been conducted using SO_2/EtOH, in an overnight reaction.[43] The present method provides straightforward, scalable access to the expensive *N*-oxide **6** (commercially ca. $1−3/mg) from readily prepared *N*,*N*′-dioxide **5**.

Finally, reaction of *N*,*N*′-dioxide **5** with 2 mol equiv of $(pinB)_2$ showed formation of *N*-oxide **6** within 10 min at room temperature, and complete reduction to (*S*)-(−)-nicotine (**3**) was then

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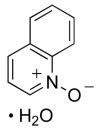
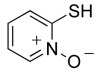
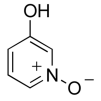
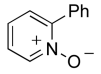
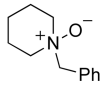
Table 2. Use of Water as Reaction Medium for Reductions Using $(pinB)_2$[a]

entry	amine *N*-oxide	conditions	yield[b]
1		70 °C, 6 h	78%
2		110 °C, 10 h	72%
3		70 °C, 8 h	80%
4		70 °C, 7 h	82%
5		rt, 15 min	94%

[a] Reactions were conducted at 1 M amine *N*-oxide concentration in water. [b] Yields reported are of isolated and purified products.

achieved within 1 h, by heating the reaction mixture to 70 °C (93% yield). In contrast to the workup procedure with the simpler amines, which required addition of ethylenediamine to completely remove boron-containing byproducts, reactions of **4** and **5** did not require this step. The chiral center adjacent to the pyrrolidine nitrogen atom remains unaffected in the reduction, as seen from the optical rotation of the total reduction product **3** in comparison to the (*S*)-(−)-nicotine sample used for this work.

Use of Water as Reaction Medium. Because the water of hydration in the amine *N*-oxides did not seem to affect the reductions by $(pinB)_2$ (entries 3 and 5 in Table 1; also see the NMR studies described below), we queried whether water could be used as a reaction medium. Results from the reactions of five amine *N*-oxides in water are shown in Table 2. Not only did these reactions prove comparable to those accomplished in organic solvents, but also product isolation was just as readily achieved.

Comparison of Reductions by Triethylborane and $(pinB)_2$. Although pinB−H has been used for preparing $(pinB)_2O$ by reduction of trimethylamine *N*-oxide,[44] its utility as a reducing reagent is limited by functional group compatibility issues and by moisture sensitivity considerations. Further, pinB−OH initially formed in the reaction of pinB−H and the amine *N*-oxide consumes 1 equiv of pinB−H, releasing hydrogen.[44] Formation of hydrogen by reaction of B−H containing organoboranes and amine *N*-oxides is known.[36,37] Thus, minimally 2 mol equiv of pinB−H will be required for reducing amine oxides. In principle, trialkylboranes can be used to reduce amine *N*-oxides, as has been demonstrated with trimethylamine *N*-oxide.[36−39] Although 3 mol of a *N*-oxide can be reduced per 1 mol of a trialkylborane, it has been shown that the rate for each sequential B−C oxidation step is slower than the previous one.[37] For example, reaction of 2 mol equiv of trimethylamine *N*-oxide with 1 mol equiv of *n*-Bu_3B is rapid.[45] However, reaction with the third molar equivalent of the *N*-oxide required 24 h at reflux.[45] On the basis of these

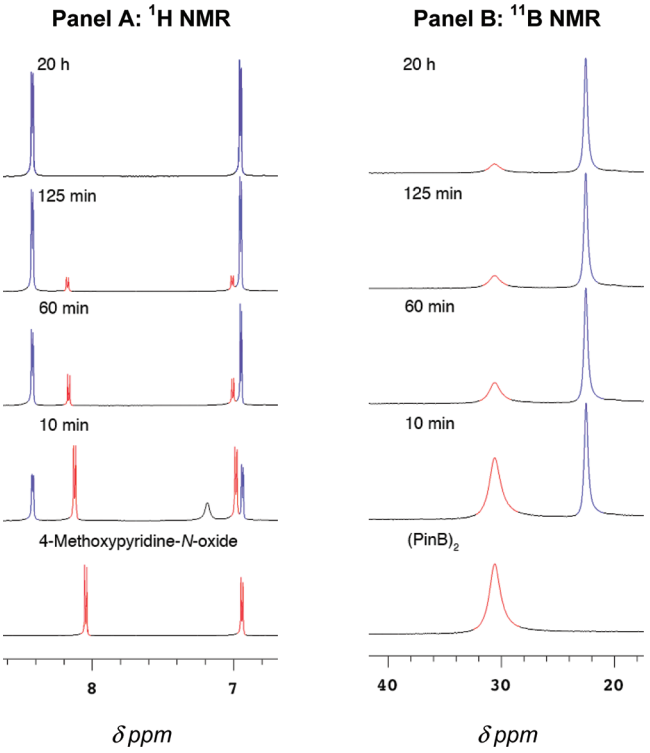


Figure 2. Monitoring the reaction between 4-methoxypyridine *N*-oxide hydrate and $(pinB)_2$ in CD_3CN, by NMR.

results, we conducted several experiments. First, we assessed selectivity of the reduction by exposing a solution of nicotine *N*,*N*′-dioxide **5** in CH_3CN to 0.3 mol equiv of commercially available Et_3B, at room temperature. This reaction yielded exclusively *N*-oxide **6** in 53% yield. Because only two alkylamine *N*-oxides can be expected to undergo reduction per Et_3B, at room temperature,[45] in theory the maximal yield should be 60%. Second, we conducted a reaction of *N*-benzylpiperidine *N*-oxide with 1 mol equiv of Et_3B, also in CH_3CN. This reaction was complete within 10 min, affording *N*-benzylpiperidine in 83% yield. Finally, with 1 mol equiv of Et_3B, practically no reduction of pyridine *N*-oxide was observed at room temperature in CH_3CN, and just a trace of pyridine was observed by TLC, after heating at 80 °C for 20 h. It has been reported that in boiling xylene, only a single B−C bond of an alkylborane is oxidized by 4-methylpyridine *N*-oxide.[37] Thus, reactions of alkylboranes with *N*-oxides of alkylamines are facile in comparison to reactions with pyridine *N*-oxides. On the basis of these collective data, $(pinB)_2$ appears to be a reagent endowed with broad *N*-oxide reducing ability as well as selectivity.

Evaluation of the Reaction Mechanism. To gain insight into the mechanism of this reaction, we conducted some ^{1}H and ^{11}B NMR experiments. A 0.28 M solution of 4-methoxypyridine *N*-oxide in CD_3CN was exposed to 1.05 mol equiv of $(pinB)_2$ in an NMR tube. Figure 2, panel A, shows that within 10 min at room temperature, a fast reaction ensued. Continued monitoring of this reaction showed that substantial reduction was complete within 125 min, and finally no trace of the *N*-oxide was detectable at 20 h. The disappearance of the OCH_3 resonance in 4-methoxypyridine *N*-oxide (δ = 3.90 ppm) and formation of the corresponding resonance in 4-methoxypyridine (δ = 3.89 ppm) was also observed (not shown in Figure 2, panel A). The

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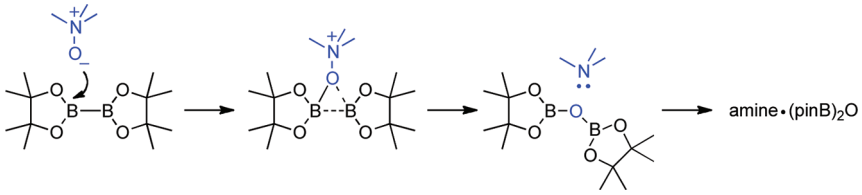
Scheme 4. Plausible Mechanism for the *N*-Oxide Reduction



resonances of $(pinB)_2$ and its oxidation product appear at δ = 1.25−1.26 ppm but are not particularly informative.

^{11}B NMR (Figure 2, panel B) showed disappearance of the resonance at δ = 30.6 ppm corresponding to $(pinB)_2$ and formation of a single new entity with a resonance at δ = 22.5 ppm. From the ^{11}B NMR chemical shift, it is plausible that the oxidation product formed is $(pinB)_2O$ because the chemical shift is consistent for a boron bonded to an oxygen atom.[46] For comparison, authentic $(pinB)_2O$ was synthesized as reported,[44] and its ^{11}B resonance was recorded in several solvents.[47] The chemical shift of the boron-containing product from the deoxygenation reaction is consistent with $(pinB)_2O$. Because it is not of particular relevance to the chemical methodology, we have not determined whether this product is or contains hydrolyzed pinB−OH. The literature indicates very similar chemical shifts for $(pinB)_2O$ and pinB−OH,[44,48,49] and amine can form a $(pinB)_2O$ adduct.[33]

To investigate by NMR whether water in the *N*-oxide hydrate had any influence on the reaction course, the reduction of 4-phenylpyridine *N*-oxide (which was not a hydrate) was also monitored by ^{1}H and ^{11}B NMR. The results from the ^{11}B NMR experiment in this case were comparable to those from the reduction of 4-methoxypyridine *N*-oxide hydrate.

On the basis of the ^{11}B NMR experiments, where only two boron resonances ascribable to $(pinB)_2$ and a final product were discernible, a plausible mechanism is shown in Scheme 4 that is consistent with the one proposed previously.[33] An N−O−B bond is formed by reaction of the *N*-oxide at a boron center, and in a subsequent step $(pinB)_2O$ is produced with liberation of the amine that can remain bound to the boron. The ^{1}H NMR results, where only two sets of resonances were observed during the course of the reduction, also support this proposal. Consistent with the mechanism proposed, the highly electron-depleted *p*-nitropyridine *N*-oxide was a recalcitrant substrate, whereas the electron-rich *p*-methoxypyridine *N*-oxide underwent reaction at room temperature.

CONCLUSIONS

We have described a facile reduction method for alkylamino-, anilino-, and pyridyl-*N*-oxides. The reactions rely on a simple exposure of the *N*-oxide to $(pinB)_2$, in a suitable solvent, and at a suitable temperature to attain a reasonable reaction rate. The reductions are generally mild, require no specialized handling, are compatible with a wide range of functionalities, and can be conducted with stoichiometric $(pinB)_2$. Product isolation is also straightforward. In addition to the broad range of amine oxides that can be reduced, $(pinB)_2$ offers selectivity in reduction. Thus, an alkylamino-*N*-oxide can be reduced in the presence of a pyridyl-*N*-oxide, as demonstrated with the *N*,*N*′-dioxide of (*S*)-(−)-nicotine. Water of hydration does not impact the reductions, and notably reductions of amine *N*-oxides can be conducted in water as reaction medium. In recent years, heterocyclic *N*-oxides have proven to be excellent substrates for metal-catalyzed C−H bond activation processes, wherein the *N*-oxide moiety is finally reduced using Pd/HCO_2NH_4, Zn/NH_4Cl, or PCl_3.[50,51] In this context, the present approach provides an excellent, mild, and functional group-compatible method for the deoxygenation. Also, deoxygenative functionalization of pyridines has been recently reported.[52] Thus, various natural products containing both pyridyl and alkylamino groups can be functionalized at the pyridine ring via the selectivity offered by this route. All these factors render this method attractive for wide ranging applications in organic synthesis, and our efforts are focused on tapping its utility for more complex functionalizations.

EXPERIMENTAL SECTION

General Experimental Considerations. Thin layer chromatography was performed on 250 μm silica plates, and column chromatographic purifications were performed on 200−300 mesh silica gel. MeCN was distilled over CaH_2, and 1,4-dioxane was distilled over $LiAlH_4$ and then over Na. All other reagents were obtained from commercial sources. *N*-Oxides in entries 1−6, 8, 9, 11, 12, 16−19 were obtained from commercial suppliers and were used without further purification, whereas *N*-oxides in entries 7, 10, 13, 14, 15 were synthesized. Trisilyl adenosine *N*1-oxide **1** was prepared via a known route (ref 40). Nicotine *N*-oxide **4** and the *N*,*N*′-dioxide **5** were synthesized by reported routes (ref 41). ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$ or DMSO-d_6 and are referenced to the residual protonated solvent resonance. All products are known compounds and, except for *N*-benzylmorpholine, are commercially available. Characterication data of *N*-benzylpiperidine and *N*-benzylmorpholine are reported in the literature.[53,54]

General Procedure for Synthesis of Amine *N*-Oxides. To a stirred solution of amine (5.5−6.7 mmol) in $CHCl_3$ (2 mL) was added 70% *m*-CPBA (1 mol equiv), portionwise at 0 °C. The resulting mixture was stirred at room temperature for 12 h, at which time complete comsumption of starting material was observed by TLC. The reaction mixture was diluted with $CHCl_3$, and solid K_2CO_3 (4 mol equiv) was added. The resulting mixture was stirred for an additional 10 min. The solid was separated by filtration, and the filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to afford the amine *N*-oxide in yields of 86−90%.

General Procedure for the Reduction of Amine *N*-Oxides. Reactions were conducted on a 0.5−1.0 mmol scale. Caution: These reductions, particularly those of alkylamine *N*-oxides, can be quite vigorous and exothermic. Hence, appropriate precautions should be taken while conducting them.

For High Boiling Amines. A 1 M solution of amine *N*-oxide in the appropriate solvent (see Table 1) was stirred in an oven-dried reaction vial. $(PinB)_2$ (1 mol equiv) was added, the vial was flushed with nitrogen gas, and the mixture was stirred at the appropriate temperature (see Table 1 for details). When TLC indicated the reaction to be complete,

ethylenediamine (20 mol equiv) was added to the mixture, and the stirring was continued for 1 h at room temperature. Then the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then purified via a silica gel column using EtOAc/hexanes as eluting solvent.

For Low Boiling Amines. A 1 M solution of amine *N*-oxide in MeCN was stirred in an oven-dried reaction vial. $(CatB)_2$ (1.5 mol equiv) was added, the vial was flushed with nitrogen gas, and the mixture was stirred at 120 °C. When TLC indicated the reaction to be complete, ethylenediamine (20 mol equiv) was added to the mixture, and the stirring was continued for 1 h at room temperature. Then the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was extracted with 1 N HCl. The aqueous layer was separated and carefully neutralized with 1 N NaOH. The free amine was extracted into Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then purified via a silica gel column using EtOAc/hexanes as eluting solvent.

General Procedure for the Reduction of Amine *N*-Oxides in Water. To a 1 M solution of amine *N*-oxide in water was added $(pinB)_2$ (1 mol equiv) with stirring. The mixture was stirred at the appropriate temperature (see Table 2 for details). When TLC indicated the reaction to be complete, ethylenediamine (20 mol equiv) was added to the mixture, and the stirring was continued for 1 h at room temperature. Then the reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then purified via a silica gel column using EtOAc/hexanes as eluting solvent.

*2′,3′,5′-Tri-O-(tert-butyldimethylsilyl)adenosine N1-Oxide (**1**).*[40] In an oven-dried 10 mL round-bottom flask, equipped with a stirring bar, was placed a solution of 2′,3′,5′-tri-*O*-(*tert*-butyldimethylsilyl)adenosine (**2**, 200 mg, 0.32 mmol) in MeOH (5 mL). To this well-stirred mixture was added 70% *m*-CPBA (79 mg, 1.4 mol equiv), the vial was flushed with nitrogen gas, and the mixture was stirred at room temperature. After 12 h, TLC indicated the reaction to be complete. The mixture was diluted with $CHCl_3$ (30 mL) and washed with aqueous $NaHCO_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified via a silica gel column using 10% MeOH in EtOAc to give **1** as a brown solid (179 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 5.98 (d, 1H, H-1′, J = 5.4 Hz), 4.57 (t, 1H, H-2′, J = 4.4 Hz), 4.28 (t, 1H, H-3′, J = 3.9 Hz), 4.27 (q, 1H, H-4′, J = 3.1 Hz), 4.00 (dd, 1H, H-5, J = 3.9, 11.5 Hz), 3.78 (dd, 1H, H-5′, J = 2.4, 11.5 Hz), 0.96, 0.92, and 0.80 (3s, 27H, *t*-Bu), 0.15, 0.13, 0.10, 0.09, −0.03, and −0.23 (6s, 18H, $SiCH_3$). HRMS (ESI) calcd for $C_{28}H_{56}N_5O_5Si_3$ $[M + H]^+$ 626.3584, found 626.3608.

*Reduction of 2′,3′,5′-Tri-O-(tert-butyldimethylsilyl)adenosine N1-Oxide (**1**).* In an oven-dried reaction vial equipped with a stirring bar was placed the adenosine *N*-oxide **1** (50.0 mg, 0.08 mmol) in diglyme (1 mL). $(PinB)_2$ (20.0 mg, 0.08 mmol) was added, the vial was flushed with nitrogen gas, and the mixture was stirred at 120 °C. After 2 h, TLC indicated the reaction to be complete. Ethylenediamine (20 mol equiv) was added to the mixture, and the stirring was continued for 1 h at room temperature. The mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then purified via a silica gel column using 30% EtOAc in hexanes as eluting solvent to give 42 mg (87% yield) of **2** as a white solid.

*Nicotine N-Oxide **4**.*[41] Synthesized by the procedure reported in ref 41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (dd, 1H, Ar-H, J = 1.4, 4.8 Hz), 8.58 (d, 1H, Ar-H, J = 1.4 Hz), 8.29 (d, 1H, Ar-H, J = 7.8 Hz), 7.36 (dd, 1H, Ar-H, J = 4.8, 7.8 Hz), 4.24 (dd, 1H, J = 7.3, 11.7 Hz), 3.78 (t, 1H, J = 8.7 Hz), 3.63 (app q, 1H, J_{app} ∼ 9.9 Hz), 2.98 (s, 3H, CH_3), 2.78−2.69 (m, 1H), 2.63−2.54 (m, 1H), 2.31−2.25 (m, 1H), 2.10−2.03 (m, 1H). $[\alpha]^{25}_D$ = −73.5 (c = 2 mg/mL, $CHCl_3$).

*Nicotine N,N′-Dioxide **5**.*[41] Synthesized by the procedure reported in ref 41. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (br s, 1H, Ar-H), 8.22 (d, 1H, Ar-H, J = 6.3 Hz), 7.84 (d, 1H, Ar-H, J = 7.8 Hz), 7.30 (t, 1H, Ar-H, J = 7.0 Hz), 4.14 (dd, 1H, J = 7.6, 11.2 Hz), 3.85 (t, 1H, J = 8.7 Hz), 3.62 (app q, 1H, J_{app} ∼ 9.8 Hz), 3.06 (s, 3H, CH_3), 2.70−2.52 (m, 2H), 2.35−2.29 (m, 1H), 2.12−2.03 (m, 1H). $[\alpha]^{25}_D$ = +109.3 (c = 5 mg/mL, $CHCl_3$).

*Reduction of Nicotine N-Oxide **4** to (S)-(−)-Nicotine (**3**).* In an oven-dried reaction vial equipped with a stirring bar was placed the nicotine *N*-oxide **4** (50.0 mg, 0.280 mmol) in CH_3CN (0.25 mL). $(PinB)_2$ (71.0 mg, 0.280 mmol) was added, the vial was flushed with nitrogen gas, and the mixture was stirred at the room temperature. After 10 min, TLC indicated the reaction to be complete. The reaction mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was then purified via a silica gel column using 80% Et_2O in hexanes as eluting solvent to give 43 mg (95% yield) of **3** as a yellowish liquid. For ^{1}H NMR data see reduction of **5** to **3** below.

*Reduction of Nicotine N,N′-Dioxide **5** to Nicotine N-Oxide **6**.* In an oven-dried reaction vial equipped with a stirring bar was placed the nicotine *N*,*N*′-dioxide **5** (50.0 mg, 0.257 mmol) in CH_3CN (0.25 mL). $(PinB)_2$ (65.0 mg, 0.257 mmol) was added, the vial was flushed with nitrogen gas, and the mixture was stirred at the room temperature. After 10 min, TLC indicated the reaction to be complete. The reaction mixture was directly loaded onto a silica gel column and purified using 10% MeOH in Et_2O as eluting solvent to give 45 mg (96% yield) of **6** as a yellowish liquid. $[\alpha]^{25}_D$ = −146.7 (c = 3.5 mg/mL, $CHCl_3$). R_f (SiO_2/40% MeOH in EtOAc) = 0.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (br s, 1H, Ar-H), 8.10 (d, 1H, Ar-H, J = 5.8 Hz), 7.26 (m, 1H, Ar-H), 7.21 (app triplet, 1H, Ar-H, J_{app} ∼ 7.0 Hz), 3.21 (t, 1H, J = 7.8 Hz), 3.08 (t, 1H, J = 7.8 Hz), 2.33 (app q, 1H, J_{app} ∼ 8.7 Hz), 2.29−2.20 (s, 3H, CH_3 superimposed on m, 1H), 1.98−1.89 (m, 1H), 1.85−1.75 (m, 1H), 1.71−1.64 (m, 1H).

*Reduction of Nicotine N,N′-Dioxide **5** to (S)-(−)-Nicotine (**3**).* In an oven-dried reaction vial equipped with a stirring bar was placed the nicotine *N*,*N*′-dioxide **5** (50.0 mg, 0.257 mmol) in CH_3CN (0.25 mL). $(PinB)_2$ (130.0 mg, 0.514 mmol) was added, the vial was flushed with nitrogen gas, and the mixture was stirred at the room temperature for 10 min and then heated to 70 °C for 1 h. TLC indicated the reaction to be complete. The reaction mixture was directly loaded onto a silica gel column and purified using 80% Et_2O in hexanes as eluting solvent to yield 39 mg (93% yield) of **3** as a yellowish liquid. $[\alpha]^{25}_D$ = −165.5 (c = 1.5 mg/mL, $CHCl_3$). For the commercial sample of nicotine used for this chemistry $[\alpha]^{25}_D$ = −167.2 (c = 1.5 mg/mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (d, 1H, Ar-H, J = 1.9 Hz), 8.51 (dd, 1H, Ar-H, J = 1.4, 4.8 Hz), 7.71 (dt, 1H, Ar-H, J = 1.9, 7.8 Hz), 7.24 (dd, 1H, Ar-H, J = 4.8, 7.8 Hz), 3.24 (t, 1H, J = 7.8 Hz), 3.07 (t, 1H, J = 8.3 Hz), 2.30 (app q, 1H, J_{app} ∼ 8.7 Hz), 2.23−2.16 (s, 3H, CH_3 superimposed on m, 1H), 1.98−1.91 (m, 1H), 1.85−1.78 (m, 1H), 1.74−1.70 (m, 1H).

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR spectra of all *N*-oxides and their reduction products, as well as the ^{1}H−^{1}H COSY spectrum for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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