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$B(C_6F_5)_3$-promoted hydrogenations of N-heterocycles with ammonia borane

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A transition-metal-free method for the $B(C_6F_5)_3$-promoted hydrogenations of N-heterocycles using ammonia borane under mild reaction conditions has been developed. The reaction affords a broad range of hydrogenated products in moderate to good yields. The enantioselective versions for corresponding products were also investigated by our approach, showing good feasibility.

The past decade has witnessed spectacular advances in metal-free catalytic reductions,[1] which in particular hydrogenations of unsaturated nitrogen-containing compounds are one of the simplest and most practical chemical processes in organic synthesis. Although a variety of insightful methods provide alternative ways to direct hydrogenations, the frustrated Lewis pairs (FLPs) have received considerable attention as powerful tools for metal-free hydrogenations.[2] The feasibility of FLPs systems to activate H_2 and hydrogenate unsaturated substrates, particularly heteroaromatic rings, has been examined.[3-8] In 2010, Stephan firstly reported metal-free reductions of N-heterocycles via FLPs.[9] Repo described the asymmetric hydrogenations of unsaturated nitrogen-containing compounds (up to 37% ee).[10] Soós developed the size-exclusion design of Lewis acids, and completed the synthesis of cuspareine under the FLPs conditions.[6] In addition, Du had a breakthrough on hydrogenations of pyridines,[11] 2,3-disubstituted quinoxalines[8] and substituted quinolines[12,13] by using homogeneous borane catalysts generated in situ from alkenes and $HB(C_6F_5)_2$. Besides the H_2 activation, FLPs can also activate the Si–H bond.[6,14-17] The reductions of substituted indoles,[15] quinolines[16] and pyridines[18] were investigated using silane and $B(C_6F_5)_3$.

In recent years, ammonia borane (**AB**) has also received considerable attention owing to its ideally high storage capacity and good stability against air and moisture compare to hydrosilanes. Although hydrosilanes are employed as low toxic, highly active and handling easily hydrogen donors, silane is not atom economic.[19] Ammonia borane is usually employed as hydrogen source in the reductive reactions.[20-28] It is notable that the transfer hydrogenations of N-heterocycles with ammonia borane by FLPs has been less reported. In 2016, Du and co-workers described a frustrated Lewis pair catalyzed asymmetric transfer hydrogenation of imines[29] and borane-catalyzed transfer hydrogenations of pyridines[19] and quinoxalines[30] with ammonia borane. However, the hydrogenations of quinoline and indole derivatives have not been reported. Our group has been devoting our efforts towards hydrogenations of complex N-heterocycles.[31] Herein, a new method $B(C_6F_5)_3$-promoted hydrogenations of N-heterocycles with ammonia borane under transition-metal-free conditions is presented.

Initially, the hydrogenation of quinaldine with ammonia borane was chosen as the model reaction to optimize the reaction conditions, and the results were summarized in Table 1. When quinaldine was treated with ammonia borane (3 equiv.), $B(C_6F_5)_3$ (5 mol%) in toluene at room temperature for 24 h, the expected product was obtained in 15% yield (Table 1, entry 1). Surprisingly, when the reaction temperature was raised to 80 °C, the yield of **2a** was dramatically increased to 81% (Table 1, entry 2). However, when the reaction was carried out at 60 °C or 100 °C, the yields of **2a** were achieved in 43% and 79% yields, respectively (Table 1, entries 3-4). Subsequently, various solvents were investigated in the presence of 5 mol% of $B(C_6F_5)_3$ and three equivalents of ammonia borane at 80 °C (Table 1, entries 5-8). Results showed that toluene as solvent was better than MeCN, THF, dioxane and 1,2-dichloroethane. Moreover, when the reaction was carried out in the absence of $B(C_6F_5)_3$ at 80 °C, only 9% yield of **2a** was obtained (Table 1, entry 9). The amount of ammonia borane was also investigated, three equivalents of ammonia borane was suitable for the reaction (Table 1, entries 10-11). Thus, the optimum reaction condition is as follows:

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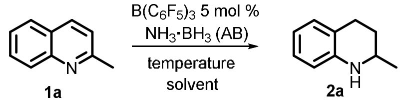
substrates (1 equiv.) ammonia borane (3 equiv.), $B(C_6F_5)_3$ (5 mol %) in toluene at 80 °C for 8 h.

Table 1 Optimization studies for the hydrogenation of quinaldine catalyzed by $B(C_6F_5)_3$[a]

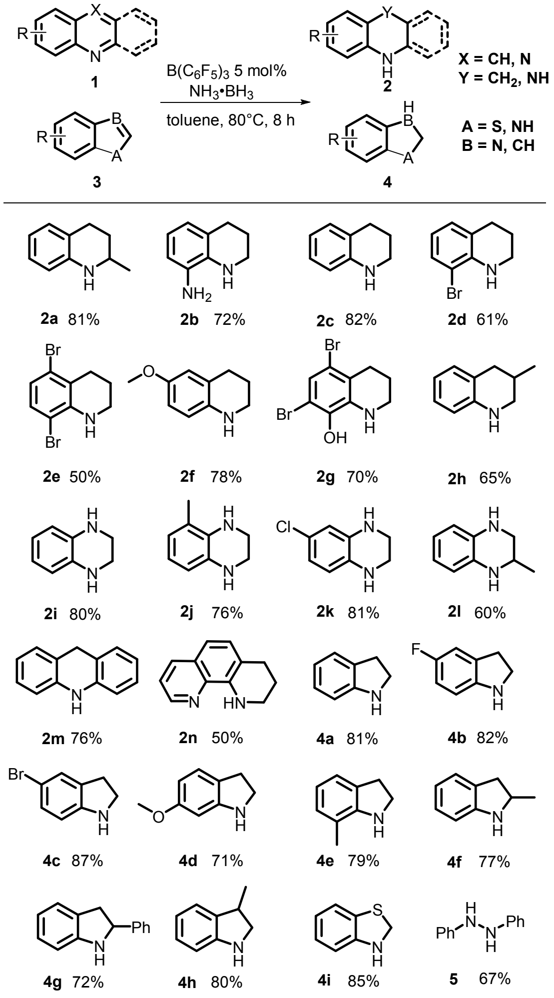


Entry	AB (equiv)	Solvent	T (°C)	Yield[b] (%)
1	3.0	toluene	rt	15
2	3.0	toluene	80	81
3	3.0	toluene	60	43
4	3.0	toluene	100	79
5	3.0	dioxane	80	65
6	3.0	THF	80	71
7	3.0	MeCN	80	73
8	3.0	DCE	80	76
9[c]	3.0	toluene	80	9
10	2.0	toluene	80	77
11	4.0	toluene	80	81

[a] Reactions were performed on a 0.5 mmol scale using $B(C_6F_5)_3$ (5 mol%) and ammonia borane (3 equiv.) with solvent (1.5 mL) at the investigated temperature for 8 h. [b] Yield of isolated product. [c] No catalyst.

With optimum procedure in hand, substrates of this protocol were investigated and the results are represented in the Table 2. At first, various N-heterocycles with six-membered ring, such as quinoline derivatives and quinoxaline derivatives, were allowed to react with ammonia borane under the optimized reaction conditions. Quinolines with substituents in the 2- or 8- position, which provide sufficient bulk to hinder adduct formation, were explored for FLPs reactivity. As shown in the Table 2, all the reactions were completed within 8 h, and led to the desired products in moderate to good yields. For example both **1a** with electron-donating group (R = 2-Me) and **1f** with electron-withdrawing group (R = 6-OCH_3) gave the corresponding products **2a** and **2f** in 81% and 78% yields, respectively. In addition, The substituting effects were also investigated. To our satisfaction, even polysubstituted **1g** formed the product **2g** in 70% yield. The remarkable functional group tolerance of our experimental conditions was observed in the hydrogenations of N-heterocycles. Bromo and chloro substituted N-heterocycles afforded the corresponding products (**2d**, **2e**, **2g**, and **2k**) in moderate to high yields, which might be employed for further structural manipulations such as the coupling reaction. Furthermore, it could be further modified at the hydroxy or amino group (**2b** and **2g**), which is useful in synthetic chemistry and pharmaceutical chemistry. Comparing to quinoline derivatives, quinoxaline derivatives afforded corresponding products in good yields. It was found that the property and the position of substitutes did not obviously effect on the yields. **1i**, **1j**, **1k** and **1l** gave the target products ranging from 60% to 81%.[30]

Table 2 Hydrogenations of various N-heterocycles catalyzed by $B(C_6F_5)_3$[a,b]



[a] Reaction conditions: substrates (0.5 mmol, 1 equiv.) and ammonia borane (1.5 mmol, 3 equiv.) with $B(C_6F_5)_3$ (5 mol%) in toluene (1.5 mL) at 80 °C for 8 h. [b] Yield of isolated product.

Due to achievement of the reduction of N-heterocycles with six-membered ring, it seems to be suitable for hydrogenations of other N-heterocycles. So we made a further investigation of the hydrogenations of N-heterocycles with five-membered ring. Taking various indole derivatives into consideration in the Table 2. Specially, indoles with substituents in the 2- or 7-position, which provide sufficient bulk to hinder adduct formation, were explored for transfer hydrogenations via FLPs. All the substituded indoles proceeded smoothly, affording corresponding Indolines (**4a**-**4h**) in good to excellent yields. It is notable that other N-heterocycles (**1m**, **1n** and **3i**) and N=N bond containing open chain compound were successfully hydrogenated to corresponding product by FLPs.

After accomplishment of the hydrogenations of N-heterocycles with ammonia borane, we further devoted our efforts to the catalytic asymmetric transformation of quinolines and 1,4-benzoxazine derivatives. The reaction conditions for the asymmetric transfer hydrogenation of **1o**

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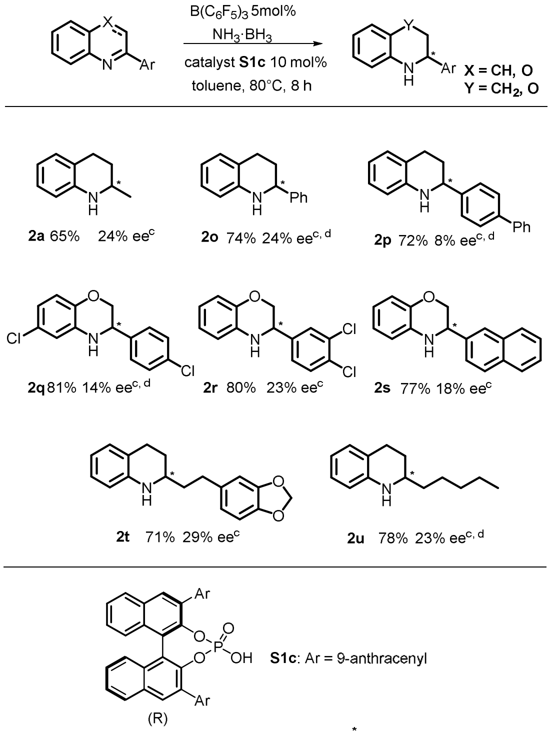
Table 3 Asymmetric transfer hydrogenations of quinolines and 1,4-benzoxazine derivatives[a,b]



[a] More details please see Supporting Information. [b] Yield of isolated product. [c] The ee values were determined by HPLC. [d] Reactions were treat with additive (1 equiv of 4-morpholinopyridine).

were optimized to improve the enantioselectivity (Table S1, S2 in the Supporting Information). Under the optimal reaction conditions, a variety of 2-substituted quinolines and 1,4-benzoxazine derivatives were examined for the asymmetric transfer hydrogenations. As shown in the Table 3, all of these reactions proceeded smoothly to give the desired products **2a**, **2o**–**2u** in 65–81% yields with 8–29% ee. It is worth mentioning that biologically active tetrahydroquinoline alkaloids **2t** and **2u** were obtained with 29% ee and 24% ee, respectively. Subsequently, we also investigated other catalysts, such as quinine and chinchonine. Although, high enantioselectivities were not observed, this result presented here confirmed the feasibility and potential of developing FLPs/chiral ligands mediated asymmetric hydrogenations of N-heterocycles.

In conclusion, a wide range of N-heterocycles were successfully reduced to corresponding products with ammonia borane by FLPs, which provided a promising and practical method for the transition-metal-free transfer hydrogenations. In contrast to the FLPs-catalyzed hydrogenations with H_2, the $B(C_6F_5)_3/NH_3•BH_3$ system successfully avoids use of high pressure H_2, and this finding provides a new approach for hydrogenation of unsaturated nitrogen-containing compounds. Moreover, enantioselectivities for some N-heterocycles were primarily investigated, affording up to 29% ee.

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