Communication

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Metal-Free Borane-Catalyzed Highly Stereoselective Hydrogenation of Pyridines

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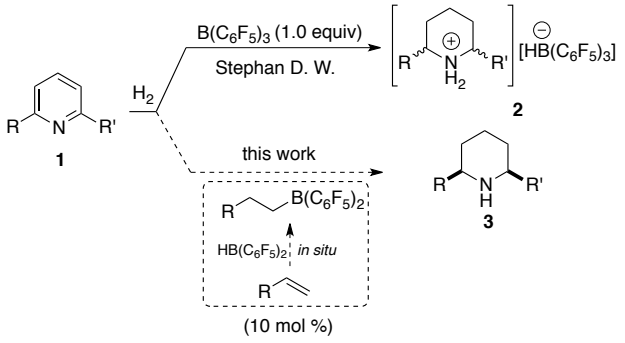
Supporting Information Placeholder

ABSTRACT: A metal-free direct hydrogenation of pyridines was successfully realized by using homogeneous borane catalysts generated from alkenes and $HB(C_6F_5)_2$ via an *in situ* hydroboration to afford a broad range of piperidines in high yields with excellent *cis*-stereoselectivities.

Piperidines are very important moieties contained in a wide range of biologically active compounds, and numerous methodologies have been established for their synthesis.[1] The catalytic hydrogenation of pyridines with H_2 undoubtedly provides a simple and straightforward approach for accessing piperidines, although it is essential to overcome some inherent challenges on the catalyst deactivation and the pyridine dearomatization.[2] Various heterogeneous transition-metal catalysts and several homogeneous Rh, Ir, and Ru complexes have been studied for the direct hydrogenation of pyridines, but harsh reaction conditions and/or specific pyridines bearing activating groups are often required due to the low activity and selectivity of catalysts.[3,4] Recently, an organocatalytic transfer hydrogenation for partial reduction of electron-deficient pyridines with Hantzsch esters has also been reported.[5] Moreover, the hydrogenation of relatively more reactive pyridine derivatives, such as pyridinium salts, pyridine *N*-oxides, and *N*-iminopyridium ylides, by either heterogeneous or homogeneous catalysts, provides an alternative and efficient strategy for the synthesis of piperidines.[6,7] Despite these advances, the direct hydrogenation of pyridines is still a challenge. In particular, the metal-free catalytic hydrogenation of simple pyridines is of great interest and has rarely been reported.

The lately emerging frustrated Lewis pairs (FLPs) have become one promising class of catalysts for the metal-free homogeneous hydrogenation.[8,9] A broad range of substrates, such as imines,[10] *N*-heterocycles,[11] nitriles,[10a] alkenes,[10b,c,h,i,12] and so on,[13] can be efficiently hydrogenated under the catalysis of FLPs. In particular, Stephan and coworkers achieved an amazing aromatic hydrogenation of anilines with $B(C_6F_5)_3$ (1.0 equiv) to afford cyclohexyl-amine derivatives.[13d] Very recently, Stephan and coworkers also described an interesting example for the reduction of pyridines **1** under H_2 using a stoichiometric amount of $B(C_6F_5)_3$ to furnish piperidium salts **2** (Scheme 1).[14] The replacement of one pentafluorophenyl group of $B(C_6F_5)_3$ by other groups, for example, mesityl and alkenyl substitutents by Soós[10h,11b] and Erker,[13c] respectively, provides a number of efficient FLP catalysts for hydrogenation.[9] Previously, we accomplished a highly enantioseletive hydrogenation of imines on the basis of an *in situ* catalyst generation strategy by hydroboration of alkenes with $HB(C_6F_5)_2$.[15,16] We envision that this strategy also provides a good opportunity to develop the challenging metal-free catalytic hydrogenation for simple pyridines, especially for 2,6-disubstituted pyridines which are often inert substrates in the reported work (Scheme 1). Herein, we report our preliminary results on this subject.

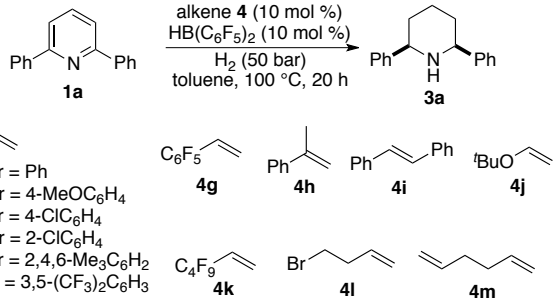


Scheme 1. Metal-free hydrogenation of pyridines by boranes.

We initially selected a variety of commercially available alkenes to examine the hydrogenation of 2,6-diphenylpyridine (**1a**) with H_2 (50 bar) in toluene at 100 °C for 20 h (Table 1). Piers' borane $HB(C_6F_5)_2$ itself can catalyze this reaction to give 2,6-diphenylpiperidine (**3a**) in 21% conversion (Table 1, entry 1). While, the majority of boranes generated *in situ* by the hydroboration of alkenes with $HB(C_6F_5)_2$ exhibited obviously high-

er activities to furnish piperidine **3a** with an excellent *cis*-selectivity (Table 1, entries 2-14). The electron-deficient alkenes were found to be more effective for this transformation (Table 1, entries 7-8 and 12), and terminal alkene **4g** gave a satisfactory conversion and 98/2 dr (Table 1, entry 8). Further decreasing the reaction temperature to 60 °C or the catalyst loading to 5 mol % led a slight loss of reactivity (Table 1, entries 15 and 16).

Table 1. *Evaluation of alkenes for hydrogenation of pyridines*[a]



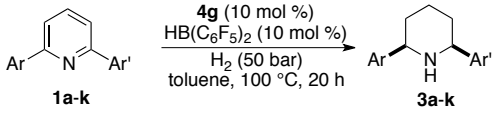
entry	4	conv (%)[b]	*cis:trans*[b]	entry	4	conv (%)[b]	*cis:trans*[b]
1[c]	--	21	nd[d]	9	**4h**	31	nd[d]
2	**4a**	59	95:5	10	**4i**	21	nd[d]
3	**4b**	72	95:5	11	**4j**	15	nd[d]
4	**4c**	62	96:4	12	**4k**	89	96:4
5	**4d**	67	96:4	13	**4l**	34	nd[d]
6	**4e**	65	96:4	14[e]	**4m**	44	nd[d]
7	**4f**	95	97:3	15[f]	**4g**	79	98:2
8	**4g**	>99	98:2	16[g]	**4g**	93	98:2

[a] All reactions were carried out with pyridine **1a** (0.25 mmol) and toluene (2.0 mL). [b] Determined by crude ^{1}H NMR. [c] Without alkene. [d] Not determined. [e] 5 mol % of alkene **4m**. [f] At 60 °C. [g] 5 mol % of catalyst.

With this interesting result in hand, we next examined the substrate scope under the optimal condition (Table 1, entry 8). As shown in Table 2, the metal-free hydrogenation of 2,6-diarylpyridines **1a**-**i** went smoothly to give piperidines **3a**-**i** in 97-99% yield with 98/2->99/1 dr (entries 1-9). 2,6-Difurylpyridine (**1j**) was also an effective substrate to give a high yield but with a relatively lower *cis*-selectivity (Table 2, entry 10). When piperidine **1k** containing both electron-withdrawing and electron-donating substituents was used, the desired product **3k** was obtained in 92% yield with 99/1 dr (Table 2, entry 11). However, the electron-deficient 2,6-bis(4-fluorophenyl)pyridine was not a suitable substrate to lead only 23% conversion. The *cis*-configuration of piperidines **3** is supported by an X-ray structure of piperidine **3c** (see Supporting Information).

A series of 2-aryl-6-methylpyridines **1l**-**u** were also subjected to the metal-free catalytic hydrogenation. Both electron-donating and electron-withdrawing aryl substituents were well tolerated to produce piperdines **3l**-**u** in 80-99% yield with excellent *cis*-selectivity (Table 3, entries 1-10).

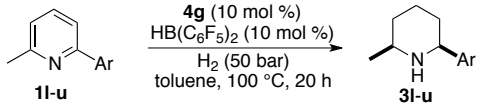
Table 2. *Hydrogenation of 2,6-diarylpyridines*[a]



entry	product (**3**)	yield (%)[b]	*cis:trans*[c]
1	**3a**: Ar = Ar' = Ph	98	98:2
2	**3b**: Ar = Ar' = 4-MeC$_6$H$_4$	97	98:2
3	**3c**: Ar = Ar' = 4-MeOC$_6$H$_4$	99	98:2
4	**3d**: Ar = Ar' = 4-^{t}BuC$_6$H$_4$	99	98:2
5	**3e**: Ar = Ar' = 3-MeC$_6$H$_4$	99	98:2
6	**3f**: Ar = Ar' = 3-MeOC$_6$H$_4$	97	98:2
7	**3g**: Ar = Ar' = 2-MeC$_6$H$_4$	98	>99:1
8	**3h**: Ar = Ar' = 2-MeOC$_6$H$_4$	99	>99:1
9	**3i**: Ar = Ar' = 2-naphthyl	99	98:2
10	**3j**: Ar = Ar' = 2-furyl	93	90:10
11	**3k**: Ar = 4-FC$_6$H$_4$ Ar' = 4-MeOC$_6$H$_4$	92	99:1

[a] All reactions were carried out with pyridine **1** (0.25 mmol) in toluene (2.0 mL). [b] Isolated yield. [c] Determined by crude ^{1}H NMR.

Table 3. *Hydrogenation of 2-aryl-6-methylpyridines*[a]



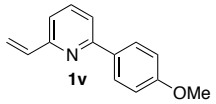
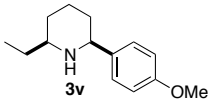
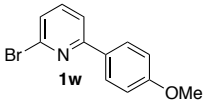
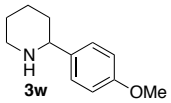
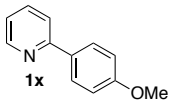
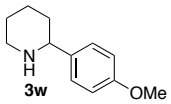
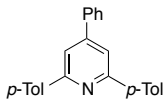
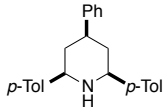
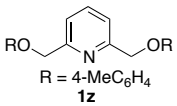
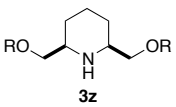
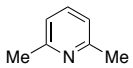
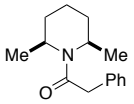
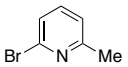
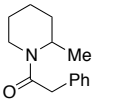
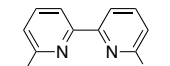
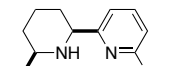
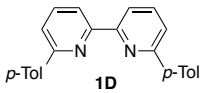
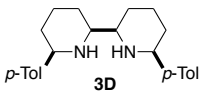
entry	product (**3**)	yield (%)[b]	*cis:trans*[c]
1	**3l**: Ar = Ph	96	95:5
2	**3m**: Ar = 4-MeOC$_6$H$_4$	98	96:4
3	**3n**: Ar = 4-PhC$_6$H$_4$	96	96:4
4	**3o**: Ar = 4-CF$_3$C$_6$H$_4$	86	97:3
5	**3p**: Ar = 4-ClC$_6$H$_4$	88	96:4
6	**3q**: Ar = 3-MeOC$_6$H$_4$	96	96:4
7	**3r**: Ar = 3,5-Me$_2$C$_6$H$_3$	93	96:4
8	**3s**: Ar = 2-MeOC$_6$H$_4$	99	97:3
9	**3t**: Ar = 2-naphthyl	99	96:4
10	**3u**: Ar = 4-allyloxyC$_6$H$_4$	80	96:4

[a] All reactions were carried out with pyridine **1** (0.25 mmol) in toluene (2.0 mL). [b] Isolated yield. [c] Determined by crude ^{1}H NMR.

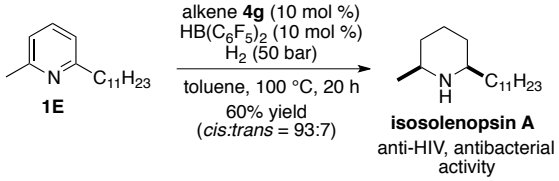
Moreover, the hydrogenation scope can be further expanded to some interesting pyridine substrates. A reduction of the vinyl group occurred under the current reaction conditions when using pyridine **1v** as a substrate to give piperidine **3v** in 96% yield with 94/6 dr

(Table 4, entry 1). For 2-bromopyridines, an unexpected dehalogenation was observed, which provides an alternative approach for the synthesis of mono-substituted piperidines (Table 4, entries 2 and 7). In comparison, the direct hydrogenation of mono-substituted pyridine **1x** required a higher catalyst loading and gave a lower yield (Table 4, entry 3). 2,4,6-Triaryl and 2,6-dialkyl substituted pyridines were hydrogenated to give moderate yields (Table 4, entries 4-6). Significantly, 2,2'-bipyridines proved to be effective substrates for the current catalytic system (Table 4, entries 8 and 9). For 6,6'-dimethyl-2,2'-bipyridine (**1C**), one of the pyridine cycles was selectively hydrogenated to give compound **3C** as the predominant product in 59% yield. While, both pyridine cycles were preferred to be reduced for 6,6'-ditolyl-2,2'-bipyridine (**1D**). Moreover, under the current conditions, pyridine **1E** can be hydrogenated to furnish racemic isosolenopsin A in 60% yield with 93/7 dr (Scheme 2).

Table 4. *Hydrogenation of simple pyridines*[a]

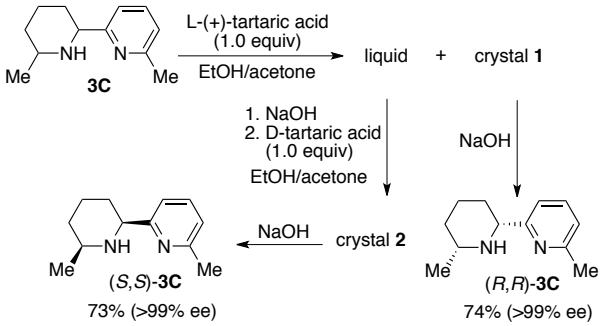
entry	pyridine (**1**)	product (**3**)	yield (%)[b,c]
1	 **1v**	 **3v**	96 (94:6)
2	 **1w**	 **3w**	80
3[d]	 **1x**	 **3w**	64
4[d]	 **1y**	 **3y**	44 (98:2)
5	 R = 4-MeC$_6$H$_4$ **1z**	 **3z**	58 (92:8)
6[e]	 **1A**	 **3A**	51
7[e]	 **1B**	 **3B**	68
8[f]	 **1C**	 **3C**	59 (96:4)
9[g]	 **1D**	 **3D**	75 (>99:1)

[a] All reactions were carried out with pyridine **1** (0.25 mmol), alkene **4g** (10 mol %) and HB(C_6F_5)$_2$ (10 mol %) under H_2 (50 bar) in toluene (2.0 mL) at 100 °C for 20 h unless other noted. [b] Isolated yield. [c] The ratio (*cis*/*trans*) in parenthesis was determined by crude ^{1}H NMR. [d] The reaction was run with 20 mol % of catalyst under H_2 (75 bar) at 120 °C for 30 h. [e] The resulting piperidines were directly treated with phenylacetyl chloride and Et_3N, the yield for two steps. [f] Pyridine **1D** (1.0 mmol) was used.



Scheme 2. Synthesis of isosolenopsin A

Our strategy for generation of borane catalysts *in situ* from alkenes and Piers' borane also provides a possible opportunity to achieve the asymmetric hydrogenation of pyridines by using chiral alkenes. Several chiral dienes[15] were therefore tentatively tested for the asymmetric hydrogenation of pyridine **1C**. Unfortunately, only moderate conversion and very low enantioselectivity (<10% ee) were obtained. The asymmetric version of this transformation is still a formidable challenge and awaits further studies. Alternatively, both enantioisomers of compounds **3C** can be easily accessed via a simple resolution process using L- or D-tartaric acid as a resolution reagent (Scheme 3). The absolute configuration was determined by the X-ray structure of crystal **1**. The interesting structures of enantiomericallyl pure compounds **3C** make them have a potential utilization as chiral organocatalysts or ligands for asymmetric catalysis.



Scheme 3. Resolution of racemic piperidine.

In summary, a broad range of pyridines have been directly hydrogenated under H_2 using catalytic amount of simple borane catalysts generated *in situ* from commercially available alkenes and HB(C_6F_5)$_2$ to furnish important piperidines in high yields with excellent *cis*-stereoselectivities. To the best of our knowledge, the current study represents the first successful example of metal-free catalytic hydrogenation of pyridines with H_2. Further studies on searching for more efficient borane catalysts, expanding substrate types, and exploring asymmetric transformations, are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Procedures for the synthesis of pyridines, hydrogenation of pyridines, and resolution of racemic piperidine, characterization of products, X-ray structures of **3c**, **3D**, and crystal **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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No competing financial interests have been declared.

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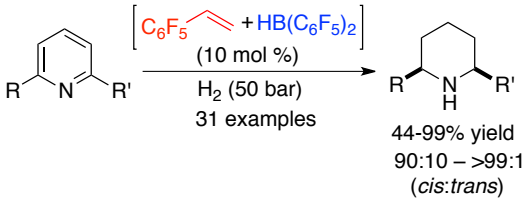
C6F5
+HB(C6F5)2
(10 mol %)
H2 (50 bar)
31 examples
R
N
R'
R
N
H
R'
44-99% yield
90:10 – >99:1
(cis:trans)