Organic LETTERS

Letter

pubs.acs.org/OrgLett

Borane-Catalyzed Transfer Hydrogenations of Pyridines with Ammonia Borane

Qiwen Zhou,[†] Lanqiong Zhang,[†] Wei Meng,[‡,§] Xiangqing Feng,[‡,§] Jing Yang,[*,†] and Haifeng Du[*,‡,§]

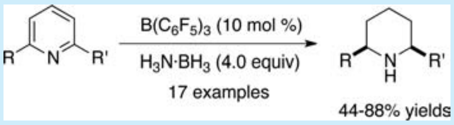
[†]State Key Laboratory of Chemical Resource, Beijing Key Laboratory of Bioprocess, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing 100029, China

[‡]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[§]University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

ABSTRACT: With the use of ammonia borane as a hydrogen source, a borane catalyzed metal-free transfer hydrogenation of pyridines was successfully realized for the first time to furnish a variety of piperidines in 44−88% yields with moderate to excellent *cis*-selectivities. The ease in handling without requiring high pressure H_2 makes this transfer hydrogenation practical and useful.

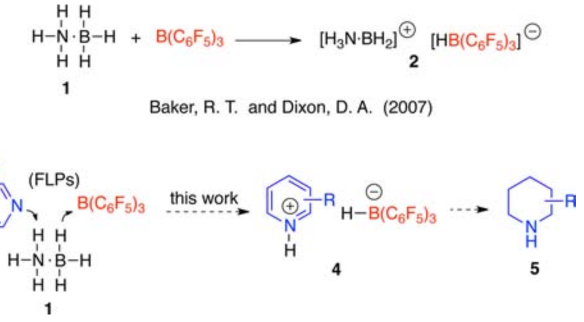


The chemistry of frustrated Lewis pairs (FLPs) provides an important and powerful approach for metal-free hydrogenations. Since the seminal discovery of H_2 splitting with FLPs by Stephan and co-workers in 2006, numerous unsaturated compounds have become effective substrates for the FLP catalysis.[1,2] In particular, rapid growth for the challenging asymmetric hydrogenation has been witnessed in recent years.[3,4] Notably, besides the H_2 activation, FLP can activate the Si−H bond as well, which leads to an interesting Piers type hydrosilylation.[5,6] As a hydrogen donor, silane is not atom economic, but the generally required high pressure in the hydrogenation is unnecessary in the hydrosilylation. Exploring novel hydrogen donors with high hydrogen capacity for the FLP catalysis is therefore an interesting subject with great importance.

Ammonia borane (**1**) has been intensively investigated as an ideal hydrogen storage material owing to its 19.6 wt % hydrogen capacity, low molecular weight, ease in handling, and good stability against air and moisture.[7] Moreover, ammonia borane is also often used as a reagent in the transfer hydrogenations.[8] In 2010, Berke and co-workers described a metal-free transfer hydrogenation of imines with ammonia borane via a concerted six-membered transition state.[9] Later on, the same group extended the transfer hydrogenation to polarized olefins and carbonyl compounds.[10] In 2014, Kinjo, Hirao, and co-workers reported a 1,3,2-diazaphospholene catalyzed transfer hydrogenation of the N═N bond.[11] Ammonia borane was also used in the transition metal catalysis. For example, in 2015, Li and co-workers reported an ammonia-borane activation with cobalt nanoparticles.[12] Very recently, Liu, Luo, and co-workers described a cobalt-catalyzed transfer hydrogenation of alkynes.[13] Despite these advances, to the best of our knowledge, the activation of ammonia borane by FLPs has been less reported. In 2010, Stephan and co-workers used ammonia borane to reduce the zwitterion intermediate generated from the reaction of CO_2 with Al-based FLPs instead of being activated by FLPs.[14] Miller and Bercaw reported a dehydrogenation of ammonia borane with an FLP.[15] In 2016, Aldridge and co-workers described a catalytic dehydrogenation of ammonia borane by a dimethylxanthene-derived FLP.[16]

As an ongoing project in our group, we have been exploring readily accessible FLPs for metal-free hydrogenation and hydrosilylation. Using the *in situ* generated boranes by the hydroboration of alkenes or alkynes with $HB(C_6F_5)_2$,[17] highly stereoselective and/or enantioselective hydrogenations and hydrosilylations have been successfully achieved.[18,19] In the search for novel hydrogen donors other than H_2 and silane for the FLP catalysis, Dixon and Baker's findings on the formation of zwitterion species **2** by treating ammonia borane with $B(C_6F_5)_3$ in 2007 (Scheme 1)[20] provided enlightenment. Based on our previous work on the FLP-catalyzed hydrogenation of simple pyridines,[19b,21] we envision that the FLPs of pyridines **3** and $B(C_6F_5)_3$ can split the N−H and B−H bonds of ammonia

Scheme 1. Our Proposal for FLPs-Catalyzed Transfer Hydrogenations with Ammonia Borane



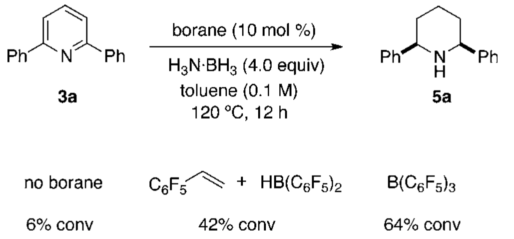
Received: August 31, 2016
Published: September 28, 2016

DOI: 10.1021/acs.orglett.6b02610
Org. Lett. 2016, 18, 5189−5191

borane to generate zwitterion species **4**, which leads a subsequent reduction to produce piperidines **5** (Scheme 1).[22,23] Herein, we wish to report our preliminary results on this subject.

An initial study was carried out with the transfer hydrogenation of pyridine **3a** with ammonia borane (4.0 equiv) as a model reaction. As shown in Scheme 2, ammonia borane itself can react with pyridine **3a** in toluene at 120 °C without any catalysts, but the conversion was very low. With the use of borane (10 mol %) generated from pentafluorostyrene and $HB(C_6F_5)_2$, a 42% conversion was obtained. $B(C_6F_5)_3$ exhibited higher activities to give piperidine **5** in 64% conversion with excellent *cis*-selectivity (99:1).

Scheme 2. Initial Studies on the Transfer Hydrogenation with Ammonia Borane



Optimization of reaction conditions was next conducted to further improve the reactivities. It was found that increasing the reaction concentration largely improved the conversions, and the reaction can be completed in 6 h at a concentration of 0.4 M (Table 1, entries 1–4). Lowering the catalyst loading to 5 mol % led to a dramatic drop in conversion to 45% (Table 1, entry 5). Reducing the amount of ammonia borane (**1**) resulted in lower reactivities (Table 1, entries 6 and 7). Solvents were found to influence this reaction largely, and toluene proved to be a better solvent (Table 1, entries 3 vs 8–14). A ^{11}B NMR study on the crude reaction mixture disclosed that ammonia borane (**1**) was converted into borazine, cyclotriborazane, and poly(borazylene) after the transfer hydrogenation (see Supporting Information), which is similar to the observation by Berke and co-workers.[9]

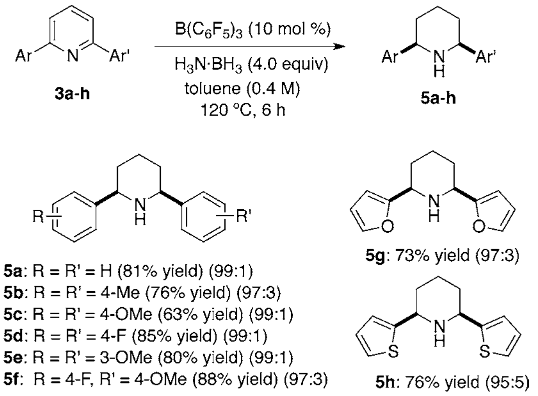
Table 1. Optimization on the Transfer Hydrogenation of Pyridine 3a[a]

entry	**1** (equiv)	solvent	concn (M)	time (h)	conv (%)[b,c]
1	4.0	toluene	0.1	12	64
2	4.0	toluene	0.2	12	83
3	4.0	toluene	0.4	6	99
4	4.0	toluene	0.6	6	96
5[d]	4.0	toluene	0.4	24	45
6	3.0	toluene	0.4	6	88
7	2.0	toluene	0.4	6	59
8	4.0	C_6H_5F	0.4	6	46
9	4.0	C_6H_5Br	0.4	6	85
10	4.0	mesitylene	0.4	6	75
11	4.0	CH_2Cl_2	0.4	6	36
12	4.0	CH_3CN	0.4	6	nr[e]
13	4.0	dioxane	0.4	6	nr[e]
14	4.0	hexane	0.4	6	33

[a] All reactions were carried out with pyridine **3a** (0.20 mmol) and borane (10 mol %) in solvent at 120 °C unless other noted. [b] The conversion was determined by crude ^1H NMR. [c] *Cis*/*trans* = 99:1. [d] 5 mol % of $B(C_6F_5)_3$ was used. [e] No reaction.

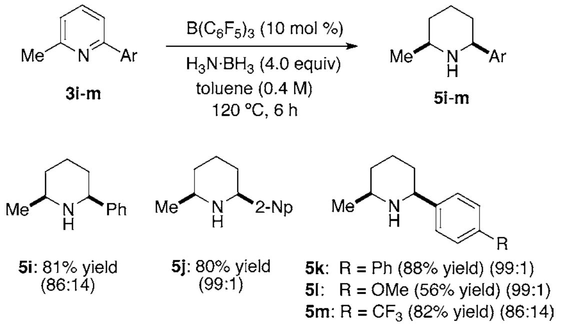
A variety of 2,6-diarylpyridines **3a–h** were then subjected to the transfer hydrogenation under the optimal reaction conditions. As shown in Scheme 3, all these reactions proceeded smoothly to furnish the desired piperidines **5a–h** in 63–88% yields with high *cis*-selectivities. Both substituted phenyl and aromatic heterocyclyl groups were tolerated well in this reaction. 2-Aryl-6-methylpyridines **3i–m** were also effective substrates for this transfer hydrogenation, and *cis*-piperidines **5i–m** as predominate isomers were obtained in 56–88% yields (Scheme 4). When pyridine **5l** bearing an electron-donating substituent was used, a relatively lower yield was given.

Scheme 3. Transfer Hydrogenation of 2,6-Diarylpyridines



Moreover, 2,6-dialkylpyridine **3n** was a suitable substrate to give product **5n** in 80% yield (Figure 1). Monosubstituted pyridine **3o** was a less reactive substrate and gave piperidine **5o** in a moderate yield. Notably, the transfer hydrogenation of 2,3-disubstituted pyridines **3p** and **3q** can also occur to furnish the desired **5p** and **5q** in 44–53% yields with moderate *cis*-selectivities.

Scheme 4. Transfer Hydrogenation of 2-Aryl-6-methylpyridines



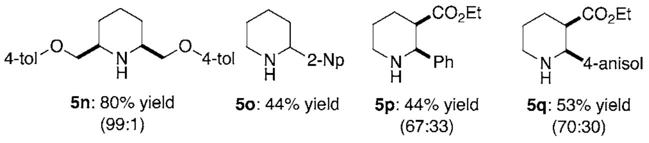


Figure 1. Transfer hydrogenation of other simple pyridines.

In summary, a borane catalyzed metal-free transfer hydrogenation of pyridines with ammonia borane as the hydrogen source was successfully realized to furnish the desired piperidines in 44−88% yields with moderate to excellent *cis*-selectivities. In contrast to the FLP-catalyzed hydrogenation with H_2, the current transfer hydrogenation with ammonia borane successfully avoided use of high pressure H_2 (50 bar),[19b] which will provide a promising and practical approach for the transfer hydrogenations. Studies to further understand the mechanism and explore the application of ammonia borane in other transfer hydrogenations are underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02610.

Procedure for the metal-free transfer hydrogenation of pyridines, characterization of products along with the NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yangj@mail.buct.edu.cn.
*E-mail: haifengdu@iccas.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the generous financial support from the National Natural Science Foundation of China (21222207, 21374005, and 21572231).

■ REFERENCES

(1) For a seminal work, see: Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124.

(2) For leading reviews, see: (a) Kenward, A. L.; Piers, W. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 38. (b) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46. (c) Soós, T. *Pure Appl. Chem.* **2011**, *83*, 667. (d) Erker, G. *Pure Appl. Chem.* **2012**, *84*, 2203. (e) Paradies, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3552. (f) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400. (g) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018. (h) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 306.

(3) For leading reviews, see: (a) Liu, Y.; Du, H. *Huaxue Xuebao* **2014**, *72*, 771. (b) Feng, X.; Du, H. *Tetrahedron Lett.* **2014**, *55*, 6959. (c) Shi, L.; Zhou, Y.-G. *ChemCatChem* **2015**, *7*, 54.

(4) For selected examples, see: (a) Chase, P. A.; Jurca, T.; Stephan, D. W. *Chem. Commun.* **2008**, 1701. (b) Chen, D.; Wang, Y.; Klankermayer, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9475. (c) Sumerin, V.; Chernichenko, K.; Nieger, M.; Leskelä, M.; Rieger, B.; Repo, T. *Adv. Synth. Catal.* **2011**, *353*, 2093. (d) Lindqvist, M.; Borre, K.; Axenov, K.; Kótai, B.; Nieger, M.; Leskelä, M.; Pápai, I.; Repo, T. *J. Am. Chem. Soc.* **2015**, *137*, 4038.

(5) For a recent review, see: Oestreich, M.; Hermeke, J.; Mohr, J. *Chem. Soc. Rev.* **2015**, *44*, 2202.

(6) For selected examples, see: (a) Parks, D. J.; Piers, W. E. *J. Am. Chem. Soc.* **1996**, *118*, 9440. (b) Blackwell, J. M.; Sonmor, E. R.; Scoccitti, T.; Piers, W. E. *Org. Lett.* **2000**, *2*, 3921. (c) Chen, D.; Leich, V.; Pan, F.; Klankermayer, J. *Chem. - Eur. J.* **2012**, *18*, 5184. (d) Hermeke, J.; Mewald, M.; Oestreich, M. *J. Am. Chem. Soc.* **2013**, *135*, 17537. (e) Süsse, L.; Hermeke, J.; Oestreich, M. *J. Am. Chem. Soc.* **2016**, *138*, 6940.

(7) For leading reviews, see: (a) Marder, T. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 8116. (b) Hamilton, C. W.; Baker, R. T.; Staubitz, A.; Manners, I. *Chem. Soc. Rev.* **2009**, *38*, 279. (c) Staubitz, A.; Robertson, A. P. M.; Manners, I. *Chem. Rev.* **2010**, *110*, 4079. (d) Huang, Z.; Autrey, T. *Energy Environ. Sci.* **2012**, *5*, 9257. (e) Houghton, A. Y.; Hurmalainen, J.; Mansikkamäki, A.; Piers, W. E.; Tuononen, H. M. *Nat. Chem.* **2014**, *6*, 983. (f) Rossin, A.; Peruzzini, M. *Chem. Rev.* **2016**, *116*, 8848.

(8) For leading reviews on transfer hydrogenations, see: (a) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (b) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (c) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282. (d) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498. (e) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621. (f) Oestreich, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 494.

(9) Yang, X.; Zhao, L.; Fox, T.; Wang, Z.-X.; Berke, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 2058.

(10) (a) Yang, X.; Fox, T.; Berke, H. *Chem. Commun.* **2011**, *47*, 2053. (b) Yang, X.; Fox, T.; Berke, H. *Org. Biomol. Chem.* **2012**, *10*, 852. (c) Yang, X.; Fox, T.; Berke, H. *Tetrahedron* **2011**, *67*, 7121.

(11) Chong, C. C.; Hirao, H.; Kinjo, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 3342.

(12) Zhao, T.-J.; Zhang, Y.-N.; Wang, K.-X.; Su, J.; Wei, X.; Li, X.-H. *RSC Adv.* **2015**, *5*, 102736.

(13) Fu, S.; Chen, N.-Y.; Liu, X.; Shao, Z.; Luo, S.-P.; Liu, Q. *J. Am. Chem. Soc.* **2016**, *138*, 8588.

(14) Ménard, G.; Stephan, D. W. *J. Am. Chem. Soc.* **2010**, *132*, 1796.

(15) Miller, A. J. M.; Bercaw, J. E. *Chem. Commun.* **2010**, *46*, 1709.

(16) Mo, Z.; Rit, A.; Campos, J.; Kolychev, E. L.; Aldridge, S. *J. Am. Chem. Soc.* **2016**, *138*, 3306.

(17) (a) Parks, D. J.; Spence, R. E. H.; Piers, W. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 809. (b) Parks, D. J.; Piers, W. E.; Yap, G. P. A. *Organometallics* **1998**, *17*, 5492.

(18) (a) Cao, Z.; Du, H. *Org. Lett.* **2010**, *12*, 2602. (b) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204.

(19) (a) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 6810. (b) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 12968. (c) Wei, S.; Du, H. *J. Am. Chem. Soc.* **2014**, *136*, 12261. (d) Zhang, Z.; Du, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 623. (e) Ren, X.; Du, H. *J. Am. Chem. Soc.* **2016**, *138*, 810.

(20) Stephens, F. H.; Baker, R. T.; Matus, M. H.; Grant, D. J.; Dixon, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 746.

(21) For a mechanistic study by DFT calculation, see: Zhao, J.; Wang, G.; Li, S. *Dalton Trans.* **2015**, *44*, 9200.

(22) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979.

(23) For recent examples on hydrogenation and transfer hydrogenation of pyridines, see: (a) Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. *Chem. Commun.* **2000**, 1925. (b) Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850. (c) Lei, A.; Chen, M.; He, M.; Zhang, X. *Eur. J. Org. Chem.* **2006**, *2006*, 4343. (d) Wang, X.-B.; Zeng, W.; Zhou, Y.-G. *Tetrahedron Lett.* **2008**, *49*, 4922. (e) Tang, W.; Sun, Y.; Xu, L.; Wang, T.; Fan, Q.; Lam, K.-H.; Chan, A. S. C. *Org. Biomol. Chem.* **2010**, *8*, 3464. (f) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562. (g) Mahdi, T.; del Castillo, J. N.; Stephan, D. W. *Organometallics* **2013**, *32*, 1971.