<u>Creanic</u> LETTERS

44-88% yields

Borane-Catalyzed Transfer Hydrogenations of Pyridines with Ammonia Borane

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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 H₂ makes this transfer hydrogenation practical and useful.

T he 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 ammoniaborane 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 CO₂ 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-

B(C₆F₅)₃ (10 mol %)

H₃N·BH₃ (4.0 equiv)

17 examples

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 H₂ 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







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

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



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).

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

Table 1. Optimization on the Transfer Hydrogenation of Pyridine $3a^a$

entry	1 (equiv)	solvent	concn (M)	time (h)	conv (%) ^{<i>b,c</i>}
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 ₆ H ₅ Br	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 ₃ CN	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*}S mol % of B(C₆F₅)₃ was used. ^{*c*}No reaction.

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 ¹¹B 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

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

Scheme 3. Transfer Hydrogenation of 2,6-Diarylpyridines



proceeded smoothly to furnish the desired piperidines 5a-hin 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 51 bearing an electron-donating substituent was used, a relatively lower yield was given.

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



Moreover, 2,6-dialkylpyridine **3n** was a suitable substrate to give product **5n** in 80% yield (Figure 1). Monosubstituted



Figure 1. Transfer hydrogenation of other simple pyridines.

pyridine **30** was a less reactive substrate and gave piperidine **50** in a moderate yield. Notably, the transfer hydrogenation of 2,3disubstituted pyridines **3p** and **3q** can also occur to furnish the desired **5p** and **5q** in 44–53% yields with moderate *cis*-selectivities.

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.or-glett.6b02610.

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

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Notes

The authors declare no competing financial interest.

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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.