ChemComm

This article is part of the

Hydrogen web- based thematic issue

showcasing the latest research on all aspects of hydrogen generation, storage and activation

Guest editors: Professors Ferdi Schüth, Douglas Stephan, Daniel DuBois and Mary DuBois

All articles in this issue are gathered together online at www.rsc.org/chemcomm/hydrogen

Metal-free reductions of N-heterocycles *via* Lewis acid catalyzed hydrogenation†‡

Stephen J. Geier, Preston A. Chase and Douglas W. Stephan*

Received 1st April 2010, Accepted 2nd June 2010
First published as an Advance Article on the web 14th June 2010
DOI: 10.1039/c0cc00719f

N-Heterocycles form weak adducts with $B(C_6F_5)_3$ that exist in equilibrium with the corresponding FLP; nonetheless, these heterocycles are reduced in the presence of a catalytic amount of the borane $B(C_6F_5)_3$ and H_2.

The growing field of organocatalysis is providing a variety of strategies to non-toxic catalysts for a variety of organic reactions.[1] While a number of organic species, such as a Hantsch ester,[2] have been used as stoichiometric sources of H_2, it has only been recently that metal-free systems capable of H_2 activation[3] have been extended to reveal catalysts that can utilize H_2 directly for catalytic hydrogenation.[4] These latter systems have been based on the concept of frustrated Lewis pairs (FLPs).[5] These combinations of Lewis acids and Lewis bases which cannot interact directly due to steric bulk are capable of the heterolytic activation of H_2 and the delivery of the resulting proton and hydride to organic substrates. The initial report on catalysis described the use of the phosphinoborane $Mes_2P(C_6F_4)B(C_6F_5)_2$ as a catalyst for the hydrogenation of imines, Lewis acid protected nitriles and the reductive ring-opening of aziridines.[4b] In a subsequent work, this concept has been subsequently expanded.[6] The Erker research group in Germany have developed related FLP catalysts for the hydrogenation of enamines and silyl-enol-ethers.[6a–c] The mechanistic details of these FLP hydrogenations continue to be the subject of theoretical study. Early computational studies[7] support the view that the electrostatic approach of the Lewis acid and base yields an "encounter complex" which polarizes H_2 for heterolytic cleavage. A recent refinement of this model suggests "side-on" and "end-on" interactions with B and P, respectively.[8] Regardless, these reactions offer an atom-economical, metal-free alternative to conventional stoichiometric reductions. While the variety of bases including carbenes,[9] amines,[4a] imines,[4a,10] pyridines,[11] phosphinoboranes[12] and boranes have been found to activate H_2, an important extension of this work recognized that the sterically hindered imines can act as the Lewis base partner of an FLP.[4] This permits the catalytic reduction of imine by simply employing a catalytic amount of $B(C_6F_5)_3$ in the presence of the imine and H_2.

Department of Chemistry, 80 St. George St., University of Toronto, Toronto, Ontario, Canada M5S 3H6.
E-mail: dstephan@chem.utoronto.ca

† This article is part of a *ChemComm* 'Hydrogen' web-based themed issue.

‡ Electronic supplementary information (ESI) available: Experimental data. CCDC 772138. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00719f

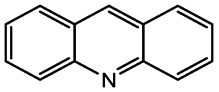
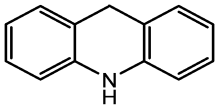
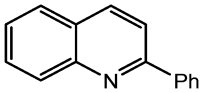
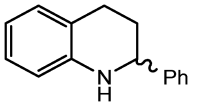
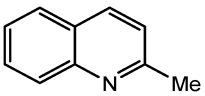
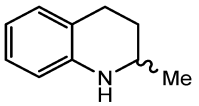
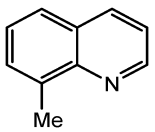
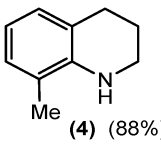
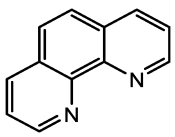
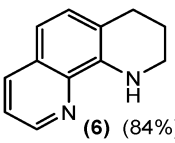
In seeking to expand further the array of substrates that undergo FLP hydrogenation, we noted that bulky pyridines, in combination with $B(C_6F_5)_3$, can activate H_2[11] to generate the corresponding pyridinium hydridoborate. More recent studies have examined analogous reactions of electron deficient pyridines such as 2,6-dimethyl-3,5-pyridinedicarboxylate resulting in the formation of the corresponding 1,2-dihydropyridine as a result of hydride transfer to the pyridinium cation.[13] This result suggested that the reactions of other electron deficient N-heterocycles with the borane $B(C_6F_5)_3$ in the absence and presence of H_2 should be examined.

Acridine and substituted quinolines have been previously hydrogenated by a variety of methods,[14] including Birch reduction,[15] transition metal catalyzed hydrogenation,[16] transfer hydrogenation,[17] stoichiometric reduction using a boro-hydride source[18] and H_2 transfer from Hantsch's ester.[19] These known reactions suggest these compounds may be viable substrates for metal-free catalytic hydrogenations. Stoichiometric combinations of acridine with $B(C_6F_5)_3$ establish an equilibrium in $CDCl_3$ involving the frustrated Lewis pair and the classical Lewis-acid–base adduct. The ratio of the two is approximately 1 : 1 as determined by ^{19}F NMR spectroscopy. The ^{19}F and ^{11}B NMR spectra show signals typical of a pyridine–borane adduct (^{19}F: δ = −130.3, −157.0, −163.7 ppm; ^{11}B: δ = −2.8 ppm) as well as resonances corresponding to free $B(C_6F_5)_3$ while the ^1H NMR spectrum showed only one set of broad peaks, indicative of an exchange process. The green colour of the solution is similar to that described for the acridine–BCl_3 adduct.[20]

The formation of an FLP suggested the possibility of reaction with H_2. Treatment of acridine with 5 mol% $B(C_6F_5)_3$ over 2 hours under 4 atm of H_2 at room temperature led to catalytic hydrogenation of the central ring of acridine. The product (**1**) was easily identifiable by characteristic peaks in the ^1H NMR spectrum at δ = 4.11 and 5.79 ppm, arising from the methylene and N–H protons, respectively. Flash chromatography afforded (**1**) in 80% isolated yield. This reduction is believed to proceed *via* heterolytic activation of H_2 by acridine and borane. Subsequent hydride attack at the strongly electrophilic 9-position affords (**1**) (Table 1).

In a similar fashion quinolines with substituents in the 2- or 8-position, which provide sufficient bulk to hinder adduct formation, were explored for FLP reactivity. Stoichiometric reactions of 2-phenylquinoline, 8-methylquinoline and 2-methylquinoline with $B(C_6F_5)_3$ were monitored by NMR spectroscopy. 2-Phenylquinoline and 8-methylquinoline showed only trace (<5%) signs of adduct formation with $B(C_6F_5)_3$, while the mixture of 2-methylquinoline with $B(C_6F_5)_3$ also showed an equilibrium mix of free Lewis acid

Table 1 Catalytic hydrogenations of N-heterocycles

Substrate	Cat/mol%	t/h	T/°C	Product (yield)
	5	2	25	 **(1)** (80%)
	5	4	25	 **(2)** (80%)
	5	16	50	 **(3)** (74%)
	10	6	80	 **(4)** (88%)
	5	3	25	 **(6)** (84%)

and classical adduct. Again free $B(C_6F_5)_3$ and the adducts were observed in approximately a 1 : 1 ratio in $CDCl_3$ at room temperature.

2-Phenylquinoline was reduced quantitatively to 1,2,3,4-tetrahydro-2-phenyquinoline (**2**) using 5 mol% $B(C_6F_5)_3$ under similar conditions described for the acridine reduction above. The product (**2**) was isolated following chromatography in 80% yield. 2-Methylquinoline and 8-methylquinoline were similarly reduced although these systems required heating to 50 °C. Nonetheless, the respective products (**3**) and (**4**) were isolated in yields of 88 and 74%, respectively.

The related heterocycle 1,10-phenanthroline reacts stoichiometrically with $B(C_6F_5)_3$, to form a new species (**5**). The ^{11}B NMR spectrum of (**5**) showed a signal at $\delta = -3.2$ ppm while the ^{19}F NMR spectrum was consistent with 15 inequivalent fluorine environments. This latter observation has been seen previously for asymmetrically substituted pyridine adducts and for systems where steric congestion inhibits fluoroarene ring rotation.[11] The X-ray crystal structure of (**5**) (Fig. 1) confirmed the anticipated connectivity and revealed extraordinarily long B–N bond lengths of 1.691(3) Å and 1.692(3) Å for the 2 crystallographically independent molecules.§ This bond length is substantially longer than that observed in the $B(C_6F_5)_3$ adduct of 2,6-lutidine (1.661(2) Å), which is in equilibrium with the free Lewis acid and base.[12] While no such equilibrium was observed for 1,10-phenanthroline, the long B–N bond length and broad signals in the ^{19}F NMR spectrum suggested that the free Lewis acid and base may be accessible. Indeed, treatment of 1,10-phenanthroline with 5 mol% $B(C_6F_5)_3$ for 3 hours under 4 atm of H_2 at 80 °C

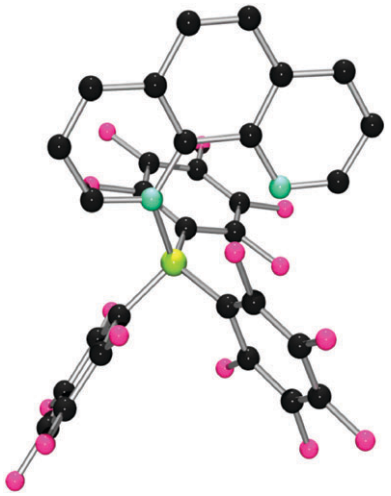
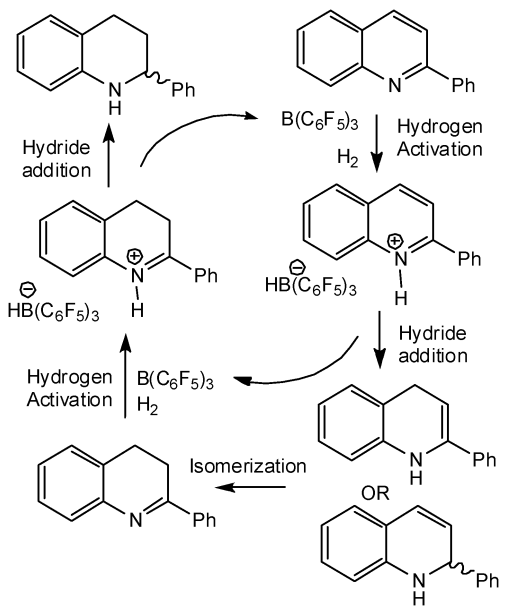


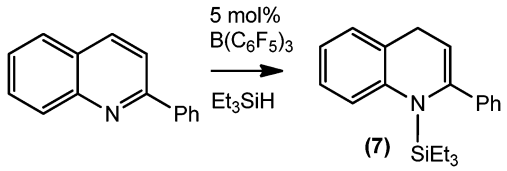
Fig. 1 POV-ray depictions of the cation of **5**. C: black, N: blue-green, F: pink, B: yellow-green; H atoms are omitted for clarity.

resulted in the hydrogenation affording 1,2,3,4-tetrahydro-1,10-phenanthroline (**6**) in 84% isolated yield.

In contrast to the acridine reduction, the quinoline and phenanthroline reduction products incorporate two equivalents of H_2. In the proposed mechanism (Scheme 1), it is thought that following FLP activation of H_2, the location of the subsequent hydride attack could be either at the 2- or 4-position as both sites are electrophilic in protonated quinoline or phenanthroline. Attack at the 4-position would generate a transient enamine. Nonetheless, attack by hydride at the 2-position would give the corresponding 1,2-dihydro-quinoline or phenanthroline which can undergo 1,3 proton shifts to regenerate an imine which could be subsequently hydrogenated. In this regard, it is also noteworthy that 1,2- or 1,4-dihydro-quinoline are known to redistribute to quinoline and tetrahydroquinoline in the presence of a Brönsted acid.[21] Direct reaction of the enamine may also occur.



Scheme 1 Proposed mechanism of hydrogenation of 2-phenylquinoline.



Scheme 2 Hydrosilylation of 2-phenylquinoline.

It is noteworthy that analogous catalytic hydrosilylation[22] of 2-phenyquinoline using Et_3SiH gives exclusively the 1,4 *N*-$SiEt_3$ product (**7**) (Scheme 2). The inability of the silyl-group to migrate to regenerate an imine precludes further reduction.

In conclusion, the N-heterocycles acridine and bulky quinolines form weak adducts with $B(C_6F_5)_3$ that exist in equilibrium with the corresponding FLP. In the case of phenanthroline, the isolated adduct exhibits a long N–B bond. Nonetheless, all of these heterocycles are reduced in the presence of a catalytic amount of borane $B(C_6F_5)_3$ and H_2 to dihydroacridine substituted 1,2,3,4-tetrahydroquinolines and 1,2,3,4-tetrahydro-1,10-phenanthrolines, respectively. These are the first such metal-free, atom economic reductions of N-heterocycles. The utility of such reductions continues to be the subject of study in our laboratories.

Financial support from NSERC of Canada is gratefully acknowledged. DWS is grateful for the award of a Killam Research Fellowship and a Canada Research Chair. SJG is grateful for the award of an NSERC-PGS-D fellowship.

Notes and references

§ Crystallographic data for **5**: $C_{30}H_8BF_{15}N_2$, MW = 692.19, T = 150 K, space group triclinic, $P\bar{1}$, a = 12.4522(10) Å, b = 12.8361(10) Å, c = 16.6764(13) Å, α = 79.106(4)°, β = 79.436(4)°, γ = 85.941(4)°, V = 2571.3(4) Å^3, Z = 4, μ = 0.182 mm^{-1}, measured reflections = 42719, independent reflections = 11857, parameters = 865, R_{int} 0.0512, R = 0.0443, R_w = 0.1161, GOF = 1.009.

1 (*a*) X. Bantreil, J. Broggi and S. P. Nolan, *Annu. Rep. Prog. Chem., Sect. B*, 2009, **105**, 232–263; (*b*) B. R. Buckley, *Annu. Rep. Prog. Chem., Sect. B*, 2009, **105**, 113–128; (*c*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304–308; (*d*) I. McCort-Tranchepain, M. Petit and P. I. Dalko, *Handb. Green Chem.: Green Catal.*, 2009, **1**, 255–318; (*e*) T. Werner, *Adv. Synth. Catal.*, 2009, **351**, 1469–1481.

2 (*a*) S. G. Ouellet, A. M. Walji and D. W. C. Macmillan, *Acc. Chem. Res.*, 2007, **40**, 1327–1339; (*b*) S.-L. You, *Chem.–Asian J.*, 2007, **2**, 820–827.

3 G. C. Welch, R. R. S. Juan, J. D. Masuda and D. W. Stephan, *Science*, 2006, **314**, 1124.

4 (*a*) P. A. Chase, T. Jurca and D. W. Stephan, *Chem. Commun.*, 2008, 1701; (*b*) P. A. Chase, G. C. Welch, T. Jurca and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2007, **46**, 9136–9136; (*c*) P. A. Chase, G. C. Welch, T. Jurca and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2007, **49**, 8050.

5 (*a*) D. W. Stephan, *Org. Biomol. Chem.*, 2008, **6**, 1535; (*b*) D. W. Stephan and G. Erker, *Angew. Chem., Int. Ed.*, 2010, **49**, 46–76.

6 (*a*) K. V. Axenov, G. Kehr, R. Frohlich and G. Erker, *J. Am. Chem. Soc.*, 2009, **131**, 3454–3455; (*b*) P. Spies, S. Schwendemann, S. Lange, G. Kehr, R. Frohlich and G. Erker, *Angew. Chem., Int. Ed.*, 2008, **47**, 7543–7546; (*c*) H. D. Wang, R. Frohlich, G. Kehr and G. Erker, *Chem. Commun.*, 2008, 5966–5968; (*d*) V. Sumerin, F. Schulz, M. Atsumi, C. Wang, M. Nieger, M. Leskela, T. Repo, P. Pyykkö and B. Rieger, *J. Am. Chem. Soc.*, 2008, **130**, 14117.

7 (*a*) Y. Guo and S. Li, *Inorg. Chem.*, 2008, **47**, 6212–6219; (*b*) T. A. Rokob, A. Hamza, A. Stirling, T. Soos and I. Papai, *Angew. Chem., Int. Ed.*, 2008, **47**, 2435–2438; (*c*) A. Hamza, A. Stirling, T. A. Rokob and I. Papai, *Int. J. Quantum Chem.*, 2009, **109**, 2416–2425; (*d*) A. Hamza, A. Stirling, T. A. Rokob and I. Papai, *Int. J. Quantum Chem.*, 2009, **109**, 2416–2425; (*e*) J. Nyhlen and T. Privalov, *Dalton Trans.*, 2009, 5780–5786; (*f*) J. Nyhlen and T. Privalov, *Eur. J. Inorg. Chem.*, 2009, 2759–2764; (*g*) T. Privalov, *Eur. J. Inorg. Chem.*, 2009, 2229–2237; (*h*) T. Privalov, *Dalton Trans.*, 2009, 1321–1327; (*i*) T. Privalov, *Chem.–Eur. J.*, 2009, **15**, 1825–1829; (*j*) T. A. Rokob, A. Hamza and I. Papai, *J. Am. Chem. Soc.*, 2009, **131**, 10701–10710; (*k*) T. A. Rokob, A. Hamza, A. Stirling and I. Papai, *J. Am. Chem. Soc.*, 2009, **131**, 2029–2036.

8 S. Grimme, H. Kruse, L. Goerigk and G. Erker, *Angew. Chem., Int. Ed.*, 2010, **49**, 1402.

9 (*a*) P. A. Chase and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2008, **47**, 7433; (*b*) D. Holschumacher, T. Bannenberg, C. G. Hrib, P. G. Jones and M. Tamm, *Angew. Chem., Int. Ed.*, 2008, **47**, 7428.

10 (*a*) V. Sumerin, F. Schulz, M. Nieger, M. Leskela, T. Repo and B. Rieger, *Angew. Chem., Int. Ed.*, 2008, **47**, 6001; (*b*) K. V. Axenov, G. Kehr, R. Frohlich and G. Erker, *Organometallics*, 2009, **28**, 5148–5158.

11 (*a*) S. J. Geier, A. L. Gille, T. M. Gilbert and D. W. Stephan, *Inorg. Chem.*, 2009, **48**, 10466–10474; (*b*) S. J. Geier and D. W. Stephan, *J. Am. Chem. Soc.*, 2009, **131**, 3476–3477.

12 S. J. Geier, T. M. Gilbert and D. W. Stephan, *J. Am. Chem. Soc.*, 2008, **130**, 12632–12633.

13 J. D. Webb, V. S. Laberge, S. J. Geier, D. W. Stephan and C. M. Crudden, *Chem.–Eur. J.*, 2010, **16**, 8.

14 (*a*) F. Fadel, S. L. Titouani, M. Soufiaoui, H. Ajamay and A. Mazzah, *Tetrahedron Lett.*, 2004, **45**, 5905–5908; (*b*) H. Friebolin and C. Ruchardt, *Liebigs Ann.*, 1995, 1339–1341; (*c*) A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031–15070; (*d*) A. Sahin, O. Cakmak, I. Demirtas, S. Okten and A. Tutar, *Tetrahedron*, 2008, **64**, 10068–10074; (*e*) S. Singh, S. Chhina, V. K. Sharma and S. S. Sachdev, *J. Chem. Soc., Chem. Commun.*, 1982, 453–454; (*f*) V. Sridharan, C. Avendano and J. Carlos Menendez, *Tetrahedron*, 2009, **65**, 2087–2096; (*g*) L. P. Yunnikova and O. V. Tigina, *Zh. Org. Khim.*, 1993, **29**, 651–652.

15 P. W. Rabideau and Z. Marcinow, *Org. React.*, 1992, **42**, 1.

16 (*a*) M. Hoenel and F. W. Vierhapper, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1933–1939; (*b*) S.-M. Lu, X.-W. Han and Y.-G. Zhou, *J. Organomet. Chem.*, 2007, **692**, 3065–3069; (*c*) G. Radivoy, F. Alonso and M. Yus, *Tetrahedron*, 1999, **55**, 14479–14490; (*d*) M. Rosales, J. Castillo, A. Gonzalez, L. Gonzalez, K. Molina, J. Navarro, I. Pacheco and H. Perez, *Transition Met. Chem.*, 2004, **29**, 221–228; (*e*) M. Rosales, R. Vallejo, L. J. Bastidas, B. Gonzalez and A. Gonzalez, *React. Kinet. Catal. Lett.*, 2007, **92**, 99–104.

17 (*a*) K.-i. Fujita, C. Kitatsuji, S. Furukawa and R. Yamaguchi, *Tetrahedron Lett.*, 2004, **45**, 3215–3217; (*b*) A. M. Voutchkova, D. Gnanamgari, C. E. Jakobsche, C. Butler, S. J. Miller, J. Parr and R. H. Crabtree, *J. Organomet. Chem.*, 2008, **693**, 1815–1821.

18 (*a*) B. C. Ranu, U. Jana and A. Sarkar, *Synth. Commun.*, 1998, **28**, 485–492; (*b*) A. Srikrishna, T. J. Reddy and R. Viswajanani, *Tetrahedron*, 1996, **52**, 1631–1636.

19 (*a*) M. Rueping, A. R. Antonchick and T. Theissmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 3683–3686; (*b*) M. Rueping, T. Theissmann and A. P. Antonchick, *Synlett*, 2006, 1071–1074.

20 R. Snyder and A. C. Testa, *J. Lumin.*, 1990, **47**, 35–39.

21 T. P. Forrest, G. A. Dauphinee and S. A. Deraniyagala, *Can. J. Chem.*, 1985, **63**, 412–417.

22 (*a*) J. M. Blackwell, W. E. Piers and M. Parvez, *Org. Lett.*, 2000, **2**, 695–698; (*b*) J. M. Blackwell, E. R. Sonmor, T. Scoccitti and W. E. Piers, *Org. Lett.*, 2000, **24**, 3921–3923.

