Lewis acid-catalyzed hydrogenation: $B(C_6F_5)_3$-mediated reduction of imines and nitriles with H_2†‡

Preston A. Chase, Titel Jurca and Douglas W. Stephan*§

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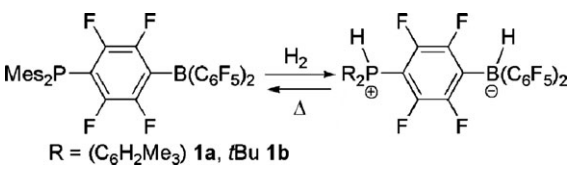
The Lewis acid $B(C_6F_5)_3$ has been found to be an efficient catalyst for the direct hydrogenation of imines and the reductive ring-opening of aziridines with H_2 under mild conditions; addition of a bulky phosphine allows for the reduction of protected nitriles.

Hydrogenation is one of the most utilized and important reactions in chemistry. Typically, the hydrogenation of organic substrates using H_2 directly is mediated by a transition metal catalyst.[1] Alternatively, main group hydrides such as $NaBH_4$ and $LiAlH_4$[2] afford stoichiometric reductions, with complementary chemo- and regioselectivity to metal catalysis. For these reagents in industrial scale reduction processes, cost, chemical efficacy and waste disposal are significant concerns. Thus, catalytic hydrogenations employing transition metal-free catalysts could address the cost and waste remediation issues associated with main group hydrides, as well as avoid the expense and potentially toxic nature of precious metal catalysts.

A number of transition metal-free hydrogenation reactions are known within the realm of organocatalysis.[3–7] These systems do not use H_2 directly but rather a surrogate, such as a Hantzsch ester, as a source of H_2. Alternatively, as H_2 is known to react directly with trialkylboranes to give R_2BH and RH, a hydrogenation cycle by successive hydroboration/hydrogenolysis reactions can be used to effect the reduction of alkenes. However, the required conditions are rather forcing (>200 °C, 15 atm).[8–11] Similarly, Berkessel *et al*. reported the catalytic reduction of benzophenone using KO*t*Bu/H_2, although the conditions were again quite harsh (180 °C, 50 bar).[12] The key to developing main group hydrogenation catalysis utilizing H_2 has been the discovery of main group compounds that react directly with H_2.[13] Power and co-workers reported the addition of H_2 to a germyne,[14] and Bertrand *et al*. demonstrated the addition of H_2 and NH_3 to certain amino alkyl carbenes.[15] We have recently reported that H_2 can be heterolytically cleaved under ambient conditions by a reaction with a combination of bulky boranes and phosphines.[16] Such sterically "frustrated Lewis pairs" (FLPs) provide unquenched acceptor and donor abilities to the acid and base, respectively, opening new modes of reactivity.[16–18] Such FLPs furnished the first main group system (**1a**, Scheme 1) that *reversibly* reacts with H_2.[19] Moreover, FLP mixtures of $B(C_6F_5)_3$ and PR_3 have been shown to react with alkenes,[20] while compounds **1** have recently been shown to catalyze the reduction of imines and nitriles under H_2.[21] Herein, we show that simple combinations of the commercially available Lewis acid $B(C_6F_5)_3$[22] with sterically demanding aldimines and ketimines constitute FLPs that react with H_2, affording direct and catalytic reduction to amines. In addition, aziridines are shown to undergo reductive ring-opening, while protected nitriles are also reduced, although in the latter case, addition of a bulky phosphine Lewis base is required.

The direct hydrogenation of a number of aldimines and ketimines[23,24] catalyzed by $B(C_6F_5)_3$ is shown in Table 1.† In accordance with the results of imine hydrogenation with **1**, the bulkier, more basic aldimines (Table 1, E1 and E2) were hydrogenated more rapidly than an electron poor system (Table 1, E3) (*vide infra*). Indeed, reactions E1 and E2 proceeded in similar times to the hydrogenations catalyzed by **1**. Ketimines (Table 1, E4 and E5) are also efficiently reduced under these conditions, with one exception (Table 1 E6), which does not show any reactivity due to the steric bulk at the imine C. *cis*-Triphenylaziridine (Table 1, E7) is reductively ring opened to racemic *N*-(1,2-diphenylethyl)aniline. Notably in E1, reduction continues after the addition of an extra equivalent of *t*BuN=CPh(H) to the completed reaction, demonstrating the living nature of the catalysis.

The above catalysis supports the view that the splitting of H_2 occurs by the action of an FLP, generated by the combination of the *N*-Lewis base and $B(C_6F_5)_3$, in a similar fashion to that previously described for P-donors.[16,19] The ability of an imine and an amine to act as the basic FLP partner was established unambiguously as follows. The stoichiometric



Scheme 1 Reactivity of H_2 with $R_2PC_6F_4B(C_6F_5)_2$ (R = $C_6H_2Me_3$ (**1a**) and *t*Bu (**1b**)) (note: the reaction is reversible for **1a**).

Department of Chemistry and Biochemistry, University of Windsor, 401 Sunset Ave. Windsor, Ontario, Canada N9B 3P4. E-mail: dstephan@chem.utoronto.ca

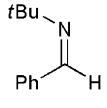
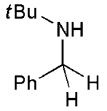
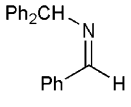
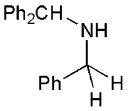
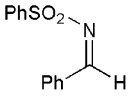
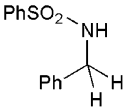
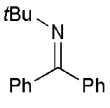
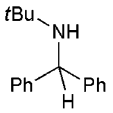
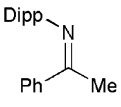
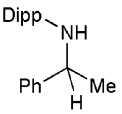
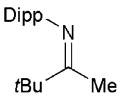
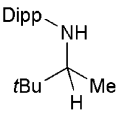
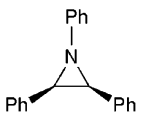
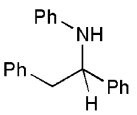
† Electronic supplementary information (ESI) available: Catalysis procedures and full experimental data for **2–4**. See DOI: 10.1039/b718598g

‡ Crystallographic data for **3**: space group monoclinic, $P2_1/n$, a = 10.2932(10), b = 13.9127(14), c = 20.747(2) Å, β = 104.0340(10)°, V = 2882.4(5) Å^3, Z = 4, μ = 0.159 mm^{-1}, measured reflections = 5088, independent reflections = 3004, parameters = 427, R_{int} = 0.0440, R = 0.869, R_w = 0.1228, GOF = 0.996. CCDC 669400. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b718598g

§ Current address: Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ontario, Canada, M5S 3H6.

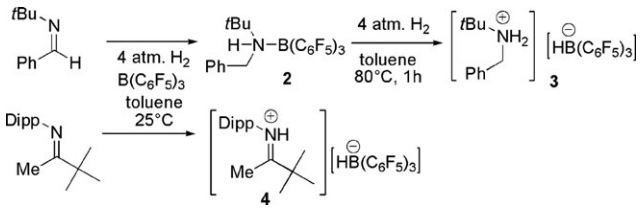
Table 1 Catalytic hydrogenations by $B(C_6F_5)_3$ and H_2

substrate $\xrightarrow[5\text{ atm. }H_2,\,120\,^{\circ}C\text{ toluene}]{5\text{ mol\% }B(C_6F_5)_3}$ product

Entry	Substrate	Time/h	Yield (%)	Product
E1		2[a]	89	
E2		1	99	
E3		41	94	
E4		1	98	
E5		8	94	
E6		48	0	
E7		2	95	

[a] Alternate conditions: 80 °C, 1 atm. H_2. Dipp = 2,6-$(Me_2CH)C_6H_3$.

reaction between imine *t*BuN=CPh(H) and $B(C_6F_5)_3$ with H_2 at room temperature gave the amine–borane adduct *t*Bu$(PhCH_2)$NH·$B(C_6F_5)_3$ (**2**) by reduction of the C=N bond (Scheme 2). Heating of the adduct (80 °C) for 1 h under H_2 (4–5 atm) resulted in thermal dissociation of the B–N dative bond and hydrogen splitting to generate the salt $[t\text{BuNH}_2(CH_2Ph)][HB(C_6F_5)_3]$ (**3**), which was identified by NMR spectroscopy. Furthermore, an X-ray crystal structure of **3** confirmed the proposed formulation (Fig. 1).‡ The structural parameters are unexceptional, although it is noted that the refined N*H*$_2$ and B*H* hydrogens display a B–H···H–N close contact of 1.87(3) Å, consistent with a non-traditional proton–hydride hydrogen bond[25] between one of the NH_2 protons and the B–H hydride. Similar protic–hydridic hydrogen bonding was also observed in the X-ray crystal structure of $[t\text{Bu}_3PH][HB(C_6F_5)_3]$.[16] In addition, the analogous reaction of the ketimine DippN=CMe(*t*Bu) with $B(C_6F_5)_3$ under H_2 afforded the ion pair [DippN(H)=CMe(*t*Bu)][$HB(C_6F_5)_3$] (**4**, Scheme 2), as evidenced by multinuclear NMR spectroscopy. The ^{11}B NMR (δ −24.4, $^1J_{BH}$ = 80 Hz) and ^{19}F NMR



Scheme 2 Synthesis of **2**–**4**.

signals (δ −132.9, −162.7 and −166.0) are indicative of the formation of the $[HB(C_6F_5)_3]^-$ anion. In the ^{1}H NMR spectrum, signals for the N*H* (δ 10.50) and B*H* (δ 3.85) groups are readily apparent. The formation and isolation of **4** suggests that the steric bulk about the iminium cation precludes hydride transfer from the borate to the iminium carbon, allowing observation of this mechanistically relevant intermediate.

Thus, the isolation of **2**–**4** permit the formulation of a catalytic cycle (Scheme 3). As none of the imines in Table 1, E1–E6 form an adduct with $B(C_6F_5)_3$,[26] the first step involves heterolytic H_2 splitting by the imine/borane FLP to generate an iminium hydridoborate ion pair analogous to **4**. The protonated imine is activated to nucleophilic attack of the iminium carbon by the BH unit of the borohydride, collapsing the ion pair to an amine–borane adduct. Dissociation of the B–N bond releases the product amine and regenerates the free borane to re-enter the cycle. It appears that this latter step of amine dissociation is rate-determining. This mechanism also accounts qualitatively for the observed relative rates. The elongated reaction time necessary in Table 1, E3 is consistent with the diminished basicity of the imine N slowing down the H_2 cleavage, whereas hydrogenation of more basic imines proceeds more quickly due to facile reactions with H_2. This mechanism has direct parallels with that proposed by Piers and co-workers for the $B(C_6F_5)_3$-catalyzed hydrosilylation of imines,[26] ketones,[27,28] enones and silyl enol ethers,[29] in which borane activation of the silane reagent generates a silylium-activated substrate and $[HB(C_6F_5)_3]^-$. Similar Lewis acid-catalyzed main group hydride additions to alkenes,[30,31] alkynes[32] and allenes[33] have been described by Gevorgyan *et al.*

The sluggish reduction of $PhSO_2N$=CPh(H) (Table 1, E3) stands in contrast to the corresponding reduction of this imine

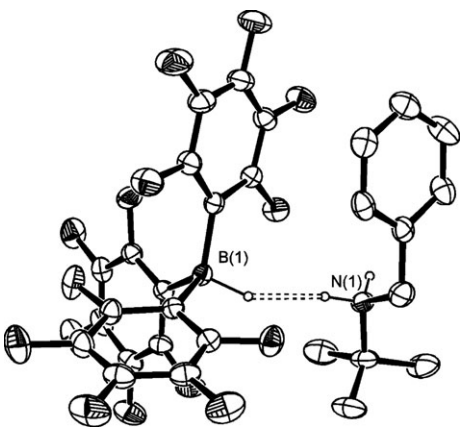
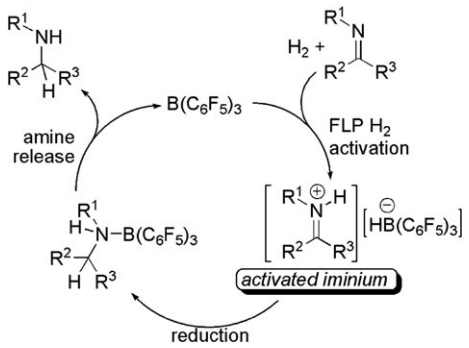


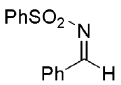
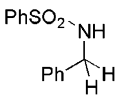
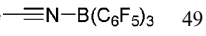
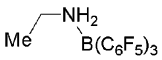
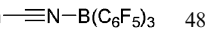
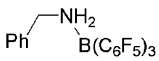
Fig. 1 ORTEP drawing of **3**. 30% probability thermal ellipsoids are shown; all protons are omitted for clarity, except the BH and NH_2 groups.



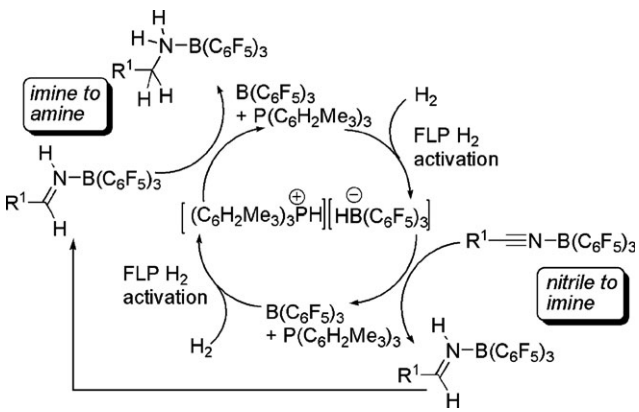
Scheme 3 Proposed mechanism of the hydrogenation of imines.

Table 2 Catalytic hydrogenations by $B(C_6F_5)_3/P(C_6H_2Me_3)_3$ and H_2

substrate $\xrightarrow[5\ \text{atm. } H_2,\ 120\ ^\circ\text{C toluene}]{5\ \text{mol\% } B(C_6F_5)_3,\ 5\ \text{mol\% } P(C_6H_2Me_3)_3}$ product

Entry	Substrate	Time/h	Yield (%)	Product
E8		8	98	
E9		49	91	
E10		48	94	

by linked phosphonium–borates **1** in 10–16 h.[21] Addition of 5 mol% $P(C_6H_2Me_3)_3$ to the present reaction greatly increased the reaction rate (see Table 2, E8). The rate acceleration was presumably due to the rapid reaction of $P(C_6H_2Me_3)_3/B(C_6F_5)_3$ with H_2, giving $[(C_6H_2Me_3)_3PH][HB(C_6F_5)_3]$,[16] which reduces the imine. In a similar fashion, the reaction of $MeCN–B(C_6F_5)_3$ or $PhCN–B(C_6F_5)_3$ with 5 mol% $B(C_6F_5)_3$ and H_2 alone gave no reduction. However, the addition of 5 mol% $P(C_6H_2Me_3)_3$ resulted in the clean hydrogenation of the imine–borane adducts to their corresponding amine–borane adducts (Table 2, E9 and E10). Mechanistically, the protected



Scheme 4 Proposed mechanism of the hydrogenation of protected nitriles.

nitriles cannot act as proton acceptors to facilitate H_2 cleavage. However, the addition of phosphine expedites H_2 activation and consequently reduction catalysis. The proposed mechanism is depicted in Scheme 4. We have previously reported analogous reductions employing **1b** as a catalyst.[21]

In conclusion, the combination of basic, sterically-hindered imines and the Lewis acid $B(C_6F_5)_3$ act as a "frustrated Lewis pair" to activate H_2, which facilitates the catalytic hydrogenation of sterically-hindered imines directly with H_2. In addition, $B(C_6F_5)_3$ and the additional base $P(C_6H_2Me_3)_3$ were found to catalyze the reduction of electron poor imines and protected nitriles.

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