A family of N-heterocyclic carbone-stabilized borenium ions for metal-free imine hydrogenation catalysis†

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This manuscript probes the steric and electronic attributes that lead to “frustrated Lewis pair” (FLP)-type catalysis of imine hydrogenation by borenium ions. Hydride abstraction from [(tBu)HB(C6F5)2]2 prompts intramolecular C–H bond activation to give (CHN)2(tBu) (CMe2CH2)CB(C6F5)2, defining an upper limit of Lewis acidity for FLP hydrogenation catalysis. A series of seven N-heterocyclic carbene–borane (NHC–borane) adducts ((R’CNR)2Cl(HBC6H14) (R’ = H, R = dipp 4a, Mes 5a, Me 8a; R = Me R’ = Me 9a, Cl, 10a) and ((H)C2(NMe1[NR2]C[HBC6H14] (R = tBu, 6a, Ph 7a) are prepared and converted to corresponding borenium salts. These species are evaluated as catalysts for metal-free imine hydrogenation at room temperature. Systematic tuning of the carbene donor for the hydrogenation of archetypal substrate N-benzylidene-tert-butylamine achieves the highest reported turnover frequencies for FLP-catalyzed hydrogenation at amongst the lowest reported catalyst loadings. The most active NHC–borenium catalyst of this series, derived from 10a, is readily isolable, crystallographically characterized and shown to be effective in the hydrogenation catalysis of functional group-containing imines and N-heterocycles.

Introduction

As the global consciousness awakens to the environmental and fiscal costs associated with energy and material-intensive chemical processes, the development of new and effective catalytic strategies grows ever more significant. The hydrogenation of unsaturated bonds is one such chemical transformation that is employed on a terrific industrial scale.1–4 Currently these processes employ highly effective transition metal catalysts despite oft associated high cost, toxicity and significant carbon footprint. These drawbacks have led to the intense pursuit of alternative or complimentary technologies. For example, hydrogenation catalysis by cheap and non-toxic transition metals such as iron5–8 and cobalt,9,10 as well as early metals such as titanium11,12 and calcium13 has drawn considerable attention. Our group14–23 and others24–46 have focused on main-group alternatives motivated by our report of metal-free hydrogen activation by a linked phosphino-borane.44 Indeed, soon after this initial report, we described the use of “frustrated Lewis pairs” (FLPs) in the catalytic hydrogenation of imines and protected nitriles.23 This prompted a flurry of developments in FLP hydrogenation catalysis. While substrate scope has since been dramatically broadened, the catalytic activities of FLP systems and the catalyst loadings required are not yet competitive with transition metal catalysts. Perhaps more importantly, the synthetic challenge of preparing electrophilic boranes limits the range of potential catalysts that are readily accessible for a systematic evaluation of structure–activity relationships. Indeed, although studies involving families of closely related FLP hydrogenation catalysts are rare,29,38,39,42 some examples in the literature suggests that subtle changes to FLP catalysts can have dramatic impact on activity and selectivity. For example, the group of Soós and co-workers has shown that substitution of one C6F5 in B(C6F5)3 with the bulkier mesityl group effects selectivity control through size exclusion.34,38 Moreover, careful choice of Lewis base in FLP hydrogenation catalysis has extended the substrate scope to include silyl enol ethers,27 olefins18,33 and most recently ketones and aldehydes.43,44

Borenium ions are three-coordinate boron cations.45–47 These relatively underexplored Lewis acids have attracted recent attention for use in catalysis48–55 and selective carboxaborations and haloborations.56–66 In an earlier communication, our group showed that an N-heterocyclic carbene-stabilized borenium salt [(iPr)BC6H14] [B(C6F5)3] (iPr = 1,3-di-isopropylimidazol-2-ylidine) can be used as a catalyst for the metal-free hydrogenation of imines and enamines.67 In this case, the borenium cation and the imine act as an FLP to cleave H2. This affords an NHC–borane that delivers hydride to a transient iminium ion.
(Scheme 1). Borenium-based catalyst 1b derives its Lewis acidity from a cationic charge rather than electron-withdrawing fluoroaryl groups on boron. Moreover, the precursor NHC–borane adduct is robust and easily accessible. During the review process of this paper Crudden and co-workers described triazolium derived borenium cations as catalysts.69

Herein, we exploit our previous findings to access a family of FLP catalysts. The reactivity of these borenium cations is evaluated in the metal-free hydrogenation catalysis of imines and N-heterocycles. This systematic study of the steric and electronic attributes of NHC–borenium catalysts provides insight into the structure–activity relationship of this new class of FLP hydrogenation catalyst.

Results and discussion

Our initial efforts to enhance reactivity with respect to previously reported catalyst 1b focused on the incorporation of electron withdrawing C₆F₅ substituents in NHC–borenium ions. To this end, the reaction of 1,3-di-tert-butylimidazol-2-ylidene (tBu) with HB(C₆F₅)₂ led to the formation of NHC–borane adduct (tBu)HB(C₆F₅)₂ 2 (Scheme 2), which was isolated in 76% yield. Crystallographic characterization revealed the anticipated pseudo-tetrahedral geometry about boron, an average C₉H₇C–B bond length of 1.645(4) Å and an average B–C₆F₅ bond length of 1.639(4) Å (Fig. 1(a)). The expected upfield doublet for 2 is observed by ¹¹B NMR spectroscopy at −22.9 ppm with a J_B-H coupling of 88 Hz. The ¹H NMR and ¹⁹F NMR spectra indicate hindered rotation about the C₉H₇C–B bond in 2 on the NMR time scale. Broad and inequivalent resonances were observed for the tert-butyl protons and fluorine atoms at room temperature; however, these were resolved upon cooling to −40 °C.

Attempts to generate an NHC–borenium ion derived from 2 via treatment with the hydride abstraction reagents [Ph₃C][B(C₆F₅)₄], Me₂SiOTf or HOTf showed no reaction. This stands in contrast to the facile hydride donation typically demonstrated by NHC–boranes.66–69 However, upon heating 2 with HNTf₂ in toluene to >100 °C for four days the clean conversion to a new product was evident from the appearance of the ¹¹B resonance at −14.8 ppm. ¹H NMR spectroscopy showed sharp singlet resonances at 0.86 ppm and 1.04 ppm and a broad singlet resonance at 1.80 ppm integrating in a 9 : 6 : 2 ratio. These combined NMR data suggest the new species (CHN)₂(B(C₆F₅)₂) as catalysts.

Fig. 1  POV-ray depiction of (a) 2 and (b) 3. C: black, B: yellow-green, N: blue, F: pink, H: grey. H-atoms except for borohydride omitted for clarity.

The C–H activation that yields 3 suggests that the proposed C₆F₅-substituted borenium ion derived from 2 is too Lewis acidic for application in catalysis. This prompted us to further examine 9-BBN based borenium cations. To this end 9-BBN was reacted with 1,3-bis(2,6-di-iso-propylphenyl)imidazol-2-ylidene (Idipp) at 60 °C for one hour to afford Idipp–borane adduct 4a in 79% yield (Scheme 3). Compound 4a exhibits a broad ¹¹B NMR signal at −15.3 ppm. Reaction of 4a with [Ph₃C][B(C₆F₅)₄] at 45 °C overnight results in the generation of Ph₃CH and the quantitative conversion of the NHC–borane to a new species as evidenced by ¹¹B NMR signals at 82.6 ppm and −16.6 ppm. These are consistent with the formation the borenium–borate salt [(Idipp)BC₆H₁₄]([B(C₆F₅)₄]) 4b. Alternatively, treatment of 4a with tBuN=CHPh and the addition of a stoichiometric equivalent of [(tBu)₃PH][B(C₆F₅)₄] results in generation of 4b with...
To further probe the steric and electronic factors impacting on the reactivity of NHC–borenium cations, a series of NHC-9-BBN adducts were prepared exercising judicious variation of the NHC. This was achieved by either directly reacting 9-BBN dimer with the isolated carbene or by reacting 9-BBN dimer with a carbene generated in situ through the combination of an imidazolium salt with [K[N(SiMe3)2]]. This latter one-pot approach is similar to that described by Brahmi et al. to prepare a series of NHC–BH3 compounds.74 A series of seven adducts including [(R’CNR)2C]HBC8H14 (R’ = H, R = dipp 4a, Me5a,75 Me8a;76 R = Me R’ = Me 9a, Cl, 10a) and [(HC)2(NMe)(NR)C]HBC8H14 (R = tBu, 6a, Ph 7a) were prepared (Scheme 3). The NHC–borane adducts 4a–10a were isolated and purified via recrystallization from pentane or toluene in yields ranging from 72–95%. The spectral data reported for these compounds were as expected and crystallographic data for 5a, 7a, (see ESI†) and 8a–10a (Fig. 2) further corroborated these formulations.

Each of these adducts reacts with [Ph3C][B(C6F5)4] to give the corresponding borenium salts [[(R’CNR)2C]B(C6F5)4] (R’ = H, R = dipp 4b, Mes 5b,75 Me8b; R = Me R’ = Me 9b, Cl, 10b) and [(HC)2(NMe)(NR)C]B(C6F5)4 (R = tBu, 6b, Ph 7b) concomitant with the generation of a stoichiometric amount of Ph3CH (Scheme 3). The most diagnostic spectroscopic change in each case is the appearance of a broad 11B resonance in the range of 81–88 ppm attributable to a three-coordinate B center. The expected resonances for the [B(C6F5)4]− anion were seen at −16.7 ppm. The species 10b was isolated as colorless crystals in 72% yield via recrystallization from CH2Cl2/pentane at −35 °C. Crystallographic data (Fig. 3) revealed trigonal planar geometry about the B center in the cation with a B–NHC bond length of 1.576(3) Å similar to that observed for 1b (1.580(3) Å).67

For comparative purposes the phosphine–borane adduct (Me5P)[HBC8H14] (11) was also synthesized and isolated as colorless crystals in 82% yield. The 11B NMR signal was observed at −14.9 ppm and exhibited both B–H coupling of 88 Hz and B–P coupling of 48 Hz. The 31P(1H) resonance for 11 is at −13.0 ppm and possesses similar B–P coupling. Single crystal X-ray diffraction confirmed the formulation (see ESI†). In contrast to the carbene complexes described above, treatment of 11 with stoichiometric [Ph3C][B(C6F5)4] gave a complex mixture of products as evidenced by 31P(1H) and 11B NMR-spectroscopy.
Hydrogenation catalysis

Compounds 4b–10b were tested for catalytic activity using the hydrogenation of tBuN=CHPh as a comparative screen. A solution of each was generated in situ, added to the imine substrate and pressurized with 102 atm H$_2$(g) for 30 minutes. After the reaction, the extent of conversion to amine was assessed by $^1$H NMR spectroscopy. These data reveal an inverse correlation between the steric demands of the NHC and the hydrogenation activity of the borenium catalyst (Table 1). The bulkiest catalyst 5b shows no catalytic activity, while the slightly less bulky catalyst 6b shows only trace conversion of imine to amine at 1 mol% catalyst loading after 30 minutes of reaction time. A sharp increase of catalytic activity is observed as the steric demands of the catalyst are further reduced. The previously reported catalyst 1b allows for 35% conversion to amine at 1 mol% catalyst loading after 30 minutes while catalysts 7b and 8b show quantitative conversion.

Reducing the loadings of these catalysts to 0.5 mol% under otherwise identical conditions reduced the conversions and demonstrated that the least bulky catalyst 8b effects 68% conversion while 7b and 9b reach only 35% and 21% conversion, respectively. In contrast, 10b gave complete conversion. Even when the loading was dropped to 0.25 mol% under otherwise identical conditions 10b gave complete conversion of imine to amine. Further reduction to 0.1 mol% gave 47% conversion representing a turn-over frequency (TOF) of 940 h$^{-1}$. A slight increase of catalyst loading to 0.15 mol% and an extension of the reaction time to 2 h at room temperature under 102 atm H$_2$(g) led to complete conversion to tBuNHCH$_2$Ph and the product could be isolated in 83% yield (Table 1, entry 13).

These observations reveal that the least sterically encumbered NHCs stabilize the most active borenium catalysts despite the fact that FLP reactivity hinges upon the steric protection of an acidic center. This suggests that the bulkier catalysts impede either H$_2$ activation or hydride delivery in the catalytic cycle. Since bulky NHC–borane 4a readily delivers hydride to an iminium ion it seems most likely that the bulkiest borenium ions are sterically prevented from generating the “encounter complex” with the imine that is required for H$_2$ activation. Similarly diminished reactivity has been observed for FLPs incorporating excessively bulky boranes.$^{14}$ It is noteworthy that computations suggest that a donor–boron distance of 4.2 Å is necessary to effect heterolytic cleavage of H$_2$. Thus, it is reasonable to suggest that bulky peripheral substituents inhibit such a close approach.

Comparison of the isosteric catalysts 8b–10b reveals that reduced donation from the NHC$^{9}$ to the B center has a positive impact on the catalytic activity. This is thought to result from an increase in the Lewis acidity at B. That being said, further reduction of the donor ability of the stabilizing ligand$^{7}$ jeopardizes the stability of the borenium cation as evidenced by the efforts to abstract hydride from 11. Apparently the donor ability and steric demands of the NHC are suitably balanced in 10b as it provides, to our knowledge, the highest TOF reported to date.

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$^a$ Yields determined by $^1$H NMR spectroscopy, isolated yields in parentheses. All reactions were carried out using 0.500 mmol substrate in CH$_2$Cl$_2$. Reaction times were 30 minutes. Catalyst loadings: 5 mol% except: $^b$ 2.5 mol%.

Fig. 3  POV-ray depiction of 10b. C: black, B: yellow-green, N: blue, F: pink, Cl: green. H-atoms omitted for clarity.
for the metal-free hydrogenation of imines. With the optimized catalyst 10b in hand, a variety of N-containing unsaturated substrates were reduced affording products in high isolated yields (Table 2). In these cases a catalyst loading of 5 mol% was employed to ensure high conversions in 30 minutes and to overcome the impact of adventitious water. The imine o-CI-C6H4CH=NtBu is readily reduced (Table 2, entry 1) as is p-(MeO2C) C6H4CH=NtBu (Table 2, entry 2). The latter stands in contrast to previous FLP hydrogenations where sterically unencumbered esters preclude or inhibit reductions using the borane B(C6F5)3.20 While the steric demands of C6H4CH=NCHPh2 slow imine reduction (Table 2, entry 3), the aniline-derived ketimines Ph(Me)C=NPh and p-EtOC6H4(Me)C=NPh are readily hydrogenated to corresponding amines (Table 2, entries 4 and 5). In stark contrast, no hydrogenation of Ph(Me)C≡NCH2Ph was observed (Table 2, entry 6). This was attributed to the greater basicity and lesser steric demands about the N-donor. 1,3,3-Trimethyl-2-methylideneindoline is hydrogenated to afford 1,2,3,3-tetramethylindoline (Table 2, entry 7), however 2,3,3-trimethylindoline is not reduced (Table 2, entry 8). Nonetheless, in contrast to 1b,67 10b smoothly catalyzes the hydrogenation of 8-methylquinoline to 1,2,3,4-tetrahydro-8-methylquinoline (Table 2, entry 9), illustrating the subtlety of sterical and electronic effects on substrate scope.

Conclusions

In this manuscript we have probed the electronic and steric parameters that impact on the ability of ligand stabilized borenium cations to act as metal-free hydrogenation catalysts. Although this catalysis proceeds via an FLP mechanism, perturbations that enhance the Lewis acidity at B or the steric demands of the NHC ligand can serve to deactivate the catalyst. At the same time, sterically unencumbered NHCs bearing electron withdrawing substituents enhance catalyst activity. Crudden and co-workers86 have very recently described related triazolium derived borenium cations and their use as catalysts for hydrogenation. Nonetheless, the present systematic examination of NHC stabilized borenium ion has led to catalysts that are highly efficient. Indeed the isoalable catalyst 10b is an effective catalyst for imine and N-heterocycle reduction at low catalyst loadings and it affords the highest TOF yet reported for metal-free hydrogenation catalysis. Efforts are continuing to systematically develop borenium-based metal-free hydrogenation catalysts and to further broaden their applications.

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Notes and references