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Abstract: Lower Lewis acidity boranes demonstrate greater tolerance to combinations of water/strong Brønsted bases than B(C6F5)3, this enables Si–H bond activation by a frustrated Lewis pair (FLP) mechanism to proceed in the presence of H2O/arylamines. Specifically, BPh3 has improved water tolerance in the presence of arylamines as the Brønsted acidic adduct H2O–BPh3 does not undergo irreversible deprotonation with aliphatic amines in contrast to H2O–B(C6F5)3. Therefore BPh3 is a catalyst for the reductive amination of aldehydes and ketones with arylamines using silanes as reductants. A range of amines inaccessible using B(C6F5)3 as catalyst, were accessible by reductive amination catalysed by BPh3 via an operationally simple methodology requiring no purification of BPh3 or reagents/solvent. BPh3 has a complementary reductive amination scope to B(C6F5)3 with the former not an effective catalyst for the reductive amination of arylamines, while the latter is not an effective catalyst for the reductive amination of alkylamines. This disparity is due to the different pKa values of the water–borane adduct and the greater susceptibility of BPh3 species towards protodeboronation. An understanding of the deactivation processes occurring using B(C6F5)3 and BPh3 as reductive amination catalysts led to the identification of a third triarylborane, B(3,5-Cl2C6H3)3, that has a broader substrate scope being able to catalyse the reductive amination of both aryl and alkyl amines with carbonyls.

Introduction

Considerable progress in frustrated Lewis pair (FLP) chemistry has been achieved in the last decade principally using tris(pentafluorophenyl)borane, B(C6F5)3. Compared to BPh3, the presence of fluorine atoms dramatically increases the Lewis acidity. While high Lewis acidity is essential in enabling certain FLP reactivity, it also poses challenges including the compatibility of FLPs with water (e.g. from unpurified reactants/solvents or as a reaction by-product)/base combinations, a topic which has attracted recent attention. A fluorinated triarylborane with a high Lewis acidity towards hydride (which is desirable for H−H and Si−H bond activations) also has considerable oxophilicity, with the corresponding triarylborane–water adduct exhibiting much greater Brønsted acidity than water itself. Indeed, the Brønsted acidity of H2O–B(C6F5)3 was determined by Parkin and co-workers (pKa = 8.4 in MeCN) to be comparable to that of HCl (8.5 in MeCN). This poses a limit to the water tolerance of these fluorinated arylboranes in the presence of certain Brønsted bases because irreversible deprotonation of the borane–water adduct yields an inactive (for FLP chemistry) hydroxytriarylborate anion.

Ashley, Stephan, and co-workers pioneered ROH-tolerant FLP reactions and demonstrated that B(C6F5)3 could be used for the hydrogenation of carbonyls (Scheme 1A). Importantly, the alco-
hol–borane adducts are not irreversibly deprotonated under these weakly basic conditions (which use ethereal solvents such as 1,4-dioxane as Lewis bases to activate H$_2$ via an FLP mechanism).\cite{6,11} Demonstration of the water tolerance of B(\text{CF$_3$})$_3$ was subsequently reported proving that the hydrogenation of ketones could be performed using non-purified, “wet” reactants and solvents (H$_2$O–B(\text{CF$_3$})$_3$ also is not irreversibly deprotonated by ethereal solvents).\cite{6} Recently, we reported the water tolerance of a B(\text{CF$_3$})$_3$-catalysed system involving more basic arylamines (conjugate acid pH$_K$ ca. 11 in MeCN, Scheme 1B).\cite{5} In particular we found that B(\text{CF$_3$})$_3$ is able to catalyse the reductive amination of aldehydes and ketones with anilines using 1.2 equivalents of silane as reductant.\cite{8} This proceeds in the presence of a super-stoichiometric amount of water derived from imine formation and the use of non-purified solvents. An elegant extension of this approach was recently reported using B(\text{CF$_3$})$_3$ to catalyse the tandem Meisenwald rearrangement and reductive amination of epoxides with anilines and silanes.\cite{12} However, in the latter, as in our work, reductive amination could not be extended to alkylamines (conjugate acid pH$_K$ $\geq$ 16 in MeCN) due to the irreversible deprotonation of H$_2$O–B(\text{CF$_3$})$_3$. Thus, the compatibility of H$_2$O–B(\text{CF$_3$})$_3$ with bases appears to be limited to those bases with conjugate acids that have pK$_a$ values $\leq$ 12 (in MeCN). A broader amine scope catalytic reductive amination methodology using a simple triarylborane is desirable as a one-pot method (thus preferable from an efficiency perspective) to rapidly access amines that are ubiquitous functionalities in natural products, pharmaceuticals and agrochemicals.

To circumvent the limitation of B(\text{CF$_3$})$_3$ towards water/strong Brønsted base combinations, Lewis acids that are less oxophilic are required. These could be “hydride selective” Lewis acids, such as Group 14 based Lewis acids (which maintain high hydridophilicity but have lower oxophilicity)\cite{13,14} or Lewis acids that are globally less Lewis acidic (e.g., less oxophilic and less hydridophilic).\cite{15} The latter approach was utilised by Papai, Sós and co-workers who employed less Lewis acidic partially halogenated triarylboranes for example, (2,3,5,6-C$_6$F$_5$H)$_2$B(2,6-C$_6$H$_4$Cl)$_3$, for the catalytic hydrogenation of carbonyls in ethereal solvents, with some water tolerance demonstrated.\cite{16} Taking this approach further, the non-halogenated triarylborane BPh$_3$ should have enhanced tolerance to water and strong base combinations due to its lower Lewis acidity. BPh$_3$ does however still possess sufficient hydridophilicity to be useful as a catalyst in FLP-type reactions as recently demonstrated.\cite{17,18} While H$_2$O–B(\text{CF$_3$})$_3$ is well documented,\cite{5} the corresponding H$_2$O–BPh$_3$ adduct is less studied, particularly its ability to act as a Brønsted acid.\cite{19,20,21,22} Herein we report an extension to the water and base tolerance of boranes to strong amine bases, focusing, in particular on the triarylborane-catalysed reductive amination of aldehydes/ketones with alkylamines using silanes as reducing agents. This demonstrates that BPh$_3$ is an effective catalyst for the reductive amination of alkylamines and carbonyls (Scheme 1C), including examples challenging to reduce with borohydride salts (e.g., [\text{IOAc}]_2BH$^+$). Furthermore, B(3,5-C$_6$H$_4$Cl)$_3$ is effective for the reductive amination of carbonyls and both aryl and alkylamines without requiring any inert atmosphere techniques or solvent/reagent purification (Scheme 1D).

### Results and Discussion

To determine if H$_2$O–BPh$_3$ protonates alkylamines, BnNH$_3$ (conjugate acid pH$_K$ $= 16.6$ in MeCN)$^{[5]}$ was added to a solution of H$_2$O–B(\text{CF$_3$})$_3$ in [D$_3$]-MeCN. $^1$H NMR spectroscopy showed coordination of BnNH$_3$ to BPh$_3$ as indicated by a 2H integral resonance at $\delta = 5.3$ ppm (for BnNH$_3$) shifted downfield from free BnNH$_3$ in [D$_3$]-MeCN (1.5 ppm). Identical $^1$H NMR resonances are observed for Ph$_3$B–N(H)$_2$Bn formed under anhydrous conditions in [D$_3$]-MeCN (for both $\delta_{1H} = -1.7$ ppm). Coordination of BnNH$_3$ to BPh$_3$ is reversible at room temperature as addition of benzaldehyde led to rapid imine formation, thus the absence of any observable [HO–BPh$_3$]$^+$ is attributed to the lower Brønsted acidity of H$_2$O–BPh$_3$. In contrast, the addition of BnNH$_3$ to H$_2$O–B(\text{CF$_3$})$_3$ led to formation of [HO–B(\text{CF$_3$})$_3$]$^+$ as the major product (by $^1$H and $^15$F NMR spectroscopy) as expected based on relative pK$_a$ values. With no observable deprotonation of H$_2$O–BPh$_3$ with BnNH$_3$, the utility of BPh$_3$ as a catalyst was explored in the reductive amination of benzaldehyde (1.0 equiv) with benzylamine (1.2 equiv), under air using non-purified BPh$_3$ non-purified solvents, and silane as reductant (Table 1). In this reaction, upon imine formation, water is produced as a by-product, so both excess (relative to BPh$_3$) water and a good Brønsted base (BnNH$_3$, used in slight excess to favour imine formation) are present in the reaction mixture.
tromethane. Changing the solvent from $\alpha$-DCB to MeCN now resulted in the desired product being obtained in moderate yield. On increasing the amount of silane from 1.2 to 3.5 equivalents, dibenzylamine was obtained in good yield (87% NMR yield and 80% isolated yield). The requirement for excess silane is due to imine reduction and H$_2$/silanol dehydrosilylation occurring concurrently. The activity of this system is not due to initial consumption of all H$_2$O by excess silane and then imine reduction proceeding under anhydrous conditions as indicated by the absence of any induction period in this reductive amination. This was further confirmed by analysis of the reaction mixture after 3 hours at 100 °C, at which point considerable imine reduction had occurred (ca. 30%) but significant water and PhMe$_2$SiOH were still present. Decreasing the catalyst loading to 5 mol% resulted in a lower yield (entry 5), while 100 °C was found to be critical (entry 6). The applicability of other silanes was then investigated: when Ph$_2$SiH$_2$ was viable in the reductive amination (entry 7), the increase in the steric hindrance of the silane going from PhMe$_2$SiH to Ph$_2$MeSiH$_2$ resulted in a significant drop in imine reduction (entry 4 vs. 8). When smaller silanes were employed (entries 9 and 10), dibenzylamine was the major component among multiple products, including EtNH$_2$ presumably deriving from MeCN reduction.

With the compatibility of BnNH$_2$ and H$_2$/O-BPh$_3$, mixtures confirmed by the successful reductive amination of benzaldehyde and BnNH$_2$, a direct comparison between B(C$_6$F$_5$)$_3$ and BPh$_3$ was performed. In our previous work we found that B(C$_6$F$_5$)$_3$ catalysed reductive aminations of anilines and aldehydes in $\alpha$-DCB at 100 °C, but not the more basic alkylamines due to irreversible deprotonation of H$_2$/O-B(C$_6$F$_5$)$_3$.[5] To avoid any disparities arising from the solvent employed, comparative reductive aminations using benzaldehyde and aniline or benzylamine with B(C$_6$F$_5$)$_3$ or BPh$_3$ as catalyst were performed in MeCN (Table 2). Although the coordination of MeCN to B(C$_6$F$_5$)$_3$ is well documented,[21] the reductive amination of benzaldehyde and aniline still proceeded to high yield (96%) in 1 h at 100 °C on replacing $\alpha$-DCB with MeCN. As previously reported, 1.2 equivalents of silane is sufficient with anilines with imine reduction occurring preferentially to water dehydrosilylation. Interestingly, on replacing B(C$_6$F$_5$)$_3$ with BPh$_3$, under identical conditions, minimal (8%) imine reduction and minimal water dehydrosilylation were observed after 1 h on heating at 100 °C. A similar outcome was observed using 0.1 equivalent BPh$_3$ loading and 3.5 equivalents of silane (entry 2) with a low reductive amination conversion even after 25 h. In contrast, in the reductive amination of benzaldehyde/benzylamine under identical conditions the use of BPh$_3$ results in an excellent conversion, whilst B(C$_6$F$_5$)$_3$ is effectively inactive (entry 3).

Notably, during reductive aminations using BPh$_3$ as catalyst four-coordinate boron species (such as imine—BPh$_3$, and amine—BPh$_3$) and $^{13}$B resonances consistent with Ph$_3$BOH and PhB(OH)$_2$ are all observed. Importantly, attempts to catalyse the reductive amination of benzaldehyde/benzylamine with PhB(OH)$_2$, Ph$_3$B(OH) or Ph$_3$BO$_2$H$^-$ (whilst not observed the latter is feasibly present in low concentration through a small degree of H$_2$/O-BPh$_3$ deprotonation) in place of BPh$_3$, led to very low conversions (e.g., 10% using Ph$_3$BOH) after 25 h at 100 °C in MeCN. The use of Brønsted acids such as HCl and HNO$_3$ also resulted in minimal reductive amination. Combined these control reactions indicate the importance of the triarylborane as the catalyst in this process, presumably for activation of the silane via established (for B(C$_6$F$_5$)$_3$) mechanistic pathways.[22]

To better understand the disparities between PhNH$_2$ and BnNH$_2$ in reductive aminations catalysed by BPh$_3$, a number of control reactions were performed. A solution of BPh$_3$ in anhydrous MeCN was heated at 100 °C sealed under air, with no significant reaction (e.g., protodeboronation) observed. However, adding 10 equivalents of water to this solution led to significant protodeboronation after 2 hours at 100 °C (PhB(OH)$_2$, Ph$_3$B(OH) and PhH observed by $^1$H and $^{13}$B NMR spectroscopy) presumably via an intramolecular protodeboronation process from H$_2$/O-BPh$_3$, as recently calculated for H$_2$/O-B(C$_6$F$_5$)$_3$.[23] Having identified that H$_2$/O-BPh$_3$ can undergo protodeboronation to produce catalytically inactive products the effect of amine basicity on protodeboronation was investigated. The addition of 10 equivalents of PhNH$_2$ to a solution of H$_2$/O-BPh$_3$ (made by mixing 1 equivalents of BPh$_3$ with 10 equivalents of water in MeCN to approximate the catalysis conditions) did not prevent protodeboronation on heating. Notably, when 10 equivalents of the more basic amine BnNH$_2$ was added to an identical solution containing H$_2$/O-BPh$_3$, protodeboronation proceeded to a significantly lower extent (by monitoring the appearance of benzene in the $^1$H NMR spectrum and by $^{13}$B NMR spectroscopy). Even upon heating at 100 °C for 20 hours (Figure 1) four-coordinate L—BPh$_3$ compounds were still the dominant species with BnNH$_2$ in contrast to that with PhNH$_2$.

The disparity between PhNH$_2$ and BnNH$_2$ in reductive amination catalysed by BPh$_3$ will be due to different amine (or imine) basicity, however this will affect a number of processes, therefore to identify the origin of this disparity a number of control reactions were performed. The disparity is not due to the less nucleophilic imine derived from aniline/benzaldehyde leading to a significantly greater barrier to an $S_{N}2$ type reaction with the $R$$_3$Si—H’—BPh$_3$ species. This was confirmed by the fact that under anhydrous conditions using catalytic BPh$_3$, and stoichiometric PhMe$_2$SiH, N-benzylidene aniline and N-benzylidene benzylamine were both reduced (Scheme 2, left). However,

Table 2. Reductive amination catalysed by BPh$_3$ or B(C$_6$F$_5$)$_3$.

| Entry | R | Mol % | Equiv. Silane | Time (h) | Yield [%]$^a$ |
|-------|---|------|--------------|---------|---------------|
|       |   | Catal. |              |         | B(C$_6$F$_5$)$_3$, BPh$_3$ |
| 1     | Ph | 5     | 1.2          | 25      | > 96          |
| 2     | Ph | 10    | 3.5          | 25      | > 96          |
| 3     | Bn | 10    | 3.5          | 25      | < 5           |

Reactions performed in sealed tubes. [a] Yield by $^1$H NMR spectroscopy versus mesitylene.
under catalytic reductive amination conditions the key electrophile could be the silylated iminium cation (if the BPh₃ activated silane is directly attacked by the imine) or the protonated iminium cation (via imine protonation by [R₂Si–OH][HB₃Ph]) formed from initial attack by H₂O on R₂Si–H–BPh₃). Although no silylated amine was observed during reductive amination, the exact nature of the iminium cation could not be unambiguously defined in this process due to the fast hydrolysis of silylated amine under these conditions. Nevertheless, further control reactions showed that both protonated N-benzylidene aniline and N-benzylidene benzylamine were reduced by [HB₃Ph]⁺ (consistent with Okuda and co-workers report on imine hydroboration catalyzed by [HB₃Ph]⁺ salts). There was no evidence for differing degrees of side reactions (such as evolution of PhH (by protodeboronation)) or significant differences in the rate of reduction during the control reactions with the iminium cations (Scheme 2, right). Whilst the iminium cations derived from N-benzylidene aniline do undergo slower reductions (than those derived from N-benzylidene benzylamine) this should only result in longer reaction times being required for complete reductive amination using PhNH₂/benzaldehyde under BPh₃ catalysis. However, this is not observed, as no further increase in conversion is observed on longer reaction times in reductive aminations. Combined these observations indicate that the difference in reactivity is due to more rapid catalyst decomposition in the presence of PhNH₂ relative to BnNH₂ and not any intrinsic barrier to N-benzylidene aniline reduction.

As BPh₃ decomposition most probably proceeds via H₂O–BPh₃ (based on its fast protodeboronation), reducing the concentration of this species in solution should be key to provide enhanced catalytic activity. At least two scenarios are feasible for achieving this: i) the more basic species (BnNH₂ or its derived imine) retards protodeboronation by deprotonating H₂O–BPh₃ resulting in a different catalyst resting state, [HO–BPh₃]⁺ – that is more stable to protodeboronation; ii) the more nucleophilic amine/imine (e.g., BnNH₂ or its derived imine) forms a Lewis adduct L–BPh₃, which is more stable to protodeboronation than Ph₃B–OH₂. Based on the in situ NMR data for H₂O–BPh₃/BnNH₂ the latter is more probable as only Bn(H)N–BPh₃ is observed with no [Ph₃B–OH]⁺ detectable. In contrast, with the less basic/nucleophilic aniline, the adduct Ph(H)N–BPh₃ (which when formed under anhydrous conditions has a characteristic integral 2H singlet in the ¹H NMR spectrum at δ = 5.7 ppm for the NH₂ group) reacts with equimolar water as indicated by a drastic shift in the ¹H NMR spectrum to a broad resonance at δ = 2.1 ppm (integral four for the combined NH2/ OH₂ resonance). This suggests an equilibrium between Ph(H)N–BPh₃ and H₂O–BPh₃ consistent with the more rapid protodeboronation observed. The ¹¹B NMR spectra are inconclusive for this system as H₂O–BPh₃ and Ph₃B–(N(H))₂Ph have extremely similar chemical shifts, whilst the slow exchange regime is not reached even at −38 °C in [D₂]–MeCN.

With the disparity between BnNH₂ and PhNH₂ in reductive aminations catalyzed by BPh₃ clarified, we next investigated the highly Brønsted basic but less nucleophilic amine tBuNH₂. Significantly, tBuNH₂ and PhNH₂ have similar Mayr nucleophilicity values in MeCN (N = 12.35 and 12.64, respectively) but the conjugate acid of tBuNH₂ has a pKₐ of 18.4. Under standard conditions (3.5 equiv. silane, 10 mol% BPh₃, MeCN), the reductive amination of tBuNH₂ and benzaldehyde proceeded to a 93% conversion after 25 h at 100 °C. Again the ¹¹B NMR spectrum after 25 h was dominated by four-coordinate boron species with minimal PhB(OH)₂ and Ph₂B(OH) observed. To investigate the origin of the enhanced stability of BPh₃ in the presence of tBuNH₂, the ¹H and ¹¹B NMR spectra of BPh₃/tBuNH₂/
H₂O mixtures was examined, which revealed broad resonances at 25 °C, (e.g., a 1'H resonance at δ = 3.7 ppm) shifted downfield with respect to tBuNH₂ and H₂O–BPh₃ (δ = 1.3 and 2.6 ppm, respectively). Cooling this solution to below −10 °C resulted in the appearance of tBuNH(H)–BPh₃ however, this was a minor component (ca. 10%). The major resonance in the 1'H NMR spectrum was still broad with a chemical shift not consistent with H₂O–BPh₃ or free tBuNH₂, instead it is assigned as H₂O–BPh₃ and [HOBPh₃][H,NBu] in fast exchange, a process which was not frozen out at −38 °C in [D₅]-MeCN. Based on these observations feasible key processes occurring in situ in the reductive amination reactions are summarised in Scheme 3.

Upon heating, enough BPh₃ is generated from a Lewis acid or the hydroxyborate to activate the silane to nucleophilic attack. Nucleophilic attack leads to the formation of [HBP₃]⁺ that in turn would reduce the iminium cation (either silylated or protonated) by hydride transfer thus regenerating the catalyst. The protodeboronation pathway deactivates the catalyst, and is a process which most probably proceeds from H₂O–BPh₃. The concentration of this species can be minimized in solution by using stronger bases/nucleophiles which lead to formation of LB → BPh₃ or [LB–H][HOB₃] (LB = amine or imine). Notably, in the presence of both BnNH₂ and N-benzylidene benzylamine, BPh₃ binds the former preferentially. As the optimal catalysis conditions uses a slight excess of amine, the continued presence of free amine presumably helps reduce the quantum of H₂O–BPh₃ present and thus limit protodeboronation.

With an understanding of the limitations of using BPh₃ for catalytic reductive amination, the substrate scope was then explored with the reactions performed under air, using non-purified solvent and reactants with everything combined at the start in an operationally simple process (Table 3).

A range of functionalised benzaldehydes were amenable in the reductive amination with benzylamine, with good in situ conversions and isolated yields (1a–e). It is noteworthy that ester and cyano substituents were compatible, with no evidence for their reduction under these conditions (1f,g). However, the reaction was less tolerant to nitro substituents (due to trans-imination and formation of dibenzylamine observed as the major by-product). It is noteworthy that when electron-withdrawing groups are present in the para position of benzaldehyde (e.g. -CO₂Me or -CN), minimal siloxane (and silanol) were observed after 25 h (by ¹H and ²⁹Si NMR spectroscopy), with significant reduction of the imine still occurring. Furthermore >50% imine reduction to 1i was observed with only 1.2 equivalents of silane after 25 h. This indicates that more electrophilic imines effectively out compete H₂O for reaction with the borohydride, whereas with less electrophilic imines the rates of water/silanol dehydrosilylation and iminium cation reduction are comparable hence excess silane is required. Reductive amination also proceeded in the presence of a terminal C=C triple bond without significant reduction of the latter (1k), or any observable side reactivity, for example, dehydroboration.⁴⁰ When aliphatic aldehydes (n-butyraldehyde and propionaldehyde) were used, full consumption of the in situ formed imine was observed, but the desired product was only a minor component due to over-alkylation to the tertiary amine or enamine isomerization reactions, as reported for B(C₆F₅)₃.⁴¹ However, when ketones were utilised, the reaction was successful, allowing a secondary carbon centre to be attached to the nitrogen (1j,k). Notably, the reductive amination of acetaldehyde and benzylamine is challenging with widely used reducing agents such as Na[triacetoxyborohydride] (Na[OAc]BH₃, 55% yield after 10 days), in contrast using BPh₃/silane 1j is produced in higher yield in shorter reaction times. The reductive amination of 1-acetyl-1-cyclohexene and morpholine to

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**Table 3. Substrates screening of the reductive amination.**

| Substrate | % Yield | Reaction Conditions |
|-----------|---------|---------------------|
| 1a (74%)  | 1.0 equiv | H₂N–Alk, PhBH₃ |
| 1b (55%)  | 1.2 equiv | H₂N–Alk, PhBH₃ |
| 1c (55%)  | 3.5 equiv | PhMe₂SiH, “wet” MeCN, 100°C, 25 h |

Reactions performed in sealed tubes. [a] ¹H NMR yields versus mesitylene. [b] Isolated yield. [c] 48 h. [d] 40 h. [e] 30 h.
yield 11 is also challenging using [(OAc)₂BH]⁻ (only 10% yield after 4 days), but it proceeds to 87% yield using BPh₃/silane. This demonstrates that the BPh₃-catalysed process is applicable to systems where established borohydride reductive amination approaches struggle. Furthermore, the formation of 11 shows the compatibility of this methodology with C–C double bonds. The inclusion of substituents on benzylamine, as well as the use of nBuNH₂, as another C-primary amine, was also realized (e.g. 1 m–o), although using the latter amine over-alkylation also occurred to some extent (e.g. forming nBuNBNB). C-secondary amines, such as cyclo-hexylamine and isopropylamine, or a C-tertiary amine tBuNH₂, gave good conversions to the desired products (1 p–r). It is noteworthy that a common product could be formed from a different combination of aldehyde/amine (e.g. 1 k and 1 p), offering two retrosynthetic strategies. Finally, when a secondary amine such as BnNHMe was used in combination with an enolizable ketone the reaction still proceeds successfully to form 1 s in excellent yield. It should be emphasized that these amines are not accessible by reductive amination using B(C₆F₅)₃ as catalyst due to it being limited to aniline derivatives. To demonstrate scalability the reductive amination of benzaldehyde and 1-adamantylamine was performed on gram-scale under air, using 10 mol% of unpurified BPh₃ in non-purified acetonitrile and using PhMe₂SiH as reductant (Scheme 4). Combining all the reactants at the start and heating the reaction mixture at 100 °C for 25 hours enabled the desired product to be isolated in a 90% isolated yield (1.1 g).

Scheme 4. Gram-scale synthesis of N-benzyl-1-adamantylamine.

The results discussed above indicate that B(C₆F₅)₃ and BPh₃ have complementary tolerance to water/amine combinations in reductive aminations (Figure 2). B(C₆F₅)₃ is a viable catalyst for aryl amines (conjugate acids pKa < 12 in MeCN) but not alkyamines (conjugate acids pKa > 16 in MeCN) due to irreversible protodeboronation of H₂O–B(C₆F₅)₃ with the latter. In contrast, BPh₃ is a viable reductive amination catalyst for alkyamines but not arylamines due to more rapid protodeboronation in the presence of the latter. We were thus interested in exploring an amine with an intermediate pKa, specifically the reductive amination of benzaldehyde and benzylhydrazine (conjugate acid pKa 15 in MeCN) was performed with both these boranes using 10 mol% catalyst loading. In all cases the in situ conversions were only moderate at best (less than 30%) under a range of conditions with both boranes (e.g., in MeCN or o-DCB at 100 °C), indicating that an amine whose conjugate acid has a pKa between 12–16 is particularly challenging for both boranes. Again in situ analysis revealed that with BPh₃ significant protodeboronation proceeded upon heating (by 11B NMR spectroscopy), whilst with B(C₆F₅)₃ the deactivation was due to the effectively irreversible protodeboronation of H₂O–B(C₆F₅)₃ (by 11B/15F NMR spectroscopy).

Given the respective limitations of B(C₆F₅)₃ and BPh₃, a single triarylborane that is a viable catalyst for the reductive amination of both aryl and alkyl amines (including benzylhydrazine) was targeted. To have a broad amine scope, the triarylborane must form a H₂O–BArNH₂ adduct that is both more resistant to protodeboronation than H₂O–BPh₃ and less Brønsted acidic than H₂O–B(C₆F₅)₃. Furthermore, a triarylborane that does not contain ortho-halogen ary substituents is desirable, as ortho substituents increase the steric bulk around boron and thus can significantly hinder amine/imine coordination to boron.[12] The latter is actually desired in this process as it reduces the concentration of H₂O–BArNH₂ in solution, thus also helping to limit protodeboronation. Given these requisites B(3,5-Cl₂C₆H₄)₃ was selected and its synthesis via the protolytic decomposition of its tetraarylborate salt was utilised as the borate salt is air and moisture stable as a solid in contrast to the free triarylboranes (see subsequent discussion). Teraarylborate anion decomposition has significant precedent for [BPh₃]⁻ salts which react with Brønsted acids to release BPh₃ compounds.[28] Furthermore, we recently observed decomposition of Na[B(3,5-Cl₂C₆H₄)₃] (termed Na[BArCl] herein) in wet solvents on heating. To confirm that Na[BArCl] decomposition by protonolysis generates B(3,5-Cl₂C₆H₄)₃ species, the strong Brønsted acid HNTf₂ was added to NaBArCl. This resulted in the appearance of a major new resonance at δ = 67 ppm in the 19B NMR spectrum assigned as B(3,5-Cl₂C₆H₄)₃, with this chemical shift consistent with other reported tri(aryl)boranes.[29] Applying this in situ B(3,5-Cl₂C₆H₄)₃ generation procedure (using an excess of NaBArCl relative to HNTf₂ to preclude any trace Brønsted acid remaining as strong Brønsted acids can also activate Si–H bonds),[30] B(3,5-Cl₂C₆H₄)₃ catalyzed the reductive amination of benzaldehyde and benzylhydrazine to give the desired product in good yield (Scheme 5). The use of both B(C₆F₅)₃

Figure 2. Water/amine tolerance of B(C₆F₅)₃ and BPh₃ under the reductive amination reaction conditions.

Scheme 5. Reductive amination with benzaldehyde and benzylhydrazine using B(C₆F₅)₃, BPh₃ or B(3,5-Cl₂C₆H₄)₃ (generated in situ) as catalyst.
and BPh₃ as catalysts under these conditions gave low conversions.

Seeking a catalytically simpler process, the decomposition of Na[BArCl] by action of H₂O was investigated as a route to generate B(3,5-Cl₃C₆H₃)₃ in situ.₁² This approach was successful for the catalytic reductive amination of benzylidymine and benzaldehyde using 10 mol% Na[BArCl] in o-DCB (Scheme 6), with all manipulations performed in air using non-purified solvent/reagents. Weakly coordinating solvents are essential as attempts using MeCN as solvent led to no reductive amination. The solvent dependency is attributed to the formation of [H₂O]Na⁺ species in o-DCB that have enhanced Brønsted acidity (relative to H₂O) and are thus key to effecting anion protodeboronation and generation of the triarylborane, as previously discussed for NaBPh₃.²⁸ In contrast in MeCN, the solvent is presumably solvating the Na cations, resulting in a less Brønsted acidic solution and no anion protodeboronation.

With an in situ catalyst generation protocol in hand, a brief amine substrate scope exploration was undertaken. Most notably, the triarylborane derived in situ from Na[BArCl] was able to catalyse the reductive amination of benzaldehyde with PhNH₂, BnNH₂, and tBuNH₂ amines whose conjugate acids span the pKₐ range from 10.6 to 18.4 in MeCN. This indicates a reduced acidity of the corresponding H₂O–B(3,5-Cl₃C₆H₃)₃ adduct (relative to that of H₂O–B(C₆F₃)₃) and an improved stability of B(3,5-Cl₃C₆H₃)₃ species to protodeboronation (relative to BPh₃). The amount of silane required for good conversion to the reductive amination product was explored and again found to depend on the imine electrophilicity, with the more electrophilic imine (derived from aniline) reduced using only 1.2 equivalents of silane, whilst the less electrophilic imines again required an excess of silane due to competitive dehydro-silylation reactions.

The ability to use Na[BArCl] as a precursor to the active triarylborane catalyst has practical advantages since it is readily synthesized and is bench stable for at least 6 months. In contrast, whilst BPh₃ is commercially available its storage as a solid under ambient atmosphere leads to gradual decomposition (even after only 14 days significant PhB(OH)₂ and Ph₃B(OH) are observed by ¹B NMR spectroscopy). This negatively impacts conversion; for example using pristine BPh₃ gives 87% conversion of benzaldehyde and benzylamine to the reductive amination product whereas the same batch of BPh₃ stored as a solid in air for 2 weeks results in only 52% conversion when used as the catalyst under otherwise identical conditions. In contrast, Na[BArCl] stored as a solid for 6 months in air shows no deterioration in reductive amination catalytic activity. Thus Na[BArCl] is a useful bench-stable catalyst precursor for reductive aminations, with its utility further demonstrated in the rapid synthesis of the more complex drug molecule Piribedil (used in the treatment of Parkinson’s disease)³³ in good yield (Scheme 7) under air using non-purified reagents/solvents.

**Scheme 6.** Reductive aminations under air employing Na[BArCl] as precursor catalyst.

**Scheme 7.** Synthesis of Piridebil by reductive amination.

**Conclusions**

In summary, BPh₃ has a higher tolerance to H₂O and alkylamine combinations than B(C₆F₃)₃ due to the lower Brønsted acidity of H₂O–BPh₃. This extends the water/base tolerance of FLP systems to strong bases (conjugate acid pKₐ = 18.5). This enables the utilisation of BPh₃ as a catalyst for the reductive amination of aldehydes and ketones with many different aliphatic amines, ranging from C-primary to C-tertiary. This system is even effective for the reductive amination of substrates that are challenging with conventional borohydrides (e.g., [(OAc)₂BH]⁻). BPh₃ and B(C₆F₃)₃ exhibit complementary amine scope in reductive aminations, with the former limited by the protodeboronation of H₂O–BPh₃ in the presence of weaker amine Brønsted bases/nucleophiles, while the latter is limited by H₂O–B(C₆F₃)₃ undergoing irreversible deprotonation by stronger Brønsted basic amines such as alkylamines. Finally, a third triarylborane, B(3,5-Cl₃C₆H₃)₃, of intermediate Lewis acidity, was shown to be effective for the reductive amination of a range of amines whose conjugate acids span pKₐ values of 10.6 to 18.5 in MeCN. Furthermore, in situ tetraarylborate anion decomposition by H₂O in non-coordinating solvents represents a simple route to generate the active triarylborane catalyst from a readily accessible bench-stable precursor. The reductive amination methodologies presented herein are operationally simple (e.g. no purification of any materials/solvent is required and the reactions are performed under air) and are applicable to gram-scale and complex molecule synthesis.

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[1] For recent reviews on FLP chemistry see: a) M. Oestreich, J. Hermke, J. Mohe, Chem. Soc. Rev. 2015, 44, 2207–2220; b) D. W. Stephan, J. Am. Chem. Soc. 2015, 137, 10018–10032; c) D. W. Stephan, G. Erker, Angew. Chem. Int. Ed. 2015, 54, 6400–6441; Angew. Chem. 2015, 127, 6498–6541; d) Topics in Current Chemistry, Vol. 332, Frustrated Lewis Pairs II (Eds.: B. G. C ox), O xford University P ress, 2016.

[2] For the Lewis acidity of perfluoroarylboranes see: a) V. Fasano, J. E. Radcliffe, M. J. Ingleson, Angew. Chem. Int. Ed. 51, 2012, 5231–5244.

[3] For alcohol tolerant FLP reductions see: a) D. J. Scott, M. J. Fuchter, A. E. Ashley, J. Am. Chem. Soc. 2016, 138, 15813–15816; b) T. Mahdi, D. W. Stephan, J. Am. Chem. Soc. 2014, 136, 15809–15812; c) T. Mahdi, D. W. Stephan, Angew. Chem. Int. Ed. 2015, 54, 8511–8514; Angew. Chem. 2015, 127, 8631–8634.

[4] For the decomposition of [B(C6F5)4]2+ see: a) D. J. Scott, R. T. Simmons, E. J. Lawrence, G. G. Wildgoose, M. J. Fuchter, A. E. Ashley, ACS Catal. 2015, 5, 5540–5544.

[5] V. Fasano, J. E. Radcliffe, M. J. Ingleson, ACS Catal. 2016, 6, 1793–1798.

[6] A. Győmöre, M. Bakos, T. Földes, I. Papai, N. A. Domjá, T. Soós, ACS Catal. 2015, 5, 5363–5372.

[7] For bransted acidity of water-borate adduct see: a) C. Bergquist, B. M. Bridgewater, C. J. Harlan, J. R. Norton, R. A. Friesner, A. E. Ashley, Bull. Chem. Soc. Jpn. 2000, 73, 1058–1059; b) A. Di Saverio, F. Focante, I. Camurati, L. Resconi, T. Beringhelli, G. D’Alfonso, D. Donghi, D. Maggioni, P. Mercandelli, A. Sironi, Inorg. Chem. 44, 5030–5041.

[8] For example the pKa of protonated Et3O is 0.2 in MeCN. For the pKa values cited in the article see: a) R. H. Morris, Chem. Rev. 2016, 116, 8588–8634; b) I. M. Kolthoff, M. K. Chantooni, S. Bhowmik, J. Am. Chem. Soc. 1968, 90, 23–28; c) J. T. Muckerman, J. H. Skone, M. Ying, Y. Wasada-Tsutsui, Biochim. Biophys. Acta Bioenerg. 2013, 1827, 882–891.

[9] Fu and co-workers reported the reductive amination of hexanal/amine with large excess of Si–H (5 equiv) to afford the amine in moderate conversion. M. C. Fu, R. Shang, W.-M. Cheng, Y. Fu, Chem. Eur. J. 2016, 22, 9170–9174.

[10] For the decomposition of [BPh4]2+ by Brønsted acids see: a) H. Jacobsen, H. Berke, S. Döring, G. Kehr, G. Erker, R. Fröhlich, O. Meyer, Organometallics 1999, 18, 1724–1735.

[11] For the mechanism of silane activation with [B(C6F5)4]2+ see: a) D. J. Parks, J. M. Blackwell, W. E. Piers, J. Org. Chem. 2000, 65, 3090–3098; b) S. Rendler, M. Oestreich, Angew. Chem. Int. Ed. 2008, 47, 5997–6000; Angew. Chem. 2008, 120, 6086–6089; c) J. Hermke, M. Mewald, M. Oestreich, J. Am. Chem. Soc. 2013, 135, 17537–17546; d) A. F. Houghton, J. Hurnalainen, A. Mansikkanimi, W. E. Piers, H. M. Tuomonen, Nat. Chem. 2014, 6, 983–986; e) W. E. Piers, A. J. V. Marwitz, L. G. Mercier, Inorg. Chem. 2011, 50, 12252–12262.

[12] a) G. Erçs, H. Mehdi, I. Pirkányi, T. Sósk, Topics in Current Chemistry, Vol. 332, Frustrated Lewis Pairs II (Eds.: B. G. C ox), O xford University P ress, 2016.

[13] For the decomposition of [BPh4]2+ by Brønsted acids see: a) M. H. Chisholm, J. C. Gallucci, H. Yin, Dalton Trans. 2007, 4811–4821; b) O. Stenzel, H. G. Raubenheimer, C. Estheruysen, Dalton Trans. 2002, 1132–1138.

[14] A. J. Blake, J. A. Greig, M. Schröder, J. Chem. Soc. Dalton Trans. 1988, 2645–2647.

[15] V. Kelsen, C. Vallée, E. Jeanneau, C. Bidal, C. C. Santini, Y. Chauvin, H. Olivier-Bourbigou, Organometallics 2011, 30, 4284–4291.

[16] R. Menye-Biyogo, F. Delpech, A. Castel, V. Pirmienta, H. Gornitzka, P. Rivière, Organometallics 2007, 26, 5091–5101.

[17] For as B(C6F5)4+ (Ref. [5]) the presence of amine retards water dehydrolysis, so its actual rate during the reductive amination is slower.

[18] H. Jacobsen, H. Berke, S. Döring, G. Kehr, G. Erker, R. Fröhlich, O. Meyer, Organometallics 1999, 18, 1724–1735.

[19] Numerous attempts (under a range of conditions) to synthesise and isolate B(3,5-Cl2-C6F4)3 have all been unsuccessful, producing the desired compound in low conversion in mixtures that proved intractable in our hands.

[20] For the decomposition of [BPh4]2+ by Brønsted acids see: a) J. H. Fowler, C. A. Kraus, J. Am. Chem. Soc. 1940, 62, 1143–1144.

[21] V. Kelsen, C. Vallée, E. Jeanneau, C. Bidal, C. C. Santini, Y. Chauvin, H. Olivier-Bourbigou, Organometallics 2011, 30, 4284–4291.

[22] a) Ref. [9]; and b) Q. Zhang, M.-C. Fu, H.-Z. Yu, Y. Fu, J. Org. Chem. 2016, 81, 6235–6243.

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