Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 4032

Received 20th February 2021,
Accepted 13th April 2021

DOI: 10.1039/d1ob00316j

rsc.li/obc

$B(C_6F_5)_3$-catalyzed tandem protonation/deuteration and reduction of *in situ*-formed enamines†

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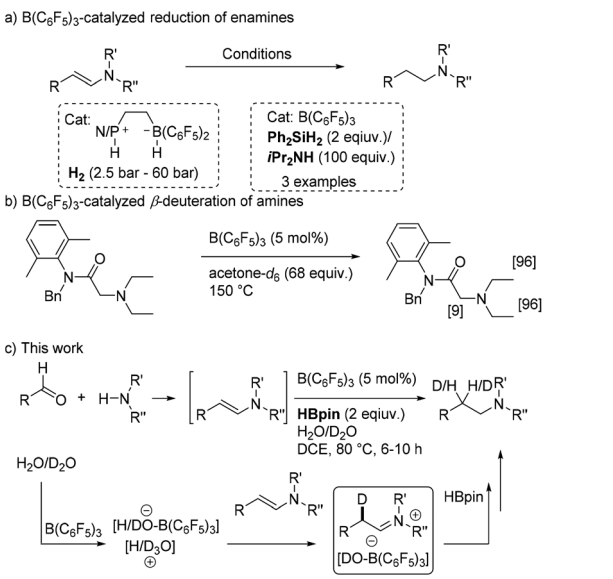
A highly efficient $B(C_6F_5)_3$-catalyzed tandem protonation/deuteration and reduction of *in situ*-formed enamines in the presence of water and pinacolborane was developed. Regioselective β-deuteration of tertiary amines was achieved with high chemo- and regioselectivity. D_2O was used as a readily available and cheap source of deuterium. Mechanistic studies indicated that $B(C_6F_5)_3$ could activate water to promote the protonation and reduction of enamines.

The bulky Lewis acid $B(C_6F_5)_3$ usually forms the acidic component of a Frustrated Lewis Pair (FLP). It has been used as a versatile catalyst for various metal-free reduction reactions,[1] such as the reduction of carbonyl groups,[2] imines,[3] pyridines[4] and enamines.[5] Among them, the reduction of enamines provides an efficient method to synthesize various tertiary amines, which are predominantly found in pharmaceuticals and natural products.[6] Erker and Repo have developed various phosphine/borane (P/B) or amine/borane (N/B) intramolecular FLP catalysts for the hydrogenation of enamine using H_2 as the reducing agent (Scheme 1a).[5] However, the complexity of the catalyst and the high pressure of hydrogen (2.5–60 bar) required for the effective reduction of enamine limit the application of the process. Reports on the use of commercially available $B(C_6F_5)_3$ as the catalyst for the reduction of enamine are scarce. To the best of our knowledge, only a few examples of $B(C_6F_5)_3$-catalyzed enamine reduction reactions have been reported in the presence of diphenylsilane (an expensive reagent) or diisopropylamine (used in an excess amount) as reducing agents (Scheme 1a).[7] Therefore, there are still challenges and there is room for a comprehensive study of $B(C_6F_5)_3$-catalyzed reduction of enamines.

Recently, regioselective deuteration of *N*-alkyl amines has gained immense attention as the products can be potentially used for target-labelling pharmaceutical compounds.[8] Beyond the transition-metal-catalysed β-deuteration of amines,[9] Wasa has reported that $B(C_6F_5)$ exhibits comparable reactivity to transition-metals in the β-amino deuteration of amines. Acetone-d_6 was used both as the deuterium source and the solvent (Scheme 1b).[10] However, the use of expensive deuterium sources and harsh reaction conditions (150 °C) limits the practical application of this method.

To address these problems, we aimed to use tandem protonation (deuteration) and reduction processes in the presence of enamine to efficiently synthesize various tertiary amines or β-deuterated tertiary amines. To realize this, $B(C_6F_5)_3$ was chosen as the catalyst as it can activate H_2O/D_2O[11] to generate acidic H/D^+ and borenium anions, respectively (Scheme 1c). The activation of the moieties is followed by protonation/deuteration of enamine to form borenium activated iminium,[3f] which accelerated the reduction with pinacolborane to afford



Scheme 1 Synthesis of tertiary amines using $B(C_6F_5)_3$ as a catalyst.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ob00316j

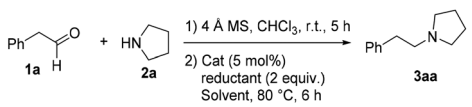
the corresponding tertiary amines or β-deuterated amines. Herein, we report the development of a simple and efficient method for the reduction of enamines for the synthesis of various tertiary amines using $B(C_6F_5)_3$ as the catalyst under mild conditions. Furthermore, the present protocol can be potentially used to achieve regioselective β-deuteration of amines in the presence of D_2O, which is a readily available and cheap deuterium source.

We initially chose phenylacetaldehyde **1a** and pyrrolidine **2a** as the model substrates. The corresponding enamine was generated *in situ* and used in the next step without further purification (reaction conditions: 4 Å molecular sieves (MS) in $CHCl_3$ for 5 h). The reduction reaction proceeded in the presence of $B(C_6F_5)_3$ (5 mol%) and pinacolborane (2 equiv.) in non-purified 1,2-dichloroethane (DCE) at 80 °C to afford the reduced product phenylethylpyrrolidine **3aa** in 89% yield (Table 1, entry 1). Following this, various solvents were screened to study the influence of solvents (entries 2–4). It was observed that $B(C_6F_5)_3$ exhibited better catalytic efficiency in nonpolar solvents (hexane and toluene). Subsequently, we studied various reducing agents for the reduction reaction. Strong reducing agents such as the borane–trimethylamine complex and $NaBH_4$ promoted the reduction reaction to afford **3aa** in lower yields (entries 5 and 6). In sharp contrast, in the presence of diphenylsilane, **3aa** was produced in significantly low yield under the reaction conditions reported herein (entry 7).[7a] Various boron catalysts, such as $BF_3{\cdot}OEt_2$ and $BH_3{\cdot}SMe_2$ exhibited low catalytic efficiencies during the reduction reactions (entries 8 and 9). The reaction could proceed in the absence of $B(C_6F_5)_3$, albeit in low yield (entry 10).

After optimizing the reaction conditions, we examined the substrate scope of the amines. As shown in Table 2, cyclic amines, such as pyrrolidine, piperidine, morpholine, and indoline, reacted with **1a** to afford the corresponding tertiary amines in good yields (**3aa–3af**). It is noteworthy that the reaction with 1,2,3,4-tetrahydroquinoline could be performed on multigram scale to afford **3ae** in 77% yield. The reactions of acyclic amines also proceeded efficiently to afford various tertiary amines in good yields (**3ag–3ar**). Anilines bearing both electron-donating and electron-withdrawing groups did not significantly influence the reaction efficiency (**3aj–3ao**, **3ar**). Various functional groups, such as pyridyl (**3ai**), methoxy (**3aj**), and halides (**3al–3ao**) were tolerated under the optimized reaction conditions.

We next examined the substrate scope of the reaction using various aldehydes (Table 3). Sterically hindered aldehydes, such as 2-(*o*-tolyl)acetaldehyde and 2-mesitylacetaldehyde, reacted with morpholine to afford **3bc** and **3ic** in 68% and 61% yields, respectively. The reaction of aldehydes with electron-donating groups afforded the corresponding products with higher efficiency than did those bearing electron-withdrawing groups (**3dc–3hc**). Functional groups such as methoxy (**3fc**), bromo (**3gc**), and hydroxyl (**3hc**) groups were tolerated under the optimized conditions. Notably, the reducible olefin group also could be tolerated (**3kc** and **3mh**). Aldehydes bearing long chains underwent the reduction reaction, affording **3lc** and **3mh** in 51% and 91% yields, respectively.

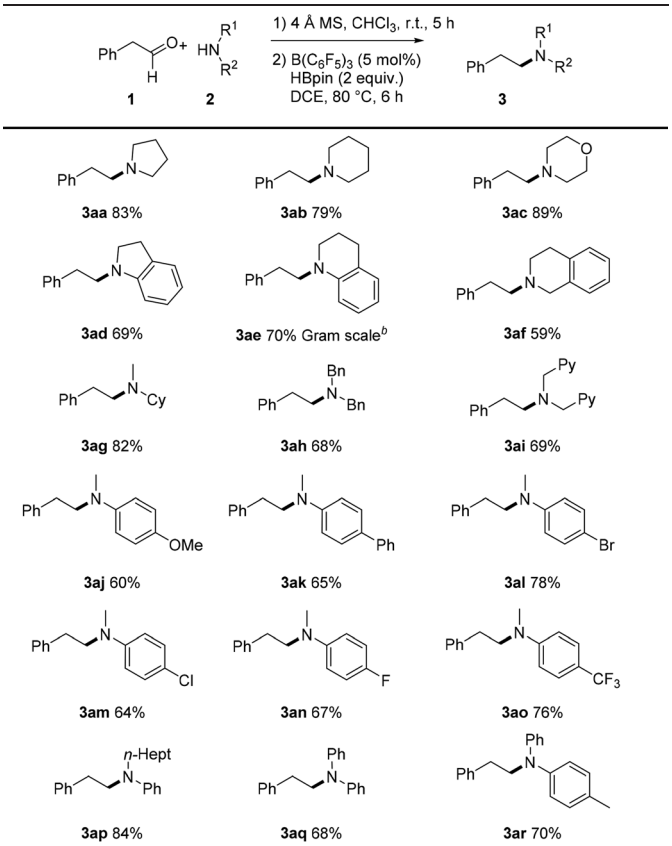
Table 1 Optimization of $B(C_6F_5)_3$-catalyzed reduction of *in situ*-formed enamine[a]



Entry	Catalyst	Reducing agent	Solvent	Yield[b] (%)
1	$B(C_6F_5)_3$	HBpin	DCE	89
2	$B(C_6F_5)_3$	HBpin	MeCN	53
3	$B(C_6F_5)_3$	HBpin	Hexane	80
4	$B(C_6F_5)_3$	HBpin	Toluene	83
5	$B(C_6F_5)_3$	$BH_3{\cdot}NMe_3$	DCE	46
6	$B(C_6F_5)_3$	$NaBH_4$	DCE	40
7	$B(C_6F_5)_3$	Ph_2SiH_2	DCE	15
8	$BF_3{\cdot}OEt_2$	HBpin	DCE	56
9	$BH_3{\cdot}SMe_2$	HBpin	DCE	18
10	—	HBpin	DCE	32

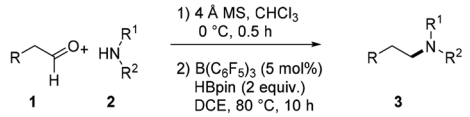
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), 4 Å MS (135 mg), $CHCl_3$ (0.4 mL), 5 h; HBpin (pinacolborane) (0.4 mmol), catalyst (5 mol%), solvents (0.4 M), 80 °C, 6 h. [b] Determined by NMR using 1,1,2,2-tetrachloroethane as an internal standard.

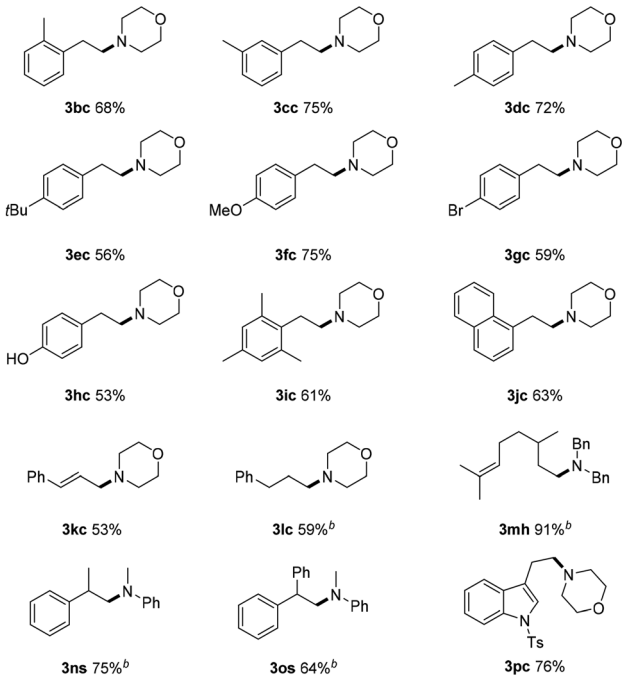
Table 2 Scope of the reaction: study of amines[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), 4 Å MS (135 mg), $CHCl_3$ (0.4 mL), 5 h; HBpin (0.4 mmol), $B(C_6F_5)_3$ (5 mol%), DCE (0.8 mL), 80 °C, 6 h. [b] 8 mmol scale.

Table 3 Scope of the reaction: study of aldehydes[a]



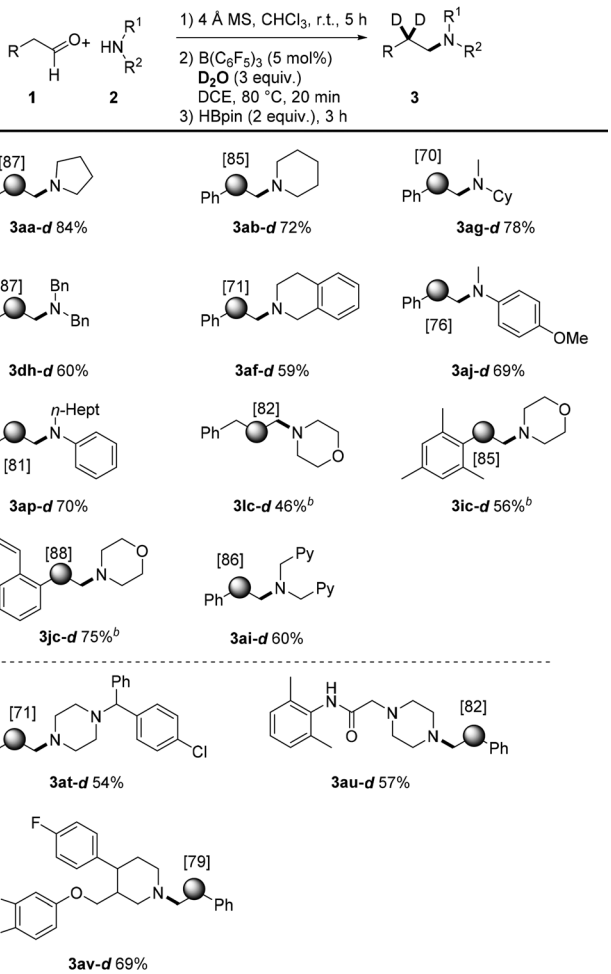


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), 4 Å MS (135 mg), $CHCl_3$ (0.4 mL), 0.5 h; HBpin (0.4 mmol), $B(C_6F_5)_3$ (5 mol%), DCE (0.8 mL), 80 °C, 10 h. [b] Enamine formation reaction was carried out at r.t. for 5 h, and then 6 h for $B(C_6F_5)_3$-catalyzed reduction.

2-Phenylpropionaldehyde and 2,2-diphenylacetaldehyde reacted with *N*-methylaniline to afford **3ns** and **3os**, respectively, in good yields. An indole-based aldehyde was well tolerated to produce **3pc** in 76% yield.

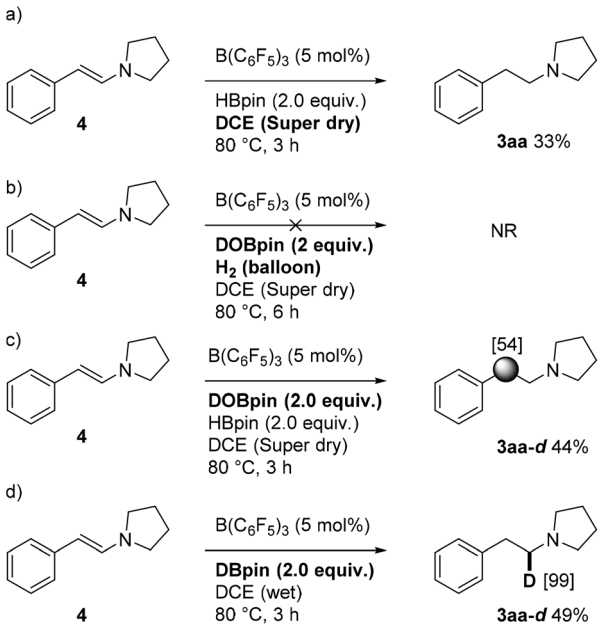
Encouraged by the above results, we next explored whether the present protocol could be used for achieving regioselective deuteration of amines. The standard reaction conditions were modified to realize regioselective β-deuteration of amines in the presence of 3 equiv. of D_2O. Notably, a similar deuterium incorporation ratio was obtained by using purified or *in situ*-formed enamine **4**. With the optimized reaction conditions in hand, we explored the versatility of $B(C_6F_5)_3$-catalyzed β-deuteration reactions with a variety of aldehydes and amines (Table 4). In particular, some commercially available drugs were also suitable for regioselective β-deuteration. In most cases, deuterium could be incorporated to good degrees (70–87%). Both cyclic and acyclic amines reacted smoothly to afford β-deuterated amines in good yields. Particularly, no aromatic C–H deuterium incorporation was observed (see **3aj-*d*** and **3ap-*d***), and only the β-deuteration on aliphatic C–H bonds was achieved to a good degree. In contrast to Werner's work on $B(C_6F_5)_3$-catalyzed deuteration on aromatic C–H bonds,[11] our methods showed high regioselective deuteration on aliphatic C–H bonds. Aldehydes such as 2-mesitylacetaldehyde and 1-naphthylacetaldehyde could be efficiently deuterated at the β-amino position (**3ic-*d*** and **3jc-*d***). Notably, this highly synthetically relevant transformation could be used for regioselective deuterium-labelling of drug derivatives. For example, the chlorcyclizine derivative **3at-*d*** was synthesized in good yield from 1-(4-chlorobenzhydryl)piperazine with phenylacetaldehyde **1a**. Good deuterium incorporation was achieved at the benzylic position. The reduction of a ranolazine based compound with **1a** afforded the deuterated compound **3au-*d*** in good yield. The percentage of deuterium incorporation was determined to be 82%. The late-stage modification of paroxetine afforded the deuterium-labelled product **3av-*d*** in good yield.

Table 4 β-Deuteration of amines[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), 4 Å MS (135 mg), $CHCl_3$ (0.4 mL), 5 h; $B(C_6F_5)_3$ (5 mol%), D_2O (3 equiv.), DCE (0.8 mL) for 20 min, HBpin (0.4 mmol), 80 °C, 3 h. The percentage of deuteration is shown in parentheses. [b] 0.5 h for enamine formation at 0 °C.

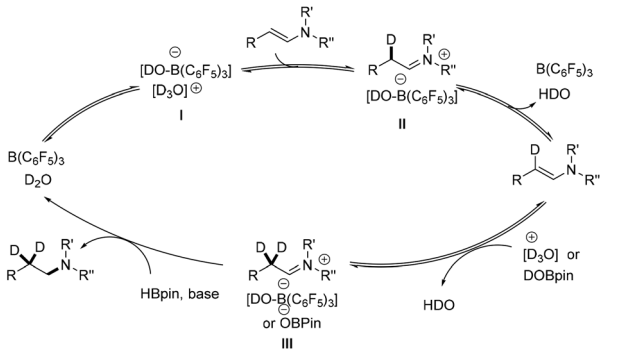
To gain more insight into the reaction mechanism, we performed several control experiments (Scheme 2). The rate of reduction of enamine **4** decreased in the absence of water,



Scheme 2 Mechanistic studies.

affording **3aa** in 33% yield (Scheme 2a). This result, coupled with the results from β-deuteration experiments (Table 4), indicates that water acts as the proton source. We also observed that the rapid dehydrogenation of pinacolborane with water afforded the boric acid pinacol ester. H_2 was simultaneously released during the process. These results prompted us to investigate whether $B(C_6F_5)_3$ could activate the boric acid pinacol ester or H_2 to promote the reduction reaction of enamine.[5] Thus, the reaction was performed in the presence of the deuterated boric acid pinacol ester (DOBpin) under an atmosphere of H_2. However, the reaction did not proceed under these reaction conditions (Scheme 2b). Thus, it was confirmed that H_2 was not the reducing agent. Surprisingly, we observed that H/D exchange could be achieved using DOBpin as the proton source (Scheme 2c). This revealed that DOBpin could potentially act as a proton source. We also observed that 99% of the H/D exchange occurred at the α-position of the amines in the presence of deuterated pinacolborane (Scheme 2d). This indicated that the proton at the α-position of the amine was derived from pinacolborane. In addition, no deuterium incorporation was observed in the reaction of **3aa** under the standard conditions. This result revealed that the enamine unit is essential for the deuterium incorporation.

Based on the above results, a putative mechanism was proposed (Scheme 3). The equilibrium between $B(C_6F_5)_3$ and D_2O resulted in the formation of the zwitterionic adduct **I** under basic conditions (base = tertiary amines),[12] initiating the catalytic cycle. The nucleophilic attack by enamine on the acidic D_3O^+ afforded the β-deuterated iminium **II**. The deuteroxide moiety assisted in deprotonating the substrate to afford the monodeuterated enamine. The secondary nucleophilic attack of enamine on D_3O^+ or DOBpin (generated from D_2O and



Scheme 3 Proposed mechanism for $B(C_6F_5)_3$-catalyzed β-deuteration of amines.

pinacolborane) formed the di-deuterated iminium **III**. The reduction of iminium **III** with HBpin with the aid of a base and a borenium anion[3f] afforded the deuterated tertiary amines and regenerated the catalyst.

In summary, we have developed efficient $B(C_6F_5)_3$-catalyzed tandem protonation and reduction reactions of *in situ*-formed enamines with water and pinacolborane under mild conditions. The present protocol was applied to a wide variety of amines and aldehydes to synthesize various tertiary amines. In addition, the reaction also achieved β-deuteration of tertiary amines with high regioselectivity and good degree of deuterium incorporation with D_2O, which is a readily available and cheap source. This would provide an alternative protocol for the synthesis of β-deuterated tertiary amines. Mechanistic studies indicated that $B(C_6F_5)_3$ could activate water to promote the protonation and reduction of enamines.

Author contributions

R. W. performed the experiments and data analysis. K. G. conceived the project and wrote the paper. R. W. and K. G. contributed to the editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the NNSFC (no. 21702071) and the Fundamental Research Funds for the Central Universities (no. CCNU18QN012) for the financial support. The Program of Introducing Talents of Discipline to Universities of China (111 program, B17019) is also acknowledged.

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