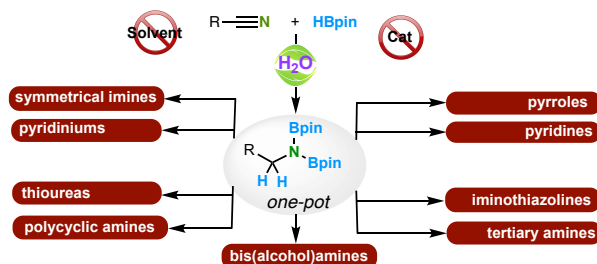


# Moisture-Assisted Hydroboration of Nitriles and Conversion Thereof to *N*-Heterocycles and *N*-Containing Derivatives

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**ABSTRACT:** The recent revelation of hidden-borane catalysis has revolutionized the field of catalytic hydroboration in organic synthesis. Many nucleophilic reaction promoters, previously believed to be the catalysts, in fact primarily facilitated the formation of borane (BH<sub>3</sub>), which subsequently acted as the true catalyst. This revelation prompted us to explore the untapped potential of these unexpected transformations, with a view to simplify hydroboration using more cost-effective and environmentally friendly nucleophilic pre-catalysts. Via computational studies, we were able to identify that water can actually undertake that role. Herein, we report a study on simple hydroboration of nitriles, a notoriously challenging yet synthetically valuable class of substrates, using nothing more than moisture as an activating agent. This moisture-assisted nitrile hydroboration process can seamlessly integrate with a range of downstream transformations in a one-pot fashion to produce valuable *N*-containing products such as symmetrical imines, thioureas and *bis*(alcohol)amines as well as *N*-heterocyclic derivatives such as pyrroles, pyridines, pyridinium salts, 2-iminothiazolines and carbazoles.

## INTRODUCTION

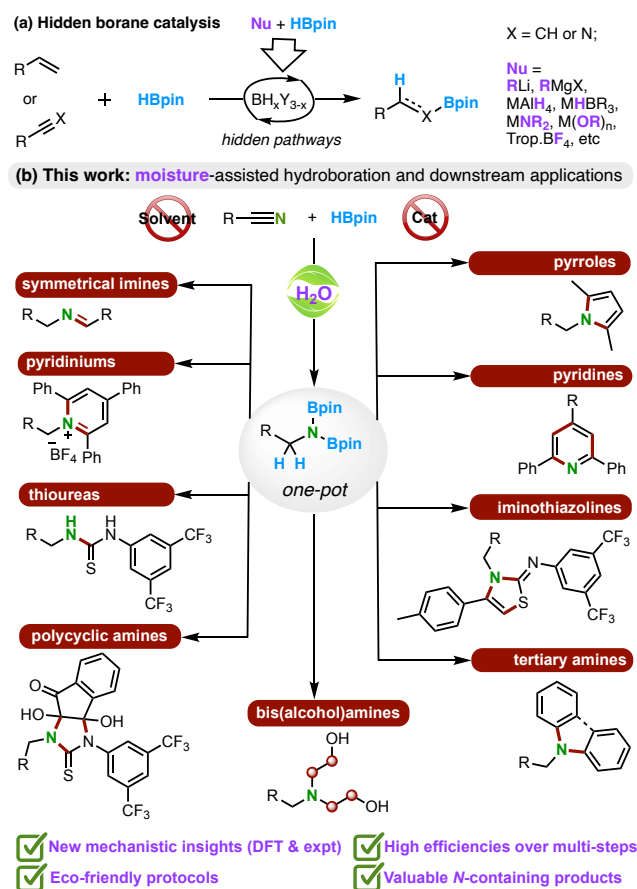
In recent years, the principles advocated by Sheldon, emphasizing that "the best catalyst is no catalyst" and "the best solvent is no solvent,"<sup>1</sup> have gained widespread acceptance in the chemical community. This growing awareness of sustainable chemistry has fueled the emergence of solvent- and catalyst-free methods for modern synthetic challenges,<sup>2</sup> which significantly contribute to a more sustainable and eco-friendly chemical landscape by reducing waste generation.

Hydroboration of nitriles is considered to be an important synthetic challenge due to the inertness of the C≡N bond with high bond dissociation energy of 212 kcal mol<sup>-1</sup>.<sup>3</sup> To the best of our knowledge, no catalyst-free procedures to achieve this transformation have been described previously.<sup>4</sup> Given the significant value of the hydroboration of nitriles, we were motivated to develop a new method for this transformation that aligns with the principles of sustainable chemistry. More importantly, the tremendous synthetic potential of *N,N*-diborylamines, which feature two boryl groups on a single nitrogen atom, remains largely unexplored.<sup>4b</sup> In this work, we introduce an operationally

straightforward solvent-free method for hydroboration of nitriles, aided by water/moisture (Figure 1b). Additionally, we establish multi-step one-pot protocols that facilitate the efficient transformation of *N,N*-diborylamine products into a diverse array of valuable *N*-containing compounds and *N*-heterocycles. This work not only addresses a longstanding challenge but also unlocks new avenues for the synthesis of new chemical building blocks in a sustainable manner.

Our inspiration for this work came from the recognition of hidden borane catalysis in hydroboration chemistry by the Thomas group in 2020 (Figure 1a),<sup>5</sup> which has transformed and revolutionized the field tremendously. Thomas and co-workers meticulously re-investigated the role of a range of commonly used nucleophilic catalysts for hydroboration reactions, and found that many of them merely act as activating agent to facilitate the formation of borane BH<sub>3</sub> from HBcat and HBpin. Borane subsequently acted as the true catalyst to promote the hydroboration reaction of unsaturated substrates.<sup>5</sup> Having done prior works on catalytic hydroboration,<sup>6</sup> this revelation prompted us to explore and exploit the untapped potential of these unexpected transformations, with a view to simplify hydroboration using

more cost-effective and environmentally friendly nucleophilic pre-catalysts. Water is always present in synthetic reactions in the form of moisture or hidden contaminant in reagents. Water is environmentally friendly and it is considered to be a relatively good nucleophile.<sup>7</sup> Therefore, we believe that it is possible to activate the hidden borane catalysis in hydroboration of nitriles with HBpin just by allowing it to interact with water/moisture.



**Figure 1.** Divergent synthesis of N-containing compounds via water-assisted hydroboration of nitriles.

## RESULTS AND DISCUSSIONS

**Computational mechanistic studies:** To gain more insights into this hypothesis, we carried out density functional theory (DFT) calculations<sup>8</sup> (see page S156 in the SI for further details) to check if water can assist the hydroboration of nitriles with HBpin. Our calculations revealed that HBpin can be hydrolyzed by water in two steps via **TS-1** and **TS-2** to give HB(OH)<sub>2</sub>. This species can further react with HBpin via two transborylation steps over **TS-3** and **TS-4**, leading to the formation of B<sub>2</sub>H<sub>6</sub> (Figure 2a). The rate-determining step for the formation of B<sub>2</sub>H<sub>6</sub> is calculated to be the first transborylation step via **TS-3**, which is 34.8 kcal/mol higher in energy than HBpin.

Upon the formation of B<sub>2</sub>H<sub>6</sub>, this species can subsequently facilitate the hydroboration of react with nitrile substrate giving the diboryl product (Figure 2b). The first step of this reaction is calculated to be the 1,2-*syn*-addition of ½ B<sub>2</sub>H<sub>6</sub> to nitrile via **TS-5** to give intermediate **INT6**, which has an activation energy barrier of 25.4 kcal/mol relative to **INT5**. To

proceed, transborylation (B–N/B–H  $\sigma$ -bond metathesis) between **INT6** and HBpin can take place via **TS-6** to generate mono-boryl species **INT7**. The transborylation step is found to occur via a concerted fashion rather than a stepwise manner<sup>9</sup> with the calculated barrier of 24.4 kcal/mol relative to **4**. From **INT7**, the reaction continues with another 1,2-*syn*-addition of BH<sub>3</sub> followed by a concerted transborylation with HBpin to give *N,N*-diboryl product **3a**. Therefore, it can be concluded that it is possible for water to activate the hidden boron catalysis pathway in hydroboration with HBpin. However, the high activation barrier of **TS-3** likely requires elevated reaction temperature, which is consistent with our experimental studies (*vide infra*).

**Proof of concept and optimization studies:** We were delighted to immediately confirm our theoretical hypothesis with experimental investigations.<sup>10</sup> Treatment of benzonitrile **1a** with a slight excess of HBpin **2** in the presence of 10 mol% of water without any solvent led to quantitative conversion to *N,N*-diborylamine **3a** after 20 hours at 110 °C (Figure 2c). Control studies heating HBpin with 10 mol% water or without water (typical water content of neat HBpin was found to be ~ 70-100 ppm, even after re-distillation) showed evidence for the formation of BH<sub>3</sub> via <sup>11</sup>B NMR spectroscopy (Figure 2d-e, also see page S5 in the SI).

**Table 1.** Optimization of nitrile hydroboration<sup>a</sup>

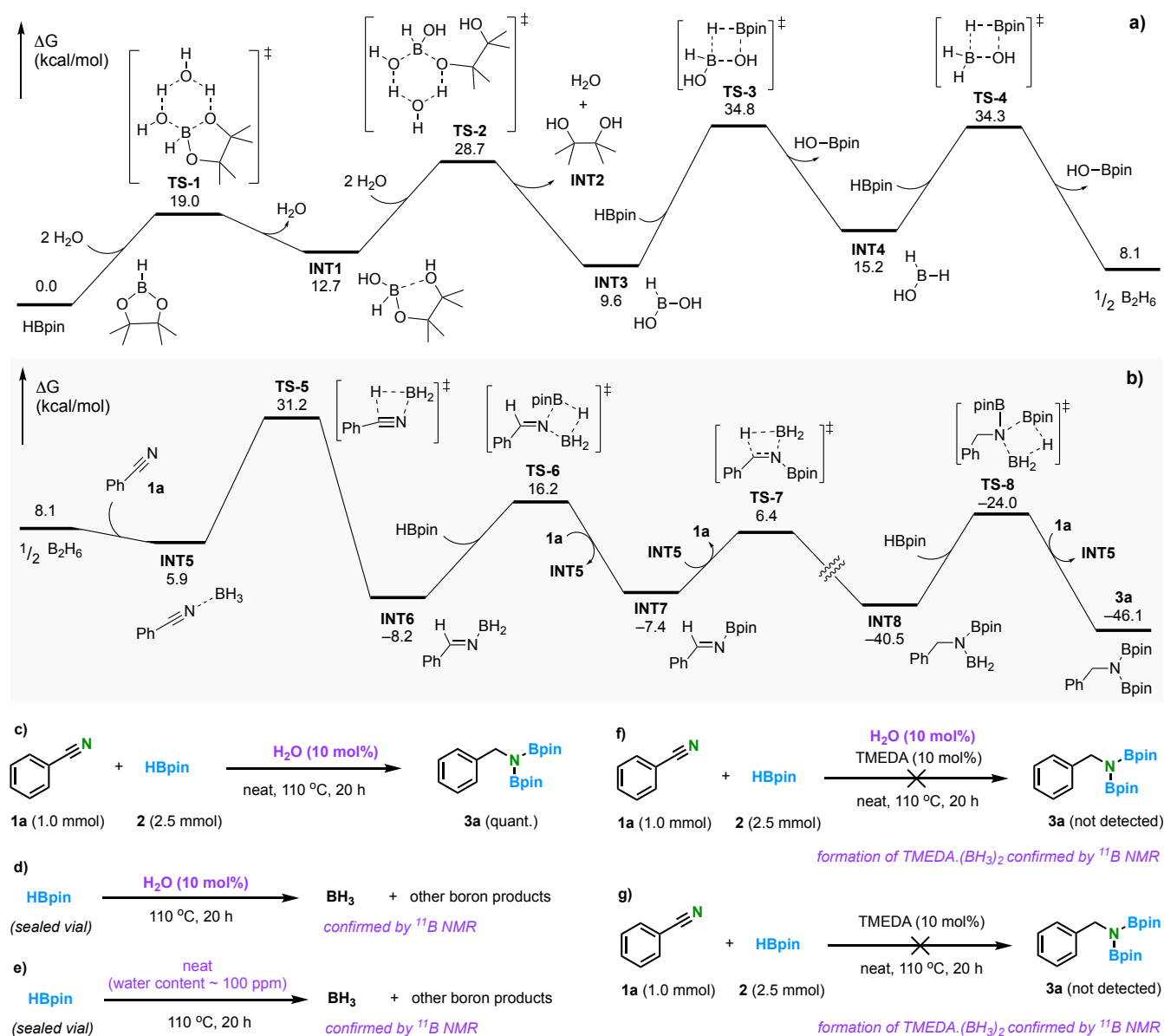
| 1a                  | 2          | 3a          |             |                         |                                 |
|---------------------|------------|-------------|-------------|-------------------------|---------------------------------|
| En-try <sup>a</sup> | T (°C)     | HBpin equiv | Solvent     | Additive (10 mol%)      | Yield <sup>b</sup> of <b>3a</b> |
| 1                   | 110        | 2.5         | neat        | H <sub>2</sub> O        | 99%                             |
| 2                   | 110        | 2.5         | neat        | -                       | 99%                             |
| 3                   | 90         | 2.5         | neat        | -                       | 46%                             |
| 4                   | 70         | 2.5         | neat        | -                       | n.d                             |
| 5                   | 110        | 2.0         | neat        | -                       | 78%                             |
| <b>6</b>            | <b>110</b> | <b>2.2</b>  | <b>neat</b> | -                       | <b>96%</b> <sup>c</sup>         |
| 7                   | 110        | 2.2         | hexane      | -                       | n.d                             |
| 8                   | 110        | 2.2         | PhMe        | -                       | 10%                             |
| 9                   | 110        | 1:2.2       | THF         | -                       | n.d                             |
| 10                  | 110        | 1:2.2       | neat        | H <sub>2</sub> O, TMEDA | n.d                             |

<sup>a</sup>Reaction conditions: benzonitrile **1a** (0.5 mmol); 4,4,5,5-tetramethyl-1,3,2-dioxaborolane HBpin **2**, 20 h; <sup>b</sup>Yield determined by <sup>1</sup>H NMR with mesitylene as internal standard; <sup>c</sup>Yield of **3a** after purification via recrystallization was 92% (see page S7 in the SI).

It should be noted here that HBpin precursor was confirmed to be free of BH<sub>3</sub> or any other borane species before use. When we add tetramethylethylenediamine (TMEDA) to the hydroboration mixtures of **1a** with or without water, the reactions were suppressed. <sup>11</sup>B NMR spectroscopy also revealed the formation of the TMEDA.(BH<sub>3</sub>)<sub>2</sub> complex in these mixtures (Figure 2f-g, also see page S5 in the SI). These experiments clearly demonstrated that moisture/water can indeed act as a nucleophile to transform HBpin into BH<sub>3</sub>, which in turn can catalyze the hydroboration of nitriles.

With the proof-of-concept in hand, we subsequently carried out the optimization study for the hydroboration of benzonitrile **1a** (Table 1). We confirmed that addition of the extra 10 mol% of water is not essential to facilitate the reaction (entries 1-2). This reaction worked better without solvent (entries 7-9). 110 °C and 2.2 equivalents of HBpin is required to give product **3a** in excellent yield (entry 6). It

should be noted that we also successfully applied this newly developed optimal reaction setup to the hydroboration of styrene and phenylacetylene (see page S8 in the SI). This verifies that this protocol is amenable to hydroboration chemistry of alkenes and alkynes, but it is not the focus of our current study.



**Figure 2.** (a-b) Mechanism hypothesis: Free energy profile for the dihydroboration of nitrile catalyzed by *in situ* generated B<sub>2</sub>H<sub>6</sub>; (c-g) Experimental control and proof-of-concept studies.

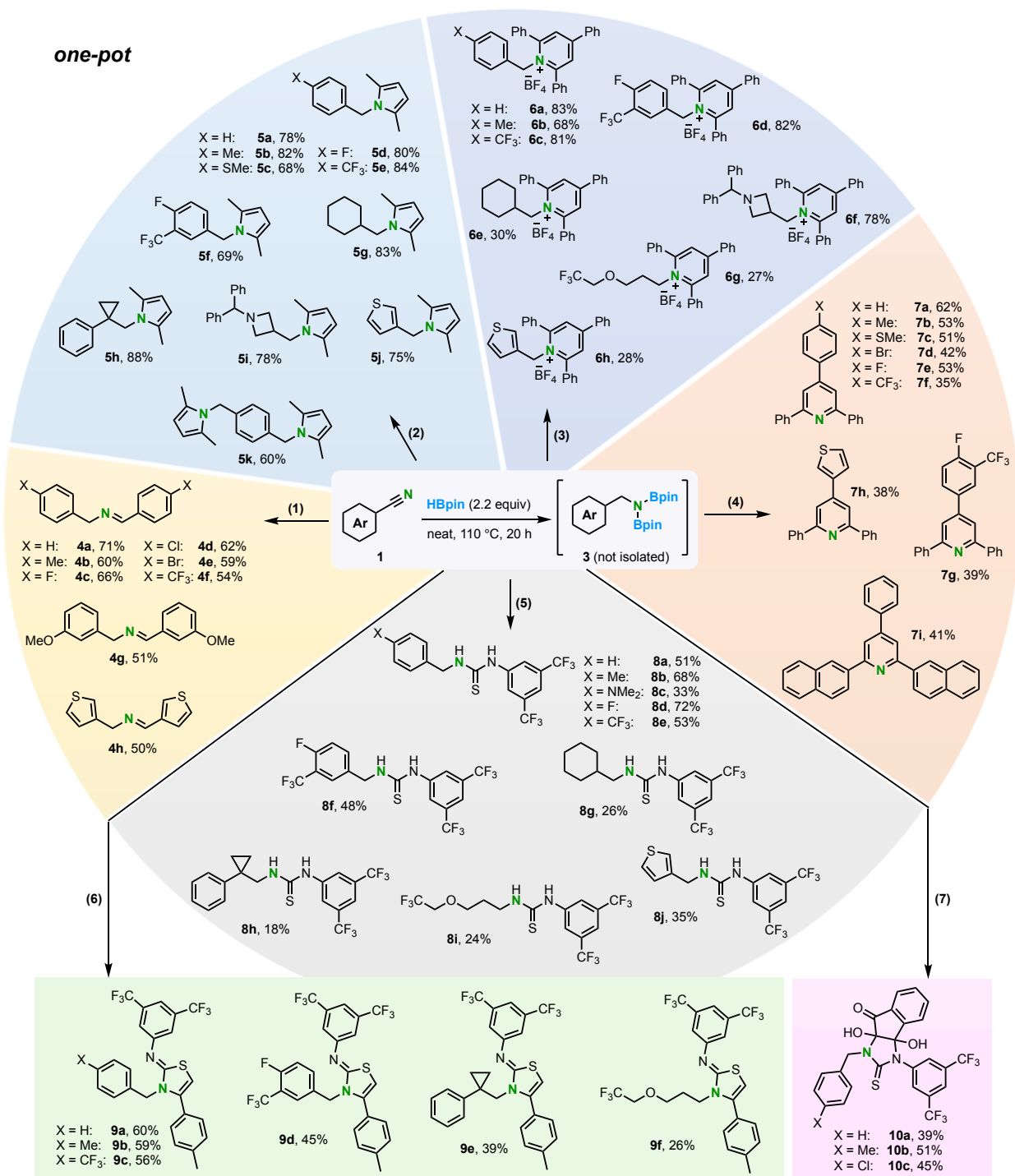
**One-pot synthesis of N-containing derivatives:** The transformation of nitriles, first via hydroboration reaction, into other valuable N-containing derivatives has become of significant interest in both academic research and modern industrial processes and due to the abundance and cost-effectiveness of nitriles as feedstocks.<sup>4a,4b</sup> Furthermore, the synthetic potential of the *N,N*-diborylamine functional group, which feature two boryl groups on a single nitrogen atom, has not been adequately explored.<sup>4b</sup> We were interested in developing a new synthetic toolbox to convert these species directly to other valuable N-containing

compounds in the same hydroboration reaction pot without isolation. The benign nature of water/moisture and the excellent reaction efficiency to *N,N*-diborylamine are highly suitable for us to carry out such sequential reactions.

Thus, we carried out a variety of synthetic transformations directly to the crude hydroboration reactions of a range of nitriles (Scheme 1). The first one was a two-step one-pot oxidative dimerization of the resulting *N,N*-diborylamines with elemental sulfur to 'symmetrical' imines **4a-h** (protocol **(1)**, Scheme 1) in good to high over yields. Next, by simply adding diacetyl or pyrylium salt to the

crude hydroboration reaction mixtures, we were able to produce 2,5-dimethylpyrroles **5a-k** (protocol (2), Scheme 1) or the corresponding Katritzky's pyridinium salts **6a-h** (protocol (3), Scheme 1),<sup>11</sup> respectively, in excellent

efficiency. Both of these are valuable synthetic precursors in organic synthesis, with the latter attracting significant attention recently in photo-mediated and transition metal catalyzed coupling chemistry.<sup>11b-d</sup>



**Scheme 1.** Two-step and three-step one-pot synthesis of *N*-containing derivatives and *N*-heterocycles from moisture-assisted hydroboration of nitriles. Details of experimental protocols (1) to (7) can be found in pages S9-S12 in the SI.

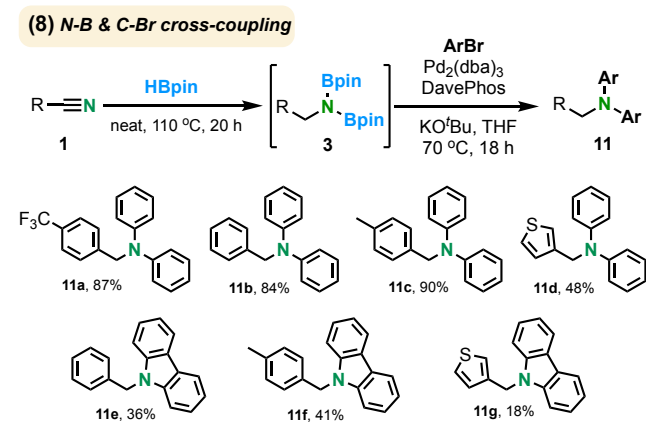
Furthermore, treatment of the crude *N,N*-diborylamines with acetophenone or acetonaphthone led to the formation of 2,4,6-trisubstituted pyridines **7a-i** (protocol (4), Scheme 1).<sup>12</sup> A number of Schreiner-type<sup>13</sup> thioureas **8a-j** were produced by reacting the hydroboration crude mixtures with an isothiocyanate (protocol (5), Scheme 1). On the other

hand, another component such as 2-bromo-1-*p*-tolylethanone together with the isothiocyanate (protocol (6), Scheme 1) to form a range of 2-iminothiazolines **9a-f**.<sup>14</sup> Using a modified approach from protocol (4), indane-1,2,3-trione<sup>15</sup> was added to the resulting crude thiourea product mixtures with longer reaction time (protocol (7), Scheme

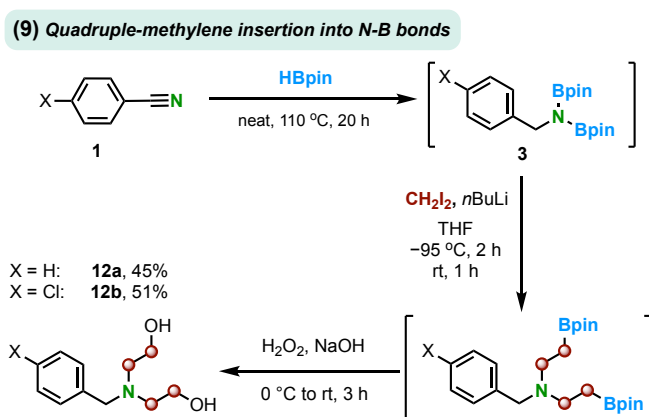
1). This three-step one-pot process afforded indeno[1,2-d]imidazole derivatives **10a-b** in relatively good efficiencies. Specific details of all experimental protocols (**1**) to (**7**) are available in pages S9-S12 in the SI.

Next, we aimed to develop further one-pot synthetic applications directly targeting the reactivity of the two N-B bonds of our *N,N*-diborylamines. In contrast to the well-developed Suzuki-Miyaura deborylative C-C cross-coupling, the deborylative N-C cross-coupling was much less studied.<sup>16</sup> Thus, the crude hydroboration mixtures were subjected to palladium-catalyzed coupling conditions with either bromobenzene or 2,2'-dibromobiphenyl (Scheme 2). Gratifyingly, this led to the formation of tertiary amines **11a-d** or carbazoles **11e-g** in moderate to good overall yields.

On the other hand, Matteson reaction represents an excellent tool for the stereoselectively controlled and



programmable synthesis of alkylboronates, which are highly versatile synthetic building blocks. However, up to this point, these controlled boron-homologation reactions have been predominantly limited to carbenoid insertion into C-B bonds.<sup>17</sup> Taking inspiration from the research conducted by Dong and co-workers,<sup>18</sup> we investigated the feasibility of double-methylene insertions into both N-B bonds of *N,N*-diborylamines. It should be noted that the previously reported work is only applicable to mono boryl amines, with no reactions observed with alkyl boronates. Thus, the crude hydroboration mixtures were treated with carbenoid  $\text{CH}_2\text{Li}$ , generated *in situ* from  $\text{CH}_2\text{I}_2$  and *n*BuLi, at  $-95^\circ\text{C}$ , followed by oxidative hydrolysis (Scheme 2), resulting in the production of bis(alcohol)amines **12a** and **12b** in moderate yields. Specific details of all experimental protocols (**8**) to (**9**) are available in page S13 in the SI.



**Scheme 2.** (left) Deborylative C-N cross-coupling of *N,N*-diborylamines; (right) Quadruple-methylene insertions into *N,N*-diborylamines. Details of experimental protocols (**8**) to (**9**) can be found in page S13 in the SI.

## CONCLUSIONS

In conclusion, water/moisture can react with HBpin to form borane, which in turn catalyze hydroboration reactions. We have demonstrated the viability of this pathway in a new synthetic method to reduce a broad range of nitriles into their corresponding *N,N*-diborylamines. Furthermore, this is an alert for future development in this field to check background reaction of HBpin and analogues with water/moisture to fully eliminate the possibility of hidden borane catalysis. On the other hand, the no-catalyst no-solvent nature of our newly developed synthetic protocol allows for multi-step one-pot direct conversion of *N,N*-diborylamines to a diverse library of synthetically valuable *N*-containing compounds and *N*-heterocycles with good to excellent efficiencies.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge: general experimental procedures, characterization data of all compounds, NMR spectra, computational methods, energies and Cartesian coordinates.

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### Author Contributions

SHD and TVN conceived the project. All experimental work was carried out by SHD. All computational studies were carried out by BKM. The manuscript was written by TVN with contributions from BKM. All authors have given approval to the final version of the manuscript.

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