Revisiting the Reduction of Indoles by Hydroboranes: A Combined Experimental and Computational Study

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ABSTRACT: A combined experimental and density functional computational study was used to probe the mechanism for the reduction of indoles using simple borane BH·-DMS (DMS = dimethyl sulfide). Experimental and computational studies all steer to the formation of the reduced species 1-BH3-indolines as the resting state for this reaction, as opposed to the historically presumed formation of the unreduced 1-BH3-indoles, before the addition of a proton source to form the final product indolines. Furthermore, it was observed that molecular H2 was generated and consumed in the reaction. Computations put forward hydroboration followed by protodeborylation as the very reasonable mechanistic route for the formation of experimentally observed major intermediate 1-BH3-indolines. For the H2 consumption in the reaction, computations suggest the frustrated Lewis pair-type heterolytic splitting of H2 by a bis(3-indolyl)borane intermediate.

INTRODUCTION
The reduction of N-H indoles to indolines has been an ubiquitous reaction within the organic chemistry community and can be done using either transition metal catalysis or simple stoichiometric reduction using hydroboranes. For the latter, borohydrides such as NaBH4, NaBH3(CN) or boranes, mostly on the form BH3-Lewis base, were employed along with a proton source. Reduction of indoles using borohydrides in the presence of a proton source was commonly presumed to proceed via an indolium ion, by protonation of an indole substrate, followed by the addition of a hydride, leading to the desired indoline (Scheme 1a). The same reaction using boranes, either B3H6 or BH3-base, was postulated to proceed via the 1-BH3-indole intermediate, formed through dehydrogenative coupling of an initial B-N complex (BH3-indole) (Scheme 1b). This intermediate subsequently abstracts a proton and a hydride in sequence to form the final indoline. While the latter mechanism for the reduction of indoles using boranes seems reasonable, indoles were generally regarded to exhibit enamine reactivity from the heterocyclic chemistry perspective. Hydroboration of enamines using boranes, leading to vicinal aminoboranones, at ambient and low temperature is well documented. Our recent exploration of the reactivity of ambiphilic aminoboranones and simple hydroboranes toward N-protected indoles revealed that hydroboration of indoles takes place when an electron withdrawing group (EWG) is present at the N-position, leading to formation of air and moisture-sensitive 3-boryl indoline intermediates (Scheme 1c). These unstable intermediates were trapped using HBpin, which led to stable 3-Bpin indolines. Recent studies on the reactivity of boranes without any hydride substituent toward N-protected indoles and enamines also showed compelling evidences for a strong interaction between boranes and the C3 of indoles and enamines. With this fresh understanding on the reactivity of protected indoles with a variety of boranes and the availability of new trapping techniques and modern instrumentalations, we report herein our exploration of the reactivity of unprotected indoles with catalytic and stoichiometric amount of simple hydroboranes (Scheme 1d), and the various mechanistic possibilities for this deep-rooted reduction reaction.

RESULTS AND DISCUSSION
Catalytic reactions. In analogy to our previous report on the BH3-catalyzed borylative dearomatization of 1-arylsulfonyl indoles, we looked at the effect of a catalytic quantity of borane dimethyl sulfide complex (BMS, 5 mol%) in presence of the unprotected parent indole and 2 equiv of pinacoloborane (HBpin). When the reaction was carried out under strict water-free conditions either at room temperature (RT) for 16 h or at 60 °C for 3 h, 1-Bpin indoline (2a) was observed along with ~1 equiv of unreacted HBpin (Scheme 2). This result is surprising since the expected 1,3-diboryl indoline, which should form by the tandem BH3-catalyzed hydroboration of the alkene part of the pyrrole ring and dehydrogenative N-B coupling, was not observed.

Scheme 1. Previously established mechanistic pathways (a-c) for reaction of protected and unprotected indoles with hydroboranes, and this current work (d) of a proposed reaction pathway for the reduction of indoles using hydroboranes. BMS = trihydridoborane dimethyl-sulfide complex.

Scheme 2. Reduction of indole using HBpin in the presence of catalytic BMS. BMS = trihydridoborane dimethylsulfide complex.
The reduction of the aromatic C(2)-(3) moiety to two chemically inequivalent methylene units in product 2a was apparent from NMR spectroscopy, where the $^1$H NMR spectrum showed two triplets at δ 3.06 and 3.78 and the $^1$C(APT) spectrum unambiguously showed two negative phase signals at δ 29.6 and 47.1. $^{11}$B NMR spectroscopy and mass spectrometry also confirm the identity of 2a. Other unprotected indoles that bear synthetically useful functionalities on the benzene ring, as shown in Scheme 3, provided similar results. Substrates such as 7-fluoro indole (1m) and 7-methyl indole (1n), however, led only to a moderate conversion, and no catalytic reaction was observed with 2,3-dimethyl indole (1o) and 1,2,3,4-tetrahydrocarbazole (1p). While most of the 1-Bpin indoline products were formed quantitatively, their purification by means of crystallization or column chromatography was not possible because of their facile hydrolysis, leading to the formation of indoline derivatives. Formation of 1-Bpin indoline derivatives is also viable through dehydrogenative coupling between unprotected indolines and HBpin in the presence of catalytic amount of BMS.\(^{9}\) Albeit, the use of indoles to form such products can be ideal in the perception of atom economy, as this synthetic route accumulates no by-product.

**Stoichiometric reactions.** To gain some mechanistic insight into how this catalytic reaction occurs, indole was treated with different molar ratios of BMS at different temperatures and reaction time in J. Young NMR tubes. The reaction conditions and results of these reactions are displayed in Table 1. With 1 equiv of BMS, the indole substrate disappeared completely after one hour at RT. Nevertheless, the reaction was incomplete as the $^1$H NMR spectroscopy revealed that a substantial amount of unreacted BMS was present in addition to the indoline-BH\(_3\) complex (3a), molecular H\(_2\), 1-BH\(_3\) indoline (presumably in its dimeric form 4a), and diaminoborane 5a.

**Table 1. Outcomes of the reaction of indole with few different equivalents of BMS at different temperature.**

<table>
<thead>
<tr>
<th>entry</th>
<th>1a:BMS</th>
<th>x (°C)</th>
<th>y (%)</th>
<th>BMS (%)</th>
<th>3a (%)</th>
<th>4a (%)</th>
<th>5a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1</td>
<td>RT</td>
<td>1</td>
<td>45</td>
<td>8.5</td>
<td>12°</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>1:1</td>
<td>60</td>
<td>2</td>
<td>25</td>
<td>0</td>
<td>44°</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>1:2</td>
<td>60</td>
<td>2</td>
<td>19</td>
<td>0</td>
<td>76</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>1:0.5</td>
<td>60</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6°</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^*\) The percentage is based on $^1$B NMR integration.  
\(^\dagger\) The percentage mentioned is for the amount of boron atoms and is based on monomeric species (4a) instead of the dimeric species 4a, which would be half.  
\(^\ddagger\) Based on the $^1$H NMR integration, some amount of H\(_2\) is present in solution.

Heating the same solution to 60 °C for 2 h resulted in a decrease of the proportion of BMS, complete disappearance of the indoline-BH\(_3\) complex (3a) and molecular H\(_2\), and appearance of species 4a in major proportion and species 5a in a significant proportion (entry 2).\(^{10}\) With 2 equivalents of BMS at 60 °C after 2 h, species 4a was observed as the major species (entry 3). On the other hand, under the same reaction conditions but with 0.5 equivalent of BMS, the formation of species 5a was observed in majority (entry 4). Since indoline-BH\(_3\) complex (3a) is only observed at room temperature, it becomes obvious that it is an intermediate that transforms to the more stable 1-BH\(_3\) indoline (4a).

Furthermore, comparison of the last two reactions (entries 3 and 4) with entry 2 suggests that disproportionation can take place where species 4a can form 5a with a concomitant release of BMS. The extent of the disproportionation depends on the stoichiometry of BMS used in the reaction. This relation is important when looking at the catalytic transformations in Scheme 3 since a 20:1 ratio of indole to BMS should favor the presence of analogues of 5a rather than species 4a. In all cases, we did not observe any evidence of the presence of species 1-BH\(_3\) indoline, although we cannot definitely confirm that it cannot exist in undetectable concentrations.

Next, in an attempt to understand the generation of 1-Bpin indoline (2a), a stoichiometric amount of HBpin was added to the mixture of 1-BH\(_3\) indoline (4a) and diaminoborane (5a) arising from the 1:1 reaction between indole and BMS. This reaction resulted in complete disappearance of the diaminoborane species 5a and appearance of product 2a at RT after 16 h (Scheme 4). Surprisingly, only a small portion of major species 4a was consumed, even at elevated temperature (60 °C). Interestingly, it suggests that higher yields of 2 are expected under catalytic conditions where a deficiency of BMS will be present relative to the parent indoles.

Revisiting the mechanism of indole reduction using BH\(_3\) solvates. Reduction of unprotected indoles to indolines using a stoichiometric amount of BH\(_3\)-THF and the mechanistic details of this reaction have been studied half a century ago by Schmidt et al.\(^{7a}\) In their study, formation of the species 1-BH\(_3\) indole was postulated as the resting state (Scheme 1b). Furthermore, it was reported that the establishment of this resting state accompanies a stoichiometric amount of H\(_2\) liberation. Lastly, to obtain the final indoline product a prerequisite for a
stoichiometric amount of a proton source, such as methanol, which involves in protonation of the 1-BH$_3$ indole intermediates, was mentioned. While their mechanistic proposal seems logical, our experimental observations as mentioned in the previous section for the reaction between indole and BMS evidently diverges from their mechanistic proposal. Some of our experimental inferences include formation of the reduced species 1-BH$_3$ indole (4a) without addition of any external proton source and generation of minor amount of H$_2$ in the reaction.

Due to the disparity between the previous and current experimental outcomes from the reaction of indole with simple hydroboranes, a further mechanistic scrutiny for this reaction is warranted. For this purpose, DFT computations at the wb97xd/d-31g(d,p) level of theory were performed and are discussed in the following sections.

**Computed dehydrogenative coupling route vs hydroboration route.** Computations were first aimed at comprehending if the dehydrogenative N-borylation of indoles occurs first, as proposed by Schmidt and coworkers.$^{29}$ In line with their proposal, the formation of 1-boryl indole intermediate (12) and H$_2$ from indole and BMS is thermodynamically favorable (ΔG = -14.6 kcal/mol; Figure 1, red and green lines). However, in contrast to their hypothesis, the formation of initial N-B complex (11) from indole and BMS is less favored as this step is endergonic by 9.1 kcal/mol. Moreover, formation of the postulated species 1-BH$_3$ indole (12) and H$_2$ from reactants via a direct dehydrogenative coupling transition state (TS(1-2), green line), as proposed by Bertrand et al., for the dehydrocoupling of primary and secondary amines with HBpin,$^{11}$ is kinetically favorable compared to the previous route, as the transition state holds a barrier of 26.3 kcal/mol. Nevertheless, both processes are significantly higher in energy compared to the hydroboration of indole, which has a transition state (TS) barrier of 19.6 kcal/mol. As expected, the syn addition of H and BH$_3$ groups at C2 and C3 position, respectively, is kinetically more favored over the addition of boron at the C2 position (ΔG$^\ddagger$ = 23.0 kcal/mol).

**Pathways for the formation of 1-BH$_3$ indole (4a) from 3-BH$_3$ indole intermediate (14).** As the hydroboration route seems favored, we explored next the possible pathways to generate 1-BH$_3$ indole intermediate (4a) from the 3-BH$_3$ indole intermediate (14). For this purpose, it was first considered for species 14 to undergo a bimolecular protodeborylation process, leading to formation of indole and 1,3-di-BH$_3$ indole (A; Scheme 5, first step). As we have initially observed the species indole-BH$_3$ complex (3a) from the stoichiometric reaction conducted at RT (see Table 1, entry 1), we next supposed that Lewis basic indole can coordinate with the unreacted BMS to form 3a. From this species, two pathways were conceived for the formation of the observed 1-BH$_3$ indole (4a). In the first pathway, species 3a reverses back to give indole, which in turn reacts with 1,3-di-BH$_3$ indole (A) through a protodeborylation transition state to afford only species 4a (Scheme 5, pathway a).

In the second pathway, the indole-BH$_3$ complex 3a undergoes either direct or BH$_3$-assisted dehydrogenative coupling to furnish 2a along with equimolar amount of H$_2$ (Scheme 5, pathway b).
From the analysis of the computed free energy profile for these two pathways (Figure 2), the pathway a (black line) that involves protodeborylation is slightly favored over pathway b (red and green lines) that encompasses the dehydrogenative coupling processes. For pathway a, the protodeborylation step from indole-BH$_3$ complex (3a) was rate limiting ($\Delta G^\ddagger = 23.1$ kcal/mol, step 18 to TS(9-10)). For pathway b, the BH$_3$-assisted dehydrocoupling step from species 3a was rate limiting ($\Delta G^\ddagger = 24.5$ kcal/mol, step 18 to TS(8-11)). Since the rate limiting barriers of both pathways are only 1.4 kcal/mol apart from each other, the BH$_3$-assisted dehydrocoupling route of pathway b should be considered as kinetically competitive to pathway a. This phenomenon clarifies how a minor amount of H$_2$ was generated from the reaction of indole with BMS. The facile hydroboration of indole by BMS, and the succeeding deborylation processes of the formed 3-BH$_3$ indoline intermediate to furnish the observed 1-BH$_3$ indoline species (4a) clearly demonstrates that no external proton source is needed for the reduction of indole. The N-H functionality of indoline or 3-BH$_3$ indoline serves as an internal proton source. Experiments carried out using 1-D indole also support this view, as the deuterium atom was transferred exclusively to the C3 of 1-BH$_3$ indoline product (see Figure S7 in the Supplementary Material).

Pathways for formation of 1-BH$_3$ indoline (4a) via the 3H-indole-BH$_3$ complex (6a). As another possible pathway for the formation of 1-BH$_3$ indoline (4a) from indole and BMS, a tautomeric switch of indole from its 1H form to 3H form, followed by coordination of it to BH$_3$ of BMS, and subsequent rearrangements to the desired 4a was considered (Scheme 6). Indoles are generally known to exist in two tautomeric forms, 1H and 3H. The equilibrium is dependent on the nature of the substituents on indoles and the pH of the solution. For example, 2-alkoxy indoles were reported to predominantly exist in their 3H tautomeric form. The spontaneous 1H-to-3H tautomeric switch was also observed for certain indoles under aqueous conditions. To ascertain the extent by which this tautomerism contributes to the formation of the observed species 4a from the reaction between indole and BMS, the spontaneous equilibrium between the two tautomeric forms of selected indoles were computed. From the results listed in Table 2, only 2-methoxy indole was shown to spontaneously exist in its 3H form (entry 1). For other derivatives, the equilibrium lies far towards their 1H form, although with different endergonic energetics (entries 2-10). Therefore, presumably none of the indoles we examined experimentally may undergo a spontaneous switch to their 3H tautomer.

![Figure 2](image-url)

**Scheme 6.** A pathway conceived for the formation of 1-BH$_3$ indoline (4a) from indole and BMS via 3H-indole-BH$_3$ complex (6a).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>$\Delta G$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-methoxy-1H-indole</td>
<td>-1.6</td>
</tr>
<tr>
<td>2</td>
<td>1H-indole</td>
<td>8.6</td>
</tr>
<tr>
<td>3</td>
<td>5-methoxy-1H-indole</td>
<td>6.1</td>
</tr>
<tr>
<td>4</td>
<td>5-fluoro-1H-indole</td>
<td>8.4</td>
</tr>
<tr>
<td>5</td>
<td>5-chloro-1H-indole</td>
<td>8.9</td>
</tr>
<tr>
<td>6</td>
<td>5-nitro-1H-indole</td>
<td>10.1</td>
</tr>
<tr>
<td>7</td>
<td>6-fluoro-1H-indole</td>
<td>8.7</td>
</tr>
<tr>
<td>8</td>
<td>6-chloro-1H-indole</td>
<td>9.1</td>
</tr>
<tr>
<td>9</td>
<td>6-nitro-1H-indole</td>
<td>10.7</td>
</tr>
<tr>
<td>10</td>
<td>4-chloro-1H-indole</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Whereas several 1H-indoles may not undergo spontaneous tautomerization, Resconi and coworkers have demonstrated that in the presence of a strong Lewis acidic borane, B(C$_6$F$_5$)$_3$, various indoles can be converted to 3H-indole-B(C$_6$F$_5$)$_3$ complexes. The computed thermodynamics for the formation of the 3H-indole-B(C$_6$F$_5$)$_3$ complex from 1H-indole and B(C$_6$F$_5$)$_3$ shows that this
The step going from 6a to 4a was exergonic with a ΔG of -25.3 kcal/mol (Figure 3; step I13 to I14). However, the barrier for this step through a direct 1,3-hydride shift from boron to C2 was found higher (ΔG1 = 28.5 kcal/mol; red line). Interestingly, the BH3-assisted transition state lowered the barrier down to 19.6 kcal/mol (black line). Despite the fact that the 1,3-hydride shift step from stage I13 to I14 to form the ultimate 1-BH3 indoline (4a) seems feasible both thermodynamically and kinetically, the formation of the 3H-indole-BH3 complex (6a) from 1H-indole and BMS appears to be less possible. This step through an initial B-N adduct (I12) formation followed by the DMS-assisted 1,3-proton shift from nitrogen to C3 appears kinetically inaccessible as it expresses a barrier of 34.8 kcal/mol (the first two mechanistic steps of Figure 3). Hence, if an alternative lower energy pathway exists to reach 3H-indole-BH3 complex (6a) from 1H-indole and BMS, then this whole mechanistic pathway should be considered as a competing route to the first proposed hydroboratization/self protodeborylation route, but none was found in our hands.

Figure 3. Computed mechanistic pathways for rearrangement of 3H-indole-BH3 complex (6a) to 1-BH3 indoline (4a).

Pathways for consumption of H3. One important experimental feature of the stoichiometric transformation was the consumption of initially evolved minor dihydrogen towards generation of 4a and 5a. For the investigation of mechanistic pathways for H3 consumption, two pathways were considered (Scheme 7). In the first pathway (pathway a), the monomeric form (14') of 3-BH3 indoline intermediate (I4) was viewed as an intramolecular vicinal frustrated Lewis pair (FLP), where the Lewis acid is the borane and the Lewis base is the nitrogen of indoline. Frustrated Lewis pairs, both intra- and intermolecular varieties, are widely known to activate the H-H bond of molecular hydrogen.15 Repo demonstrated that a similar BH3 containing aminoborane can reversibly activate dihydrogen.16 As a result, the species 14' was anticipated to cleave molecular H3 and afford a zwitterion intermediate (I16), which may subsequently transform to the indoline-BH3 complex (3a) through a self protodeborylation process. In the second pathway (pathway b), the 3-BH3 indoline intermediate (14) initially hydroborates another indole substrate and forms the secondary borane (I18). This thought came from the fact that several examples of dihydroboration by treating BH3-base with over 2 equiv of alkenes, including cyclic

Scheme 7. Pathways for the consumption of generated H3 in the reduction reaction. Pathway a involves H3 cleavage by 3-BH3 indoline (14'), and pathway b involves H3 cleavage by the dialkylborane 120. olefins, and 1-arylaufonyl indoles have been previously report- ed.19 In the next step of pathway b, the secondary borane I18 cleaves H3 in a similar fashion as that of 14' and forms the zwitterionic 119, which may further transform to the indoline-3-BH3 indoline complex (120) by a self protodeborylation process. For pathway a, the computed structure of the monomeric 3-BH3 indoline intermediate (14') is displayed in Figure 4a. The structure of this species indeed exhibits an important property of intramolecular frustrated Lewis pairs, which is the right orientation of the Lewis acid center to the non-bonding orbital of the Lewis basic center. The distance between the two Lewis centers of this species was found to be 3.073 Å, which is optimal for enabling H-H activation.20 For comparison, its closed form (14'-closed), with a strong B-N interaction (R_{B,N} = 1.761 Å), was optimized (Figure 4b), and found that this species is 10.3 kcal/mol higher in energy than its open form. Our computational attempts to enable H-H activation by species 14'-open form disclosed that there are two thermodynamically less favorable steps involved in this process (Figure 5, red line): (i) formation of the σ-complex I15, and (ii) formation of

Figure 4. DFT optimized structures of: (a) 14'-open, (b) 14'-closed, and (c) double hydroborated borane I18. Selected distances (Å) and angles (°) for: 14'-open, B-N = 3.073, B-C-N = 100.96; 14'-closed, B-N = 1.761, B-C-N = 53.89; I18, B-N1 = 3.186, B-C-N1 = 105.66.
zwitterion I16 through splitting of H2, with an overall TS barrier of 27.7 kcal/mol. Thus, foreseeing intermediate I14’ as an FLP to split H2 is less promising. Alternatively, in the second pathway (pathway b), the diindolyl borane intermediate I18 lies relatively in a favored position at the free energy scale (2.8 kcal/mol), which is only slightly endergonic (ΔG = 4.3 kcal/mol) from the 3-BH2 indoline intermediate (I14). The hydoroboration energy barrier for this step to establish species I18 is also achievable (ΔG = 22.0 kcal/mol) under RT or 60 °C. The optimized structure of species I18 and its selected structural parameters are shown in Figure 4c. As shown in this structure, this species displays the required orthogonal geometry around the Lewis centers to act as an intramolecular FLP for H2 splitting. Like that of the 3-BH2 indoline species I14’, the H2 splitting process using species I18 is endergonic (ΔG = 21.9 kcal/mol) with respect to the 3-BH2 indoline intermediate (I14) with a barrier of 25.2 kcal/mol. Yet, in comparison of this step to that of I14’ (pathway a) the H2 splitting route enabled by species I18 should be highly considered, especially at 60 °C. Therefore, for the consumption of H2 in the reaction we postulate the heterolytic splitting of H2 by I18, leading to a zwitterion I19, which might undergo the self-bimolecular protodeborylation reaction as shown in pathway b of Scheme 7.

Pathways for the formation of 1-Bpin indoline (2a) from 1-BH2 indoline (4a). As mentioned above in Scheme 4, the stoichiometric reaction among indole, BMS and HBpin proceeds through intermediates 1-BH2 indoline (4a) and diaminoborane (5a) to afford the product 1-Bpin indoline (2a). Noteworthy of this stoichiometric reaction is that the intermediate 4a was only partially consumed while the intermediate 5a is completely consumed for the formation of product 2a. To understand the formation of 2a from species 4a and HBpin, computations were performed. First, the DFT results suppose that species 1-BH2 indoline (4a’) is in equilibrium with dimer 4a that has two dative N-B interactions, forming a four-membered B-N-B-N cycle. The dimeric species 4a was found to be exergonic by 1.3 kcal/mol, and a barrier of 9.4 kcal/mol is required for the dissociation of 4a to occur. From 4a’ two pathways are possible to form 1-Bpin indoline (2a). First, metathesis can occur directly between HBpin and 4a’ (Scheme 8, pathway a). Second, species 4a’ can first disproportionate to observed diamino borane species 5a, which will then react with HBpin (Scheme 8, pathway b). Computationally, for the whole first pathway (pathway a) a high barrier was found for the initial metathesis step (ΔG‡ = 17.2 kcal/mol) (Figure 6, red line). This energy barrier is easily attainable at RT or 60 °C. Albeit, the reason for the observation of some unreacted species 4a and HBpin in the stoichiometric reaction is due to the fact that species 4a and HBpin may exist in equilibrium with 1-Bpin indoline and BMS. This can be inferred from the computed pathway where the starting stage I21 and the product stage I18 were found to be nearly equal in energy. For the second pathway (pathway b), computations show that disproportionation is much facile (Figure 6, black line). The high barrier in this pathway was for the metathesis step between diamino borane (5a) and HBpin. Between these two pathways for the transformation of species 1-BH2 indoline (4a) to 1-Bpin indoline (2a), pathway b involves disproportionation followed by metathesis is highly favored.

Scheme 8. Pathways perceived for the transformation of 1-BH2 indoline to 1-Bpin indoline. Pathway a involves a direct metathesis step, and pathway b entails disproportionation and metathesis steps.
Figure 6. Mechanistic pathways for conversion of 1-BH$_2$ indoline (4a) to 1-Bpin indoline (2a) using HBpin and its disproportionation to diamino-borane (5a) and BMS. [B] = Bpin.

Overall, based on the experimental and computational insights, the plausible catalytic cycles for the formation of 1-Bpin indolines from indoles, HBpin and the catalyst BMS are presented in Figure 7. Between the two catalytic cycles proposed, cycle B is more favored.

Figure 7. Plausible catalytic cycles for the transformation of 1-BH$_2$ indoline to 1-Bpin indoline.

Conclusions

According to our experiments on the reaction of indoles with simple hydroboranes of the form BH$_3$·base, in either stoichiometric or catalytic quantity, the major resting state arose was 1-boryl indoline in an atom economical manner. In addition, only a minor proportion of H$_2$ was generated through a relatively less competitive side reaction. These insights overturn the earlier mechanistic proposal of generation of stoichiometric amount of H$_2$ along with the formation of the resting state intermediate 1-boryl indole. Through DFT computations we recognized that H$_2$ generated through a competing side reaction was observed to be consumed in the reaction. For its consumption, computations suggest the FLP-type heterolytic splitting of H$_2$ by a dihydroborated borane intermediate. Other computational mechanistic possibilities pursued based on the recent experimental observations from the reaction of unprotected and protected indoles with tertiary boranes can be ruled out for the formation of 1-BH$_2$ indolines from indoles and simple hydroboranes.

Experimental section

General comments.

All procedures were carried out in a glovebox under a nitrogen atmosphere. All unprotected indoles were used as received from commercial suppliers. Dichloromethane, chloroform and CDCl$_3$ were purified by vacuum-distillation from P$_2$O$_5$. C$_6$D$_6$ was purified by vacuum distillation from Na/benzophenone. Pinacolborane (HBpin) was freshly prepared from BMS and pinacol in dichloromethane by following a literature procedure.$^{21}$ The prepared HBpin contains residual dichloromethane. The NMR spectra were recorded either on Agilent Technologies NMR spectrometer at 500.00 MHz (1H), 125.757 MHz (13C), 160.46 MHz (11B) and 470.385 MHz (19F) or on Varian Inova NMR AS400 spectrometer, at 400.0 MHz (1H), 100.580 MHz (13C) and 376.29 (19F) in CDCl$_3$ or C$_6$D$_6$. Mass Spectrometry analyses were carried out on an Agilent 6210 LC Time of Flight Mass Spectrometer, by means of electrospray ionization (ESI) method.

Catalytic reactions.

All catalytic reactions for the formation of 1-Bpin indolines were carried out using either J. Young NMR tubes or sealable 20 mL microwave vials. Indoles in a 0.1 to 0.5 millimole scale was first dissolved in chloroform or CDCl$_3$ (0.5 – 2 mL), then HBpin (1.0 – 1.3 equiv) and catalytic quantity of BMS (5 mol%) were introduced. This was followed by the tube was quickly sealed. The reaction mixture was subsequently heated at 60 °C for 2 – 3 h. Afterwards, solvent and other volatiles were evaporated in vacuo at RT for 2 h. Our attempts to crystallize the obtained products as residue in the form of either oil or powder led to decomposition under inert atmosphere and hydrolyzes if kept outside in a sealed flask. As a result, isolated yields were not...
3.75 (s, 3H), 3.02 (t, J = 8.6, 2H), 6.63 (dd, J = 7.4, 1.1 Hz, 1H), 3.78 (t, J = 8.8 Hz, 2H), 3.06 (t, J = 8.8 Hz, 2H), 1.31 (s, 12H). 13C NMR (126 MHz, CDCl3): δ 148.3, 131.4, 127.2, 124.4, 119.5, 112.6, 83.1, 47.0, 29.9, 24.7. 11B NMR (160 MHz, CDCl3): δ 23.8. HRMS (ESI-TOF) m/z: Calcd for C19H20BCINO + H+: 276.1766; Found: 276.1756.

5-Methoxy-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (2c). Reaction time: 3 h. Conversion: 98%. 1H NMR (500 MHz, CDCl3): δ 7.15 (s, 1H), 7.03 – 6.91 (m, 2H), 6.41 (dd, J = 8.8, 2H), 3.80 (t, J = 8.8 Hz, 2H), 1.31 (s, 12H). 13C NMR (126 MHz, CDCl3): δ 148.3, 131.4, 127.2, 124.4, 119.5, 112.6, 83.1, 55.9, 47.3, 29.9, 24.7. 11B NMR (160 MHz, CDCl3): δ 23.5. HRMS (ESI-TOF) m/z: Calcd for C21H22BCINO + H+: 280.1273; Found: 280.1251.

5-Fluoro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (2d). Reaction time: 3 h. Conversion: > 99%. 1H NMR (500 MHz, CDCl3): δ 7.15 (s, 1H), 7.03 – 6.91 (m, 2H), 6.78 – 6.72 (m, 1H), 3.78 (t, J = 9.0 Hz, 2H), 3.03 (t, J = 8.9 Hz, 2H), 1.30 (s, 12H). 13C NMR (126 MHz, CDCl3): δ 157.3 (d, J = 236.1 Hz), 144.3, 125.9, 113.1 (d, J = 22.9 Hz), 112.6 (d, J = 8.1 Hz), 111.6 (d, J = 23.8 Hz), 83.1, 47.4, 29.6, 24.7. 11B NMR (160 MHz, CDCl3): δ 23.5. HRMS (ESI-TOF) m/z: Calcd for C21H20BCINO + H+: 264.1568; Found: 264.1565.

5-Chloro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (2e). Reaction time: 3 h. Conversion: > 99%. 1H NMR (500 MHz, CDCl3): δ 7.14 (dd, J = 8.4, 0.4 Hz, 1H), 7.05 – 6.95 (m, 2H), 3.75 (t, J = 9.2 Hz, 2H), 3.01 (t, J = 8.8 Hz, 2H), 1.28 (s, 12H). 11B NMR (160 MHz, CDCl3): δ 23.7. HRMS (ESI-TOF) m/z: Calcd for C21H20BCINO + H+: 280.1273; Found: 280.1259.

5-Bromo-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (2f). Reaction time: 3 h. Conversion: > 99%. 1H NMR (500 MHz, CDCl3): δ 7.18 – 7.13 (m, 1H), 7.12 – 7.08 (m, 2H), 3.74 (t, J = 9.0 Hz, 2H), 3.01 (t, J = 8.8 Hz, 2H), 1.28 (s, 12H). 11B NMR (160 MHz, CDCl3): δ 23.6. HRMS (ESI-TOF) m/z: Calcd for C21H20BCINO + H+: 294.1620; Found: 294.1592.

6-Chloro-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline (2h). Reaction time: 3 h. Conversion: > 99%. 1H NMR (500 MHz, CDCl3): δ 7.21 (s, 1H), 6.96 (d, J = 7.0 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 3.77 (t, J = 8.8 Hz, 2H), 2.99 (t, J = 8.8 Hz, 2H), 1.29 (s, 12H). 11B NMR (160 MHz, CDCl3): δ 23.6. HRMS (ESI-TOF) m/z: Calcd for C21H20BCINO + H+: 276.1779; Found: 276.1766.
Computational details. Geometry optimizations and frequency calculations were performed at the hybrid DFT with dispersion-corrected functional oB97XD, as implemented in the Gaussian 09 (revision C.01) software program. The standard 6-31G(d,p) basis set was used. Transition state (TS) geometries were obtained using opt = (ts, nocoeff, calcfc) algorithms. Frequency calculations were performed on all optimized structures to verify the nature of the structures and to extract the thermochemistry information. From the frequency calculations we ensured that the TS structures had only one imaginary frequency and that the magnitudes of all frequencies were greater than the residual frequencies that are due to rotations and translations. Additionally, each TS was confirmed to be on the chosen reaction path by performing “plus-and-minus-displacement” minimization calculations where the TS structure was displaced ca. 0.05 Å or 5° on the imaginary frequency normal mode in both directions and subsequently the displaced geometries were optimized to the nearest minima. The energies (ÅG) given are corrected for zero-point vibrational energies.

ASSOCIATED CONTENT
Supplementary Material. Computational details, energies and Cartesian coordinates, and NMR spectra of all new compounds from catalytic and stoichiometric reactions.

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REFERENCES AND NOTES
8. In contrast, the stoichiometric reaction between these substrates and BMS led to a complete consumption of the substrate and formation of multiple unidentified species.
9. The same also works without addition of catalytic amount of BMS, but requires an elevated temperature (80 °C) and a long reaction time (16h).
10. The same products can also be obtained at room temperature but requires a long reaction time (~48 h).


TOC graphic: