Photoinduced Dehydrogenative Borylation via Dihydrogen Bond Bridged Electron Donor and Acceptor Complexes

Zhiyong Wang, Jiaxin Chen, Zhenyang Lin, Yangjian Quan

ABSTRACT: Air-stable amine- and phosphine-boranes are discovered as donors to integrate with pyridinium acceptor for generating photoactive electron-donor-acceptor (EDA) complexes. Experimental results and DFT calculations suggest a dihydrogen bond bridging the donor and acceptor. Illuminating the EDA complex enables an intramolecular single electron transfer to give boron-centered radical for dehydrogenative borylation with no need of external photosensitizer and oxidant. The deprotonation of Wheland-like radical intermediate rather than its generation is believed to determine the very good ortho-selectivity based on DFT calculations. A variety of α-borylated pyridine derivatives have been readily synthesized with good functional group tolerance.

INTRODUCTION

Hydrogen bond, one representative class of “weak” interactions, plays a crucial role in the state of molecules, secondary and tertiary structures of proteins, connection of reticular materials, catalysis, among others. As the non-conventional hydrogen bond, dihydrogen bond, generally constructed by a hydride and a proton, has attracted increasing research attention. In addition to the well-known B-H⋯H⋯N interaction, the investigation of B-H⋯H⋯C bonds is relatively less developed, although they have also proved the ability to affect the efficiency and selectivity of reactions. In addition, recent research shows that dihydrogen bonding interactions competently serve as the main forces for recognition and separation of organic isomers (Figure 1a). However, to the best of our knowledge, employment of B-H⋯H⋯C interaction for photoinduced single electron transfer to generate open-shell boron-centered radical remains elusive.

In the past few years, photoresponsive electron donor-acceptor (EDA) complexes have exhibited promising potential in photoinduced synthesis. In general, relatively photoinert electron donor and acceptor precursors aggregate to form photoactive EDA complexes, which can be excited by light to trigger single electron transfer (SET) to afford active radical species under mild reaction conditions. Different kinds of electron donors and acceptors are investigated for developing fresh EDA-based photochemical strategies. Specific to organoboron compounds, amide-coordinated bis(catecholato) diboron acts as a competent donor for the corresponding photoactive EDA adducts (Figure 1b). On the other hand, alkyl boronic acid was found as an efficient acceptor (Figure 1b). The exploration of other organoboron compounds is desired. In view of the nucleophilicity of tetracoordinated boranes, we hypothesize they would be the candidates of donor to deliver new EDA complexes for photoinduced borylation.

Despite the versatile applications of organoboron compounds ranging from synths to pharmaceuticals, their preparation still suffers from limitations of relatively low boron atom economy and/or rigorous reaction conditions. The use of air stable boranes as feedstocks brings a mild and compatible route to organoboron compounds. The tetracoordinated boranes can react with free carbene, transition metal carbene, and benzyne directly to construct B-C bonds.

Fig. 1. Dihydrogen bond and EDA complex. a) Representative examples of B-H⋯H⋯C dihydrogen bond. b) Proposed photoactive EDA complexes containing organoboron compounds. c) This work: photoinduced dehydrogenative borylation via dihydrogen bond bridged EDA complexes.

Furthermore, hydrogen atom transfer (HAT) or SET of boranes reportedly form active boron-centered radicals for useful transformations. For example, a significant breakthrough of photoinduced C-H borylation of azines catalyzed by CzIPN dye was achieved. The research however only focused on trimethylamine borane, which was used in excess as the coupling partner. Inspired by these seminal advances, we herein report the first investigation of photoresponsive EDA adducts derived from amine- or phosphine-coordinated boranes and pyridinium salts via B-H⋯H⋯C interaction. The photoexcita-
tion of the EDA adducts enables a dehydrogenative borylation through intermediacy of boron-centered radical. An unexpected sole ortho-selectivity is obtained, due to the preferred α-H deprotonation of the related Wheland-like radical intermediates based on DFT calculation results. This transformation proceeds with no need of external photosensitizer, oxidant, and excess acid.

RESULTS AND DISCUSSION

To evaluate the feasibility of employing the tetracoordinated boranes as the electron donors for photoactive EDA complexes, the electronagative trimethylamine borane 1a was chosen as the model substrate. A series of electropositive acceptors were then examined (Table S1 in SI). To our delight, N-methoxy pyridinium methosulfate 2a gave the borylation product 3a in 42% yield upon light irradiation (390 nm) with borane (entry 1, Table 1). Screening of bases proved NaHCO₃ was the optimal choice, leading to an enhanced yield of 72% for 3a (entries 2-7, Table 1). Reducing the amount of pyridinium salt resulted in a decreased yield of 60% (entry 8, Table 1). The wavelength of light is crucial. Illumination at 427 nm and 525 nm afforded 3a in only 48% and 7% yields, respectively (entries 9 & 10, Table 1). However, the addition of Ir(ppy)₃ or Eosin Y photosensitizers enhanced the yields to 78% and 60%, respectively, in the presence of blue (427 nm) or green (525 nm) LEDs (entries 11 & 12, Table 1). The absence of light provided only trace amount of 3a (entry 13, Table 1).

Table 1. Optimization of Reaction Conditions

<table>
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<tr>
<th>Entry</th>
<th>Light (nm)</th>
<th>Base (equiv)</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>390</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>390</td>
<td>NaHCO₃ (4)</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>390</td>
<td>NaHCO₃ (6)</td>
<td>72</td>
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<td>KHCO₃ (6)</td>
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<tr>
<td>5</td>
<td>390</td>
<td>Na₂CO₃ (6)</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>390</td>
<td>NaOAc (6)</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>390</td>
<td>NEt₃ (6)</td>
<td>N.D.</td>
</tr>
<tr>
<td>8</td>
<td>390</td>
<td>NaHCO₃ (6)</td>
<td>60</td>
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<tr>
<td>9</td>
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<td>60</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>NaHCO₃ (6)</td>
<td>trace</td>
</tr>
</tbody>
</table>

*Reactions were conducted by mixing 1a (0.1 mmol) with 2a (0.3 mmol) in 2 mL of CH₂CN in a closed flask, yield of isolated products. †2a (2 equiv) was used. ‡Ir(ppy)₃ (2 mol%) was added, ppy = 2-phenylpyridine. §Eosin Y (2 mol%) was added.

To understand the reaction pathway, several control experiments were carried out (Figure 2). Both coupling partners remained inert under light irradiation (Figures 2f & 2g). In addition, the individual solutions of 1a and 2a were almost colorless, but their mixture showed an obvious yellow color (Figure 2a). Then, UV-vis measurements of the above individual and mixed solutions were performed. A bathochromic shift from the individual solutions to the mixed solution was observed, indicating the existence of interaction that changed the photophysical properties of the reagents. Furthermore, †H NMR of 1a, 2a, and their mixtures with different 1a/2a ratios were collected. The α-H signal of pyridinium ring in 2a shifted upfield most significantly upon the addition of 1a (Figures 2b, S1 & S2 in SI), meanwhile the hydride signal of 1a shifted downfield obviously with the addition of 2a (Figures S3 & S4 in SI), suggesting the potential of pyridinium α-H and borane hydride as the interacting sites. The corresponding Job plot implied the 1:1 ratio of 1a/2a in the plausible EDA complex (Figure 2c & Table S2 in SI).

Fig. 2. Elucidation of EDA interaction. a) UV-vis spectra of 1a, 2a, and their mixture. b) †H NMR signals of pyridinium α-H in 2a with increased loadings of 1a. c) Job’s plot based on †H NMR data. d) Calculated surface electrostatic potentials of 1a and 2a. d) Proposed dihydrogen bond bridged EDA complex and its HOMO and LUMO. f-h) Control experiments.

To further illustrate the interaction, density functional theory (DFT) calculation was performed (see SI for the computational details). Figure 2d shows the surface electrostatic potentials of 1a and 2a. The area associated with two of the three B-H bonds in 1a possesses the most negative electrostatic potentials, while those associated with the N-methoxy pyridinium α-Hs and the center of the pyridinium ring of 2a possess the most positive electrostatic potentials. Thus, 1a is considered as the electron donor through the B-H bonds and 2a is viewed as the electron acceptor through the σ hole from the N-methoxy pyridinium α-Hs and the π hole from the center of the pyridinium ring. Our DFT results indicate that the EDA complex via a dihydrogen bond derived from the interaction.
Table 2. Scope of Substrates

<table>
<thead>
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<th>pyridinium salts:</th>
<th>boranes:</th>
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<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
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</table>

- Yield of isolated products.  
- Reactions were conducted in 3.0 mmol scale.  
- Reaction was conducted in 10.0 mmol scale.  
- Dimethylbenzylamine borane was used.

between B–Hδ and pyridinium α-Hδ+ (σ hole) is more stable by 1.6 kcal/mol than that via a B–H∙∙∙π interaction between B–Hδ and the pyridinium ring center (π hole) (Figure 2e & Table S3 in SI). The HOMO of the dihydrogen-bonded EDA complex is highly localized over the B–H bonds, while the LUMO is mainly contributed by the pyridinium π* orbitals (Figure 2e). These results indicated the possible electron transfer from B–H bonds to the pyridinium π* orbitals upon light excitation.

The time-dependent density functional theory (TDDFT) calculation showed that the vertical excitation energy (S0→S1) of the EDA complex is 3.2 eV (388 nm, Table S4 in SI), within the wavelength range of the LED lamps used in the experiment (Figure S7 in SI).

No borylation product was observed by using 2,6-dimethylpyridinium salt as the substrate at room temperature, whereas heating the mixture at 80 °C led to the product in only 5% yield (Figure 2h). These results suggested the importance
of dihydrogen bonding and the feasibility of B-H⋯π interaction.

The scope of the above dehydrogenative borylation was then investigated (Table 2). In general, all the three representative conditions (entries 3, 11 and 12, Table 1) competently afforded the target borylation products 3, although the yields were quite different in some cases. Alkyl and benzyl groups at the para-position of the pyridine ring were tolerated to give 2-borylated pyridines in up to 92% yields (3a, 3c-3g), and no obvious steric effects were observed. Cyclic substituents, including 3-, 4-, 5-, and 6-membered rings or adamantly ring, were compatible, leading to 3n-3r in moderate to very good yields. Substrates with phenyl, ester, ether, chloro, fluoro, nitro, and trimethylsilyl groups reacted with trimethylamine borane smoothly (3h-3l, 3s-3x), and no obvious electronic effects were observed. Among the various tolerated functional groups, ester, chloro, fluoro, nitro, trimethylsilyl, and alkenyl substituents could be readily used for further transformations. Pyridinium and 2-substituted pyridinium salts delivered only the ortho-borylated products (3b, 3y, 3aa, and 3ab), meanwhile 3-phenyl and 3-methyl pyridinium methosulfates also afforded only 2- and 6-borylated pyridines (3ac & 3ac', 3ad & 3ad'), implying the excellent ortho-selectivity (vide infra).

Fig. 3. Transformations of 3a. a) Oxone (4.0 equiv), acetone, r.t., 12 h. b) Cu(OAc)$_2$ (1.0 equiv), B(OH)$_3$ (2.0 equiv), 4 Å MS, CH$_2$CN, 80 ºC, 24 h. c) ArX (X= I, Br; 4.0 equiv), Pd[PPh$_3$]$_2$Cl$_2$ (5 mol%), CuCl (25 mol%), Cs$_2$CO$_3$ (4.0 equiv), THF/H$_2$O (19/1), 55 ºC, 48h.

We also examined the scope of tetracoordinated boranes. Both linear and cyclic amine boranes served as the suitable coupling partners, and the resultant pyridinyl boranes 3ae-3aj were achieved in moderate to good yields. If dimethylbenzylamine borane was employed, the unexpected product 3ak was isolated which might derive from the exchange reaction between the original product and 4-methylpyridine, given that no 3ak was observed from the reaction of 4-methylpyridine borane with pyridinium salt 2a (Table S1 in SI). Allyldimethylamine borane gave the product 3ai in relatively low yield with the detection of olefin hydroboration side product. Noteworthily, phosphate boranes worked well to produce 3an-3ap in up to 92% yields. However, N-heterocyclic carbene borane did not give the borylated product under standard reaction conditions (Table S1, SI).

Substrates bearing drug or bioactive molecules were also evaluated. For nicotinamide and myristyl nicotinate derived pyridinium salts, only 6-borylated products were isolated, due probably to the steric factors (3aq, 3av & 3aw vs 3ac vs 3ad). Furthermore, menthol, borneol, β-citronellol, and vitamin E derived substrates were also compatible to give the corresponding products 3ar-3au, indicating the versatility of the newly developed methodology. Large scale reactions were performed to give 3a in 70% (Condition 1) and 60% (Condition 3) yields, respectively, as well as 3an in 90% (Condition 1) yield.

To illustrate the synthetic utility of the developed methodology, transformations of 3a were performed (Figure 3). Treatment of 3a with oxone offered the 4-methyl-2-pyridone 5a quantitatively. The Chan-Lam esterification of 3a with 4-cresol gave the corresponding 6a in 82% yield. The Suzuki coupling of 3a with aryl halides afforded the target products 7a-10a in moderate to very good yields. Importantly, the facile introduction of pyridine moiety into drug and/or bioactive molecules, including coumarin 1, nimesulide, and pheniramine, were realized (11a-13a). This strategy also enabled the convenient synthesis of an abiraterone isomer 14a.

To shed light on the reaction mechanism, several control experiments were carried out. The addition of 3 equiv of 4-ethylpyridine showed little effect on the reaction (Figure 4b). No borylation of 4-ethylpyridine was observed, indicating the preferential attack of nucleophilic boron-centered radical at the more electron deficient pyridinium ion rather than neutral pyridine. Furthermore, the measured KIE (KIE = kinetic isotope effect) values $k_d/k_o$ of borane BH/BD and pyridinium α-CH/CD were 1.28 and 1.86 (Figure 4a), respectively, suggesting both cleavages might not be involved in the rate-determining step. The addition of radical scavenger to the reaction mixture inhibited the dehydrogenative borylation dramatically (Figure 4c). Furthermore, the light on-off experiment results showed the continuation of the reaction in the absence of light, suggesting a radical propagation pathway (Figure S6, SI).

Based on the aforementioned experimental results and DFT calculations (more will be discussed below), a plausible reaction mechanism is proposed for the photoinduced dehydrogenative borylation without photosensitizers (Figure 4d). Upon light illumination, intramolecular SET of the dihydrogen-bonded EDA complex occurs to release the boron radicalcation A, a neutral pyridine molecule and a methoxyl radical. The radical cation A undergoes deprotonation to deliver the active boron-centered radical B, which can also be generated via HAT between borane and a methoxyl radical. The nucleophilic B reacts with the pyridinium ion to form the radical intermediate C. The intermediate C then undergoes deprotonation and re-aromatization to deliver the final borylation product and regenerate the methoxyl radical. Methoxyl radical would then react with borane to start another cycle.

Figure 4d shows the DFT-calculated energy profile for the
proposed catalytic cycle starting from hydrogen abstraction reaction of methoxyl radical with borane. The barrier for the hydrogen abstraction was calculated to be 13.4 kcal/mol. The generated borane radical B then nucleophilically adds to pyridinium without a barrier to form the radical intermediate C (Figure S8 in SI). Deprotonation with the aid of pyridine occurs. The DFT results indicate that deprotonation is slightly more energy demanding (with a barrier of 15.2 kcal/mol) than the hydrogen abstraction. Clearly, the step for regeneration of methoxyl radical and release of borylated product is very facile with a very small barrier of 4.8 kcal/mol.

Figure 4e presents the DFT results explaining and clarifying the ortho regioselectivity observed experimentally (3b, 3y, 3aa, 3ab, 3ac & 3c, 3ad & 3d, 3aq, 3av, and 3aw). In theory, the borane radical B can also nucleophilically add to pyridinium’s meta and para positions (Figure S8 in SI). Our calculations show that the corresponding radical intermediates Cmeta and Cpara are only slightly less stable than C (Figure 4e). However, their barriers for deprotonation are significantly higher than their barriers for their conversion to C. In other words, even though the intermediates Cmeta and Cpara are formed, instead of undergoing deprotonation to give metal para/borylated products, it is expected that they would favorably isomerize to C followed by deprotonation to give the ortho/borylated product as observed experimentally.

The findings described above have important implications. In electrophilic substitution reactions of arenes, formation of Wheland intermediates often dictates the regioselectivity. In other words, the electrophilically-attacking aromatic ring generally takes time and is a slow process, and once a Wheland intermediate is formed, the followed deprotonation is normally very facile. In the case studied here, we found that the Wheland-like radical intermediates (C, Cmeta and Cpara) could isomerize to each other before deprotonation, leading to a situation that the site with the most favorable deprotonation determines the final substitution product (regioselectivity).

CONCLUSIONS

In summary, the readily available amine and phosphine boranes were first demonstrated as the competent donors to aggregate with the pyridinium acceptor through dihydrogen bond for generating new photoactive EDA complexes. Upon light irradiation, intramolecular SET of the EDA complexes gave the active boron-centered radicals for efficient dehydrogenative borylation. DFT calculations illustrated the deprotonation step rather than nucleophilic radical addition accounts for the very good ortho-selectivity in this pyridine borylation. This work presents a new strategy for generating boron-centered radical in the absence of photosensitizer or radical initiator. The results of this research not only pave an important avenue toward developing photoinduced EDA-complex-mediated borylation, but also provide a useful reference to control the regioselectivity for pyridine functionalization.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge.
Experimental procedures, DFT calculation details, and characterization of the products.

AUTHOR INFORMATION

Corresponding Author


