Boronyl borinic esters: preparation as B$_2$pin$_2$/secBuLi/TFAA adducts, structural insights and reactivity in Pd-catalyzed allylic borylation

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Abstract: Novel boronyl borinic ester I was generated by quenching of B$_2$pin$_2$/BuLi-ate complex with trifluoroacetic acid anhydride (TFAA) via ring-opening of 1,3,2-dioxaborolane molety on ater-boron. Detailed NMR investigations of B$_2$pin$_2$/BuLi-ate complex in solution and in solid state allowed to suggest its oligomeric nature in solids with only ater-boron involved in the oligomerization process. Initially formed on quenching with TFAA O-trifluoroacetyl pinacolate residue on borinic ester I undergo unusual intramolecular transesterification with carbonyl group of trifluoroacetyl forming orthoester moiety over hours at r.t. leading to boronyl borinic ester II. These reagent I/II solution was proved to be effective for borylation of (2-fluoroallyl)pyridinium salts that are highly base sensitive.

Introduction

Transition metal (TM) catalyzed borylation with diboron reagents is one of the most important strategies for preparation of various organoboronates. A large variety of diboron reagents is published to date including B$_2$pin$_2$ or other tetraalkoxy diborons with less hindered diols or B$_2$(OH)$_4$. Also, in the past few years, B$_2$cat$_2$ was found to be the reagent of choice in LED-induced or electrochemical borylations.

Nevertheless, B$_2$pin$_2$ is still the most frequently used borylation agent. B$_2$pin$_2$ is commercially available inexpensive crystalline solid that can be easily handled on an air and stored for years at r.t. without any special precautions. However, this stability also leads to lowered reactivity of B$_2$pin$_2$ in transmetalation processes. Sodium or potassium acetates are the most simple and widely used to enhance transmetalation Lewis bases. Recently, the superiority of potassium pivalate and 2-ethyl hexanoate on acetates was shown.

Alkoxydes are also well-known to facilitate boronyl transfer from B$_2$pin$_2$ to TM. Alkali metal alkoxydes can form ate-complexes with B$_2$pin$_2$, thus increasing its facilities for boronyl transfer reactions. In this way, many successful borylation reactions were developed, catalyzed by Pd, Ni, Cu, Zn, Fe, Mn, Co, and others. Also, B$_2$pin$_2$ ate-complexes with organolithium and organomagnesium compounds are known which was applied in a range of borylation and boronyl transfer reactions.

During our recent researches on the development of new synthetic approaches to biologically relevant fluoroalkenes,[9] we met the task of borylation of (2-fluoroallyl)pyridinium salts that was found to be challenging. These pyridinium salts are sensitive even to weak bases like alkali carbonates or tertiary amines and decompose with fluorne elimination.[9] Therefore, any alkoxydes could not be applied for B$_2$pin$_2$ activation in this case and the development of base-free activation strategy is required.

Recently, Aggarwal and co-workers[9] reported elegant method for activation of Bpin-group of allyboronates improving their reactivity toward ketones. It required transformation of Bpin-group into borinic ester by making ate-complex with secBuLi and quenching it with trifluoroacetic acid anhydride (TFAA). In the current work, we applied this strategy for activation of B$_2$pin$_2$ in order to generate more active and base-free borylation agent.

Supporting information for this article is given via a link at the end of the document.

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Scheme 1. Common diboron reagents and precursors for TM catalyzed borylation.
Results and Discussion

When the B₂pin₂-BuLi ate-complex solution generated at -82°C was warmed to r.t., a white precipitate was formed (Scheme 2). Such precipitation of ate-complexes of B₂pin₂ with organometallics was previously shown by many researchers. Solid ate-complexes were found to be poorly soluble in any solvent, but still enough to be characterized by NMR. We decided to compare structural features of solution form of B₂pin₂-BuLi ate-complex A (generated at -82°C) and solid form B if they are the same or not.

Both B₂pin₂-BuLi ate-complexes A (generated in solution at -82°C) and B (the solids precipitated at r.t.) demonstrate similar ¹¹B, ¹³C and ¹H,¹³C) characteristics. Note, solid reagent B was characterized by solid state NMR (ssNMR) under magic-angle spinning (MAS) that resulted in much broader lines and another ¹H,¹³C-correlation technique (i.e., HETCOR with ¹³C detection for solid vs. HSQC with ¹H detection for solution). Despite these differences, both A and B showed signals at ca. +5 ppm in ¹³C NMR that is typical for tetracoordinated ate-boron (Figure 1-B). Also, characteristic is the cross-peak between hydrogen and carbon in CH-group of -Bu. It has chemical shifts at +33 ppm for ¹³C and both A and B. For ¹H chemical shift is around 0 ppm for A (Figure 2-A). In solid state ¹H NMR for adduct B, chemical shift is ca. 1 ppm only. However, on the contrary to liquid state NMR, absolute chemical shift values in solid state ¹H NMR spectra are often very approximate due to various crystal lattice effects and challenging scale calibration. But as it can be seen from Figure 2-B, the key C-H cross peak is the most downfielded compared to methyl groups of pinacol residues. This is completely agreed with liquid state (¹H,¹³C)-edited HSQC for adduct A (Figure 2-A).

An important note was made when analyzing MAS NMR data of solid adduct B. ¹¹B Solid-state NMR spectra showed very broad lines that are almost independent on spinning rate. Such independence on spinning rate is unusual for low-molecular weight compounds; and therefore, this fact allowed us to assign solid complex B to be an oligomeric form (see SI for details). Moreover, ¹³C signals of quaternary carbons of pinacol residues are very similar to those observed in solution indicating that only ate-boron is involved into oligomerization process, while Bpin-group remains unchanged (Figure 1, D).

Solid state NMR is superior to usual liquid state NMR when correlation between two quadrupole nuclei in asymmetric environment is to be registered. In this way, we were succeeded to get good (¹¹B,¹³C)-correlation between both borons in solid B₂pin₂-BuLi adduct B (see SI for details). Finally, A could be assigned as monomeric form of B₂pin₂-BuLi ate-complex, while B — as oligomer. Notably, quaternary carbons of pinacol residue in ate-boron group gave 4 signals in ¹³C spectra both for A and for B. This might be attributed to 2 rotamers distinguishable due to either low temperature in solution NMR experiment or crystal lattice effects in ssNMR experiments. In each rotamer, 2 carbons are diastereotopic due to presence of asymmetric carbon in -Bu that lead finally 4 separated signals.
Figure 1. NMR monitoring of the αt-complexes A/B generation and quenching with TFAA.
Addition of TFAA into solution of A resulted in characteristic changes in $^{11}$B and $^{13}$C NMR spectra. Thus, in $^{11}$B NMR, broad signal at +5 ppm is replaced by new signal at +57 ppm that points to the cleavage of 1,3,2-dioxaborolane moiety of A forming O-trifluoroacetyl pinacol fragment of I (Figure 1-B). In $^{13}$C NMR this process causes splitting of the group of quaternary carbons of A, A into 2 distant signals at 91.4 and 80.2 ppm (Figure 1-D). Moreover, the formation of reagent I was confirmed by ESI-MS data that clearly showed a set of ions corresponding to I·OTFA$^-$ with variable amount of coordinated THF and CF$_3$CO$_2$Li.

Interesting changes were noted upon storage of the solution of I at r.t. In $^{11}$B no substantial changes could be detected besides the formation of the second diboron compound with similar boron environment. The most important changings were observed in $^{19}$F NMR where the signal at −76.8 ppm attributed to pinacol-TFA group substantially decreased while a new signal at −84.7 ppm appeared (Figure 1-C). This new signal gave good correlations in $^{19}$F,$^{13}$C-HMQC/HMBC 2D spectra allowing to determine that this new CF$_3$-group is attached to a carbon with a chemical shift value of 112.7 ppm (Figure 2-D). Such an upfield chemical shift is somewhat unusual for sp$^3$ carbon and could only be assigned to CF$_3$C(OR)$_2$ moiety. As the result, the new compound was assigned as II that is formed by cyclization of mono-O-trifluoroacetyl pinacolate residue.

The solution of boronyl borinic esters II generated in this way was next tested for borylation of 2-fluorocinnamyl pyridinium tetrafluoroborate 1a. Under model conditions (see Table 1), B$_2$pin$_2$, B$_2$cat$_2$ and B$_2$pin$_2$/tertBuOK adduct gave no trace of boroate 2a. When B$_2$pin$_2$/nBuLi was used, low yield of 2a was observed. Among various organometallics and quenching agents used for generation of boronyl borinic esters III, the combination of $^{19}$BuLi and TFAA showed superior results (Entry 6 vs. 5 and 7). Additional changing of the ligand from SPhos to CyJohnPhos and the Lewis base from NaOAc to CsOAc allowed additional improvement of the yield and regioselectivity (Entry 9 vs. 6 and 8).
Table 1. Diboron reagent screening for borylation of 1a[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diboron reagent</th>
<th>Deviation from standard conditions</th>
<th>Yield of 2a, (%)b</th>
<th>Yield of 3a, (%)b</th>
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<tbody>
<tr>
<td>1</td>
<td>B2pin2</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BuCat</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Bpin/CsOAc</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Bpin/Pd(dba)</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Bpin/BuLi/TFAA</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Bpin/CsOAc</td>
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<td>7</td>
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<tr>
<td>8</td>
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<td>—</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Bpin/BuLi/TFAA</td>
<td>—</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Reaction procedure: To the 1a (0.10 mmol), C6H6 (5–10 mg, internal standard), a solution of Pd(dba)2 (2.5 mol %) and the Ligand (5 mol %) in THF (0.50 mL) was added, followed by a solution of Diboron reagent (1.5 equiv.) in THF (0.50 mL). After 24 h at 28°C the mixture was analyzed by GC; [b] Calibrated GC yields are given to the nearest 5%.

Table 2. Preparative synthesis of allyl boronates[b]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allyl electrophile</th>
<th>Allyl boronate</th>
<th>Yield, (%)b</th>
<th>Z/E</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>Ph'PY'BF4-</td>
<td>83</td>
<td>95/5</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph'Py'BF4-</td>
<td>78</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>&quot;CyH3Ph&quot;Py'BF4-</td>
<td>&quot;CyH3Ph&quot;Py'BF4-</td>
<td>68</td>
<td>95/5</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph'Py'BF4-</td>
<td>90</td>
<td>&gt;20/1</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Me'Py'BF4-</td>
<td>53</td>
<td>&gt;20/1</td>
</tr>
</tbody>
</table>

[b] Reaction procedure: To the 1a (0.25 mmol), a solution of Ph=Ph (2.5 mol %) and the Ligand (5 mol %) in THF (1.25 mL) was added, followed by a solution of I (1.5 equiv.) in THF (1.25 mL). After 24 h at 28°C, the reaction mixture was isolated by column chromatography. Moreover, it was necessary to check if borylation conditions with I/II are suitable for isolation of pure product or not. Indeed, we were lucky to prove this by isolation of 3 examples of almost pure allyl- and allyl substituted boronates 2a-c in good yields with high Z/E-selectivity (Table 2, Entries 1–3).

Additionally, non-fluorinated cinnamyl acetate could be successfully borylated to corresponding cinnamyl boronate 2d (Table 2, Entry 4). Crotyl benzoate also reacted, but the crotyl boronate 2e obtained was contaminated with 20 w/w % of starting benzoate (Table 2, Entry 5). This experiment shows one important advantage of allyl pyridinium salts compared to any other allylic electrophiles — as being ionic compound, allyl pyridinium salt could be easily separated from the target allyl boronate if the reaction did not reach completeness.

Conclusion

In summary, we have developed new diboron compound — boronyl borinic ester I, generated as Bpin=Bpin/BuLi/TFAA adduct. Detailed NMR and ESI/MS investigations supports well the formation of reagent I upon quenching Bpin=Bpin/BuLi aecomplex with TFAA. Moreover, they revealed the “decomposition” of I into II in solution during storage at r.t. Synthetic utilities of I/II in Pd-catalyzed borylation were demonstrated on synthesis of (2-fluoroallyl)boronates from base-sensitive (2-fluoroallyl)pyridinium tetrafluoroborates. It is not yet clear, but preliminary data indicate that the reactivity of reagents
I and II might be different depending on substrate, thus, making it necessary to tune not only a ligand but also I/II ratio in real synthetic applications. Nevertheless, the reported here solution of boronyl borinic ester I/II proved to be promising mild and base-free borylation reagent.

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Keywords: Diboron reagents • Borylation • Boron ate-complexes • Allyl boronates • Solid-state-NMR


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Novel class of diboron reagent — boronyl borinic ester — was developed that were generated as $\text{B}_2\text{pin}_2$/secBuLi/TFAA adducts. Detailed NMR with solid-state 2D NMR techniques and ESI-MS investigations were used to get structural insights of these new reagent. The new boronyl borinic esters were proved to be promising for allylic borylations of base-sensitive substrates.