



Base-Free Cross-Coupling

Phenoxy-Dialkoxy Borates as a New Class of Readily Prepared **Preactivated Reagents for Base-Free Cross-Coupling**

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Abstract: One of the most useful chemical transformations of organoboronic acids is the Suzuki-Miyaura cross-coupling reaction. Although it has vast application, it possesses some limitations: boronic acids can be difficult to quantify accurately due to their tendency to form oligomeric anhydrides and they must be activated under basic conditions. To address these problems,

a new class of boronic acid derivatives is described. Phenoxydialkoxy borates are prepared under mild conditions and show good solubility in common organic solvents. These adducts can be used in base-free metal-catalysed cross-coupling reactions, including orthogonal reactions with MIDA boronates and trifluoroborates.

Introduction

Several types of organoboron compounds can be employed as nucleophilic carbon-based reagents in transition metal-catalyzed processes, such as the popular Suzuki-Miyaura crosscoupling reaction.^[1] Typically, the nucleophilic nature of the carbon-boron bond is revealed upon in situ formation of a tetrahedral boron species during the transition-metal-catalyzed reaction. Although many variants of this activation strategy have been exploited successfully, most notably with boronic acids, it still possesses limitations: 1. Often the tetrahedral boronate ion is a transient entity that is not isolated and requires strongly basic conditions in order to form; 2. Some boronic acids are sensitive to oxidation or protodeboronation, therefore they require careful handling and storage; 3. Boronic acids tend to exist as mixtures containing various proportions of dehydrated anhydrides, such as as the 6-membered boroxines, which makes it challenging to determine their accurate stoichiometry. To address these problems, a number of 'masked' boronic acids or preactivated adducts have been proposed (Figure 1). For example, air- and bench-stable trifluoroborate salts $M[RBF_3]$ (M = K or NR₄) are solids that are easy to prepare, handle, and guantify.^[2] On the other hand, they tend to display low solubility in many common organic solvents.^[3] Use of aqueous base is still required for their activation and coupling, and corrosive HF is released in the coupling process. Likewise, MIDA boronates are a stable class of protected boronic acid derivatives but they also require the use of a stoichiometric quantity of base as part of a slow-release mechanism.^[4,5]

In 2006, Cammidge and co-workers reported the preparation and characterization of discrete trihydroxy borate sodium salts $(RB(OH)_3^{-} Na^{+})$ as isolable and stable reagents for use in the Classic Suzuki-Miyaura cross-coupling with boronic acids

R ¹ –B(OH) ₂ 1	+	R ² –X	Pd(0), aq. base ► R ¹ -R ²	 Boronic acid may be sensitive to air and protodeboronation Formation of oligomeric anhydrides Requires aqueous base
Cross-coupling with trifluoroborates				
R ¹ –BF ₃ M	+	R ² –X	Pd(0) → R ¹ -R ²	Easily prepared Limited solubility in common organic solvent Release HF as corrosive side-product

Cross-coupling with Miyaura trialkoxyborates

1

 $R^2 - X$ i. refluxing PhN Pd(0) OH R¹-B(OH)₂ $R^1 - R^2$ ii. KOH. heat



Figure 1. Organoboron compounds for Suzuki-Miyaura cross-coupling reaction.

concept of direct base-free Suzuki-Miyaura cross-coupling.^[6] The absence of base is advantageous, however it is not known whether trihydroxyborate salts are orthogonal with other boron adducts such as trifluoroborate salts. Subsequently, Miyaura and co-workers reported the preparation and characterization of cyclic trialkoxyborates that can also be employed directly in base-free Suzuki-Miyaura cross-couplings and other C-C bondforming reactions (Figure 1).^[7,8]

Whereas the reaction conditions for the cross-coupling are mild, the synthesis of the requisite trialkoxyborates from free boronic acids requires high temperatures (refluxing toluene) and a strong base (KOH), which is not ideal for thermosensitive and highly functionalized boronic acids. Consequently, there is

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a need for new types of stable, preactivated adducts that can be prepared with ease under mild reaction conditions, and that are easy to handle and soluble in most common organic solvents. Herein, we report the design, facile synthesis, and crosscoupling of a new class of phenoxy-dialkoxy adducts (**3**) of organoboronic acids (**1**) and triol **2** (Figure 1). These adducts form under ambient conditions, at a significantly lower temperature and with a weaker base compared to the conditions required for the preparation of trialkoxyborates.

Results and Discussion

Triol 2 was selected because it possesses several key features for the purpose of this application: 1. It embeds a hindered 1,2alkanediol group that demonstrates a high affinity for boronic acids; 2. It includes a phenoxy moiety which, with a lower pK_a than a regular aliphatic alcohol, will allow a more facile deprotonation and concomitant guaternization of the boron atom; 3. The aromatic ring can help increase the solubility of the resulting adducts in organic solvents. Triol 2 is easily synthesized from phenol as shown in Scheme 1. To this end, ortho-hydroxyalkylation with EtO2CCHO (ethyl glyoxalate) furnishes intermediate 4, which is reacted with MeMgCl to give the desired triol 2.^[9] The preparation of phenoxy-dialkoxy adducts is also straightforward, and the conditions were optimized using phenylboronic acid (Scheme 1). Thus, the boronic acid is condensed with triol 2 at room temperature in acetone, followed by addition of potassium carbonate to yield the desired triolborate 3a in high yield. The reaction is presumed to proceed through the formation of a boronic ester intermediate (e.g. 5a), which is then converted into the corresponding phenoxy-dialkoxy borate by deprotonation of the phenol, and concomitant cyclization with quaternization of the boron atom.



Scheme 1. Preparation of triol **2** and model phenoxy-dialkoxy potassium borate **3a**.

The potassium borate **3a** was interchanged into the corresponding ammonium salt **6a**, which was recrystallized to provide crystals suitable for X-ray crystallographic analysis (Figure 2).^[10] In **6a**, the length of the B–O bonds is 1.40–1.53 Å and 1.60 Å for the C–B bond. As expected from the loss of conjugation with the boron atom, these distances are significantly longer than the values observed in boronic acids (1.36–1.37 Å for

B–O, and 1.57 Å for C–B)^[11a] and pinacol boronic esters (1.31 Å for B–O, and 1.57 Å for C–B).^[11b] The tetrahedral nature of the boron atom is clearly depicted in the ORTEP diagram: all of the C–B–O and O–B–O bond angles are relatively close to the expected value of 109 °. Quaternization of the boron center can also be inferred by NMR spectroscopy: ¹¹B-NMR analysis reveals a characteristic broad signal with upfield chemical shift, ca. $\delta = 7.5$ ppm, typical of a negatively charged tetrahedral boron species.



Figure 2. Preparation and X-ray crystal structure (ORTEP representation) of tetrabutylammonium borate salt ${\bf 6a}$.

To test the generality of the formation of phenoxy-dialkoxy borates, a prototypical set of arylboronic acids **1a–1e** with various electronic and steric characteristics were condensed with triol **2** at room temperature in acetone, followed by addition of potassium carbonate to yield the desired triolborate salts **3a–e** in high yields (Scheme 2). Most of the adducts **3a–3e** are solids^[12] that can be recrystallized with ease from diethyl ether. They are soluble in most organic solvents with the exception of halogenated hydrocarbons (i.e. dichloromethane and chloroform).



Scheme 2. Preparation of a representative set of aryl phenoxy-dialkoxy borate salts **3a-3e**.

The application of phenoxy-dialkoxy boronates in base-free Pd-catalyzed Suzuki-Miyaura cross-coupling was assessed using as model substrates the phenyl borate salt **3a** and *p*-iodoanisole (7) (Table 1). The formation of the expected coupling product 8a was optimized by examining the effect of temperature and solvent using Pd(OAc)₂ as the pre-catalyst. From the results of Table 1, it is apparent that the reaction does not proceed at room temperature and requires gentle heating to 45 °C in order to reach completion within 18 hours when using triphenylphosphine as the ligand. A variety of solvents are tolerated, making this reaction suitable for both hydrophobic as well as more polar substrates (entries 5-9). As expected, the presence of water is crucial for a successful outcome.^[7] Presumably, partial hydrolysis to a monohydroxyborate intermediate is required for an efficient transmetallation step. Initially, PPh₃ was used as the ligand and since it gave satisfying results, commercially avail-





able $Pd(PPh_3)_4$ was selected as the catalyst for the substrate scope study.

Table 1. Optimization of the model cross-coupling reaction between phenoxy-dialkoxy borate ${\bf 3a}$ and ${\bf 7}.^{\rm [a]}$



[a] Reaction conditions: **7** (0.1 mmol), **3a** (0.12 mmol), Pd(OAc)₂ (5 mol%), ligand (11 mol%), solvent (0.10 M), time (18 h). [b] Isolated yields of **8a** after flash chromatography on silica gel.

With optimized cross-coupling conditions in hand, different aryl and alkenyl halides were evaluated. Aryl halides with electron-withdrawing or electron-donating substituents both led to a successful cross-coupling with the phenoxy-dialkoxyborate **3a** (Table 2). Notably, more congested ortho-substituted aryl halides (entry 2 and entry 5) afforded the expected biphenyl products in good yields. Cross-coupling with alkenyl halides and pseudo-halides was also examined and the corresponding products were isolated in good yields (entry 7 and 8).

The same procedure was tested in the cross-coupling of a variety of aryl borates **3b**–**e** with bromobenzene (Table 3). The expected biphenyl products were isolated in good yields. Remarkably, the more sterically hindered ortho-substituted aryl borates (entry 2 and 3) successfully underwent the cross-coupling reaction in very good yields.

One attractive attribute of this new class of adducts of boronic acids is their potential chemical orthogonality with other boron containing reagents.^[13] With this view in mind, we turned our attention to the para-bromoaryl MIDA boronate **9** and trifluoroborate salt **11**, with the goal of evaluating their chemoselectivity with the phenoxy-dialkoxy borates. To our satisfaction, bifunctional substrates **9** and **11** underwent the crosscoupling reaction with **3a** uneventfully, affording the desired biaryl boron adducts **10** and **12** in good yields (Scheme 3). The slower hydrolysis rate of the MIDA boronate and the requirement of a base to activate the trifluoroborate moiety enables chemoselective cross-coupling conditions where these groups remain unreactive throughout these transformations.

Lastly, with the goal of expanding the application of these new phenoxy-dialkoxy borates to other transition metal-cataTable 2. Substrate scope study with aryl and alkenyl halides.^[a]



[a] Reaction conditions: **3a** (0.12 mmol) aryl–X or alkenyl-halide (0.10 mmol), Pd(PPh₃)₄ (5 mol%), solvent DMF/H₂O (5:1 v/v, 0.5 m). [b] Isolated yield after flash chromatography on silica gel. [c] 18 h reaction time. [d] Monitored by TLC.

Table 3. Cross-coupling reaction with different borate adducts 3b-e.[a]



[a] Reaction conditions: **3b–e** (0.12 mmol.) bromobenzene (0.10 mmol), Pd(PPh₃)₄ (5 mol%), solvent DMF/H₂O (5:1 v/v, 0.5 M), 18 h. [b] Isolated yields after flash chromatography on silica gel.







Scheme 3. Examples of orthogonal cross-coupling with MIDA ate complex 9 and trifluoroborate 11.



Scheme 4. Example of rhodium-catalyzed 1,4-conjugate addition.[14]

lyzed transformations, we tested the suitability of aryl borate **3a** in a base-free rhodium catalyzed 1,4-conjugate addition.^[14] In the event, the reaction with *trans*-methylcinnamate (**13**) proceeded smoothly under mild conditions, affording the expected biphenyl product **14** in good yield (Scheme 4).

Conclusions

In summary, we have developed a new class of phenoxy-dialkoxy borate adducts that can be employed as coupling partners in base-free Suzuki–Miyaura cross-coupling reactions. The ease of preparation using a milder base at room temperature along with their solubility in many of the commonly used organic solvents makes these phenoxy-dialkoxy adducts an advantageous alternative for base-sensitive substrates. Moreover, this methodology enables chemoselective cross-coupling reactions with other boron reagents such as MIDA esters and trifluoroborate salts. Finally, it has also been demonstrated that such boron complexes can be used for other base-free metal-catalyzed reactions, such as the rhodium-catalyzed 1,4-conjugate addition. We are planning to further expand the scope and applications of this new and complementary class of boron reagents.

Experimental Section

General synthesis of aryl triolborate 3a–3e. Triol **2** (364 mg, 1.00 equiv., 2.00 mmol) and the appropriate boronic acid **1a–1e** (1.10 equiv.) were dissolved in acetone (4 mL, 0.50 M). The reaction mixture was stirred at room temperature for 8 h. Then solid K₂CO₃ (829 mg, 3.00 equiv., 6.00 mmol) was added in one portion. The reaction mixture was stirred for a further 18 h at room temperature. The suspension was then filtered through a small plug of Celite[®] (ca. 50 mg) and rinsed with acetone. The filtrate was concentrated under vacuum to afford the desired aryl triolborate salt (see Sup-

porting Information for specific examples and characterization data).

Conflict of interest

The authors declare no conflict of interest.

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