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Aryl Trihydroxyborates: Easily Isolated Discrete Species Convenient for Direct Application in Coupling Reactions

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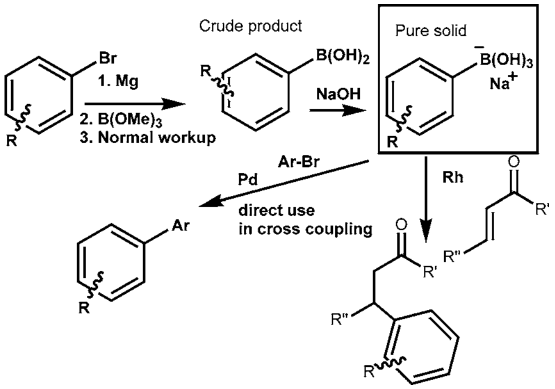
ABSTRACT



A conceptually and practically simple alternative approach to the use of arylboron species as the organometallic component in cross-coupling processes is described whereby trihydroxyborate salts are isolated and directly employed. The protocol derives practical benefit from the ease and convenience of the isolation and subsequent use of the discrete borate salts, eliminates the need for additional base, and aids the use of correct reaction stoichiometry.

The use of aryl boronic acids as cross-coupling partners in palladium and other transition metal catalyzed (e.g., Suzuki−Miyaura) reactions has received enormous interest particularly over the last 10−20 years.[1] The mechanisms of these reactions can vary subtly.[2] In a conventional Suzuki−Miyaura cross-coupling reaction (Scheme 1), aryl halide (or triflate) can be considered to undergo oxidative addition to Pd(0). The second key step in the catalytic cycle involves transfer of the second aryl residue from aryl boronic acid to the arylpalladium intermediate. Aryl boronic acids do not themselves participate in such transmetalation processes. To transmetalate, the boronic acid (or boronate ester) needs to be activated by reaction with a nucleophile to form the corresponding borate complex.[3] Conventionally, this occurs in situ with addition of a suitable base/nucleophile to the

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[‡] GSK.

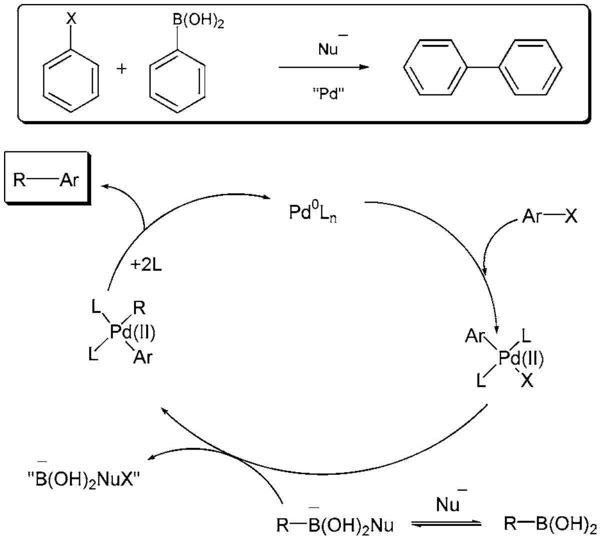
[1] Reviews on the Suzuki reaction include: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (c) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

[2] See, for example: (a) Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. *Organometallics* **2006**, *25*, 54. (b) Goossen, L. J.; Koley, D.; Hermann, H.; Thiel, W. *Chem. Commun.* **2004**, 2141. (c) Armatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314. (d) Armatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. (e) Cammidge, A. N.; Crepy, K. V. L. *J. Org. Chem.* **2003**, *68*, 6832.

[3] Braga, A. A. C.; Morgen, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298.

10.1021/ol061564w CCC: $33.50

Scheme 1. Suzuki−Miyaura Coupling Reaction and Simplified Catalytic Cycle

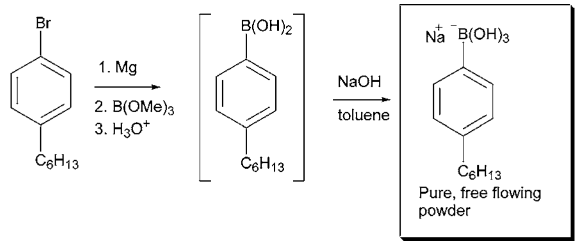


reaction mixture.[4] An alternative strategy has been occasionally employed whereby the "activated" boronate ester is formed, typically by quenching an organolithium intermediate with trialkyl borate, and used.[5] Recent innovations involve the use of trifluoroborate[6] and tetraarylborate[7] salts as the coupling partners in such reactions.

In most cases, particularly on a laboratory scale, these conventional reaction sequences (formation and isolation of boronic acid and subsequent reaction with an added base nucleophile) pose few problems. However, this sequence can present well-known problems, especially when more elaborate (often precious) aryl boronic acid derivatives are required for use. Hydrophobic boronic acids can be difficult to isolate, usually requiring chromatography. The materials tend to form waxy solids comprising a variable and unpredictable mixture of the parent boronic acid and anhydrides. Formation of the latter does not affect subsequent reactions but prohibits convenient, reproducible calculation of the reaction stoichiometry, important for large/production scale applications.

The above drawbacks were routinely encountered in our laboratories and led us to investigate a conceptually and practically simple solution based on isolation and direct use of trihydroxy borate salts. Hexylphenylboronic acid/boronate was selected as the substrate for this investigation. This boronic acid can be easily prepared, but its isolation is not convenient due to its hydrophobic/amphiphilic character. However, a simple modification to the experimental protocol permits convenient isolation of the discrete "active" borate salt suitable for direct use in cross-coupling reactions. The boronic acid is prepared in the usual manner, from 4-bromo-1-hexylbenzene via formation of the Grignard reagent followed by quenching with trimethylborate. The reaction mixture is subjected to normal aqueous workup and concentrated. The residue is dissolved in toluene and treated with a concentrated solution of sodium hydroxide. A precipitate of the corresponding sodium trihydroxyarylborate salt forms immediately (sodium hydroxide is added dropwise until no further precipitate forms) and can be isolated by filtration as a free-flowing, pure colorless powder (Scheme 2). The ^{1}H NMR spectrum clearly indicated that a single, discrete species was formed. Further evidence for formation of the borate salt came from ^{11}B NMR which shows a single resonance at 5.89 ppm, characteristic of tetrahedral boron species.[8]

Scheme 2. Preparation and Isolation of "Activated" Borates[a]



[a] After preparation of boronic acid by conventional procedures, the crude product is taken up in toluene. Concentrated NaOH is added until no further precipitate is formed. The pure borate salt is isolated by filtration.

The general applicability of this protocol for isolation of related borate salts has been investigated using a series of prepared and commercially available boronic acids. In all cases, the sodium trihydroxyarylborate salts (shown in Table 1 and in Supporting Information) were easily and conveniently isolated as described above in near quantitative yield. Crystals were grown (from water) of the sodium 4-methoxyphenylborate salt, and the X-ray crystal structure (the first of such a species) is shown in Figure 1. The $[Na(H_2O)_5]_n$ units are linked in hydrogen-bonded sheets in the crystal. The anionic p-MeOC$_6$H$_4$B(OH)$_3$ units form links between the sheets, with the borate groups forming part of the hydrogen-bonding network in one sheet and the methoxy O atom acting as an acceptor group in the neighboring sheet. The sodium atom is coordinated by six water molecules in an approximately octahedral pattern. Every hydrogen of the water molecules is involved in an O−H···O hydrogen bond. Two of the borate OH groups are also hydrogen-bond donors, and the three borate O atoms are acceptors. Other salts, as prepared, are similarly isolated as hydrates. Their water content is easily determined using NMR spectroscopy in CD$_3$OD by integration. Alternatively, anhydrous salts were obtained by drying in a desiccator overnight.

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(4) Formation of trihydroxyboronates in solution has been accepted for many years, but the species have been only rarely isolated: Fields, C. L.; Doyle, J. R. *Thermochim. Acta* **1974**, *8*, 239.

(5) (a) Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1994**, *59*, 6501. (b) Frohn, H.-J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *J. Fluorine Chem.* **2003**, *122*, 195.

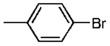
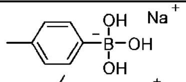
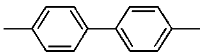
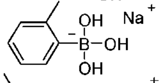
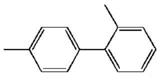
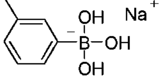
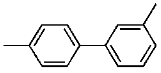
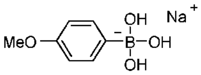
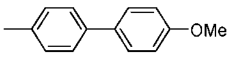
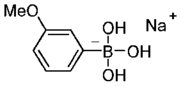
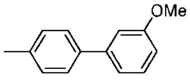
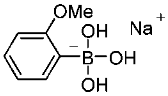
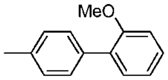
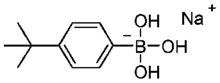
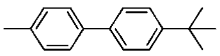
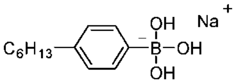
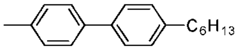
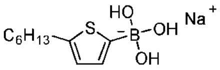
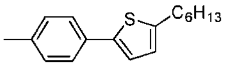
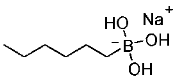
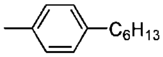
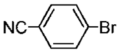
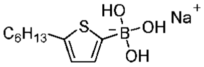
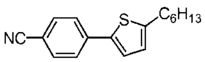
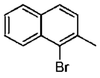
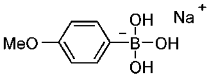
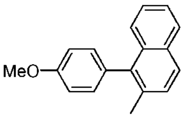
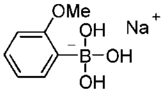
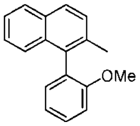
(6) (a) Darses, S.; Michaud, G.; Genêt, J.-P. *Tetrahedron Lett.* **1998**, *39*, 5045. (b) Molander, G. A.; Figueroa, R. *Aldrichchimica Acta* **2005**, *38*, 49. (c) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313.

(7) Lu, G.; Franzen, R.; Zhang, Q.; Xu, Y. J. *Tetrahedron Lett.* **2005**, *46*, 4255.

(8) Nakazawa, I.; Suda, S.; Masuda, M.; Asai, M.; Shimizu, T. *Chem. Commun.* **2000**, 879.

Table 1. Suzuki−Miyaura Couplings Employing Isolated Borate Salts

$$Ar\text{-}B(OH)_3Na \quad + \quad Ar'\text{-}Br \xrightarrow[\text{toluene, reflux}]{PdCl_2(dppf)} Ar\text{-}Ar'$$

aryl bromide	borate salt	product	yield[a]
			83
			81
			80
			90
			79
			79
			80
			80
			85
			59
			85
			90
			58

[a] Yields are of isolated material.

The main motivation for isolating these borate salts was, however, their subsequent direct use in Suzuki−Miyaura (and other) reactions. It became immediately apparent that the borate salts can indeed be used directly and conveniently in Suzuki−Miyaura coupling reactions. As expected, the reactions do not require addition of further base/nucleophile, which is itself a significant advantage. The reactions proceed cleanly under standard conditions, and (unoptimized) yields are very good (typically >90% by NMR spectroscopy of the crude reaction product). Representative examples, shown in Table 1 (further examples in Supporting Information), demonstrate that this "base-free" protocol is widely applicable. Extension to alkylborates is straightforward (*n*-hexyl is shown as an example) providing a shelf-stable, solid alkyl anion equivalent for cross-couplings. It can be seen that electron-rich and heteroaromatic borates are readily employed in this protocol, and the reaction between thiophenylborate and bromobenzonitrile further demonstrates the potential to expand substrate tolerance to include examples with base-sensitive functional groups. The reactions shown in the table were performed using the salts as isolated (1.5−2 equiv). However, a distinct advantage to isolating and employing discrete borate salts stems from the ability to calculate and use more precise stoichiometry (boronic acids themselves are typically contaminated with varying proportions of their respective anhydrides). The sodium borate salt was formed from 2-methoxyphenylboronic acid, as described above, and dried in a desiccator overnight to give the anhydrous salt. This salt (1.1 equiv) was employed in a standard Suzuki−Miyaura coupling with 4-bromotoluene and gave >95% conversion to the corresponding biphenyl. Sodium salts have been investigated most extensively, but preliminary experiments indicate that the corresponding potassium and barium salts can be similarly prepared and employed (Supporting Information).

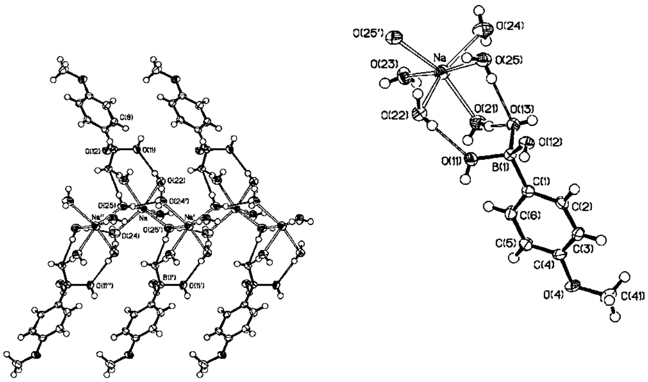


Figure 1. First X-ray crystal structure of an aryl trihydroxyborate salt ($p\text{-}MeOC_6H_4B(OH)_3Na$).

Activated boronic acids/borates are finding application in transition metal catalyzed reactions beyond Suzuki−Miyaura cross couplings. To prove the broader application of these isolated, active borates, we selected the rhodium-catalyzed conjugate addition reaction[9] between the boronate salt prepared from 4-tolylboronic acid and cyclohexenone.[10] Once again, the direct reaction proceeded cleanly and smoothly to give a good yield of the conjugate addition product (Scheme 3).

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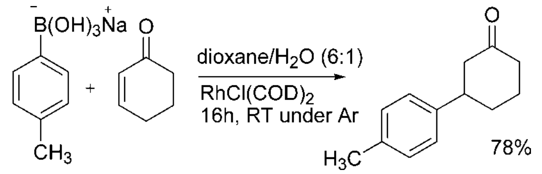
[9] (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

[10] Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.

Scheme 3. Rhodium-Catalyzed Conjugate Addition Employing an Isolated Boronate Salt



In conclusion, a conceptually and practically simple alternative approach to the use of arylboron species as the organometallic component in catalyzed processes has been demonstrated.[11] The protocol derives practical benefit from the ease and convenience of the isolation and subsequent use of the borate salts. Elimination of the base from the catalyzed reaction has both economic benefits and the potential to expand substrate tolerance.

Acknowledgment. We would like to thank EPSRC, GSK, and Merck Ltd. for financial support and the EPSRC National Mass Spectrometry Service Center (Swansea).

Supporting Information Available: X-ray structural data, experimental procedures, and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL061564W

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[11] Patent applied for.