Arylboronates

DOI: 10.1002/anie.201003191

Expanding the Limits of Organoboron Chemistry: Synthesis of Functionalized Arylboronates**

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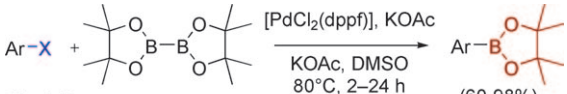
arenes · boron · boronates · cross-coupling · palladium

Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

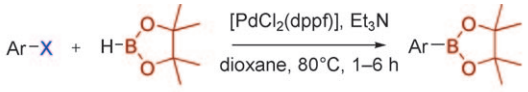
Arylboronates (arylboronic acid esters) have become a useful building block in organic chemistry because of the variety of processes in which they can take part.[1] They are an excellent alternative to aryl boronic acids in rhodium-, ruthenium-, nickel-, and palladium-catalyzed (Suzuki–Miyaura reaction) cross-coupling reactions.[2] This great versatility in scope and applicability in different fields including fine chemicals, polymer chemistry, and the pharmaceutical industry justify the crucial role of arylboronates in the synthesis of aromatic compounds. Indeed, arylboronates can be assembled easily with high efficiency under a variety of reaction conditions. Nevertheless, the potential use of arylboronates in the construction of complex molecules resides in the presence of a diverse and adequate number of functionalities; because of this, the synthesis of functionalized arylboronates constitutes a challenging research area.

Arylboronates are accessible from the parent boronic acids—that can be prepared by reaction of trialkyl borates with Grignard or lithium reagents—by treatment with alcohols or diols in organic solvent.[3] The reaction can be carried out in a one-pot procedure: although initial steps should be performed at low temperature, otherwise mixtures of boronic esters and undesired borinic acid derivatives are obtained. In some case, however, equilibration of the crude reaction mixture at 50 °C allows preparation of arylboronates on a multikilogram scale.[4] The drawback associated with the use of organometallic reagents are circumvented by the development of the Hosomi–Miyaura borylation (Scheme 1),[5] that is, the direct reaction of an aryl iodide (or bromide) with diboron reagents, typically bis(pinacolato)diboron, in the presence of Pd^0 as a catalyst and a base. In the case of less reactive bromobenzene derivatives bearing electron-rich substituents the reaction takes 24 hours to complete. Although it can be accelerated by microwave irradiation other reaction conditions have been studied.[6] By changing the catalytic system to $[Pd(dba)_2]/PCy_3$ (Cy = cyclohexyl, dba = *trans,trans*-dibenzylideneacetone) and solvent to 1,4-dioxane the reaction proceeds in 6 hours with electron-rich aryl electrophiles. Other catalytic systems including $[PdCl_2(PPh_3)]$ and $[Pd_2(dba)_3]$ have been studied but the better catalyst in terms of cost and catalyst recovery is $Pd(OAc)_2$, which can be used in the absence of any ligand.



Scheme 1. Hosomi–Miyaura synthesis of arylboronate derivatives. DMSO = dimethyl sulfoxide, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, mesityl = 2,4,6-trimethylphenyl.

One of the major advantages of the Hosomi–Miyaura borylation is its functional-group compatibility. A great variety of aryl halides bearing diverse functional groups can be utilized as substrates. Higher synthetic versatility is achieved by using dialkoxyboranes as borating agents. Only a few dialkoxyboranes are commercially available, but the most widely used is pinacolborane. Direct borylation of aryl halides or triflates with that reagent in the presence of a Pd catalyst and Et_3N gives rise to arylboronates bearing a number of functional groups such as carbonyl, cyano, and nitro groups (Scheme 2).[7] The Et_3N plays a crucial role not only by avoiding undesired dehalogenated hydrocarbons but also by favoring the C–B bond formation. The reaction proceeds in ionic liquids and shorter reaction times are observed. Aryl boronates are obtained in good purity directly from the reaction mixture by extraction, and the solution of the catalyst in the ionic liquid can be recycled. Sterically hindered phenyl bromides with substituents in the *ortho* position to the halogen atom are converted into arylboronates by using the oxidation-stable ligand dpephos (bis(*o*-diphenylphosphanylphenylether). The



Scheme 2. Direct borylation with pinacolborane. Tf = trifluoromethanesulfonyl.

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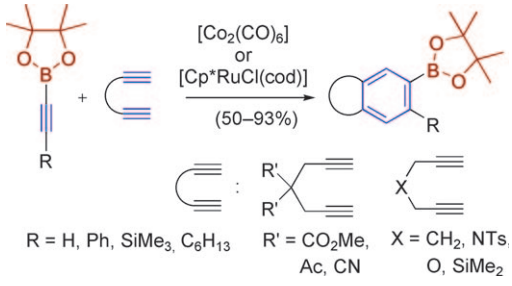
[**] We thank the Government of Aragon and Spanish Ministry of Science and Education (MEC CTQ2007-67532-CO2-01) for their support of our programs.

use of *t*Bu-dpephos as a ligand expands the scope of the reaction to both aryl bromides and chlorides, thus enabling the synthesis of a variety of *ortho*-, *meta*-, and *para*-substituted electron-rich and electron-poor arylboronates.[8] The coupling reaction of pinacolborane with aryl iodides under catalysis by CuI in the presence of NaH allows preparation of arylboronates at room temperature.[9] Arylboronates are prepared from aryl iodides or bromides through intermediate arylzinc species, which undergo transmetalation with bromocatecholborane.[10] In the case of the aromatic ring substituted with electron-rich groups the less reactive chlorocatecholborane can be used. The process is quite tolerant with several functionalities placed in different positions on the arene ring.

The high stability of arylboronates makes possible further functional group interconversions that expand considerably the synthetic utility of those compounds. It is possible to modify functionalities directly attached to the aromatic ring without altering the boronate unit, thus leading to complex and advanced synthetic intermediates.[11] Arylboronates are also compatible with the preparation of organometallic species.[12] Magnesiated aryl and heteroaryl boronates are prepared through iodine–magnesium exchange. These compounds expand considerably the possibility of preparing a huge number of functionalized boronic acid esters for further use in cross-coupling reactions. The method is extended to indole, pyridine, and quinoline derivatives of high synthetic importance. All these polyfunctional boronic acid esters are used in Suzuki coupling, thus demonstrating high functional group compatibility. Brominated arylboronates are used in lithium–halogen exchange reactions by using lithium isopropoxide as a protecting group. The resulting isopropoxide protected boronate is ready for metalation and further use in reactions with electrophiles. The protected intermediate can also be generated directly from dibromoarenes by reaction with isopropylpinacolborate and *tert*-butyllithium. Adequately functionalized arylboronates allow the generation of borylbenzynes that undergo cycloaddition reactions with both furan and pyrrole derivatives to afford fused tricyclic arylboronates of high synthetic importance.[13] The cyclotrimerization of alkynes represents a completely different approach, which focuses on the formation of the aromatic ring (Scheme 3). The one-pot formation of fused arylboronates by [2+2+2] cycloaddition of alkynylboronates to α,ω-dyines mediated by either $[Co_2(CO)_8]$ or [Cp*RuCl(cod)] shows an acceptable functional groups tolerance.[14]

In conclusion, there is no doubt about the importance of arylboronates within the field of modern synthetic chemistry,



Scheme 3. Cyclotrimerization of alkyne derivatives. cod = cycloocta-1,5-diene, Cp* = pentamethylcyclopentadienyl, Ts = 4-toluenesulfonyl.

but what is also clear is the necessity of a vast array of substrates with different functionalization that enhance the synthetic applicability of such compounds. By incorporating the boryl unit into the aromatic ring as discussed in this Highlight, it is possible to introduce a great variety of both electron-rich and electron-poor substituents that are suitable of further synthetic transformations. This feature has been used to develop a large number of functionalized arylboronates. The time is now ripe for breakthroughs in bulk chemistry by applying this chemical technology developed for fine chemicals to industrial processes.

Received: May 26, 2010
Published online: July 29, 2010

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