Efficient Preparation of 2-Aminomethylbiphenyls via Suzuki–Miyaura Reactions

Pierre-Luc Boudreault, Sébastien Cardinal, Normand Voyer*

Département de Chimie and PROTEO, Université Laval, Pavillon Alexandre-Vachon, Faculté des Sciences et de Génie, 1045 Avenue de la Médecine, Québec, QC, G1V OA6, Canada
Fax +1(418)6567916; E-mail: normand.voyer@chm.ulaval.ca

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Abstract: We prepared four 2-(aminomethyl)arylboronic acids and studied their reactivity in the Suzuki–Miyaura coupling reaction with different aryl halides. We observed significant increases in yields and shorter reaction times when the amine adjacent to the boronic acid was protected by a *tert*-butyloxycarbonyl (*t*-Boc) group. We then investigated the origin of the greater reactivity of *N*-*t*-Boc-protected substrates with regard to the potential role of an N–B bond.

Key words: Suzuki–Miyaura cross-coupling, biaryls, (aminomethyl)arylboronic acids, N–B dative bond

There has recently been a steady stream of new developments and refinements reported about the application of the Suzuki–Miyaura coupling reaction.

During the course of our investigation on the synthesis of natural products, we decided to use a retrosynthetic strategy that employs a Suzuki–Miyaura coupling between 2-(aminomethyl)arylboronic acids and aryl halides and leads to 2-aminomethylbiphenyls. Aside from being found in many types of organic compounds,[1,2] the structural motifs derived from the 2-aminomethylbiphenyl moiety are present in several natural and bioactive products.[3–5]

Despite the importance of these motifs, there are only a few examples of studies of aryl–aryl coupling leading to 2-aminomethylbiphenyl derivatives.[6,7] In most cases, the aminomethylbiphenyl unit was obtained by a multistep synthesis, such as a C–C coupling reaction followed by S_N2 reactions,[8] reductive amination,[8] and/or reduction[9] of the corresponding functional group. There are also a few examples of Suzuki–Miyaura cross-coupling reactions using boronic acid and ester derivatives like structures **1**–**4** (Figure 1) described in the literature.[6,7,10–14] We now report the results of our study on the efficient preparation of *o*-aminomethylbiphenyls.

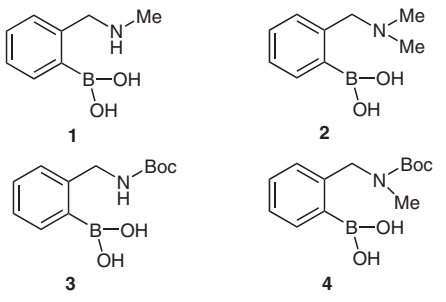
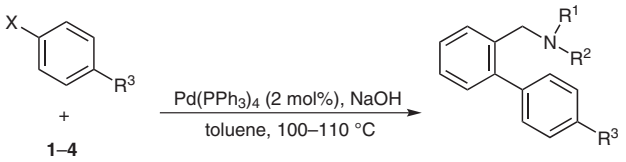


Figure 1 Structures of the four boronic acids that we studied

In the study with boronic acids **1**–**4**, we used aryl halides with electron-withdrawing and electron-donating groups at the *para* position as coupling partners. The results are shown in Table 1.

Table 1 Suzuki–Miyaura Coupling Reactions of **1**–**4**



Entry	Substrate	R^1	R^2	R^3	X	Product	Isolated yield (%)
1	**1**	Me	H	H	Br	**5**	25
2	**1**	Me	H	H	I	**5**	37
3	**1**	Me	H	NO_2	Br	**6**	75
4	**1**	Me	H	OMe	Br	**7**	23[a]
5	**2**	Me	Me	H	Br	**8**	63
6	**2**	Me	Me	H	I	**8**	65
7	**2**	Me	Me	NO_2	Br	**9**	76
8	**2**	Me	Me	OMe	Br	**10**	48
9	**3**	H	Boc	H	Br	**11**	98
10	**3**	H	Boc	H	I	**11**	96
11	**3**	H	Boc	NO_2	Br	**12**	94
12	**3**	H	Boc	OMe	Br	**13**	94
13	**4**	Me	Boc	H	Br	**14**	97
14	**4**	Me	Boc	H	I	**14**	99
15	**4**	Me	Boc	NO_2	Br	**15**	97
16	**4**	Me	Boc	OMe	Br	**16**	97

[a] 75% purity by analytical HPLC.

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When we used primary and secondary amine boronic acids **1** and **2**, yields were modest and reactions proceeded slowly (entries 1–8). It is well established that electron-rich aromatic systems, specifically those with an electron-donating group in the *para* position, are generally less susceptible to oxidative addition.[15] As expected, results obtained with the methoxy-substituted system (entries 4 and 8) showed an even slower reaction rate and led to lower yields of biaryl products with boronic acids **1** and **2**. GC-MS analysis revealed that the consumption of starting materials was not complete, even after prolonged reaction times (up to 48 h). We also observed the formation of deboronation byproducts, the loss of the methoxy group in some cases, but only a small amount of homocoupling byproduct (<2%). Using an aryl iodide instead of an aryl bromide accelerated the reactions and led to modest increases in yields (see entries 1 vs. 2 and 5 vs. 6).

However, when *N*-Boc-protected boronic acid substrates **3** or **4** were used, the reactions were much faster (<1 h compared with up to 48 h for **1** and **2**). Yields were higher than 94% in all cases. This comparison of the results obtained with boronic acids **1** and **2** vs. **3** and **4** clearly illustrates the influence of the adjacent N atom lone pair on the outcome of the Suzuki–Miyaura reaction. To get a better understanding of the results, we investigated the possible interaction between the N and B atoms.

The boronic acid functional group is frequently incorporated into synthetic receptors for recognition of diols and secondary and tertiary amines; complexes of boronic acids have been extensively studied.[5,16,17] Wulff has demonstrated that the incorporation of an amine adjacent to the boronic acid creates a tetrahedral sp^3 boron, where the lone pair on the nitrogen associates with the empty *p* orbital on the boron to form a dative bond.[18,19] The presence of such bonds surely affects the acidic character of the boron, and concomitantly, its electrophilicity.[20] On that basis, we investigated the relationship between the reactivity of **1**–**4** and the N–B coordination.

We used two methods to observe the extent of N–B dative bond formation: X-ray crystallography and ^{11}B NMR spectroscopy.

To confirm the geometry of the boronic acid, we obtained an X-ray structure of structures **1** and **3** with crystals from $CDCl_3$ solution. The structure of **1** shows that this compound co-crystallizes with cyclotrimeric anhydride (Figure 2). To the best of our knowledge, such a co-crystallization pattern has not yet been observed for this type of compound. However, analogous trimerized cyclic boronic anhydride is a structural motif often found for boronic acids.[20–22] In the cyclic form of **1**, the boron atom is tetrahedral and coordinated with the nitrogen to form a dative bond. The N–B bond length is about 1.75 Å in the boronic acid and in two of the three N–B interactions. However, in the last N–B bond, the stronger nature of the interaction is evident by a shorter N–B length of 1.67 Å, which is comparable to the one observed with the diethanolamine adduct of phenylboronic acid.[23]

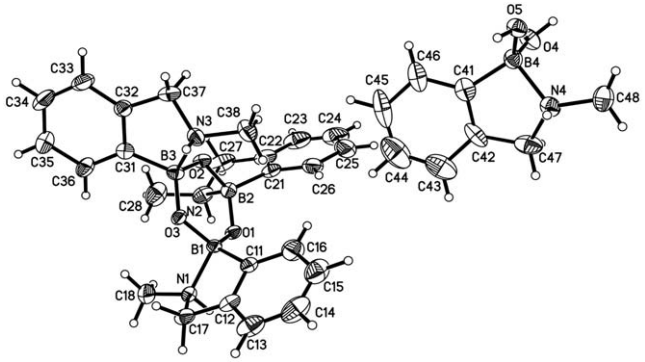

Figure 2 ORTEP X-ray crystal structure of boronic acid **1**, showing 50% probability ellipsoids

As expected, the N–B dative bond is not observed in the crystal structure of boronic acid **3** (Figure 3). As shown by the short N–C bond (1.33 Å), the lone electron pair of the nitrogen is involved in a partial double bond within the carbamate and is unavailable to coordinate with the boron atom. Interestingly, compound **3** crystallized as a dimer stabilized by hydrogen bonds between the trigonal boronic acid group.

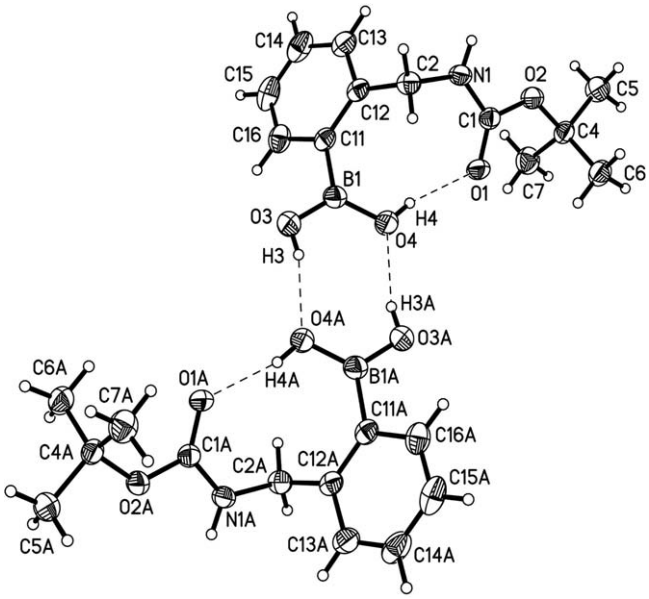

Figure 3 ORTEP X-ray crystal structure of boronic acid **3**, showing 50% ellipsoids

Internal hydrogen bonds were also observed between the B–OH group and the carbamate C=O. We were unable to obtain good quality diffraction crystals for compound **4**, but it is reasonable to believe that the boron atom of **4** is not involved in bonding with the nitrogen lone electron pair.

Interaction in solution between the boron and nitrogen atoms may be evaluated by ^{11}B NMR chemical shift.[20,21,24,25] Toyota et al. reported the presence of N–B coordination bond in the boronic ester derivative of **2** and showed that the dissociation of the dative bond proceed by

a S_N2-type mechanism.[26] A sp^2 trigonal, uncoordinated boron NMR signal and a tetragonal sp^3-coordinated signal with an amine are approximately δ = 30 and 15 ppm, respectively.[20] As shown in Table 2, the ^{11}B NMR chemical shift of boronic acids **1** and **2** indicates that the boron atom is tetracoordinated in solution. Boronic acid **1** displays a signal at δ = 12.3 ppm, while **2** displays a signals at δ = 4.6 ppm.

Table 2 ^{11}B NMR Chemical Shift of Boronic Acids **1**–**4** in $CDCl_3$

Compound	^{11}B NMR (δ, ppm, 128.34 MHz)
1	12.3
2	4.6
3	34.4
4	31.2

However, no intramolecular N–B bonding is observed in the case of boronic acids **3** and **4**, which have boron signals at δ = 34.4 and 31.2 ppm, respectively. Therefore, in chloroform, the presence of a carbamate on the N forbids the formation of N–B dative bond since the electron lone pair is delocalized on the carbonyl group, leaving the boronic acid free. Further studies more relevant to the Suzuki–Miaura conditions in pure toluene-d_8 with **3** and **4** confirmed the absence of an N–B bond (δ = 34.4 and 32.0 ppm). However, addition of increasing amounts of 0.1 M NaOH demonstrated that the boronate was formed, as indicated by sp^3 boron signals at δ = 5.6 and 3.2 ppm for **3** and **4**, respectively (see Supporting Information). Unfortunately, it was not possible to perform the toluene studies with boronic acids **1** and **2** due to solubility problems. Hence, the ^{11}B NMR studies support the absence of an N–B dative bond in **3** and **4**, but cannot confirm that the same bond in **1** and **2** is responsible for their decreased reactivity in the Suzuki–Miaura reaction.

It is worth noting that the anchimeric participation of the aminomethyl group in compounds of type **1** and **2** affect the pK_a, which influences the activation step of the Suzuki–Miyaura coupling reaction. The transmetalation step is known to be facilitated by a base-mediated tetracoordinated boronate anion,[27] although its exact role remains unclear.[28]

Finally, another possible explanation is that the enhanced reactivity of **3** and **4** in the Suzuki–Miyaura reaction can be attributed to the fact that the amine protected by an *N*-Boc group does not interact with Pd as strongly as in **1** and **2**. Hence, the catalytic cycle can proceed smoothly, leading to increased reaction rates and yields.

In summary, we have demonstrated that properly protected 2-aminomethylphenylboronic acids are useful synthons for the preparation of functionalized 2-aminomethylbiphenyl derivatives. The presence of a protonable N atom adjacent to the boronate was shown to decrease the yields and rate of the reaction. Taking into account the ease of preparation of the boronic acids, the current methodology provides an efficient way to produce useful intermediates. We are currently working to exploit this versatile synthetic method to prepare useful biphenyl derivatives.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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