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# Anthranilamide: A Simple, Removable *ortho*-Directing Modifier for Arylboronic Acids Serving also as a Protecting Group in Cross-Coupling Reactions

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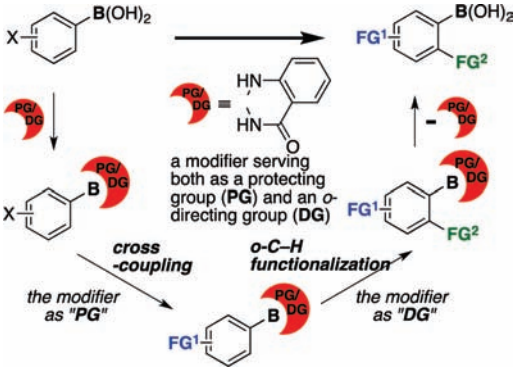
## ABSTRACT




**Anthranilamide (AAM) serves as a bifunctional modifier on the boron atom in catalytic transformations of arylboronic acids. It makes boronyl groups unreactive in Suzuki–Miyaura coupling and promotes Ru-catalyzed *ortho*-silylation. Suzuki–Miyaura coupling of AAM-modified bromophenylboronic acids with tolylboronic acid gave 1,1′-biaryl-4-boronic acid bearing AAM on the boron atom, which subsequently underwent Ru-catalyzed *ortho*-silylation at the 3-position by virtue of the *ortho*-directing effect of the AAM group.**

Much interest has focused on the synthesis and use of arylboronic acids in organic synthesis.[1] In addition to the conventional synthesis using transmetalation with more nucleophilic organometallic reagents such as Grignard and organolithium reagents, catalytic C–B bond formation reactions have gained increasing attention. Transition-metal-catalyzed C–H and C–X borylations are recognized as the most promising, efficient access to arylboronic acids.[2,3] Efforts are now devoted to the synthesis of organoboronic acids with retention of the boron functionality throughout the synthesis.[4] For this purpose, robust protecting groups for organoboronic acids, especially in

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(4) Use of a chiral diol for protection of a boronyl group: (a) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **2000**, *65*, 9194. Use of trfluoroborate for protection: (b) Molander, G.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

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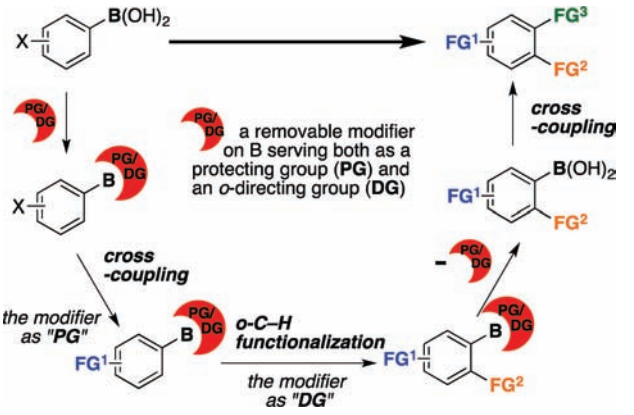
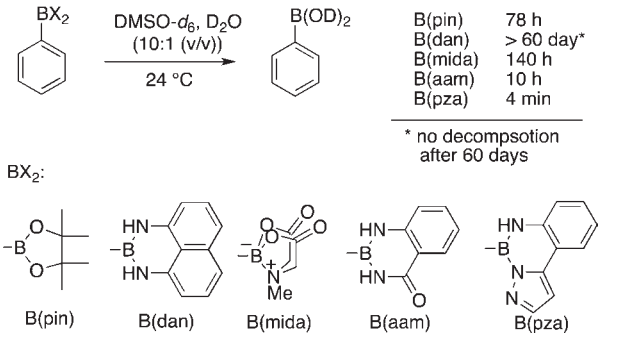
**Scheme 1.** Use of a Removable Modifier on the Boron Atom That Serves As Both Protecting and *ortho*-Directing Group for the Synthesis of Highly Functionalized Arene Derivatives




the Suzuki–Miyaura cross-coupling reaction, have been developed.[5,6] They have made possible the synthesis of rather complex organoboronic acids through iterative Suzuki–Miyaura coupling.[4,7,8] As a new boron-retaining strategy, we recently reported use of 2-(pyrazol-5-yl)-aniline (PZA) as an agent for Ru-catalyzed *ortho*-silylation,[9,10] in which coordination of the $sp^2$-nitrogen atom of PZA to the catalyst is crucial.[11−13] These boron-retaining syntheses of arylboronic acids are particularly useful in the synthesis of elaborated arylboronic acids that are otherwise difficult to synthesize. Our interest has focused on finding a simple modifier on the boron atom serving both as an *ortho*-directing group in the *o*-C−H functionalization reactions and as a protecting group in the cross-coupling reactions (Scheme 1). Such a bifunctional modifier would allow us to develop new synthetic access to highly elaborated arylboronic acids, which is in turn beneficial for the synthesis of highly functionalized arene derivatives. Herein, we describe the use of anthranilamide as such a bifunctional agent for arylboronic acid synthesis. It shows a higher ability for *ortho*-direction and much higher robustness toward SMC and isolation procedures than PZA.

**Scheme 2.** Stabilities of Modified Phenylboronic Acids




After brief screening of some 1,3,2-diazaboracyclohexane structures, we found that PhB(aam) **1a** (see Scheme 2 and Table 1 for the structure), which was prepared by condensation of $PhB(OH)_2$ with commercially available anthranilamide in toluene under reflux in high yield, shows high stability toward moisture, oxygen, and even chromatography on silica gel.[14] The stabilities of the cyclic diaminoborane derivatives were compared in DMSO/$D_2O$ (10:1) at room temperature (Scheme 2). To our surprise, even PhB(pin) decomposed gradually under these reaction conditions. The half-life was determined to be 78 h by $^1H$ NMR measurement. In contrast, PhB(dan) showed no hint of decomposition under the same reaction conditions. PhB(mida) (mida: *N*-methyliminodiacetato) was also robust, although it too underwent slow hydrolysis ($t_{1/2}$ = 140 h). Although less stable than the DAN and MIDA protecting groups, AAM exhibited much higher stability than the previous directing group PZA.

Ru-catalyzed *ortho*-silylation of PhB(aam) (**1a**) with dimethylphenylsilane proceeded in high yield in the presence of $RuH_2(CO)(PPh_3)_3$ with norbornene as a hydrogen scavenger at 135 °C (Table 1).[5b−d] The *ortho*-silylated product **2aa** was isolated by silica gel flash column chromatography. Among the hydrosilanes examined for the

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(10) For representative C−H silylations without using directing groups, see: Klare, H. F. T.; Oestreich, M.; Ito, J.; Nishiyama, H.; Ohki, Y.; Tatsumi, K. *J. Am. Chem. Soc.* **2011**, *133*, 3312 and reference therein.

(11) Ihara, H.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502.

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(13) For directed catalytic *ortho*-C−H functionalization, see: (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, N.; Chatani, N. *Nature* **1993**, *366*, 529. For earlier pioneering work, see: (b) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. Reviews: (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (d) *Handbook of C−H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005.

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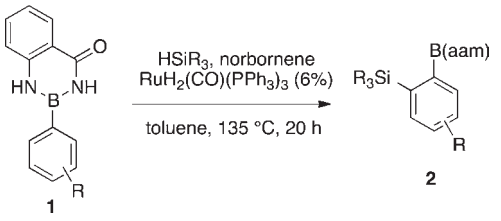
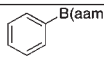
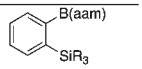
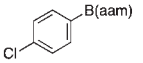
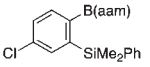
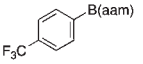
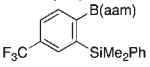
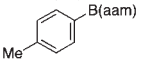
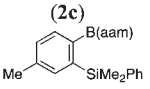
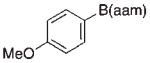
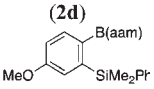
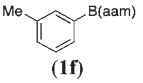
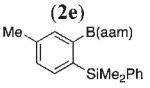
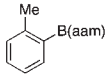
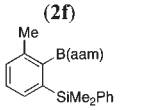
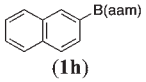
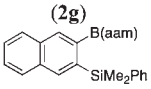
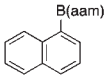
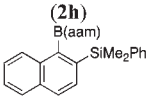
**Table 1.** *ortho*-Silylation of Arylboronic Acids Using Anthranilamide as an *ortho*-Directing Agent[a]

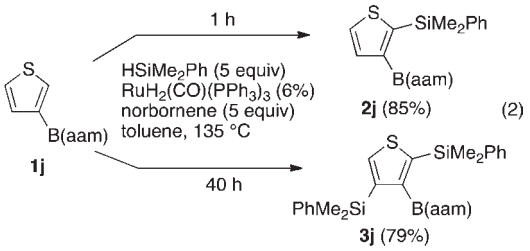



| entry | 1 | $HSiR_3$ | % yield[b] | isolated product |
|---|---|---|---|---|
| 1[c] |  | $HSiMe_2Ph$ | (88) |  |
| 2 | | $HSiEt_3$ | (64) | |
| 3 | **(1a)** | $HSiMePh_2$ | 90 (80) | **(2aa-2ad)** |
| 4 | | $HSiMe_2Bu$-*t* | 0 | |
| 5 |  | $HSiMe_2Ph$ | 97 (91) |  |
| | **(1b)** | | | **(2b)** |
| 6 |  | $HSiMe_2Ph$ | 94 (77) |  |
| | **(1c)** | | | **(2c)** |
| 7 |  | $HSiMe_2Ph$ | 96 (88) |  |
| | **(1d)** | | | **(2d)** |
| 8 |  | $HSiMe_2Ph$ | 95 (85) |  |
| | **(1e)** | | | **(2e)** |
| 9[d] |  | $HSiMe_2Ph$ | 91 (81) |  |
| | **(1f)** | | | **(2f)** |
| 10[e] |  | $HSiMe_2Ph$ | 32 (19) |  |
| | **(1g)** | | | **(2g)** |
| 11 |  | $HSiMe_2Ph$ | 97 (90) |  |
| | **(1h)** | | | **(2h)** |
| 12[e] |  | $HSiMe_2Ph$ | 54 (30) |  |
| | **(1i)** | | | **(2i)** |

[a] Reagents and conditiona: **1** (0.25 mmol), $RuH_2(CO)(PPh_3)_3$ (15 $\mu$mol), norbornene (1.25 mmol), hydrosilane (1.25 mmol), and toluene (0.13 mL) at 135 °C (bath temperature) for 20 h unless otherwise noted. [b] NMR yield. Isolated yields in parentheses. [c] 3 h. [d] 37 h. [e] 51 h.

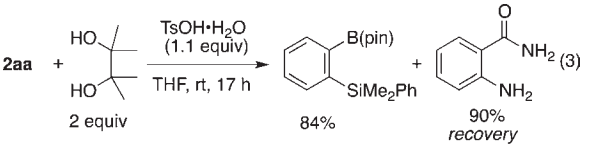
reaction, dimethylphenylsilane showed the highest reactivity. Triethylsilane, which was the most reactive in the PZA-directed reaction, resulted in a slightly lower yield. It should be remarked here that no silylation at the phenyl ring of anthranilamide took place at all. Using dimethylphenylsilane, isolated AAM-modified substituted arylboronic acids were subjected to the silylation reaction. Arylboronic acids having electron-donating and electron-withdrawing groups at their *para*-positions afforded the corresponding *ortho*-silylated products in high yields (entries 5–8). *m*-Tolylboronic acid derivative **1f** underwent silylation at the less sterically demanding *ortho*-position selectively in high yield (entry 9). Although the yield was low, *o*-Me-substituted **1g** afforded *ortho*-silylated 1,2,3-trisubstituted benzene derivative **2g** (entry 10). Note that

**Scheme 3.** AAM-Directed Silylation of 3-Thiopheneboronic Acid Derivative **1j**




PZA-modified *o*-tolylboronic acid does not give the desired *ortho*-silylation product at all. The 2-naphthyl derivative was silylated at the 3-position selectively in good yield (entry 11) as observed in the PZA system. 1-Naphthylboronic acid gave the 2-silylated product **2i** selectively, albeit in low yield, whereas the corresponding PZA derivative was not reactive at all (entry 12). A remarkable difference between the present AAM and the previous PZA system has been demonstrated by the reaction of 3-thienyl derivative **1j** (Scheme 3). In both systems, the first silylation takes place at the 2-positions. The second silylation in the AAM system took place at the 4-position of the thiophene ring, in contrast to exclusive silylation at the 5-position in the PZA system via nondirected silylation.[15] This clearly suggests that the AAM group has a stronger directing ability than does PZA. In these syntheses of *ortho*-silylated organoboronic acids, the AAM group on the boron atoms was readily converted into the PIN group by acid-catalyzed ligand exchange (Scheme 4). Hydrolysis of **2aa** was accomplished cleanly in the presence of aqueous acid at room temperature, giving the corresponding arylboroxine in high yield.

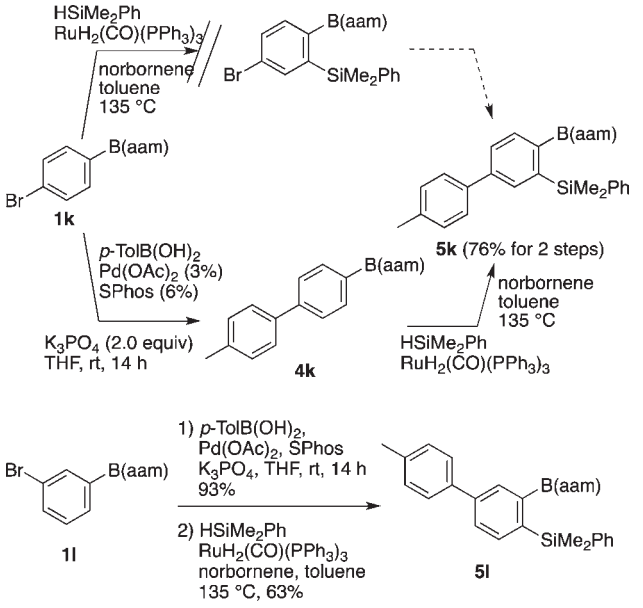
**Scheme 4.** Acid-Mediated Conversion of ArB(aam) to ArB(pin)




Attempted *ortho*-silylation of *p*-bromophenylboronic acid derivative **1k** resulted in the substitution of the bromine group by a silyl group (Scheme 5). Instead, we carried out Suzuki–Miyaura coupling of **1k** with *p*-tolylboronic acid. In the presence of SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl) as a ligand, the coupling proceeded at room temperature with complete retention of the AAM group on the boron atom. The isolated AAM derivative of biphenylboronic acid **4k**

(15) Non-directed, Ir-catalyzed silylation of thiophenes has been reported. Lu, B.; Falck, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 7508.

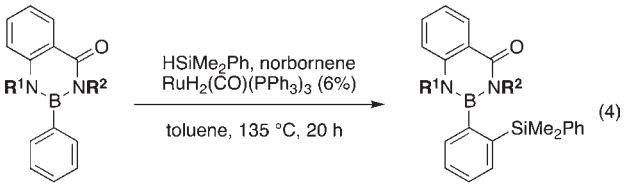
**Scheme 5.** Cross-Coupling/Silylation Sequence with Bromo-Substituted Arylboronic Acids




underwent Ru-catalyzed silylation selectively at the *ortho* position, giving silylborylbiphenyl **5k**. The sequential cross-coupling/*ortho*-silylation protocol could also be applied to *m*-bromoboronic acid derivative **1l**, affording **5l** (room temperature, 14 h). The B(aam) group was completely retained even in the attempted cross-coupling of **1l** with *p*-tolylboronic acid at 80 °C, giving the same coupling product in 94% yield (1.5 h). In the corresponding transformation of *o*-bromophenylboronic acid, the first step, i.e., coupling with $TolB(OH)_2$, proceeded in high yield, although *ortho*-silylation afforded the silylated biphenyl only in low yield. In these examples, the AAM group serves not only as a directing group but also as a protecting group for the boronyl group in the Suzuki–Miyaura coupling reaction.

To gain insight into the origin of the directing effect of the AAM group, we compared two *N*-methylated derivatives **6a** and **6b** of anthranilamides in the *ortho*-silylation reactions (Scheme 6). Anthranilamide **6a** bearing a methyl group on the aniline nitrogen atom underwent the *ortho*-silylation smoothly under the same reaction conditions as those for the parent anthranilamide. In contrast, its isomer

**Scheme 6.** Reactions of Phenylboronic Acid Drrivatives **6a** and **6b** Modified by *N*-Methylated Anthranilamides




| 6a, b | 6 | $R^1$ | $R^2$ | %yield | 7 |
|---|---|---|---|---|---|
| | 6a | Me | H | 93 (86) | |
| | 6b | H | Me | no reaction | |

**6b** bearing a methyl group on the amide nitrogen was not reactive at all. These results suggest that the amide nitrogen rather than the aniline nitrogen serves as the coordinating element in the Ru-catalyzed *ortho*-silylation. It may be presumed that a tautomerized form, which carries an $sp^2$ lone pair on the nitrogen atom, may play a key role in coordination to the catalyst.

In summary, anthranilamide has been established as a new directing agent for transition-metal-catalyzed *o*-C–H silylation. The B(aam) group exhibited higher ability in *ortho*-direction in comparison with the previously reported B(pza) group. The stronger directing effect resulted in *ortho*-silylation of sterically demanding arylboronic acids such as *o*-tolylboronic acid and 1-naphthylboronic acid, albeit in low yields, which could not be achieved with the B(pza) group. Furthermore, a sharp switch of regioselectivity was observed in the silylation of 2-silylated 3-thiopheneboronic acid. The AAM group also serves as a protecting group in the Suzuki–Miyaura coupling reaction, enabling the synthesis of silylated biphenylboronic acids through a cross-coupling/*ortho*-silylation sequence. Application of these directing groups in other catalytic C–H functionalizations is being undertaken in this laboratory.

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**Supporting Information Available.** Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.