Synthetic Methods

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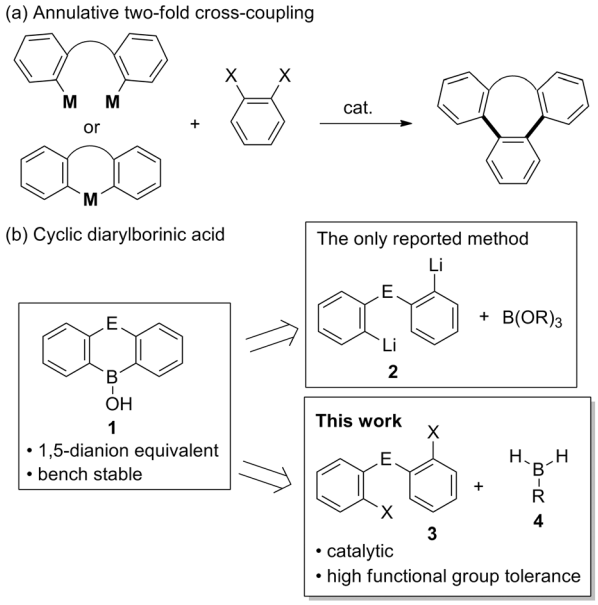
Catalytic Double Carbon–Boron Bond Formation for the Synthesis of Cyclic Diarylborinic Acids as Versatile Building Blocks for π-Extended Heteroarenes

Takuya Igarashi, Mamoru Tobisu, and Naoto Chatani**

Abstract: *The first catalytic synthesis of cyclic diarylborinic acids is developed using a dihydroaminoborane reagent as the boron source. Unlike previously reported methods that use organolithium reagents, this method allows the easy synthesis of cyclic diarylborinic acids bearing a range of functionalities including CN, CO_2Et, $CONEt_2$ and $NMeCO_2{}^tBu$. Furthermore, these cyclic diarylborinic acids provide rapid access to skeletal diversity, in particular they enable the synthesis of six- to nine-membered π-extended heteroarenes through simple cross-coupling reactions, which are important synthetic targets in both advanced materials and pharmaceuticals.*

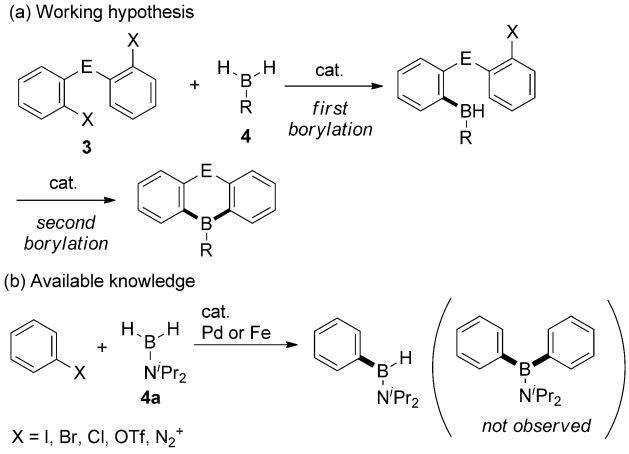
The development of synthetic methods for elaborate π-conjugated molecules is crucial for the creation of new functional organic materials, such as light emitting diodes, transistors and solar cells.[1] The annulative two-fold $C(sp^2)$–$C(sp^2)$ cross-coupling reaction between organodimetallic reagents and dihalides represents a powerful method for this purpose (Scheme 1a). Among the organodimetallic reagents reported to date,[2] cyclic diarylborinic acid **1**[3] is particularly useful, because of its stability towards air and moisture, and the low toxicity and easily removable nature of the boron-based residue generated after the cross-coupling. It thus has similar properties to those of the arylboronic acids. However, the potential utility of **1** remains limited because all of the reported syntheses of **1** require the use of organolithium reagents **2**, thus rendering the introduction of many common functional groups impossible (Scheme 1b).[3] Herein, we report the first catalytic synthesis of **1**, which allows access to a range of functionalized cyclic borinic acids, including a seven-membered derivative (Scheme 1b). The synthetic utility of **1** as a dianionic building block was also demonstrated by its elaboration into a diverse array of ring systems.

On the basis of the widespread utility of palladium-catalyzed borylation of aryl halides in the synthesis of functionalized arylboronic acids,[4] we envisioned that



Scheme 1. Cyclic diarylborinic acid **1** and methods for its preparation.

1 would be formed if borylation occurs twice between dihalide **3** and dihydroborane reagent **4** (Scheme 2a). Diisopropylaminoborane ($R = {}^iPr_2N$, **4a**)[5–8] was chosen as a readily available dihydroborane reagent. Although several catalytic borylation reactions of aryl halides using **4a** have been reported,[6] none afforded a diarylated product, even in the presence of an excess amount of the aryl halide (Scheme 2b).[6d] This suggested that it may not be possible for both



Scheme 2. Working hypothesis: two-fold borylation.

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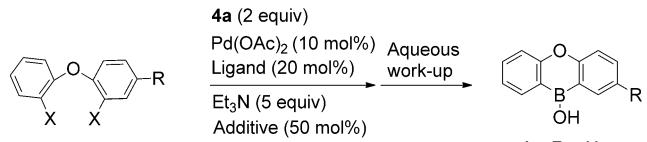
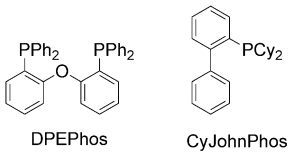
of the B–H bonds in **4a** to react, and thus raised an uncertainty with our hypothesis. Nevertheless, we expected that the second borylation would be facilitated in our system owing to its intramolecular nature (Scheme 2a).

To test our hypothesis, we initially examined the reaction of ditriflate **3a** with **4a** (2 equiv) in the presence of a palladium catalyst at 65 °C for 15 h (Table 1). The yield of borylated

Table 1: Optimization of the reaction conditions.[a]



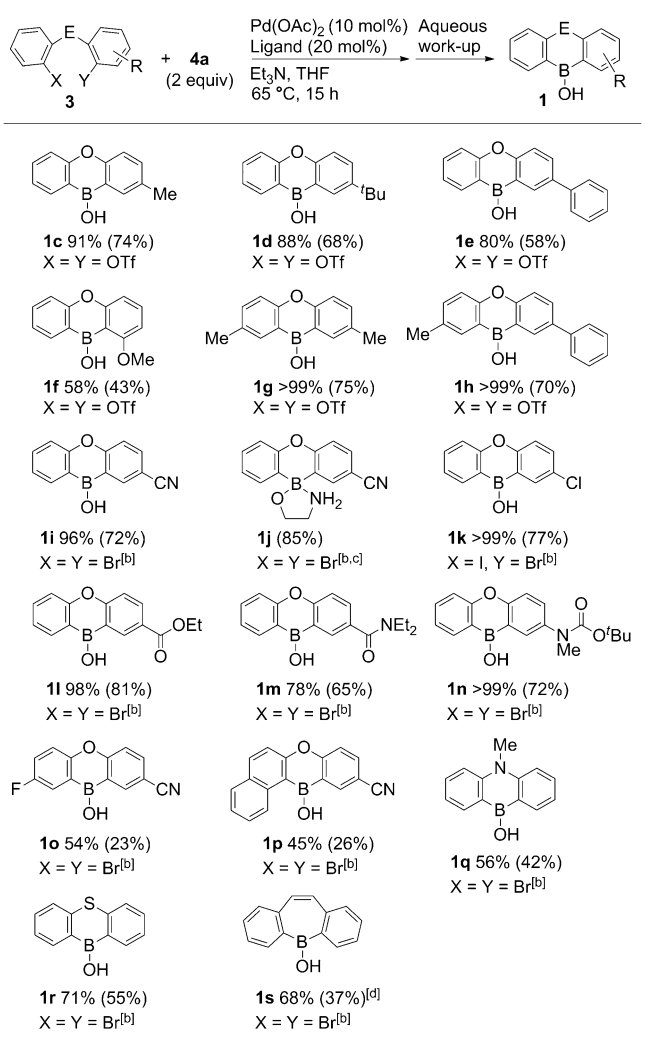
Entry	Substrate	Ligand	Additive	NMR yield of **1** [%]
1	**3a**	DPEPhos	none	>99 (76)[b]
2	**3b**	CyJohnPhos	KI	97 (75)[b]



[a] Reaction conditions: **3a** or **3b** (0.50 mmol), **4a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.10 mmol), Et_3N (2.5 mmol), additive (0.25 mmol) in THF (2 mL) at 65 °C for 15 h. [b] Isolated yields are shown.

product **1a** was estimated by ^1H NMR spectroscopy after treatment with methanol and an aqueous solution of NH_4Cl. A brief screening of the ligand revealed that a bisphosphine with a diphenyl ether backbone (i.e., DPEPhos) displayed the highest activity, giving **1a** in >99% NMR yield (entry 1). The product **1a** could be isolated in 76% yield by column chromatography. Unfortunately, however, reactions under these optimized conditions using DPEPhos failed to promote the borylation of dibromide **3b**. Reoptimization of the reaction conditions showed that using KI together with CyJohnPhos,[9] markedly improved the yield of **1b**, affording product **1b** in 97% NMR yield (entry 2, see also the Supporting Information (SI) for details of optimization and some discussion regarding the effect of KI).[6h]

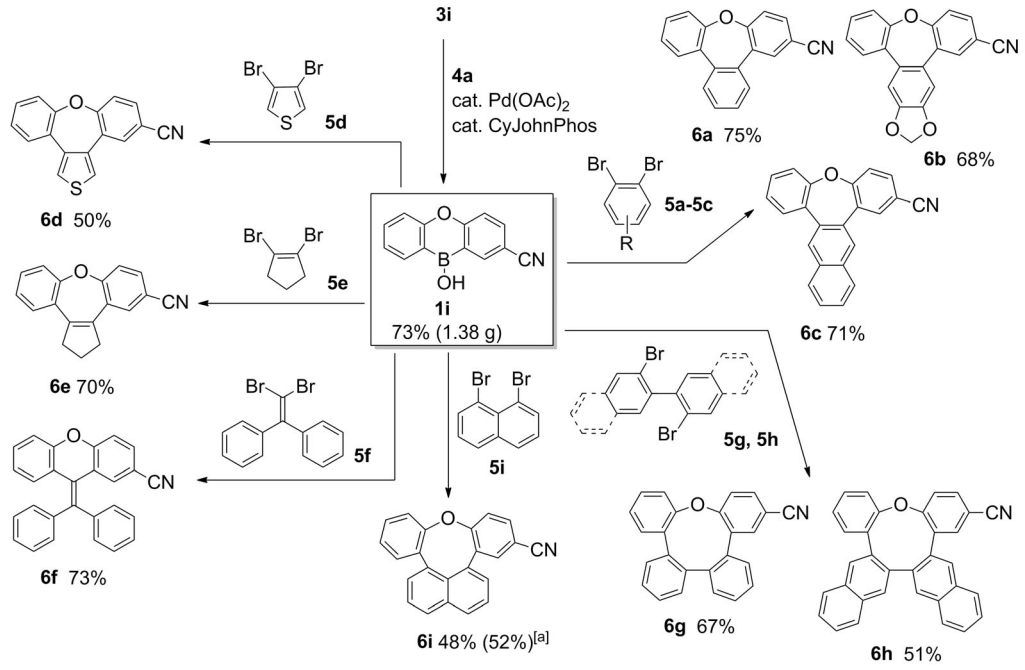
The reaction was successfully applied to the synthesis of a diverse array of cyclic diarylborinic acids (Scheme 3). In addition to diarylborinic acids bearing simple alkyl, aryl and alkoxy groups (**1c**–**1h**), those containing cyano, chloro, ester, amide, carbamate, and fluoro groups (**1i**–**1o**) were all compatible with the present catalytic conditions. This highlights the synthetic advantage of our protocol over previously reported methods using organolithium reagents.[3] In particular, the tolerance of an aryl chloride moiety, as shown for **1k**, is notable when considering that the report that the borylation of aryl chlorides occurs with **4a** using a Pd/XPhos catalyst.[6h] Our protocol also allowed the synthesis of π-extended analogue **1p** as well as diarylborinic acids containing nitrogen



Scheme 3. Pd-catalyzed synthesis of cyclic diarylborinic acids by annulative two-fold borylation.[a] [a] Reaction conditions: **3** (0.50 mmol), **4a** (1.0 mmol), $Pd(OAc)_2$ (0.050 mmol), ligand (0.10 mmol), Et_3N (2.5 mmol) in THF (2 mL) at 65 °C for 15 h. Ligand: DPEPhos for ditriflates **3c**–**3h**; CyJohnPhos for dibromides **3i**–**3o** and **3s**; XPhos for **3p** and **3r**; RuPhos for **3q**. ^1H-NMR yields are shown. Numbers in parentheses are isolated yields. [b] KI was added. [c] After the reaction, 2-aminoethanol (4.0 equiv) was added. [d] Using 1.0 g of **3s**.

(**1q**) and sulfur (**1r**) tethers. Notably, seven-membered diarylborinic acid **1s** was successfully synthesized.[10] Although we routinely isolated the product after hydrolysis in the form of borinic acid **1**, chromatographic separation led to a considerable loss of **1** in some cases (numbers in parentheses in Scheme 3 refer to isolated yields). However, this issue could be easily addressed by formation of an aminoalcohol adduct, such as **1j**,[8] which could be isolated by simple filtration and used directly for the subsequent two-fold cross-coupling (see below).

Our catalytic protocol can be readily applied to the gram scale production of cyclic diarylborinic acids (Scheme 4, **3i**→**1i**). The obtained functionalized boracycle can then serve as a 1,5-dianion equivalent in annulative cross-coupling with dihalides under palladium catalysis, and thus allows access to a diverse range of π-extended heteroarenes (Scheme 4).[3e]

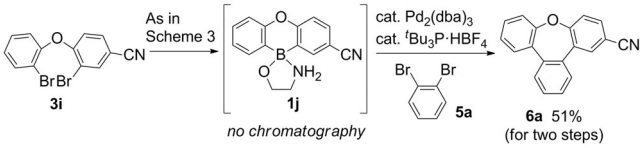


Scheme 4. Pd-catalyzed annulative two-fold Suzuki–Miyaura coupling for the synthesis of benzannulated heterocycles. Reaction conditions: **1i** (0.25 mmol), **5** (0.50 mmol), $Pd_2(dba)_3$ (0.0038 mmol), $^tBu_3P{\cdot}HBF_4$ (0.0090 mmol), Cs_2CO_3 (0.83 mmol), H_2O (2.5 mmol) in ^{t}AmOH (3 mL) at 100 °C for 24–48 h. Yields of isolated products are shown. [a] Run on a 1.0 mmol scale.

For example, cross-coupling of **1i** with 1,2-dibromo-(hetero)arenes **5a**–**5d** enabled the modular synthesis of the tribenzo[b,d,f]oxepine skeleton in **6a**–**6c** or the heteroarene-fused analogue **6d**. This structural motif is found in antidepressant drugs[11] and natural products.[12] In addition, cross-coupling of **1i** with 1,2-dibromocyclopentene **5e** proceeded efficiently to afford corresponding dibenzo[b,f]oxepin derivative **6e**. π-Extended xanthene derivative **6f** was also assembled by cross-coupling of **1i** with 1,1-dibromoalkene **5f**, valuable finding with respect to potential application in the synthesis of molecular probes for aggregation induced emission.[13] Moreover, a larger ring system can also be accessible by the reaction of **1i** with dibromobiaryl **5g** and **5h**, which led to the construction of a tetrabenzo[b,d,f,h]oxonine skeleton **6g** and **6h**.[14] Cross-coupling with 1,8-dibromonaphthalene **5i** yielded dibenzo[b,g]naphtho[1,8-de]oxocine framework **6i**, for which a synthetic method has not previously been reported. This modular assembly of six- to nine-membered π systems by simply changing the dihalide coupling partners highlights the synthetic utility of the cyclic diarylborinic acids.

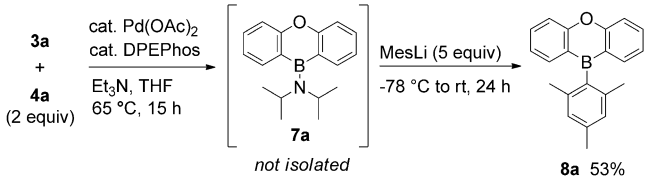
Importantly, this annulative two-fold cross-coupling can be performed directly from dihalide **3** and **4a** without the need for chromatographic isolation of borinic acid **1** (Scheme 5). The palladium-catalyzed reaction of **3i** and **4a**, followed by treatment with 2-aminoethanol, led to the formation of borinate **1j**, which could be isolated by simple filtration. This material was used directly in a subsequent annulation with **5a** to form **6a** in 51% overall yield.

In addition to their use as a 1,5-dianion equivalent, cyclic diarylborinic acid derivatives can also serve as useful precursors to functional organoboron compounds. For example,



Scheme 5. Pd-catalyzed two-fold Suzuki–Miyaura coupling using cyclic borinate **1j**.

the reaction of ditriflate **3a** with **4a**, followed by addition of MesLi instead of aqueous work up, led to the formation of 9-mesityl-9*H*-boraxanthene **8a**, a class of fluorescent compounds that are currently attracting much attention (Scheme 6).[15]



Scheme 6. One-pot synthesis of 9-mesityl-9*H*-boraxanthene **8a**.

In summary, we have developed the first catalytic method for the synthesis of cyclic diarylborinic acids through a two-fold borylation of dihalides using **4a** as the boron source. This method allows the synthesis of cyclic diarylborinic acids bearing a range of functionalities, which could not be synthesized by previously reported methods using organolithium reagents. The cyclic diarylborinic acids can serve as

air- and moisture-stable building blocks with low toxicity for the rapid synthesis of a diverse range of π-extended heteroarenes through annulative two-fold Suzuki–Miyaura cross-coupling reactions. The unique compound libraries made possible by our method promise to accelerate the discovery of new functional molecules.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aminoborane · borylation · diarylborinic acid · palladium · heteroarene

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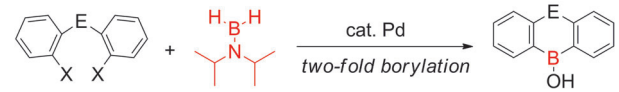

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The first catalytic synthesis of cyclic diarylborinic acids is developed using a dihydroaminoborane reagent as the boron source. The reaction products provide rapid access to skeletal diversity, in particular they enable the synthesis of six- to nine-membered π-extended heteroarenes through simple cross-coupling reactions, which are important synthetic targets in advanced materials and pharmaceuticals.