

Boron-Selective Biaryl Coupling Approach to Versatile Dibenzoxaborins and Application to Concise Synthesis of Defucogilvocarcin M

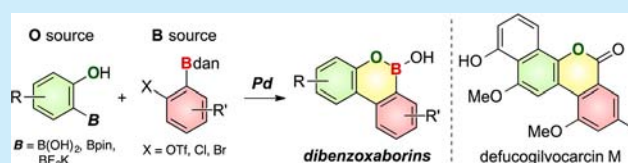
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S Supporting Information

ABSTRACT: An efficient synthetic method for versatile dibenzoxaborins based on boron-selective Suzuki–Miyaura cross-coupling between *o*-borylphenols and aryl halides or triflates bearing a 1,8-diaminonaphthalene-protected *o*-boryl group is reported. A short synthesis of defucogilvocarcin M was achieved using the proposed method in combination with several other boron-mediated transformations.

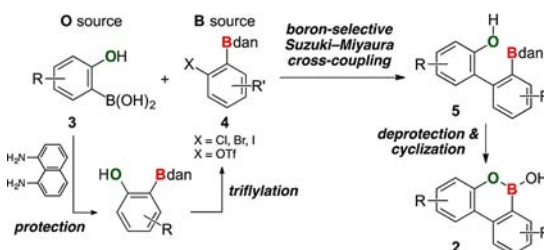


Organoboron compounds play valuable roles in a variety of disciplines, e.g., as efficient building blocks in organic synthesis and materials science and as unique pharmacophores and chemosensors in medicinal chemistry and chemical biology.¹ Recently, considerable attention has been paid to cyclic boronic half esters, such as 1,3-dihydro-1-hydroxy-2,1-benzoxaborole (1), because of their superior properties in terms of binding affinity to saccharides² and bioactivity.³ 6-Hydroxy-6H-dibenz-[c,e][1,2]oxaborin (2a),⁴ which is referred to as dibenzoxaborin in this paper, is a cyclic boronic half ester that serves as a useful building block for constructing versatile π -conjugated systems.⁵ Typically, dibenzoxaborins have been prepared by treatment of 2-hydroxybiaryl with BCl₃ followed by addition of AlCl₃^{4a,b,5a} or a monohalogen–lithium exchange reaction of 2,2'-dibromobiaryl followed by treatment with a trialkyl borate.^{5b} However, only limited dibenzoxaborins are available from the reported synthetic methods,^{4–6} and the utility of dibenzoxaborins remains largely unexplored. Herein, we show an efficient synthetic method for dibenzoxaborins that is based on boron-selective Suzuki–Miyaura cross-coupling.



Dibenzoxaborins 2 contain a biphenyl substructure; therefore, we conceived the idea of preparing 2 using Suzuki–Miyaura cross-coupling⁷ of *ortho*-hydroxyaryl boronic acid 3 with aryl halide 4 bearing a 1,8-diaminonaphthalene (dan)-protected *ortho*-boryl group,⁸ followed by deprotection of the dan group and intramolecular dehydrative cyclization (Scheme 1). We

Scheme 1. Synthetic Plan of Dibenzoxaborins based on Boron-Selective Suzuki–Miyaura Cross-coupling



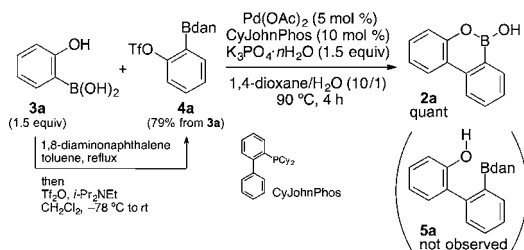
assumed that this strategy would be suitable for preparing diverse dibenzoxaborins because the oxygen source 3 could be transformed into triflate-type boron source 4 (X = OTf) by a simple two-step procedure: dan-protection of the boryl group and triflylation of the phenolic hydroxy group.

After extensive screening of the reaction conditions for cross-coupling of (2-hydroxyphenyl)boronic acid (3a) with dan-protected *ortho*-borylphenyl triflate 4a, an excellent result was obtained using CyJohnPhos^{8b,9} as a ligand for the catalytic system and potassium phosphate as a base (Scheme 2).^{10,11} Contrary to our expectation, the originally intended cross-coupling product 5a was not obtained; however, the desired dibenzoxaborin 2a was produced directly without special manipulations. This result was possibly because of the high affinity of oxygen for boron, which assisted deprotection of the dan group and formation of a stable dibenzoxaborin skeleton. Furthermore, we observed that using an equimolar amount of

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Scheme 2. Optimized Conditions



base with an arylboronic acid was important to obtain dibenzoxaborin in high yield.¹⁰ The reaction conditions using an excess amount of base significantly decreased the product yield accompanying the production of 2-phenylphenol, which should be formed through protodeborylation of dibenzoxaborin **2a** triggered by the redundant base.

Under the optimized conditions, a variety of O-sources **3** and B-sources **4** with either electron-donating or -withdrawing groups served as good substrates to afford dibenzoxaborins, including those difficult to prepare by conventional methods (Table 1). As for the oxygen source, not only boronic acids but also boronic acid pinacol esters or a trifluoroborate salt¹² were usable under the same conditions (entries 1, 4–7, 12). In particular, a Pd(PPh₃)₄ catalytic system gave better results for some pinacol ester substrates (entries 1, 5, 6). These results significantly increased the scope of the method because a variety of *o*-hydroxyarylboronic acid pinacol esters can be readily prepared in several ways: treatment of *o*-lithiated phenolates with trialkyl borate,¹³ Pd-catalyzed Miyaura borylation of *o*-halophenols,¹⁴ or iridium-catalyzed direct *o*-borylation of phenols.¹⁵ In addition to aryl triflates, chlorides and bromides with a neighboring Bdan group served as an efficient boron source substrate (entries 8–11, 13–15). The method enabled facile synthesis of disubstituted dibenzoxaborins and a heteroatom containing compound, such as pyridine-fused benzoxaborin **2m** (entries 11–13). Unique pentacyclic arylboronic ester **2n** was also available via double cyclization of dibromo boron source **4g** using an excess amount of **3a** (entry 14). The planar structure of **2n** was clearly demonstrated by X-ray structure analysis.^{10,16} Coupling of olefinic boron source **4h** with **3a** proceeded in the same fashion, providing benzoxaborin **2o** in high yield (entry 15).

Moreover, trading the boryl group of the oxygen source with the halogen group of the boron source was effective for the synthesis of bis(dibenzoxaborin) derivative **2p** with a binaphthyl skeleton, which was achieved under modified conditions (Scheme 3).^{10,17} Coupling of 3,3'-dibromo-[1,1'-binaphthalene]-2,2'-diol (**6**) with monodan-protected *ortho*-benzene-diboronic acid pinacol ester **7^{8b}** using di(1-adamantyl)-*n*-butylphosphine¹⁸ as a ligand afforded **2p** in moderate yield.^{10,19}

The boron-selective coupling approach was also applicable to the synthesis of dihydrodibenzazaborine²⁰ derivatives using *ortho*-borylated anilines as a nitrogen source (Scheme 4A). Cross-coupling of (2-aminophenyl)boronic acid (**8a**) with **4a** under the general conditions afforded dihydrodibenzazaborine **9^{5a,20a,b,d}** in 70% yield. The reaction of (2-(acetylamino)phenyl) boronic acid (**8b**) with **4a** afforded the cross-coupling product **10**, wherein the Bdan group remained untouched. This was probably due to the low nucleophilicity of amide nitrogen. In this case, the catalytic system using Pd(amphos)₂Cl₂²¹ provided a better result. Removal of the dan group of **10** under acidic conditions and purification by recrystallization afforded dehy-

Table 1. Scope of Substrates

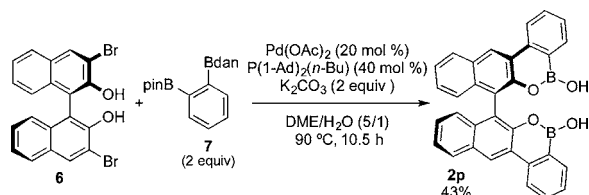
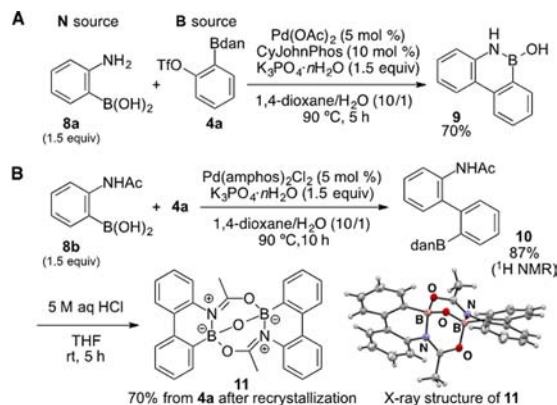
entry	O source 3^a	B source 4	time (h)	product 2	yield (%) ^b
1	3b	4a	8 (5) ^c	2a	74 (98) ^c
2	3c	4a	5	2b	88
3	3d	4a	4	2c	67
4	3e	4a	5	2d	92
5	3f	4a	4 (9) ^c	2e	78 (92) ^c
6	3g	4a	4 (9) ^c	2f	56 (74) ^c
7	3h	4a	4	2g	72
8	3a	4b	4	2h	92
9	3a	4c	4	2i	80
10	3a	4d	2	2j	83
11	3c	4d	3.5	2k	89
12	3e	4e	5	2l	85
13	3a	4f	16	2m	65
14 ^d	3a	4g	9	2n	30
15	3a	4h	5	2o	81

^aBpin = 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl. ^bIsolated yields. ^cReaction times and yields for the reaction performed using Pd(PPh₃)₄ (5 mol %) and 2 M aqueous Na₂CO₃ (1.5 equiv) in DME at 90 °C in parentheses. ^dMolar ratio: **3a**/**4g**/base = 3.0/1.0/1.5.

drated dimer **11** as the sole product in high yield (Scheme 4B).^{10,16,20c}

The utility of the synthetic method for dibenzoxaborins was demonstrated in a short synthesis of defucogilvocarin M (**12**), taking advantage of other boron-mediated transformations

Scheme 3. Bis(dibenzoxaborin) with Binaphthyl Skeleton

Scheme 4. Synthesis of Dihydrodibenzazaborines^a

^aamphos = *p*-(Me₂N)C₆H₄P(*t*-Bu)₂.

(Scheme 5). Defucogilvocarcin M is a representative aglycon of the gilvocarcin-class antibiotics, which have been considered as a challenging synthetic target by many groups.²² A previous report has shown that dibenzoxaborin is capable of converting into 3,4-benzocoumarin by a palladium-mediated deborylative CO insertion reaction.^{5a} Thus, we assumed that defucogilvocarcin M with a dibenzocoumarin structure can be prepared from benzonaphthoborin with appropriate substituents, such as **2q**. Therefore, we first prepared the coupling components, 2-boryl-1-naphthol derivative **3i** and triflate **4i**.

The oxygen source **3i** was prepared from known naphthol **16**²³ by iridium-catalyzed *ortho*-borylation¹⁵ (Scheme 5A). Previously, Suzuki and co-workers reported an efficient approach to differentially protected 1,4,5-naphthalenetriol **16** based on

regioselective [2 + 4]-cycloaddition of 3-benzyloxybenzynes with 2-methoxyfuran.²³ Recently, we have reported an efficient generation method for arynes via ate complexes of arylboronic esters bearing an *ortho*-triflyloxy group.²⁴ This method was also effective for the regioselective synthesis of naphthol **16** using aryne precursor **15**, which was easily prepared by *ortho*-borylation¹⁵ of 2-benzyloxyphenol (**13**) and subsequent triflylation. The boron source **4i** was similarly prepared by *ortho*-borylation and triflylation of 4-methylguaiaicol (**17**), followed by a simple two-step conversion of the pinacoloboryl group to the dan-protected boryl group (Scheme 5B).

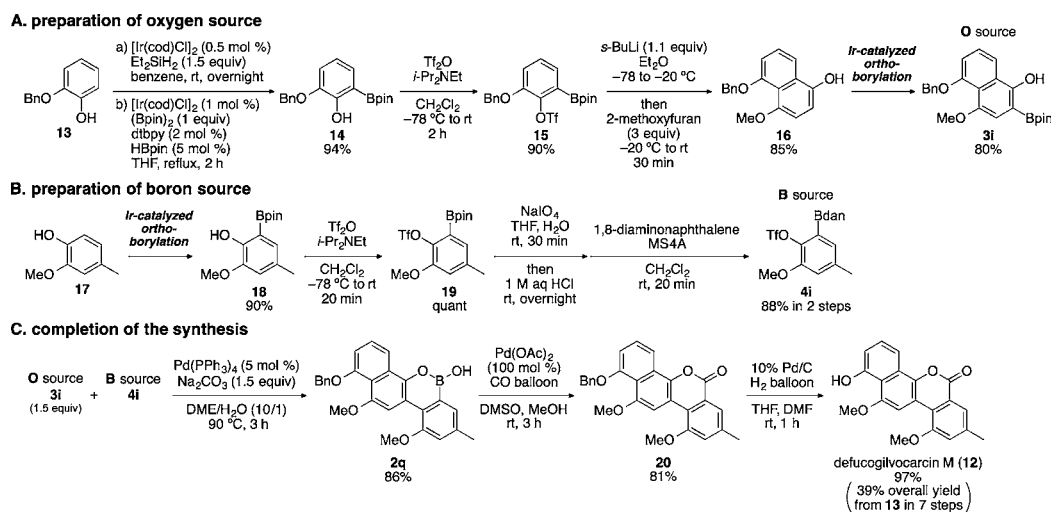
Synthesis of defucogilvocarcin M was accomplished in three additional steps (Scheme 5C). Boron-selective Suzuki–Miyaura cross-coupling of **3i** with **4i** afforded the desired benzonaphthoborin **2q** in 86% yield. Palladium-mediated deborylative CO insertion of **2q** provided dibenzocoumarin derivative **20**.^{22l} Finally, debenzoylation of **20** under reported conditions^{22l} afforded defucogilvocarcin M (**12**). The synthesis was accomplished in 7 steps with a 39% overall yield in the longest linear sequence, which compares very favorably with the previous successful syntheses: 17% in 11 steps,^{22h} 31% in 8 steps,²²ⁱ 33% in 8 steps,^{22j} 33% in 16 steps,^{22l} and 15% in 9 steps^{22m} (some of them do not include the yields for the preparation of starting materials).

In summary, we have developed a convenient synthetic method for diverse dibenzoxaborin derivatives. The method was successfully applied to the concise synthesis of defucogilvocarcin M. Further studies on dibenzoxaborins, including their application to novel transformations and molecular recognition, are currently in progress.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures and characterization data including copies of NMR spectra and the X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Scheme 5. Synthesis of Defucogilvocarcin M Using Boron-Mediated Transformations^a

^acod = cyclooctadiene, dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridyl.

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Notes

The authors declare no competing financial interest.

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