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Differentially Protected Benzenediboronic Acids: Divalent Cross-Coupling Modules for the Efficient Synthesis of Boron-Substituted Oligoarenes

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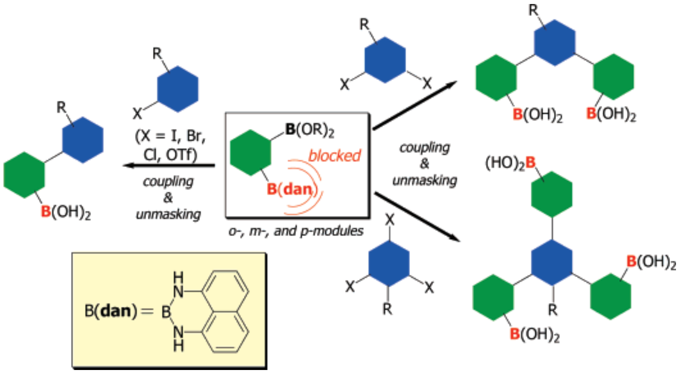
ABSTRACT



On the basis of the boron-masking strategy, new divalent cross-coupling modules have been designed for the efficient synthesis of boron-substituted oligoarenes. The modules, i.e., monoprotected *o*-, *m*-, and *p*-benzenediboronic acid derivatives, undergo highly selective Suzuki–Miyaura coupling with sp^2 iodides, bromides, chlorides, and triflates, affording coupling products in which the protected boronyl groups are left intact.

Much effort has been devoted to the exploration of new synthetic routes to organoboron compounds because of their increasing utilization in synthetic organic chemistry directed toward both material sciences and pharmaceutical sciences.[1] In particular, the chemistry of organoboronic acids[2] is growing rapidly in recognition of their reasonable stability and controllable reactivity in a variety of transition-metal-catalyzed reactions, such as Suzuki−Miyaura coupling (SMC).[3] Therefore, efficient synthetic routes to organoboronic acid derivatives are in great demand, including those having multiple $B(OH)_2$ functional groups.[4] While the majority of the newly developed methods involve boron−carbon bond formation as the key step,[5,6] it seems to be highly desirable to develop synthetic methods in which boron groups are retained intact. Although the potential of boronyl

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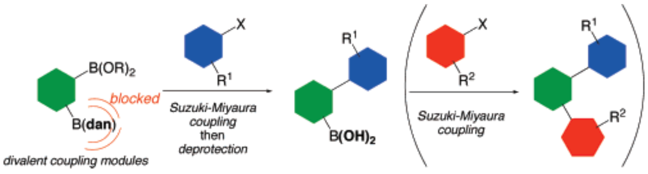
protection in organic synthesis has been successfully demonstrated by the studies of organotrifluoroborates, which are tolerable toward various reactions including oxidation, they are still reactive in SMC.[7] It seems likely that the development of effective protective groups for boronyl groups in SMC shall open up the new possibilities for the synthesis of new organoboron compounds.

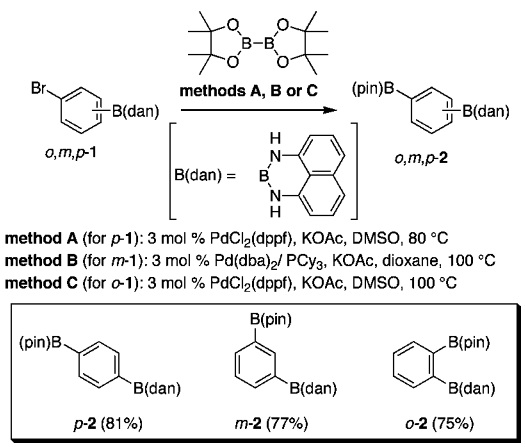
In this paper, we report benzenediboronic acid derivatives of which boronyl groups are differentially protected as new divalent cross-coupling modules for the convenient synthesis of oligoarene derivatives (Scheme 1).[8] The modules have two boronyl-derived substituents whose reactivities were differentiated by the introduction of a temporary protective group onto one of the two boron atoms. The temporary protection of otherwise reactive boronyl groups was achieved by 1,8-diaminonaphthalene, which we recently established as a masking group for boronyl groups in iterative SMC.[9−11]

Scheme 1. Synthesis of Oligoarenes by Using Monoprotected Benzenediboronic Acid Derivatives as Divalent Coupling Modules



Our initial attempts at preparing the requisite monoprotected modules by simple condensation of benzenediboronic acids with 1,8-diaminonaphthalene resulted in nonselective formation of mixtures of monoprotected and diprotected diboronic acids. We then turned our attention to use of boronyl-protecteded haloarylboronic acid derivatives as starting materials. Protected haloarylboronic acids *p*-, *m*-, and *o*-**1** were subjected to palladium-catalyzed borylation with bis(pinacolato)diboron (Scheme 2).[12] Reactions of *p*- and *o*-**1** proceeded in the presence of $PdCl_2$(dppf) in DMSO, giving benzenediboronic acid derivatives *p*- and *o*-**2**, respectively, whose boron atoms are unsymmetrically substituted with 1,8-diaminonaphthalene and pinacol. On the other hand, *m*-**1** showed an apparently lower reactivity than the corresponding *p*- and *o*-derivatives, requiring the modified catalyst system ($Pd(dba)_2/PCy_3$) to obtain a reasonable yield of *m*-**2**.

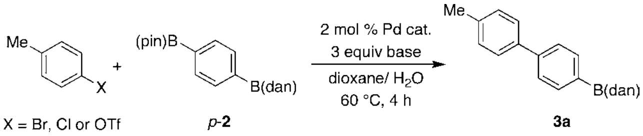
Scheme 2. Synthesis of Monoprotected Benzenediboronic Acid Derivatives



method A (for *p*-**1**): 3 mol % $PdCl_2$(dppf), KOAc, DMSO, 80 °C
method B (for *m*-**1**): 3 mol % $Pd(dba)_2$/ PCy_3, KOAc, dioxane, 100 °C
method C (for *o*-**1**): 3 mol % $PdCl_2$(dppf), KOAc, DMSO, 100 °C

The monoprotected *p*-benzenediboronic acid derivative *p*-**2** was subjected to SMC with *p*-bromotoluene under various reaction conditions (Table 1). The reaction rate was greatly influenced by bases: K_3PO_4 and NaOH were found to be most effective in promoting the reaction in dioxane/H_2O in the presence of Pd[P(*t*-Bu)$_3$]$_2$ as a catalyst, whereas KF, CsF, and Na_2CO_3 resulted in a slower reaction at 60 °C. After prolonged reaction time (18 h), however, almost quantitative yields were attained even with the less effective bases (entries 1−5). It should be noted that the 1,8-diaminonaphthalene protective group was found to be perfectly tolerable toward strong bases in the presence of water.[9] The high tolerance toward bases is characteristic of the 1,8-diaminonaphthalene

Table 1. Optimization of Suzuki−Miyaura Coupling Reaction Conditions[a]



entry	X	catalyst	base	% yield[b]
1	Br	Pd[P(*t*-Bu)$_3$]$_2$	KF	37
2	Br	Pd[P(*t*-Bu)$_3$]$_2$	CsF	51
3	Br	Pd[P(*t*-Bu)$_3$]$_2$	Na_2CO_3	58
4	Br	Pd[P(*t*-Bu)$_3$]$_2$	K_3PO_4	97
5	Br	Pd[P(*t*-Bu)$_3$]$_2$	NaOH	99 (99)
6	Br	$Pd(OAc)_2/PPh_3$ (1/2)	NaOH	99
7	Br	$Pd(OAc)_2$/dppf (1/1)	NaOH	99
8[c]	Cl	Pd[P(*t*-Bu)$_3$]$_2$	NaOH	92 (90)
9[c]	Cl	$Pd(OAc)_2/PPh_3$ (1/2)	NaOH	N.R.
10	OTf	$Pd(OAc)_2$/(2-biphenyl)PCy_2 (1/2)	NaOH	(94)

[a] A mixture of aryl halide (0.14 mmol), *p*-**2** (0.14 mmol), a catalyst (2.7 μmol), and base (0.41 mmol) was stirred at 60 °C for 4 h. [b] NMR yield. Isolated yield in the parentheses. [c] 3 mol % of catalyst at 80 °C for 24 h.

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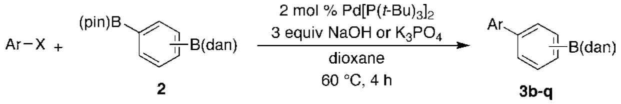
protective group in comparison with a recently reported tridentate protective group, which is reported to be deprotected easily even by weak bases.[10] For the cross-coupling with aryl bromides, PPh_3 and DPPF ligands are active enough to attain high yields (entries 6 and 7). In the coupling of aryl chloride, however, use of a t-Bu_3P-based catalyst system rather than a PPh_3-based system was essential to obtain high yields (entries 8 and 9). In the coupling of *p*-tolyl triflate, (2-biphenyl)PCy_2 was found to be most active,[13] while the t-Bu_3P-based catalyst resulted in almost no reaction under the same reaction conditions (entry 10). In general, use of NaOH as a base was preferable, and even in the presence of the strong base, there was no appreciable decomposition of the protected boronyl group during the reaction.

Under the optimized reaction conditions, *p*-, *m*-, and *o*-**2** were subjected to the cross-coupling reaction with various aryl halides (Table 2). Coupling of aryl iodides proceeded in high yields under the reaction conditions optimized for aryl bromides, regardless of the electronic nature of the *p*-substituents on the aromatic rings (entries 1−3). Products could be isolated in high yields by silica gel column chromatography. Cross-coupling of *p*-**2** with substituted aryl bromides, heteroaryl bromides, and aryl chlorides afforded the corresponding coupling products in high yields (entries 4−9). Under the same reaction conditions as *p*-**2**, *m*-**2** reacted with aryl bromides to give the corresponding coupling products in good yields (entries 10−12). In contrast to the reactions of *p*-**2** and *m*-**2**, reactions of *o*-**2** in the presence of NaOH resulted in significant decomposition of the protected boronyl group during the reaction. Using K_3PO_4 as a base, however, the cross-coupling of *o*-**2** proceeded cleanly, giving the corresponding products in high yields (entries 13−17). Note that cross-coupling of *o*-**2** with ortho-substituted aryl bromide gave sterically demanding coupling products in high yields (entries 16 and 17).

Table 2. Pd-Catalyzed Suzuki−Miyaura Coupling of Aryl Halides with Benzenediboronic Acid Derivatives[a]

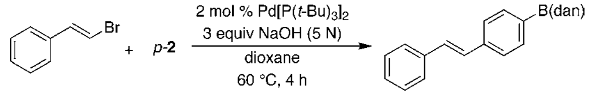


entry	aryl halide Ar	X	2	product	% yield[b]
1[c]	Ph	I	*p*-**2**	**3b**	94
2	4-$MeOC_6H_4$	I	*p*-**2**	**3c**	92
3	4-$NO_2C_6H_4$	I	*p*-**2**	**3d**	88
4	4-FC_6H_4	Br	*p*-**2**	**3e**	99
5	2,6-$Me_2C_6H_3$	Br	*p*-**2**	**3f**	93
6[c]	1-Naphthyl	Br	*p*-**2**	**3g**	85
7	2-Pyridyl	Br	*p*-**2**	**3h**	96
8	2-Thienyl	Br	*p*-**2**	**3i**	98
9[d]	4-$NO_2C_6H_4$	Cl	*p*-**2**	**3d**	93
10	4-MeC_6H_4	Br	*m*-**2**	**3j**	94
11	4-$MeOC_6H_4$	Br	*m*-**2**	**3k**	95
12[c]	4-MeC(O)C_6H_4	Br	*m*-**2**	**3l**	95
13[e]	4-MeC_6H_4	Br	*o*-**2**	**3m**	96
14[e]	4-$MeOC_6H_4$	Br	*o*-**2**	**3n**	94
15[e]	4-MeC(O)C_6H_4	Br	*o*-**2**	**3o**	99
16[e]	2-MeC_6H_4	Br	*o*-**2**	**3p**	99
17[e]	1-naphthyl	Br	*o*-**2**	**3q**	94

[a] A mixture of aryl halides (0.14 mmol), **1** (0.14 mmol), Pd[P(t-Bu)$_3$]$_2$ (2.7 μmol), and 5 N NaOH aq (0.41 mmol) was stirred at 60 °C for 4 h, unless otherwise noted. [b] Isolated yield. [c] Reaction in a 1.0 mmol scale. [d] At 80 °C. [e] K_3PO_4 as a base.

SMC of *p*-**2** with alkenyl bromide proceeded as well, giving the boron-substituted *trans*-stilbene **3r** in good yield (Scheme 3).

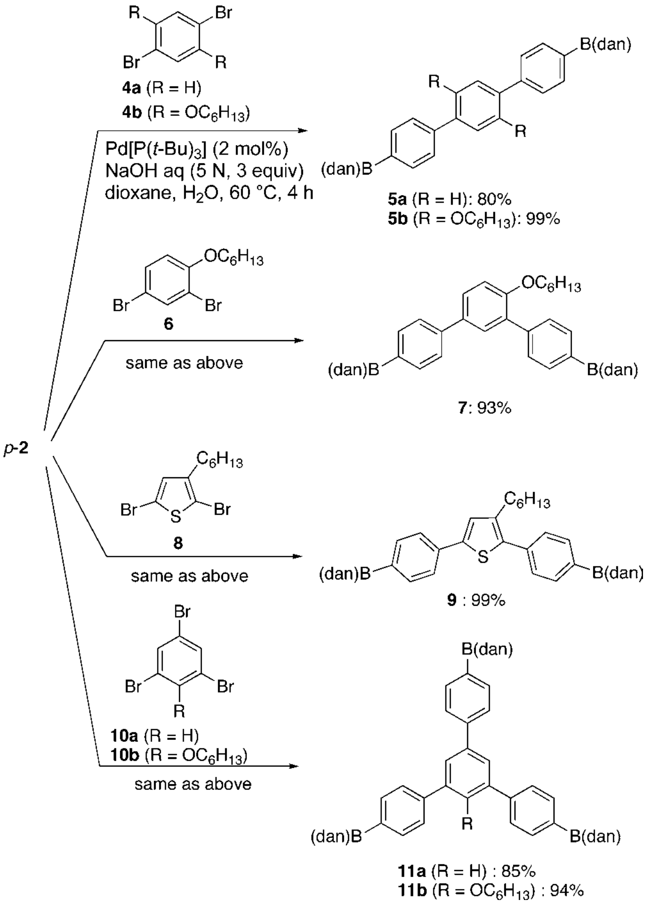
Scheme 3



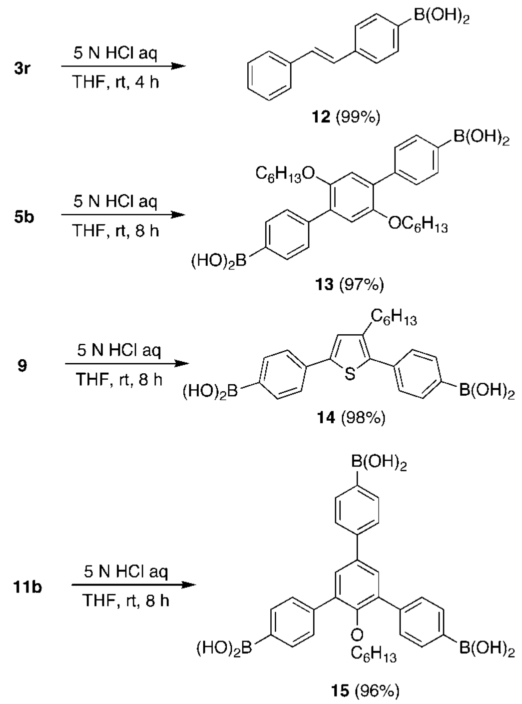
3r (90%)

To demonstrate the synthetic utility of the new divalent coupling module, reactions of di- and trihaloarene derivatives with *p*-**2** were carried out (Scheme 4). In the coupling of *p*-dibromobenzene derivatives **4a** and **4b**, 4,4″-diboronylterphenyl derivatives **5a** and **5b**, respectively, were obtained

Scheme 4. Synthesis of Boron-Substituted Oligoarene Derivatives



Scheme 5. Synthesis of Boronic Acids via Hydrolysis



in high yields. Likewise, *m*-dibromobenzene derivative **6** was coupled with *p*-**2**, giving meta-linked terphenyl **7** in high yield. The coupling system could be applied to dibromothiophene derivative **8** to give 2,5-di(*p*-boronylphenyl)thiophene derivative **9** in high yield. In an additional example, tribromobenzene derivatives **10** afforded tri(*p*-boronylphenyl)benzene derivatives **11a** and **11b** in high yields.

As demonstrated in the previous report, the diaminonaphthalene protective group features facile deprotection in the presence of aqueous acid (Scheme 5). For example, boronyl-substituted stilbene **12**, teraryl-1,4″-diboronic acid **13** and 2,5-di(4-boronylphenyl)thiophene derivative **14** were obtained in high yields by acid hydrolysis. Triply protected derivative **11b** also underwent clean deprotection of the diaminonaphthalene group at room temperature, giving triboronic acid **12** in high yield. Because cyclic boronates such as a pinacolate often meet with difficulty in clean deprotection,[14,15] the present boron-protecting strategy is attractive in that highly elaborated boronic acids are readily obtained at the final stage of their synthetic process.

In summary, we have developed new divalent cross-coupling modules for the synthesis of boron-substituted oligoarene derivatives, which can be further transformed into higher oligoarenes via a second cross-coupling. The mono-protected divalent modules undergo cross-coupling with sp^2 iodides, bromides, chlorides, and triflates under the optimized reaction conditions. The new reaction system provides convenient access to oligoarene derivatives bearing multiple boronyl groups through coupling with polyhalogenated haloarenes followed by clean deprotection of the protecting group.

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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.

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