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Preparation and Regioselective Diels–Alder Reactions of Borylbenzynes: Synthesis of Functionalized Arylboronates**

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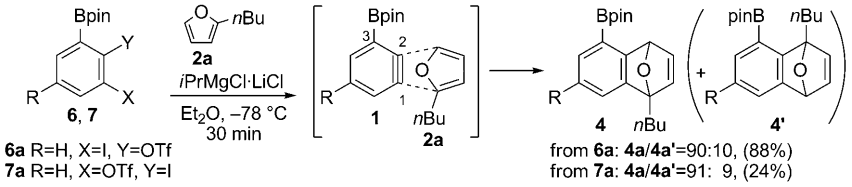
Arylboronates currently represent one of the most widely used classes of synthetic intermediates because of the versatile transformation of their C–B bonds to C–C, C–N, and C–O bonds.[1] Arylboronic acids have also been utilized in a variety of applications in saccharide sensing[2] and medicinal chemistry.[3] While arylboronic acid derivatives have been mainly prepared by the borylation of boron-free compounds,[4] the construction of carbon frameworks from boron-containing reactive species provides alternative syntheses of arylboronic acid derivatives. In particular, the latter approach is useful for the preparation of polyfunctionalized compounds, some of which are otherwise difficult to prepare.[5]

Herein we describe the preparation of 3-borylbenzynes **1**, and their Diels–Alder reaction with furans **2** or pyrroles **3** to produce highly functionalized arylboronic acid derivatives (**4** and **5**, Tables 1 and 2). The following two points are also worth noting from the viewpoint of benzyne chemistry: Firstly, the boryl groups (Bpin = pinacolboryl) were found to favor the highly regioselective Diels–Alder reactions of unsymmetrically substituted benzynes with furans **2** or pyrroles **3**, in contrast to most of the previously reported cases.[6-8] Secondly, the regioselectivities of the Diels–Alder reaction of **1** resembled those of the 3-silylbenzynes,[9] but the boryl groups exerted different effects than the silyl groups.

We investigated the efficient preparation of several precursors of the 3-borylbenzynes **1** and also benzyne generation. Although the addition of *t*BuLi to 2-boryl-6-bromo-4-methylphenyl triflate generated **1** (R = Me), which was immediately and effectively trapped by 2-butylfuran (**2a**) to give a 92:8 mixture of the regioisomeric cycloadducts **4** and **4′**(R=Me) in 67% yield, the use of *t*BuLi hampered the compatibility of various functional groups. 2-Boryl-4-methyl-6-trimethylsilylphenyl triflate was another potential precursor; however, its treatment with fluoride ions resulted in the exclusive generation of the 3-silylbenzyne. We finally discovered that 2-boryl-6-iodophenyl triflate **6a** served as an excellent precursor of **1a** (R = H) and was sufficiently compatibile with various functional groups. Thus, the addition of 1.2 equivalents of *i*PrMgCl·LiCl[10] to **6a** in Et_2O at −78 °C led to generation of **1a**, which instantaneously underwent the Diels–Alder reaction with **2a** to give a 90:10 mixture of **4a** (R = H) and **4a′** (R = H) in a total yield of 88% (Scheme 1). The use of the 2-boryl-6-iodophenyl triflates has another advantage that enabled us to prepare precursors with various



Scheme 1. Generation of borylbenzyne **1** and its Diels–Alder reaction with *n*-butylfuran (**2a**).

labile functional groups without the use of strong bases such as *n*BuLi (see below).[11] By starting from another precursor **7a**, in which the positions of the iodide and sulfonyloxy groups were interchanged, the same mixture of **4a** and **4a′** was obtained in the same ratio. Although we could not directly observe **1a** because of its extreme instability, all these results strongly suggest the generation of **1a** and its excellent reactivity as a dienophile in the Diels–Alder reaction. Another noteworthy result was the high regioselectivity of the Diels–Alder reaction, in which the major product **4a** (*anti* adduct) had the two substituents (boryl and *n*Bu groups) at a maximum distance. The steric repulsion between the boryl and *n*Bu groups does not seem to be sufficient to explain this high level of selectivity.[12]

Because the use of **6a** led to a better yield than **7a** (Scheme 1), we investigated the Diels–Alder reaction of various borylbenzynes **1**, generated from **6**, and the 2-substituted furans **2** (Table 1). The Diels–Alder reaction of **2b**, which has a methyl group as a small substituent in the 2-position, gave a significantly high regioselectivity (**4b**/**4b′** =

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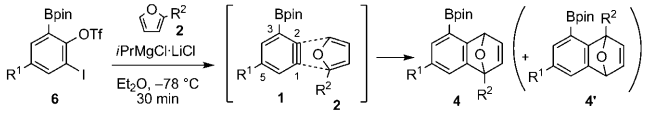
Table 1: Regioselective Diels–Alder reaction between borylbenzynes **1** (generated from **6**) and 2-substituted furans **2**.[a]



Entry	R^1	**6**, **1**	R^2	**2**	**4**	**4**/**4′**[b]	Yield [%][c]
1	Me	**6b**, **1b**	Me	**2b**	**4b**	88:12	85
2	Me	**6b**, **1b**	*n*Bu	**2a**	**4c**	92:8	93
3	Me	**6b**, **1b**	*t*Bu	**2c**	**4d**	94:6	>99
4	Me	**6b**, **1b**	$SiMe_3$	**2d**	**4e**	>98:2	91
5	Me	**6b**, **1b**	$SnBu_3$	**2e**	**4f**	>98:2	79
6	Me	**6b**, **1b**	CO_2Me	**2f**	**4g**	93:7	57
7	Me	**6b**, **1b**	COMe	**2g**	**4h**	87:13	51
8	Me	**6b**, **1b**	CN	**2h**[d]	**4i**	>98:2	46
9	Me	**6b**, **1b**	Ph	**2i**	**4j**	>98:2	40[e]
10	Me	**6b**, **1b**	OMe	**2j**	**4k**	>98:2	68[e]
11	Br	**6c**, **1c**	*n*Bu	**2a**	**4l**	84:16	64
12[f]	CO_2Me	**6d**, **1d**	*n*Bu	**2a**[g]	**4m**	83:17	68

[a] Conditions: **6** (1.0 equiv), **2** (3.0 equiv), *i*PrMgCl·LiCl (1.2 equiv) in Et_2O (0.10 M) at −78 °C for 30 min. [b] Determined from the 500 MHz ^{1}H NMR spectrum. [c] Total yield of isolated **4** and **4′**. [d] With 10 equiv of **2h**. [e] Isolated as an 8-boryl-1-naphthyl acetate (**4j**, **4k**) after acetylation of the crude reaction products. [f] *i*PrMgBr (2.1 equiv) was applied instead of *i*PrMgCl·LiCl. [g] With 10 equiv of **2a** at 0 °C.

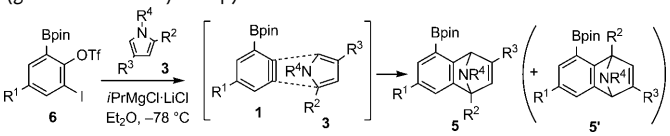
88:12; Table 1, entry 1).[7b] The larger alkyl groups of **2** increased both the selectivity and the yield (Table 1, entries 2 and 3). The steric effect of the substituents, though, was less than that of the corresponding silylbenzynes in similar Diels–Alder reactions.[9] The reactions of 2-trimethylsilylfuran (**2d**) (Table 1, entry 4) and 2-tributylstannylfuran (**2e**) (entry 5) exclusively gave the *anti* adducts (**4e** and **4f**). Substituents such as an ester (Table 1, entries 6 and 12), acyl (entry 7), nitrile (entry 8), and bromo (entry 11) were compatible under the reaction conditions. To our surprise, the reaction of furans that have both electron-donating (Table 1, entries 4, 5, and 10) and electron-withdrawing (entries 6–9) groups at the 2 position resulted in similar *anti* selectivities. The halogen and ester group substituents (R^1) at the 5 position of the benzyne led to a decrease of the *anti* selectivities (Table 1, entries 11 and 12).

3-Methylfuran (**2k**) reacted with **1b** to produce the Diels–Alder adducts (**8** and **8′**) in a 87:13 ratio. The major product **8** had the methyl group derived from **2k** located close to the boryl group (Scheme 2), whereas the use of 3-silylbenzyne resulted in a reverse selectivity.[13] This high level of regioselectivity is outstanding among the existing Diels–Alder reactions of substituted benzynes and 3-substituted furans.[7c]

These results clearly demonstrate that the effect of the boryl group on the regioselectivity of the Diels–Alder reaction is different from that of the silyl group; the former effect seems to be more electronically dominated and the latter is presumably caused by sterical factors. We hypothesize that some type of coordination of an isopropyl anion or a chloride ion to the Lewis acidic boron atom exhibits a stronger electron-donating inductive effect on the triple bond of the borylbenzynes **1** than that of the silyl group of the silylbenzynes. Therefore, the significantly polarized C1 (δ−) and C2 (δ+) atoms of **1** clearly distinguish even subtle electronic differences between the C2 and C5 atoms of slightly polarized furans such as 3-methylfuran (**2k**).

The cycloadditions of the benzynes **1** with pyrroles **3** are valuable for the synthesis of biologically active compounds.[14] The reaction of N-protected pyrroles **3** successfully produced cycloadducts **5** as the major products with high regioselectivities (Table 2). Particularly, the *N-tert*-butoxycarbonyl group

Table 2: Regioselective Diels–Alder reaction between borylbenzyne **1** (generated from **6**) and pyrroles **3**.[a]

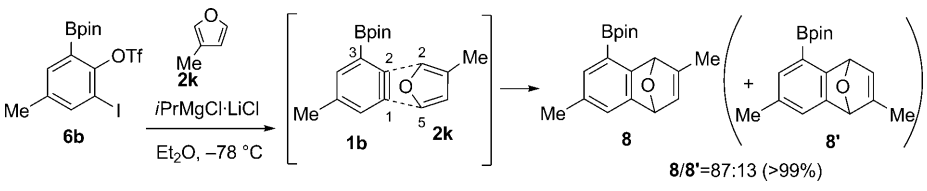


Entry	R^1	**6**, **1**	R^2	R^3	R^4	**3**	**5**	**5**/**5′**[b]	Yield [%][c]
1	Me	**6b**, **1b**	Et	H	Ts	**3a**	**5a**	87:13	63
2	Me	**6b**, **1b**	Et	H	Boc	**3b**	**5b**	>98:2	70
3	Me	**6b**, **1b**	Br	H	Boc	**3c**	**5c**	>98:2	58
4	Br	**6c**, **1c**	Et	H	Boc	**3b**	**5d**	95:5	72
5	CO_2Me	**6d**, **1d**	Et	H	Boc	**3b**	**5e**	88:12	61
6	Me	**6b**, **1b**	H	Me	Ts	**3d**	**5f**	86:14	87
7	Me	**6b**, **1b**	H	Me	Boc	**3e**	**5g**	92:8	95
8	Me	**6b**, **1b**	$(CH_2)_2Ph$	Me	Boc	**3f**	**5h**	>98:2	81

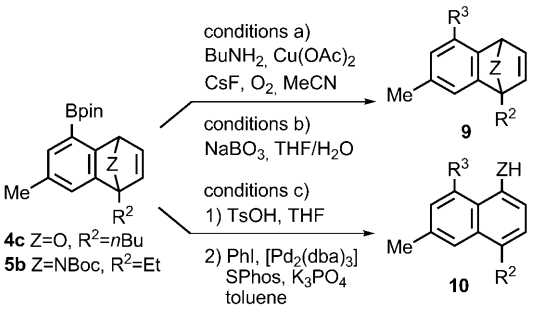
[a] Conditions: **6** (1.0 equiv), **3** (3.0 equiv), *i*PrMgCl·LiCl (1.2 equiv) in Et_2O (0.10 M) at −78 °C for 30 min. [b] Determined from the 500 MHz ^{1}H NMR spectrum. [c] Total yield of isolated **5** and **5′**.

of **3** was found to play an important role in determining the regioselectivity of the Diels–Alder reaction (compare entries 1 and 2 and entries 6 and 7 in Table 2), and the selectivities were higher than those of the furans **2** that have the same or similar substituents (entries 2, 4, 5, and 7). These results represent the first examples of highly regioselective Diels–Alder reactions between substituted benzynes and pyrroles **3**.

The boryl group of **4c** was successfully transformed into a nitrogen group (Scheme 3, conditions a) and into a hydroxyl group (conditions b) while leaving the 1,4-epoxy-1,4-dihydronaphthalene frame intact. After the acid-catalyzed isomerization of **4c** and **5b** into the corresponding 1-naphthol



Scheme 2. Regioselective Diels–Alder reaction between borylbenzyne **1b** (generated from **6b**) and 3-methylfuran (**2k**).



R^2	R^3	Z	Conditions	9, 10	Yield [%]
*n*Bu	NHBu	O	a	**9a**	71
*n*Bu	OH	O	b	**9b**	85
*n*Bu	Ph	O	c	**10a**	94
Et	Ph	NBoc	c	**10b**	82

Scheme 3. Transformation of the boryl groups of **4c** and **5b**. Boc = *tert*-butoxycarbonyl; dba = *trans*, *trans*-dibenzylideneacetone; SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; Ts = *p*-toluenesulfonyl.

and 1-naphthylamine derivatives, Suzuki coupling with phenyliodide gave the biaryl compounds **10a** and **10b** in excellent yields in two steps. Because the boryl group is easily eliminated by protodeboronation, it can additionally serve as a regioselectivity-directing auxiliary.[15] Thus, a series of reactions, namely the regioselective Diels–Alder reaction of the borylbenzynes **1** and the transformation of the boryl group of the adducts, has provided a reliable method for the synthesis of multisubstituted fused aromatic compounds.

In conclusion, we have succeeded in producing the 3-borylbenzynes **1** and have subsequently used them in regioselective cycloadditions with substituted furans **2** or pyrroles **3** to provide highly functionalized arylboronic acid derivatives. Efforts to apply the borylbenzynes **1** to other regioselective reactions are currently underway.

Experimental Section

General Procedure for the generation of borylbenzyne **1** followed by the Diels–Alder reaction with furans **2** or pyrroles **3**. (Scheme 1, Scheme 2, and Table 1, Table 2): An oven-dried pear-shaped flask was charged with borylbenzyne precursor **6** (1.0 equiv) and capped with an inlet adapter with a three-way stopcock and then evacuated and back-filled with argon. Anhydrous Et_2O (10 mL per 1.0 mmol of **6**) was added and the mixture was cooled to −78 °C. A furan (3.0 equiv) was added, followed by the slow addition of a solution of *i*PrMgCl·LiCl in THF (1.3 M, 1.2 equiv) over 5 min. The reaction mixture was stirred at −78 °C for 30 min, and subsequently quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the remaining aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

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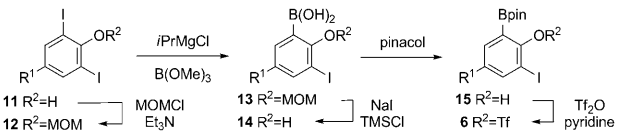
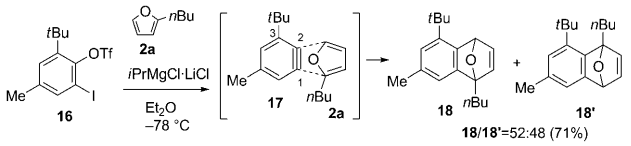
[11] The precursors **6** were generally prepared from the corresponding 2,6-diiodophenols **11** in five steps as shown below. The overall yields were fairly good (for example, **6a** (R^1 = H) was obtained in 62% overall yield). For detailed experimental procedures, see the Supporting Information. MOM = methoxymethyl; Tf = trifluoromethanesulfonyl; TMS = trimethylsilyl.



[12] The Diels–Alder reaction between 3-*tert*-butylbenzyne **17**, generated from **16** and **2a** produced no regioselectivity (unpublished results).



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