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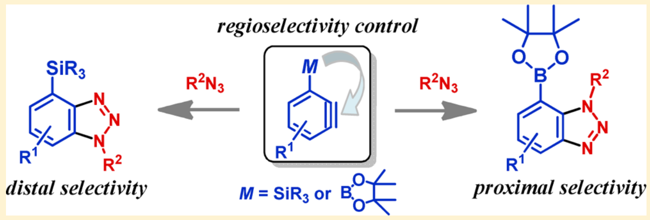
Regiocomplementary Cycloaddition Reactions of Boryl- and Silylbenzynes with 1,3-Dipoles: Selective Synthesis of Benzo-Fused Azole Derivatives

Takashi Ikawa,[†] Akira Takagi,[†] Masahiko Goto,[†] Yuya Aoyama,[†] Yoshinobu Ishikawa,[†] Yuji Itoh,[‡] Satoshi Fujii,[†] Hiroaki Tokiwa,*,[‡] and Shuji Akai*,[†]

[†]School of Pharmaceutical Sciences, University of Shizuoka, 52-1, Yada, Suruga-ku, Shizuoka, Shizuoka 422-8526, Japan
[‡]Department of Chemistry, Faculty of Science, Rikkyo University, 3-34-1, Nishi-ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

Supporting Information

ABSTRACT: Benzo-fused nitrogen-containing heterocycles are abundant in biologically active compounds. One of the most important methods for preparing such heterocycles is the (3 + 2) cycloaddition reaction of benzynes with 1,3-dipolar compounds. However, the reactions of unsymmetrically substituted benzynes generally show low selectivity and hence yield mixtures of two regioisomers. In this paper, we describe the synthesis of both regioisomers of multisubstituted benzo-fused azole derivatives such as benzotriazoles, 1*H*-indazoles, and benzo[*d*]isoxazoles through the regiocomplementary (3 + 2) cycloaddition reactions of 3-boryl- and 3-silylbenzynes with 1,3-dipoles. The improved generation of 3-borylbenzynes from new precursors was one of the most important results of this work, which produced the successful (3 + 2) cycloaddition reactions with exclusive and proximal selectivities. On the other hand, similar reactions of 3-silylbenzynes selectively afforded distal cycloadducts. Analysis of the reaction pathways of these amazing regioselectivities by density functional theory calculations revealed that the (3 + 2) cycloadditions of borylbenzynes are controlled by the electrostatic effect of the boryl group, while those of silylbenzynes are controlled mainly by the steric effect of the bulky silyl groups that produced electrostatically unfavorable adducts via anomalous transition states.



■ INTRODUCTION

Benzo-fused azole derivatives are one of the most important classes of nitrogen-containing heterocycles.[1] For example, they have been reported to have a wide range of biological activities such as anticancer,[2] antidepressant,[3] antidiabetic,[4] antimicrobial,[5] antifungal,[6] antitubercular,[7] and antilipolytic activities.[8] These compounds have traditionally been synthesized using a linear, stepwise transformation of substituted benzene derivatives.[9] However, these methods usually involve many steps and are less effective for the preparation of drug candidate libraries because each compound must be synthesized from a different starting material.

Cycloadditions of benzynes with 4π-components have attracted much attention recently. Among them, the (3 + 2) cycloaddition of benzynes with 1,3-dipole compounds has served as an effective alternative route to benzo-fused azole derivatives.[10] In 2007, Yamamoto et al. reported a synthesis of 1*H*-indazole[10b] using the (3 + 2) cycloaddition of benzynes, generated from 2-(trimethylsilyl)phenyl triflate with a fluoride source, to diazo compounds. Subsequently, a large number of benzo-fused azole derivatives such as 1*H*-indazole,[10d,h,j] 2*H*-indazole,[10k] benzotriazole,[10c,f,g] and benzo[*d*]isoxazole[10a,e,i,l] were synthesized using benzyne reactions. These transformations are valuable for convergent diversity-oriented syntheses of heterocyclic compounds and allow effective preparation of drug candidate libraries.

However, like most benzyne reactions,[11] the (3 + 2) cycloaddition of unsymmetrically substituted benzynes with 1,3-dipoles is not always regioselective. For example, the reaction of 3-methylbenzyne **1A** with 4-methoxyphenyl azide **6a** yields a 1:1 mixture of two regioisomers of benzotriazole (*proximal-* and *distal*-**7Aa**) (Table 1, entry 1),[10g] and a similar reaction of 3-fluorobenzyne **2A** also exhibited poor regioselectivity (entry 2).[10g] The reaction of 3-methoxybenzyne **3A** is one of the special cases in which the (3 + 2) cycloaddition with **6a** exclusively gave *distal*-**9Aa** (entry 3),[10g] and similar regioselective (3 + 2) reactions were also reported using 3-alkoxybenzynes.[10b,c,e,g,h,j] In addition, Suzuki et al. discovered another kind of the regioselective (3 + 2) cycloaddition reaction using (3-trialkylsilyl)benzyne with nitrone.[10a] However, since then only a few groups have focused on the regiocontrol of the (3 + 2) cycloadditions of benzynes possessing a substituent other than an alkoxy group,[10e,12,13] although so many new 1,3-dipolar cycloadditions have been reported over the last dacade.[10] Moreover, 3-silylbenzynes have

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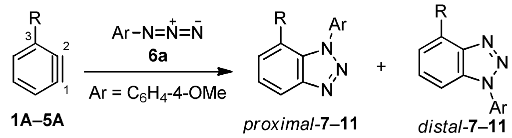
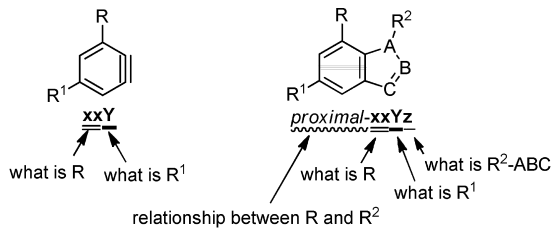
Table 1. Regioselectivities of (3 + 2) Cycloadditions of 3-Substituted Benzynes 1A–5A with 4-Methoxyphenyl Azide 6a



entry	R	1–5[a]	7–11[a]	proximal:distal	ref
1	Me	**1A**	**7Aa**	1:1	10g
2	F	**2A**	**8Aa**	1:1	10g
3	OMe	**3A**	**9Aa**	1:>50	10g
4	Bpin[b]	**4A**	**10Aa**	>50:1	this study
5	$SiMe_3$	**5A**	**11Aa**	1:5.7	this study

[a]General rules for the numbering on this paper. [b]Bpin: pinacolboryl



been generated under harsh reaction conditions using *n*-BuLi.[10a,e,12]

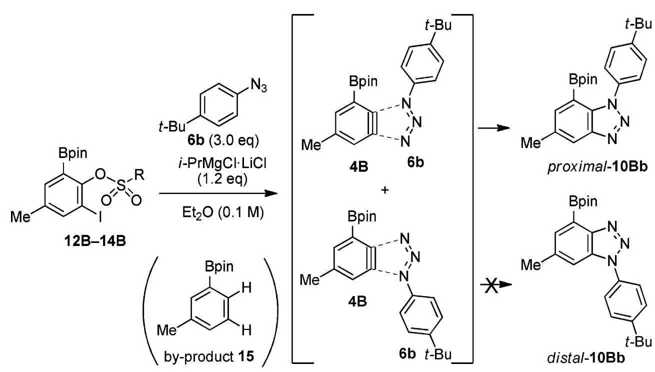
We recently reported that 3-boryl- and 3-silylbenzynes undergo Diels–Alder reactions with substituted furans and pyrroles to provide cycloadducts with high distal regioselectivity.[14] We applied these benzynes to the (3 + 2) cycloadditions with various 1,3-dipoles and discovered the following. The cycloaddition reactions of 3-borylbenzynes **4** selectively gave proximal benzo-fused azoles **10**, whereas similar reactions of 3-silylbenzynes **5** gave distal products **11**. These opposite regioselectivities were also generally obtained with a range of 1,3-dipoles (typical examples in Table 1, entries 4 and 5; for more examples, see Table 3). We applied these protocols to the regioselective synthesis of the biologically interesting triazole analogue of hippadine, vorozole, and its regioisomer. To reveal the origin of the opposite regioselectivities of the (3 + 2) cycloadditions of **4** and those of **5**, we performed theoretical analysis of the reaction pathways by density functional theory (DFT) calculations. Although a part of this work was reported in our recent brief account,[15] this paper describes the full details of this work. In particular, it provides new information about the reasons for the improvement of the borylbenzyne precursor and its development process, the experimental procedures and spectroscopic data of the benzyne precursors and products, the preparation of an aza analog of hippadine, and a full discussion about regioselectivities. Our previously published account only summarized the results without discussing them in detail, and in this paper we discuss the details of each reaction, pointing out many important features of the reactions that were not mentioned in the previous account.

■ RESULTS

Development of Improved Preparation Methods of 3-Boryl- and 3-Silylbenzynes. The most critical problems addressed in this project are the development of better precursors for the boryl- and silylbenzynes (**4** and **5**) and the optimization of the conditions for benzyne generation followed by (3 + 2) cycloaddition, because our preliminary trials, in which the generation methods for **4** and **5** (developed in our previous Diels–Alder reactions[14b]) were applied to the (3 + 2) cycloaddition with 4-(*tert*-butyl)phenyl azide **6b**, were not very successful. For example, *i*-PrMgCl·LiCl (1.2 equiv) was added to an Et_2O solution of 6-boryl-2-iodo-4-methylphenyl triflate **12B** and **6b** at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min to generate **4B** and promote the cycloaddition. We observed the formation of a cycloaddition product, *proximal*-**10Bb** as a single regioisomer; however, its yield was as low as 15%, and a significant amount of byproduct **15** (29%) along with the recovery of **12B** (26%) were observed (Table 2, entry 1). We suspected that **15** was produced by the competitive hydride reduction[16] of **4B** by another *i*-PrMgCl molecule, which would leave behind a substantial amount of **12B**.

Therefore, to improve the yield of *proximal*-**10Bb**, we attempted to suppress the formation of **15** using two approaches. First, we used Grignard reagents without *β*-

Table 2. Efficient Preparation of 3-Borylbenzyne 4B for (3 + 2) Cycloaddition to 4-(*tert*-Butyl)phenyl Azide 6b



entry	R	12B–14B	conditions	yield (%) of *proximal*-10Bb[a]
1	CF_3	**12B**	−78 °C, 30 min	15[b]
2	C_6H_4-4-Cl	**13B**	−78 °C, 30 min then 0 °C, 30 min	48
3	C_6H_2-2,4,5-Cl_3	**14B**	−78 °C, 30 min then 0 °C, 30 min	67[c]

[a]The yield of *proximal*-**10Bb** was determined by ^{1}H NMR; *distal*-**10Bb** was not detected in a crude product of each entry. [b]The formation of **15** (29% yield) and the recovery of **12B** (26% yield) were also observed. [c]Isolated yield of *proximal*-**10Bb**.

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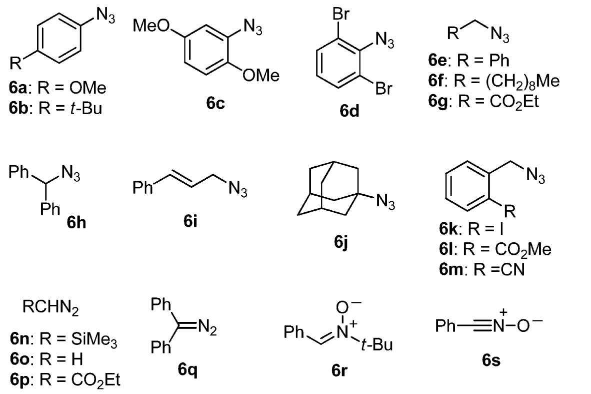

Figure 1. Structure of 1,3-dipoles **6a**–**6s**.

hydrogen atoms, such as MeMgCl, BnMgCl, and *t*-$Bu_2CHMgCl$, instead of *i*-PrMgCl; however, there was no improvement (see Table S1 in Supporting Information). We next examined leaving groups other than $-OSO_2CF_3$. Knochel et al. reported a very important method for preparing functionalized benzynes from 2-iodophenyl 4-chlorobenzenesulfonate using the reaction with *i*-PrMgCl.[17] The use of corresponding 4-chlorobenzenesulfonate **13B** significantly improved the yield of *proximal*-**10Bb** by up to 48% (Table 2, entry 2). After extensive studies on the benzyne precursors (see Tables S2 and S3 in Supporting Information), we finally found that 2,4,5-trichlorobenzenesulfonate **14B**[18,19] was the best precursor of **4B** and that its (3 + 2) cycloaddition with **6b** afforded *proximal*-**10Bb** in 67% yield (Table 2, entry 3). It was proved that the iodine–magnesium exchange reaction of **14B** proceeded rapidly at −78 °C; however, the subsequent formation of **4B** did not proceed at the same temperature when **14B** was used as a precursor (see Tables S2 and S3 in Supporting Information). **4B** was gradually generated while the reaction mixture was warmed to 0 °C and immediately reacted with **6b**. Thus, the leaving ability of the sulfonyloxy group of the benzyne precursor affected the rate of benzyne generation, and tuning this leaving ability was the key to suppressing the undesired hydride reduction and allowing the successful reaction of **4** with **6b**. The regioisomer *distal*-**10Bb** was not detected in any of the cases examined (Table 2), indicating the first successful proximal-selective (3 + 2) cycloaddition of 3-substituted benzynes with azides.

Previously, we prepared silylbenzynes **5** through the reaction of 2-bromo-6-silylphenyl triflates and *n*-BuLi and applied them in regioselective Diels–Alder reactions.[14a] In this study, we found the generation of **5** from 2,6-bis(trimethylsilyl)phenyl triflates **13** using Bu_4NF[14c,20] was more suitable for the (3 + 2) cycloaddition of **5** because of the milder reaction conditions required. In fact, the reaction of the in situ generated 5-methyl-3-(trimethylsilyl)benzyne **5B** with **6b** selectively yielded *distal*-**11Bb** (*distal*:*proximal* = 10:1) (Table 3, entry 1).[12] It is worth noting that the regioselectivity of **5B** was opposite to that of the above-mentioned borylbenzyne **4B**. This cannot be explained by the electrostatic effects of boron and silicon, which are both less electronegative than carbon (Allred-Rochow electronegativities: B, 2.0; Si, 1.7; C, 2.5).[21]

Scope and Limitation of (3 + 2) Cycloadditions of Boryl- and Silylbenzynes with Various 1,3-Dipoles.[15] We next investigated the (3 + 2) cycloadditions of 3-borylbenzynes (**4A** and **4B**) and 3-silylbenzynes **5A**–**5D** with diverse 1,3-dipoles including azides **6a**–**6m**, diazo compounds **6n**–**6q**, nitrone **6r**, and nitrile oxide **6s** (Figure 1 and Table 3). The (3 + 2) cycloaddition of **4** generally afforded *proximal*-**10**, while that of **5** selectively afforded *distal*-**11**. Many examples of opposite selectivities are presented in entries 1–9 of Table 3. On the other hand, nitrone **6r**[13] underwent cycloaddition with both **4** and **5** to give distal 2,3-dihydrobenzo[*d*]isoxazoles (**10Br** and **11Br**) with excellent selectivity (entry 10; similar reactions of **5** with **6r** were previously reported by Suzuki[10a] and Danishefsky[10e] under harsh conditions). This is the only exception in which both **4** and **5** showed the same distal selectivity.

The (3 + 2) cycloaddition of **4** with Me_3SiCHN_2 **6n** exclusively gave a desilylated indazole, *proximal*-**10Bn** (entry 9), while similar reactions of **5** with diazo compounds (**6p** and **6q**) gave distal 1*H*-indazoles (**11Bp** and **11 Bq**) (entries 18 and 19). Silylbenzyne **5B** and benzonitrile oxide **6s** were simultaneously generated from their precursors (**16B** and *N*-hydroxybenzimidoyl chloride, respectively) using Bu_4NF in a single flask and exclusively gave distal benzo[*d*]isoxazole **11Bs** (entry 20).

The following features are also worth noting: (i) Functional groups such as olefin (**6i**), ester (**6g** and **6l**), bromo (**6d**), iodo (**6k**), and cyano (**6m**) groups were tolerated under the reaction conditions when either *i*-PrMgCl·LiCl (for generating **4**) or a fluoride source (for generating **5**) was used. (ii) The reactions between **4** and most of the azides, including the bulky diphenylmethyl azide **6h**, resulted in complete proximal selectivity, and the reaction with the extremely bulky adamantyl azide **6j** also exhibited slight proximal preference (*proximal*-**10Bj**:*distal*-**10Bj** = 1.1:1) (Table 3, entry 8). (iii) The use of **5B′**, which has the more bulky *tert*-butyldimethylsilyl group, resulted in better distal selectivity (*distal*-**11Be′**:*proximal*-**11Be′** = 10:1) than did the use of 3-(trimethylsilyl)benzyne **5B** (entry 4). Similar results were also observed in the reaction with **6n** (entry 9). The distal selectivities also increased with increasing steric bulk of the alkyl chains in the azides (**6e**, **6h**, and **6j**; compare entries 4, 7, and 8). (iv) The substituent R^1 (H, Me, F, Cl) at the C5 position of **4** and **5** had little effect on the selectivity of the reaction with **6e** (entries 3, 4, 16, and 17).

Synthetic Applications of the (3 + 2) Cycloadducts. The proximal-selective cycloaddition of 3-borylbenzynes **4** was applied to the synthesis of triazole analogues (**18A** and **18B**) of a testicular function inhibitor, hippadine **19**[22] (Scheme 1a). When a suitably functionalized azide derivative **6t** was used, the (3 + 2) cycloaddition of borylbenzynes, generated from the corresponding precursors (**14A** and **14B**), gave benzotriazoles (*proximal*-**10At** and *proximal*-**10Bt**) in 69% and 67% isolated yields, respectively, with exclusive proximal selectivities. Their intramolecular Suzuki–Miyaura coupling afforded **17A** and **17B**, which were oxidized by MnO_2 to give **18A** and **18B** in 53% and 61% isolated yields, respectively, in two steps.

The formal synthesis of vorozole **21**[9] (Scheme 1b) was performed using the distal-selective cycloaddition of 3-silylbenzynes **5**.[15] First, 3-(*tert*-butyldimethylsilyl)benzyne, generated from **16E′**[23] by Bu_4NF, reacted with trimethylsilylmethyl azide **6u** to give *distal*-**11Eu′** (84% isolated yield) along with *proximal*-**11Eu′** (6% yield). Desilylation of *distal*-**11Eu′**, followed by deacetalization, afforded **20** (90% overall yield), a key intermediate for the synthesis of biologically active compounds such as aromatase inhibitor **21**[9] and a PI3K inhibitor.[24] Moreover, we synthesized a regioisomer **23** of vorozole **21** via the proximal-selective (3 + 2) cycloaddition of a 3-borylbenzyne, generated from **14C**, with **6u** (Scheme 1c).

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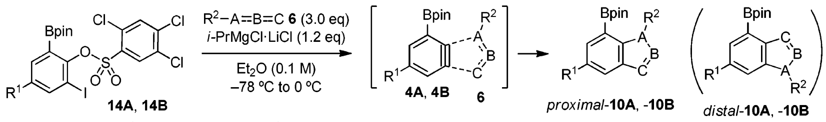
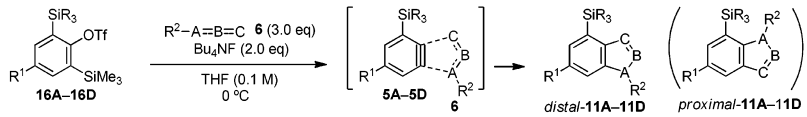
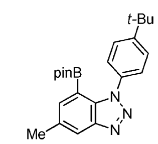
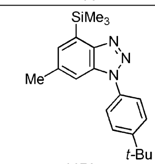
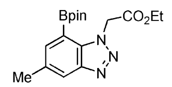
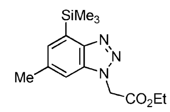
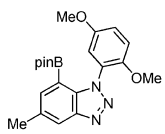
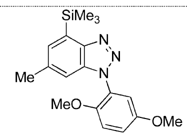
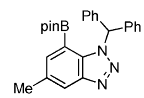
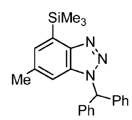
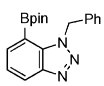
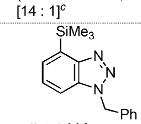
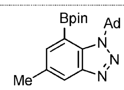
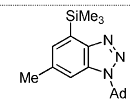
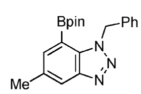
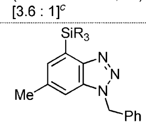
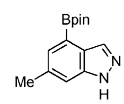
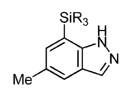
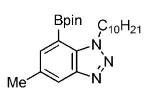
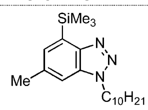
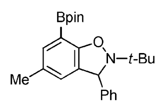
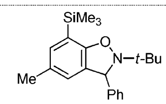
Table 3. Complementary Regioselective (3 + 2) Cycloaddition of Borylbenzynes 4 and Silylbenzynes 5



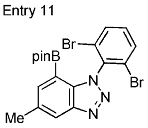
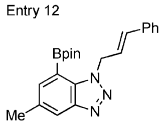
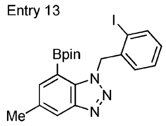
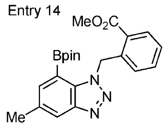
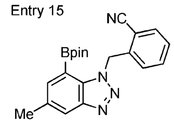
14A, **4A**, **10A**: R1 = H; **14B**, **4B**, **10B**: R1 = Me

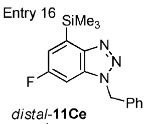
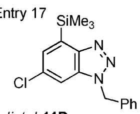
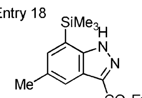
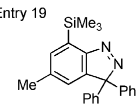
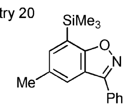


16A, **5A**, **11A**: R1 = H, SiR3 = SiMe3; **16B**, **5B**, **11B**: R1 = Me, SiR3 = SiMe3
16B', **5B'**, **11B'**: R1 = Me, SiR3 = Si(t-Bu)Me2; **16C**, **5C**, **11C**: R1 = F, SiR3 = SiMe3
16D, **5D**, **11D**: R1 = Cl, SiR3 = SiMe3

Entry	10	11	Entry	10	11
1	 *proximal*-**10Bb**[a] (67% from **14B**, **6b**)	 *distal*-**11Bb** (80%[b] from **16B**, **6b**) [10 : 1][c]	6	 *proximal*-**10Bg**[a] (74% from **14B**, **6g**)	 *distal*-**11Bg** (78%[b] from **16B**, **6g**) [3.3 : 1][c,e]
2	 *proximal*-**10Bc**[a] (65% from **14B**, **6c**)	 *distal*-**11Bc** (74%[b] from **16B**, **6c**) [14 : 1][c]	7	 *proximal*-**10Bh**[a] (65% from **14B**, **6h**)	 *distal*-**11Bh** (65%[b] from **16B**, **6h**) [5.0 : 1][c]
3	 *proximal*-**10Ae**[a] (89% from **14A**, **6e**)	 *distal*-**11Ae** (52%[b] from **16A**, **6e**) [3.6 : 1][c]	8	 *proximal*-**10Bj** (total 63% from **14B**, **6j**) [1.1 : 1][c]	 *distal*-**11Bj** (57%[b] from **16B**, **6j**) [>50 : 1][c]
4	 *proximal*-**10Be**[a] (85% from **14B**, **6e**)	 *distal*-**11Be** [73%[b] (77%)[b,d] from **16B**, **6e**] [3.3 : 1],[c] [10 : 1][c,d]	9	 *proximal*-**10Bn**[a] (54% from **12B**, **6n**)	 *distal*-**11Bn** [98%[b] (99%)[b,d] from **16B**, **6n**] [1.4 : 1],[c] [3.3 : 1][c,d]
5	 *proximal*-**10Bf**[a] (87% from **14B**, **6f**)	 *distal*-**11Bf** (73%[b] from **16B**, **6f**) [4.0 : 1][c]	10	 *distal*-**10Br**[f] (64% from **12B**, **6r**)	 *distal*-**11Br** (94% from **16B**, **6r**) [20 : 1][c]

Other examples:

Entry 11	Entry 12	Entry 13	Entry 14	Entry 15
 *proximal*-**10Bd**[a] (67% from **14B**, **6d**)	 *proximal*-**10Bi**[a] (80% from **14B**, **6i**)	 *proximal*-**10Bk**[a] (71% from **14B**, **6k**)	 *proximal*-**10Bl**[a] (74% from **14B**, **6l**)	 *proximal*-**10Bm**[a] (78% from **14B**, **6m**)

Entry 16	Entry 17	Entry 18	Entry 19	Entry 20
 *distal*-**11Ce** (84%[b] from **16C**, **6e**) [2.8 : 1][c,e]	 *distal*-**11De** (44%[b] from **16D**, **6e**) [3.0 : 1][c,e]	 *distal*-**11Bp** (81%[b] from **16B**, **6p**) [12 : 1][c]	 *distal*-**11Bq** (85%[b] from **16B**, **6q**) [21 : 1][c]	 *distal*-**11Bs** (73% from **16B**, **6s**) [>50 : 1][c]

[a]Proximal regioisomer **10** was exclusively observed in ^{1}H NMR spectra of the crude product. [b]Total isolated yield of distal and proximal isomers **11**. [c]The ratio of distal to proximal products, determined using ^{1}H NMR spectra of the crude product, is shown in brackets. [d]Results for 3-(*tert*-butyldimethylsilyl)benzyne **5B′** [SiR$_3$ = Si(*t*-Bu)Me$_2$], which was used instead of 3-(trimethylsilyl)benzyne **5B** (SiR$_3$ = SiMe$_3$) and provided a mixture of the corresponding *distal*- and *proximal*-**11B′** [SiR$_3$ = Si(*t*-Bu)Me$_2$]. The ratio of *distal*- to *proximal*-**11B′** [SiR$_3$ = Si(*t*-Bu)Me$_2$] is shown in brackets. [e]Only the corresponding desilylated product was isolated for *proximal*-**11**. [f]Distal regioisomer **10Br** was exclusively observed in ^{1}H NMR spectra of the crude product. Ad = 1-adamantyl.

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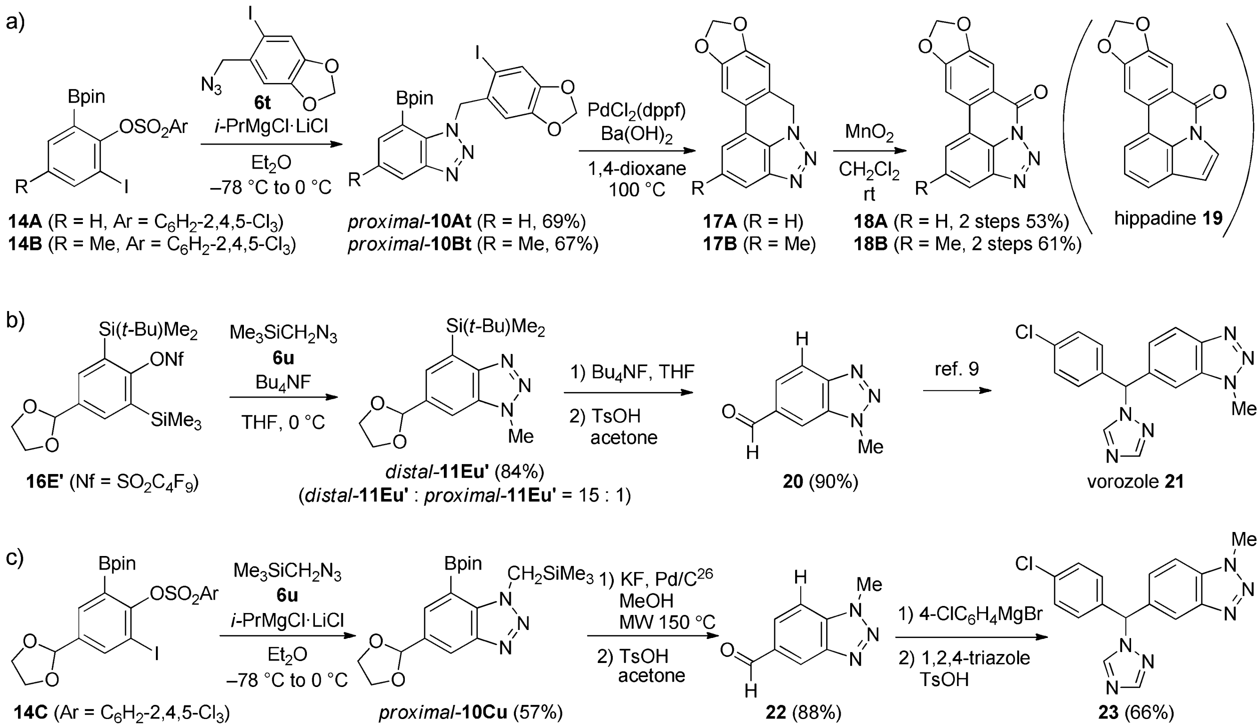
Scheme 1. Application of [3 + 2] Cycloaddition to the Syntheses of Biologically Active Compounds and Their Aza Analogues[a]



[a](a) Synthesis of hippadine analogues (**18A** and **18B**). (b) Synthesis of vorozole **21**. (c) Synthesis of a regioisomer **23** of vorozole **21**.

These regiocomplementary syntheses are valuable because the methylation of norvorozole produced a 1:1:1 mixture of **21** and its two regioisomers.[25] Our method involves fewer steps and allows the convergent synthesis of benzo-fused azoles from benzyne precursors and 1,3-dipoles. Thus, it should be useful for the combinatorial synthesis of diverse derivatives of biologically active compounds.

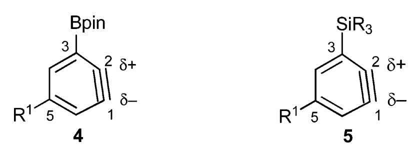
DISCUSSION

Herein, we discuss why the (3 + 2) cycloadditions of borylbenzynes **4** gave proximal products and those of silylbenzynes **5** gave distal products using the results of density functional theory (DFT) calculations.[27]

First, we checked the internal angles of the geometry-optimized 3-boryl- (**4A** and **4B**) and 3-silylbenzynes (**5A–5D**, and **5B′**) to evaluate the contribution of distortion energy,[12] and we also analyzed the charge distributions of these benzynes by performing natural population analysis in the isolated system (without solvent effect and coordination of metals) (Table 4).[28] Two important features of the benzynes were found: (i) The internal angles and the charge distribution of all these benzynes are almost exactly the same, and the substituent R^1 at the C5-position of benzyne has little effect. (ii) C2s are more electrophilic than C1s because of the electrostatic effect[10a,14,15] of the boryl and silyl groups and also because of the benzyne distortion.[12,29]

We next analyzed the experimental regioselectivities of the (3 + 2) cycloaddition reactions between two benzynes (**4B** and **5B**) and three 1,3-dipoles (**6e**, **6o**, and **6r**) (for natural charges of these 1,3-dipoles, see Figure 2) to find whether they were consistent with their calculated charge distributions and benzyne distortions. The experimental regioselectivities of the reactions between borylbenzyne **4B** and the 1,3-dipoles (**6e**, **6o**, and **6r**) are consistent with the calculated results, while those between silylbenzyne **5B** and the 1,3-dipoles (**6e** and **6o**) are not (Table 3, entries 4, 9, and 10). These contrasting results clearly indicate that the regioselectivities are accounted for by neither the electrostatic effect nor the benzyne distortion.

Table 4. Internal Angle and Natural Charge of 3-Borylbenzynes 4 and 3-Silylbenzynes 5



			internal angle (deg)		natural charge	
Bpin	R^1	**4**	C1	C2	C1	C2
	H	**4A**	122	133	−0.042	0.118
	Me	**4B**	122	132	−0.034	0.111
			internal angle (deg)		natural charge	
SiR_3	R^1	**5**	C1	C2	C1	C2
$SiMe_3$	H	**5A**	121	135	−0.037	0.081
$SiMe_3$	Me	**5B**	121	134	−0.030	0.076
$SiMe_3$	F	**5C**	121	135	−0.027	0.080
$SiMe_3$	Cl	**5D**	121	135	−0.027	0.092
$SiMe_3$	Me	**5B′**	121	134	−0.031	0.072
SiH_3	Me	**5B″**	123	132	−0.006	0.067

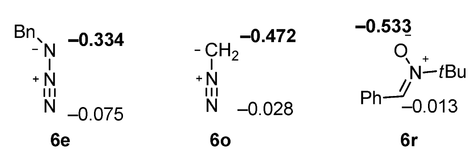


Figure 2. Natural charges of 1,3-dipolar compounds (**6e**, **6o**, and **6r**).

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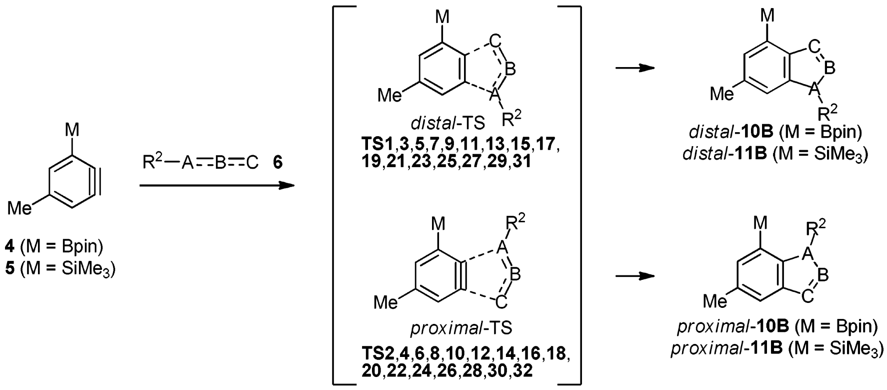
Table 5. Theoretical and Experimental Ratios in the (3 + 2) Cycloaddition Reactions of Borylbenzynes 4 and Silylbenzyne 5



					theoretical results		
entry	M	4, 5	6	TS1–TS32	$\Delta\Delta H^{\ddagger}$ or $\Delta\Delta G^{\ddagger}$ (kcal/mol)[a]	ratio of distal to proximal[30]	exptl ratio of distal to proximal from Table 3
1	Bin	**4B**	**6e**	**TS1, TS2**	+2.58[b]	1:>50	1:>50
2	$SiMe_3$	**5B**	**6e**	**TS3, TS4**	−1.11[c]	6.5:1	3.3:1
3	SiH_3	**5B″**	**6e**	**TS5, TS6**	−0.14[c]	1.3:1	
4	Bpin	**4B**	**6f**	**TS7, TS8**	+2.22[b]	1:43	1:>50
5	Bpin	**4B**	**6g**	**TS9, TS10**	+3.94[b]	1:>50	1:>50
6	Bpin	**4B**	**6h**	**TS11, TS12**	+1.96[b]	1:28	1:>50
7	Bpin	**4B**	**6i**	**TS13, TS14**	+2.36[b]	1:>50	1:>50
8	Bpin	**4B**	**6j**	**TS15, TS16**	+0.63[b]	1:2.9	1:1.1
9	Bpin	**4B**	**6k**	**TS17, TS18**	+2.78[b]	1:>50	1:>50
10	Bpin	**4B**	**6l**	**TS19, TS20**	+3.02[b]	1:>50	1:>50
11	Bpin	**4B**	**6m**	**TS21, TS22**	+3.60[b]	1:>50	1:>50
12	$SiMe_3$	**5B**	**6c**	**TS23, TS24**	−1.45[c]	11:1	14:1
13	$SiMe_3$	**5B**	**6j**	**TS25, TS26**	−2.40[c]	>50:1	>50:1
14	$SiMe_3$	**5B**	**6p**	**TS27, TS28**	−1.66[c]	20:1	>50:1
15	$SiMe_3$	**5B**	**6q**	**TS29, TS30**	−3.08[c]	>50:1	>50:1
16	$SiMe_3$	**5B**	**6s**	**TS31, TS32**	−2.73[c]	>50:1	>50:1

[a]Energy difference between *distal*-TS and *proximal*-TS. Positive $\Delta\Delta H^{\ddagger}$ or $\Delta\Delta G^{\ddagger}$ indicates that *distal*-TS is higher than *proximal*-TS, while negative $\Delta\Delta H^{\ddagger}$ or $\Delta\Delta G^{\ddagger}$ represents the opposite. [b]Activation energy difference is shown as a $\Delta\Delta H^{\ddagger}$ value. [c]Activation energy difference is shown as as a $\Delta\Delta G^{\ddagger}$ value.

Therefore, we performed a theoretical analysis of the reaction pathways, including the transition states, to quantitatively rationalize the origin of the selectivities.

The transition states (**TS1**–**TS4**) of the reactions between benzyl azide **6e** and two benzynes (3-borylbenzyne **4B** and 3-silylbenzyne **5B**) were obtained as typical cases (Table 5, entries 1 and 2). **TS2**, which leads to *proximal*-**10Be**, has an energy 2.58 kcal/mol lower than that of **TS1**, which leads to *distal*-**10Be**. This energy difference corresponds to 1:>50 proximal selectivity, which is in good agreement with our experimental result (*distal*-**10Be**:*proximal*-**10Be** = 1:>50; Table 3, entry 4 and Table 5, entry 1). On the other hand, **TS3**, which leads to *distal*-**11Be**, has an energy 1.1 kcal/mol lower than that of **TS4**, which leads to *proximal*-**11Be**. This difference corresponds to 6.5:1 distal selectivity, which is in reasonable agreement with our experimental result (*distal*-**11Be**:*proximal*-**11Be** = 3.3:1; Table 3, entry 4 and Table 5, entry 2).[30]

We also performed similar calculations for thirteen other reactions between **4B** (or **5B**) and various 1,3-dipolar compounds **6**. All of these results are in good agreement with the experimental data (Table 5, entries 4–16). These facts suggest that the calculated transition states are reliable and that their structures can provide valuable information that can be used to identify the origin of the regioselectivities.[30]

As a reference, the transition state **TS33** of the reaction of benzyne **24A** and **6e** was also calculated, in which the bond distance (2.40 Å) between the internal nitrogen of **6e** and the benzyne carbon is shorter than that (2.77 Å) between the terminal nitrogen and the benzyne carbon (Figure 3a). This is despite the fact that there should be some steric interaction between the benzylic methylene moiety of **6e** and the benzyne hydrogen. The corresponding bond distances of the **TS34**, derived from 5-methylbenzyne **24B**, and **6e** are close to those of **TS33**, which implies that a methyl group at the C5-position of benzyne hardly affects the structure of the transition state. The lengths of the two bonds forming in **TS2**, which is more stable than **TS1** because the electrostatic combination of the reacting atoms is well matched (Figure 3b), are also very similar to those of **TS34**. These facts imply that there is little steric interaction between the boryl group and the benzyl substituent and that the exclusive formation of *proximal*-**10Be** is dominated by the electrostatic interactions between the two reactants and also by the benzyne distortion, both of which are caused by the boryl group.[15]

In the case of silylbenzyne **5B**, the distance between the internal nitrogen and the benzyne C2 is much longer in **TS4** (2.51 Å) than in **TS34** (2.41 Å) because of the strong steric interaction between the trimethylsilyl group and the benzyl group. This makes the electrostatically and distortionally

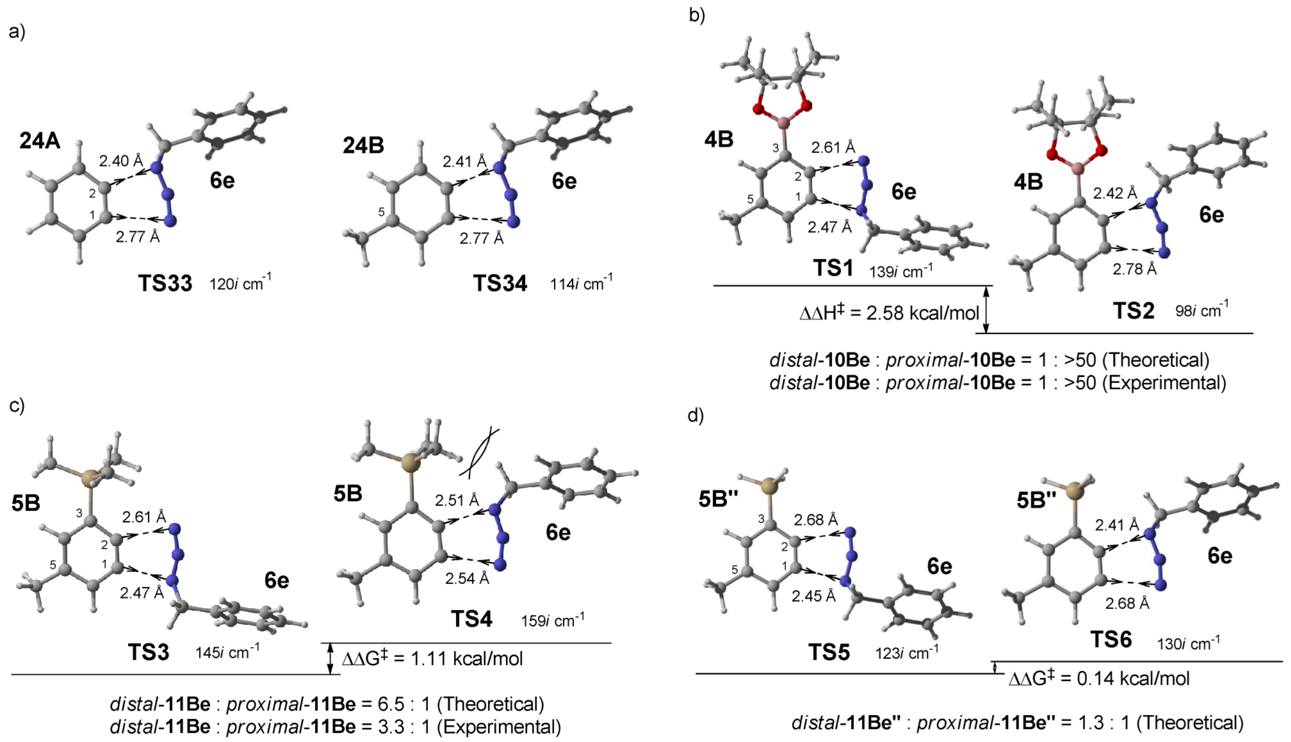


Figure 3. Transition states of (3 + 2) cycloaddition reactions of benzynes with 1,3-dipoles.[15,32] (a) Transition states of the reactions between benzyne **24A** and **6e** (**TS33**) and between 5-methylbenzyne **24B** and **6e** (**TS34**). (b) Most probable transition states (**TS1** and **TS2**) of the reaction between 3-boryl-5-methylbenzyne **4B** and benzyl azide **6e** giving *distal*-**10Be** and *proximal*-**10Be**, respectively. (c) Most probable transition states (**TS3** and **TS4**) of the reaction between 5-methyl-3-(trimethylsilyl)benzyne **5B** and **6e** giving *distal*-**11Be** and *proximal*-**11Be**, respectively. (d) Most probable transition states (**TS5** and **TS6**) of the reaction between 5-methyl-3-silylbenzyne **5B**″ and **6e**.

favorable **TS4** less stable than the unfavorable **TS3** (Figure 3c) and results in the preferential formation of *distal*-**11Be**. We also analyzed two transition states (**TS5** and **TS6**) derived from a virtual benzyne **5B**″ possessing a SiH_3 group (Figure 3d). The distance between the internal nitrogen and the benzyne C2 of **TS6** (2.41 Å) is shorter than that of **TS4** (2.51 Å) but similar to that of **TS34** (2.41 Å). Although the benzyne distortion of **5B**″ is quite similar to that of **5B** (Table 4), the energy difference between **TS5** and **TS6** is smaller than that between **TS3** and **TS4** (Figure 3c and d). These results also prove that the steric bulkiness of the silyl groups has a significant adverse influence on the electrostatically favorable proximal transition state. This steric influence even overrides the attractive electrostatic interaction and the benzyne distortion.[15,31]

■ CONCLUSIONS

In conclusion, we have achieved complementary regiocontrol of the (3 + 2) cycloaddition reaction of benzynes with 1,3-dipoles by the unique substituent effects of the boryl and silyl groups. Both regioisomers of benzo-fused azoles such as benzotriazole, 1*H*-indazole, and benzo[*d*]isoxazole can be prepared by choosing a boryl or silyl group as the benzyne substituent. In particular, the finding of an improved generation method of 3-borylbenzynes **4** from new precursors **14** was one of the most important new results of this work and led to the successful (3 + 2) cycloaddition reactions to demonstrate the first proximal-selective examples of the cycloaddition reaction of 3-substituted benzynes with 1,3-dipoles. We have clearly and quantitatively explained the regioselectivities of these reactions by analyzing the transition state structures obtained by DFT calculations. Namely, the (3 + 2) cycloaddition of borylbenzynes **4** is more electrostatically controlled, while that of silylbenzynes **5** is more sterically dominated. Because the boryl and silyl groups of the cycloaddition products can be converted into carbon, nitrogen, and oxygen substituents as well as a hydrogen atom,[33] the use of 3-boryl- and 3-silylbenzynes would be the ideal solution to the longstanding problem of the regioselectivity of substituted benzynes. Application of this chemistry to the preparation of a wide range of biologically interesting compounds and further improvement of the selectivity are in progress in our laboratory.

■ EXPERIMENTAL SECTION

General. All reactions were carried out under an argon or nitrogen atmosphere in an oven-dried flask containing a stir-bar with a rubber septum or an inlet adapter with a three-way stopcock. 1-Azido-4-methoxybenzene **6a**,[34] 1-azido-4-(*tert*-butyl)benzene **6b**,[35] 2-azido-1,4-dimethoxybenzene **6c**,[10c] 2-azido-1,3-dibromobenzene **6d**,[36] 1-azidodecane **6f**,[37] ethyl 2-azidoacetate **6g**,[10c] (azidomethylene)dibenzene **6h**,[38] (*E*)-(3-azidoprop-1-en-1-yl)benzene **6i**,[10c] (1*R*,3*R*,5*S*)-1-azidoadamantane **6j**,[10c] 1-(azidomethyl)-2-iodobenzene **6k**,[10c] methyl 2-(azidomethyl)benzoate **6l**,[39] 2-(azidomethyl)benzonitrile **6m**,[40] (diazomethylene)dibenzene **6q**,[41] *N*-hydroxybenzimidoyl chloride (for the in situ preparation of benzonitrile *N*-oxide **6s**),[42] 5-(azidomethyl)-6-iodobenzo[*d*]1,3-dioxole **6t**,[43] 2-iodo-6-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl trifluoromethanesulfonate **12A**,[14b] 2-iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)phenyl trifluoromethanesulfonate **12B**,[14b] 2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate **16A**,[14c] 4-methyl-2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate **16B**,[14c] 4-fluoro-2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate **16C**,[14c] and 4-chloro-2,6-bis(trimethylsilyl)phenyl trifluoromethanesulfonate **16D**[14c] were synthesized according to the literature. Flash chromatography[44] was performed with silica gel 60 N, spherical neutral (40−50 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded on an instrument (^{1}H, 500 MHz; ^{13}C, 125 MHz) with chemical shifts reported in ppm relative to the residual deuterated solvent or the internal standard tetramethylsilane. The high-resolution mass spectra were recorded on an ESI or APCI TOF mass spectrometer. Yield refers to isolated yields of compounds greater than 95% purity as determined by ^{1}H NMR analysis. ^{1}H NMR and melting points (where applicable) of all known compounds were taken from references. The regioselectivities were determined by 500 MHz ^{1}H NMR spectra of crude reaction mixtures. Each regiochemistry of representative cycloaddition products (*proximal*-**10Bb**, *proximal*-**10Be**, *proximal*-**10Bf**, *proximal*-**10Bg**, *proximal*-**10Bh**, *proximal*-**10 Bi**, *proximal*-**10Bj**, *proximal*-**10Bn**, *distal*-**10Br**, *distal*-**11Bc**, *distal*-**11Be**, *distal*-**11Bf**, *distal*-**11Bh**, *proximal*-**11Bh**, *distal*-**11Bj**, *distal*-**11Bn**, *distal*-**11Bp**, and *distal*-**11Bs**) was confirmed by NOESY experiment. The regiochemistries of all other cycloaddition products were predicted by the similarity of ^{1}H NMR data.

General Procedure I: Proximal-Selective (3 + 2) Cycloadditions of Borylbenzynes 4 (Tables 1−3). An oven-dried flask was charged with a borylbenzyne precursor **12**[14b]−**14** (1.0 equiv) and a dipole **6** (3.0 equiv), capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous Et_2O (0.10 M) was added, and the mixture was cooled to −78 °C. Then, a 1.0 or 1.3 M solution of *i*-PrMgCl·LiCl in THF (1.2 equiv) was slowly added to the reaction mixture over 5 min. After stirring at −78 °C for 30 min, the reaction mixture was warmed to 0 °C, stirred for an additional 30 min, and quenched with a saturated aqueous NH_4Cl solution. Then the reaction mixture was extracted with EtOAc, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The solution was filtered through a glass filter and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give boryl benzazole **10**.

1-(4-Methoxyphenyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Aa) (Table 1, entry 4). Following the general procedure I, a mixture of **14A**[14b] (61 mg, 103 μmol), 1-azido-4-methoxybenzene **6a**[34] (46 mg, 0.31 mmol), and *i*-PrMgCl·LiCl (1.0 M in THF, 0.12 mL, 0.12 mmol) in Et_2O (1.1 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to provide the titled compound *proximal*-**10Aa** (17 mg, 46%) as a colorless solid. Mp 142−145 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.08 (12 H, s), 3.89 (3 H, s), 7.03 (2 H, td, *J* = 3.0, 9.0 Hz), 7.40 (1 H, dd, *J* = 7.0, 8.0 Hz), 7.41 (2 H, td, *J* = 3.0, 9.0 Hz), 7.92 (1 H, dd, *J* = 1.0, 7.0 Hz), 8.20 (1 H, dd, *J* = 1.0, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.5, 55.6, 83.8, 114.1, 122.7, 123.5, 128.1, 131.3, 136.3, 136.8, 145.3, 160.4. IR ($CHCl_3$): 1518 cm^{-1}. HRMS calcd for $C_{19}H_{22}BN_3NaO_3$ (M + Na)$^+$ *m*/*z*: 374.1652, found 374.1661.

1-[4-(*tert*-Butyl)phenyl]-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bb) (Table 2, entry 1). An oven-dried pear-shaped flask was charged with **12B**[14b] (44 mg, 90 μmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with argon. Anhydrous Et_2O (0.90 mL, 0.10 M) and 1-azido-4-(*tert*-butyl)benzene **6b**[31] (62 mg, 0.35 mmol) were added via a syringe, and the mixture was cooled to −78 °C. *i*-PrMgCl·LiCl (1.3 M in THF, 0.080 mL, 104 μmol) was slowly added into the reaction mixture over 5 min. After being stirred at −78 °C for 30 min, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The solution was filtered through a glass filter and concentrated under reduced pressure. The product yield and ratio were determined by ^{1}H NMR [*proximal*-**10Bb** (15%), **15**[45] (29%), **12B**[14b] (26%), 1,4-dimethoxybenzene was used as an internal standard].

Table 2, entry 2. Following the general procedure I, a mixture of **13B** (25 mg, 48 μmol), 1-azido-4-(*tert*-butyl)benzene **6b**[35] (23 mg, 131 μmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 60 μL, 78 μmol) in Et_2O (0.50 mL, 0.10 M) was stirred for 30 min at 0 °C. The product yield and ratio were determined by ^{1}H NMR [*proximal*-**10Bb** (48%), 1,4-dimethoxybenzene was used as an internal standard].

Table 2, entry 3 and Table 3, entry 1. Following the general procedure I, a mixture of **14B** (21 mg, 34 μmol), 1-azido-4-(*tert*-butyl)benzene **6b**[35] (20 mg, 113 μmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 40 μL, 52 μmol) in Et_2O (0.40 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *proximal*-**10Bb** (8.9 mg, 67%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 160−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.05 (12 H, s), 1.38 (9 H, s), 2.53 (3 H, s), 7.42 (2 H, d, *J* = 8.5 Hz), 7.53 (2 H, d, *J* = 8.5 Hz), 7.72 (1 H, d, *J* = 1.0 Hz), 7.95 (1 H, d, *J* = 1.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.5, 31.3, 31.3, 34.8, 83.8, 121.6, 125.9, 126.0, 133.4, 134.9, 135.8, 137.9, 146.1, 152.2. IR ($CHCl_3$): 2968 cm^{-1}. HRMS calcd for $C_{23}H_{31}BN_3O_2$ (M + H)$^+$ *m*/*z*: 392.2509, found 392.2507.

1-(2,5-Dimethoxyphenyl)-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bc) (Table 3, entry 2). Following the general procedure I, a mixture of **14B** (31 mg, 52 μmol), 2-azido-1,4-dimethoxybenzene **6c**[10c] (50 μL, 166 μmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 50 μL, 65 μmol) in Et_2O (0.50 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *proximal*-**10Bc** (13 mg, 65%) as a colorless solid. Mp 116−120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (12 H, s), 2.52 (3 H, s), 3.58 (3 H, s), 3.79 (3 H, s), 6.93 (1 H, dd, *J* = 1.0, 9.5 Hz), 7.03−7.06 (2 H, m), 7.76 (1 H, d, *J* = 1.0 Hz), 7.95 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.6, 24.8, 24.8, 37.3, 83.6, 88.9, 92.5, 114.6, 123.1, 123.7, 128.0, 128.3, 131.4, 134.6, 135.4, 1367.0, 138.4, 145.4. IR ($CHCl_3$): 1514 cm^{-1}. HRMS calcd for $C_{21}H_{27}BN_3O_4$ (M + H)$^+$ *m*/*z*: 396.2095, found 396.2086.

1-Benzyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Ae) (Table 3, entry 3). Following the general procedure I, a mixture of **14A** (64 mg, 0.11 mmol), (azidomethyl)benzene **6e** (41 μL, 0.32 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.10 mL, 0.13 mmol) in Et_2O (1.1 mL) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *proximal*-**10Ae** (32 mg, 89%) as a colorless solid. Mp 89−92 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (12 H, s), 6.40 (2 H, s), 7.01 (2 H, d, *J* = 7.0 Hz), 7.20−7.25 (3 H, m), 7.38 (1 H, dd, *J* = 7.5 Hz, 8.0 Hz), 8.04 (1 H, dd, *J* = 1.0 Hz, 7.5 Hz), 8.21 (1 H, dd, *J* = 1.0 Hz, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.6, 52.3, 84.4, 123.3, 123.5, 126.2, 127.3, 128.4, 135.8, 137.1, 137.3, 145.9. IR ($CHCl_3$): 3010 cm^{-1}. HRMS calcd for $C_{19}H_{23}BN_3O_2$ (M + H)$^+$ *m*/*z*: 336.1883, found 336.1863.

1-Benzyl-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Be) (Table 3, entry 4). Following the general procedure I, a mixture of **14B** (61 mg, 101 μmol), (azidomethyl)benzene **6e** (40 μL, 0.30 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 90 μL, 117 μmol) in Et_2O (1.0 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to provide the titled compound *proximal*-**10Be** (30 mg, 85%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 116−118 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (12 H, s), 2.51 (3 H, s), 6.36 (2 H, s), 6.99 (2 H, d, *J* = 7.0 Hz), 7.17−7.24 (3 H, m), 7.86 (1 H, d, *J* = 1.0 Hz), 7.96 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.7, 52.3, 84.4, 122.5, 126.2, 127.2, 128.4, 133.2, 134.4, 137.2, 139.3, 146.7. IR ($CHCl_3$): 2982 cm^{-1}. HRMS calcd for $C_{20}H_{25}BN_3O_2$ (M + H)$^+$ *m*/*z*: 350.2040, found 350.2037.

1-Decyl-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bf) (Table 3, entry 5). Following the general procedure I, a mixture of **14B** (56 mg, 93 μmol), 1-azidodecane **6f**[35] (60 mg, 0.33 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 85 μL, 111 μmol) in Et_2O (0.90 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to provide the titled compound *proximal*-**10Bf** (32 mg, 87%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 70−72 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86 (3 H, t, *J* = 7.5 Hz), 1.23−1.37 (14 H, m), 1.40 (12 H, s), 1.87 (2 H, q, J = 7.0 Hz), 2.50 (3 H, s), 5.00 (2 H, t, J = 7.0 Hz), 7.85 (1 H, d, J = 1.5 Hz), 7.90 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 21.1, 22.6, 24.9, 26.6, 29.2, 29.3, 29.48, 29.50, 30.9, 31.8, 49.6, 84.3, 122.4, 132.9, 133.9, 139.0, 146.6. IR ($CHCl_3$): 2927 cm^{-1}. HRMS calcd for $C_{23}H_{39}BN_3O_2$ (M + H)$^+$ m/z: 400.3135, found 400.3156.

Ethyl 2-(5-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazol-1-yl)acetate (*proximal*-10Bg) (Table 3, entry 6). Following the general procedure I, a mixture of **14B** (57 mg, 95 μmol), ethyl 2-azidoacetate **6g**[10c] (35 μL, 0.30 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 90 μL, 117 μmol) in Et_2O (1.0 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to provide the titled compound *proximal*-**10Bg** (24 mg, 74%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 141−144 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21 (3 H, t, J = 7.5 Hz), 1.35 (12 H, s), 2.50 (3 H, s), 4.17 (2 H, q, J = 7.5 Hz), 5.83 (2 H, s), 7.88 (1 H, d, J = 1.5 Hz), 7.93 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 21.1, 24.7, 51.3, 61.5, 84.4, 122.6, 133.2, 134.8, 139.4, 146.6, 167.7. IR ($CHCl_3$): 1755 cm^{-1}. HRMS calcd for $C_{17}H_{25}BN_3O_4$ (M + H)$^+$ m/z: 346.1938, found 346.1933.

1-Benzhydryl-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bh) (Table 3, entry 7). Following the general procedure I, a mixture of **14B** (72 mg, 119 μmol), (azidomethylene)dibenzene **6h**[39] (75 mg, 0.36 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.11 mL, 143 μmol) in Et_2O (1.2 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound *proximal*-**10Bh** (33 mg, 65%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 130−133 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.37 (12 H, s), 2.51 (3 H, s), 7.26−7.33 (10 H, m) 7.91 (1 H, d, J = 1.5 Hz), 7.97 (1 H, s), 8.47 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.8, 64.9, 84.5, 122.6, 127.6, 128.3, 128.6, 133.1, 135.0, 139.5, 140.0, 146.0. IR ($CHCl_3$): 2981 cm^{-1}. HRMS calcd for $C_{26}H_{29}BN_3O_2$ (M + H)$^+$ m/z: 426.2353, found 426.2347.

1-(Adamantan-1-yl)-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bj) (Table 3, entry 8). Following the general procedure I, a mixture of **14B** (61 mg, 101 μmol), 1-azidoadamantane **6j**[10c] (54 mg, 0.30 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 95 μL, 124 μmol) in Et_2O (1.0 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound *proximal*-**10Bj** (14 mg, 34%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 239−241 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (12 H, s), 1.80−1.95 (6 H, m), 2.29 (3 H, brs), 2.48 (3 H, s), 2.57 (6 H, brs), 7.55 (1 H, d, J = 1.0 Hz), 7.88(1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0, 24.7, 29.8, 35.8, 41.6, 62.1, 84.5, 121.6, 131.4, 132.4, 136.0, 147.3. IR ($CHCl_3$): 2914 cm^{-1}. HRMS calcd for $C_{23}H_{33}BN_3O_2$ (M + H)$^+$ m/z: 394.2660, found 394.2680.

1-(Adamantan-1-yl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*distal*-10Bj) (Table 3, entry 8). This product, the regiochemistry of which was determined by NOESY spectrum, was obtained by the column chromatography (EtOAc) of the above-mentioned crude product and the following treatment with pinacol in CH_2Cl_2 to give a mixture of *distal*-**10Bj** (34%), Et_2O, and pinacol (1:0.072:0.065) as a colorless solid. Mp 174−180 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (12 H, s), 1.84 (6 H, brs), 2.29 (3 H, brs), 2.46 (6 H, brs), 2.51 (3 H, s), 7.62 (1 H, s), 7.64 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.8, 24.8, 29.5, 36.1, 42.1, 61.1, 84.1, 114.3, 131.4, 133.4, 135.4, 148.6. IR ($CHCl_3$): 2918 cm^{-1}. HRMS calcd for $C_{23}H_{32}BN_3NaO_2$ (M + Na)$^+$ m/z: 416.2485, found 416.2485.

6-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole (*proximal*-10Bn) (Table 3, entry 9). An oven-dried flask was charged with **12B** (43 mg, 88 μmol). The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous Et_2O (0.90 mL) and (diazomethyl)trimethylsilane **6n** (2.0 M in Et_2O 0.14 mL, 0.28 mmol) were added, and the mixture was cooled to −78 °C. A solution of *i*-PrMgCl (2.0 M in THF, 0.060 mL, 0.12 mmol) was slowly added to the reaction mixture over 5 min. After stirring at −78 °C for 30 min, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The solution was filtered through a glass filter and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to provide the titled compound *proximal*-**10Bn** (12 mg, 54%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 155−157 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (12 H, s), 2.48 (3 H, s), 7.37 (1 H, s), 7.52 (1 H, s), 8.42 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.7, 24.9, 83.9, 112.1, 131.2, 136.3, 136.5, 139.9. IR ($CHCl_3$): 3472 cm^{-1}. HRMS calcd for $C_{14}H_{20}BN_2O_2$ (M + H)$^+$ m/z: 259.1618, found 259.1631.

2-*tert*-Butyl-5-methyl-3-phenyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzo[*d*]isoxazole (*distal*-10Br) (Table 3, entry 10). An oven-dried flask was charged with **12B**[14b] (56 mg, 0.11 mmol). The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous Et_2O (1.2 mL) and *N*-*tert*-butyl-α-phenylnitrone **6r** (61 mg, 0.35 mmol) were added, and the mixture was cooled to −78 °C. A solution of *i*-PrMgCl·LiCl (1.3 M in THF, 0.18 mL, 0.23 mmol) was slowly added to the reaction mixture over 5 min. After stirring at −78 °C for 30 min, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The solution was filtered through a glass filter and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 11:1) to provide the titled compound *distal*-**10Br** (29 mg, 64%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 104−107 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (6 H, s), 1.13 (6 H, s), 1.19 (9 H, s), 2.34 (3 H, s), 5.78 (1 H, s), 6.78 (1 H, s), 7.12−7.13 (4 H, m), 7.19 (2 H, d, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 24.5, 24.6, 25.5, 61.3, 66.8, 83.6, 109.8, 126.8, 128.0, 128.27, 128.34, 132.4, 138.3, 144.6, 157.6. IR ($CHCl_3$): 1582 cm^{-1}. HRMS calcd for $C_{24}H_{33}BNO_3$ (M + H)$^+$ m/z: 394.2553, found 394.2546.

1-(2,6-Dibromophenyl)-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bd) (Table 3, entry 11). Following the general procedure I, a mixture of **14B** (50 mg, 0.080 mmol), 2-azido-1,3-dibromobenzene **6d**[39] (69 mg, 0.25 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.080 mL, 0.11 mmol) in Et_2O (0.80 mL) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to provide the titled compound *proximal*-**10Bd** (28 mg, 67%) as a colorless solid. Mp 181−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (12 H, s), 2.55 (3 H, s), 7.30 (1 H, t, J = 8.0 Hz), 7.68 (2 H, d, J = 8.0 Hz), 7.92 (1 H, d, J = 1.0 Hz), 8.04 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.4, 83.5, 122.7, 125.2, 131.6, 131.7, 133.7, 134.8, 137.9, 139.7, 145.9. IR ($CHCl_3$): 1478 cm^{-1}. HRMS calcd for $C_{19}H_{20}BN_3{}^{79}Br^{81}BrNaO_2$ (M + Na)$^+$ m/z: 515.9893, found 515.9882.

1-Cinnamyl-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bi) (Table 3, entry 12). Following the general procedure I, a mixture of **14B** (55 mg, 90 μmol), (*E*)-(3-azidoprop-1-en-1-yl)benzene **6i**[10c] (43 mg, 0.27 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.090 mL, 110 μmol) in Et_2O (0.90 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 40:9) to provide the titled compound *proximal*-**10Bi** (27 mg, 80%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 134−136 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (12 H, s), 2.52 (3 H, s), 5.86 (2 H, dd, J = 1.0, 6.0 Hz), 6.35 (1 H, d, J = 16 Hz), 6.43 (1 H, dt, J = 6.5, 16 Hz), 7.18−7.27 (5 H, m), 7.88 (1 H, d, J = 1.5 Hz), 7.95 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.9, 50.9, 84.4, 122.5, 124.6, 126.3, 127.7, 128.5, 132.0, 133.1, 134.0, 136.2, 139.2, 146.6. IR ($CHCl_3$): 3421 cm^{-1}. HRMS calcd for $C_{22}H_{27}BN_3O_2$ $(M + H)^+$ m/z: 376.2196, found 376.2193.

1-(2-Iodobenzyl)-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10Bk) (Table 3, entry 13). Following the general procedure I, a mixture of **14B** (58 mg, 97 μmol), 1-(azidomethyl)-2-iodobenzene **6k**[10c] (76 mg, 0.29 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.090 mL, 117 μmol) in Et_2O (1.0 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound *proximal*-**10Bk** (33 mg, 71%) as a colorless solid. Mp 185–187 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.13 (12 H, s), 2.54 (3 H, s), 5.93 (1 H, dd, J = 1.0, 7.5 Hz), 6.22 (2 H, s), 6.91 (1 H, dt, J = 1.0, 7.5 Hz), 7.05 (1 H, t, J = 7.5 Hz), 7.88 (1 H, d, J = 7.5 Hz), 7.90 (1 H, d, J = 1.0 Hz), 8.0 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.4, 58.4, 84.3, 95.9, 122.7, 125.7, 128.4, 128.6, 133.4, 134.8, 139.1, 139.7, 146.7. IR ($CHCl_3$): 2982 cm^{-1}. HRMS calcd for $C_{20}H_{24}BIN_3O_2$ $(M + H)^+$ m/z: 476.1006, found 476.1017.

Methyl 2-[(5-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazol-1-yl)methyl]benzoate (*proximal*-10Bl) (Table 3, entry 14). Following the general procedure I, a mixture of **14B** (57 mg, 95 μmol), ethyl methyl 2-(azidomethyl)-benzoate **6l**[40] (56 mg, 0.29 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.090 mL, 117 μmol) in Et_2O (1.0 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 4:1) to provide the titled compound *proximal*-**10Bl** (29 mg, 74%) as a colorless solid. Mp 127–129 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.05 (12 H, s), 2.53 (3 H, s), 3.97 (3 H, s), 6.01 (1 H, d, J = 7.5 Hz), 6.73 (2 H, s), 7.21 (1 H, dt, J = 1.0, 7.5 Hz), 7.27 (1 H, dt, J = 1.0, 7.5 Hz), 7.86 (1 H, d, J = 1.0 Hz) 8.0 (1 H, brs) 8.11 (1 H, dd, J = 1.0, 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.3, 52.0, 52.7, 84.1, 122.6, 125.4, 126.7, 126.8, 131.1, 132.9, 133.3, 134.9, 139.3, 140.5, 146.7, 167.1. IR ($CHCl_3$): 1717 cm^{-1}. HRMS calcd for $C_{22}H_{27}BN_3O_4$ $(M + H)^+$ m/z: 408.2095, found 408.2100.

2-[(5-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazol-1-yl)methyl]benzonitrile (*proximal*-10Bm) (Table 3, entry 15). Following the general procedure I, a mixture of **14B** (62 mg, 102 μmol), 2-(azidomethyl)benzonitrile **6m**[41] (49 mg, 0.31 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.10 mL, 124 μmol) in Et_2O (1.0 mL, 0.10 M) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to provide the titled compound *proximal*-**10Bm** (30 mg, 78%) as a colorless solid. Mp 174–176 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.16 (12 H, s), 2.54 (3 H, s), 6.19–6.22 (1 H, m), 6.58 (2 H, s), 7.30–7.34 (2 H, m), 7.71–7.74 (1 H, m), 7.92 (1 H, d, J = 1.5 Hz), 8.01 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.4, 51.3, 84.4, 109.8, 117.1, 122.9, 125.5, 127.5, 132.7, 133.2, 133.7, 134.7, 140.0, 141.7, 146.7. IR ($CHCl_3$): 2226 cm^{-1}. HRMS calcd for $C_{21}H_{24}BN_4O_2$ $(M + H)^+$ m/z: 375.1992, found 375.1984.

General Procedure II: Distal-Selective (3 + 2) Cycloadditions of Silylbenzynes 5 (Tables 1 and 3). An oven-dried flask was charged with a silylbenzyne precursor **16** (1.0 equiv), capped with a rubber septum, and evacuated, and backfilled with argon. Anhydrous THF (0.10 M) was added via a syringe, and the reaction mixture was cooled to 0 °C. After 5 min, a dipole **6** (3.0 equiv) and Bu_4NF (1.0 M THF solution, 2.0 equiv) were added in that order, and the reaction mixture was stirred at 0 °C for 30 min. The mixture was filtered through a short pad of silica gel (hexane/EtOAc = 10:1 as the eluent). The effluent mixture was concentrated under reduced pressure and further purified by silica gel flash column chromatography to give silyl benzazole **11**.

1-(4-Methoxyphenyl)-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Aa) (Table 1, entry 5). Following the general procedure II, a mixture of **16A**[17] (100 mg, 0.27 mmol), 1-azido-4-methoxybenzene **6a**[34] (124 mg, 0.83 mmol), and Bu_4NF (1.0 M in THF, 0.54 mL, 0.54 mmol) in THF (2.7 mL, 0.10 M) was stirred for 30 min at 0 °C. The ratio of *distal*- to *proximal*-**11Aa** (5.7:1) was determined using ^1H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 10:1 to 5:1) to provide the titled compound *distal*-**11Aa** (39 mg, 49%) as a colorless solid. Mp 97–100 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.53 (9 H, s), 3.90 (3 H, s), 7.11 (2 H, dd, J = 2.0, 8.5 Hz), 7.47 (1 H, dd, J = 1.0, 7.0 Hz), 7.51 (1 H, dd, J = 7.0, 8.0 Hz), 7.65 (1 H, dd, J = 1.0, 8.0 Hz), 7.66 (2 H, dd, J = 2.0, 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.77, 55.6, 110.7, 114.9, 124.5, 127.3, 129.6, 130.2, 131.4, 133.9, 150.2, 159.6. IR ($CHCl_3$): 1520 cm^{-1}. HRMS calcd for $C_{16}H_{19}N_3NaOSi$ $(M + Na)^+$ m/z: 320.1195, found 320.1192.

1-(4-Methoxyphenyl)-7-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*proximal*-11Aa) (Table 1, entry 5). Product (7.9 mg, 10%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 106–109 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.02 (9 H, s), 3.92 (3 H, s), 7.08 (2 H, dd, J = 2.0, 7.0 Hz), 7.39 (1 H, dd, J = 7.0, 7.5 Hz), 7.44 (2 H, dd, J = 2.0, 7.0 Hz), 7.70 (1 H, d, J = 7.0 Hz), 8.14 (1 H, d, J = 7.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.51, 55.7, 114.5, 121.3, 122.6, 123.6, 129.3, 130.9, 136.1, 138.3, 145.0, 160.9. IR ($CHCl_3$): 1518 cm^{-1}. HRMS calcd for $C_{16}H_{19}N_3NaOSi$ $(M + Na)^+$ m/z: 320.1195, found 320.1197.

1-(4-(*tert*-Butyl)phenyl)-6-methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Bb) (Table 3, entry 1). Following the general procedure II, a mixture of **16B**[14a] (70 mg, 0.20 mmol), 1-azido-4-(*tert*-butyl)benzene **6b**[35] (105 mg, 0.60 mmol), and Bu_4NF (1.0 M in THF, 0.40 mL, 0.40 mmol) in THF (2.0 mL) was stirred for 1.0 h. The ratio of *distal*- to *proximal*-**11Bb** (10:1) was determined using ^1H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 30:1) to provide the titled compound *distal*-**11Bb** (42 mg, 61%) as a yellow solid. Mp 92–94 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.52 (9 H, s), 1.40 (9 H, s), 2.53 (3 H, s), 7.32 (1 H, s), 7.49 (1 H,s), 7.61 (2 H, d, J = 8.0 Hz), 7.68 (2 H, d, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.7, 22.0, 31.3, 34.8, 110.2, 122.6, 126.6, 131.7, 131.9, 133.2, 134.7, 137.7, 149.0, 151.5. IR ($CHCl_3$): 2964, 1600, 1519, 1411 cm^{-1}. HRMS calcd for $C_{20}H_{28}N_3Si$ $(M + H)^+$ m/z: 338.2053, found 338.2055.

1-(4-(*tert*-Butyl)phenyl)-5-methyl-7-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*proxiaml*-11Bb) (Table 3, entry 1). Product (12 mg, 18%) was obtained by column chromatography of the above-mentioned crude product as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ: −0.02 (9 H, s), 1.40 (9 H, s), 2.53 (3 H, s), 7.43 (2 H, d, J = 8.0 Hz), 7.51 (1 H, s), 7.58 (2 H, d, J = 8.0 Hz), 7.89 (1 H, s). ^{13}C NMR (125 MHz, CD_3OD) δ: 0.4, 21.4, 31.3, 34.9, 120.1, 122.2, 126.3, 127.4, 133.3, 135.5, 136.7, 138.4, 145.8, 153.7. IR ($CHCl_3$): 1602, 1514, 1261, 1236 cm^{-1}. HRMS calcd for $C_{20}H_{28}N_3Si$ $(M + H)^+$ m/z: 338/.2053, found 338.2059.

1-(2,5-Dimethoxyphenyl)-6-methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Bc) (Table 3, entry 2). Following the general procedure II, a mixture of **16B**[14a] (50 mg, 0.13 mmol), 2-azido-1,4-dimethoxybenzene **6c**[10c] (69 mg, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Bc** (14:1) was determined using ^1H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 15:1) to provide the titled compound *distal*-**11Bc** (30 mg, 68%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 140–142 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.52 (9 H, s), 2.50 (3 H, s), 3.74 (3 H, s), 3.81 (3 H, s), 7.04 (1 H, d, J = 2.0 Hz), 7.07 (1 H, dd, J = 2.0, 8.0 Hz), 7.09 (1 H, d, J = 8.0 Hz), 7.13 (1 H, brs), 7.30 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.7, 22.0, 55.9, 56.5, 111.0, 113.4, 113.8, 116.2, 126.0, 131.65, 132.8, 133.3, 137.2, 147.7, 148.2, 153.8. IR ($CHCl_3$): 2959, 1595, 1514 cm^{-1}. HRMS calcd for $C_{18}H_{24}N_3O_2Si$ $(M + H)^+$ m/z: 342.1638, found 342.1622.

1-(2,5-Dimethoxyphenyl)-5-methyl-7-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*proximal*-11Bc) (Table 3, entry 2). Product (2.7 mg, 6.0%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 99–100 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.01 (9 H, s), 2.53 (3 H, s), 3.64 (3 H, s), 3.81 (3 H, s), 6.99 (1 H, d, J = 8.0 Hz), 7.02 (1 H, d, J = 2.0 Hz), 7.11 (1 H, dd, J = 2.0, 8.0 Hz), 7.49 (1 H, s), 7.90 (1 H, s). ^{13}C NMR (125 MHz, CD_3OD) δ: 1.2, 22.1, 57.2, 57.3, 115.2, 118.4, 119.3, 121.1, 124.6, 128.5, 136.1, 139.5, 140.4, 147.1, 152.6, 155.6. IR ($CHCl_3$): 2960, 1620, 1514 cm^{-1}. HRMS calcd for $C_{18}H_{24}N_3O_2Si$ $(M + H)^+$ m/z: 342.1638, found 342.1615.

1-Benzyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Ae) (Table 3, entry 3). Following the general procedure II, a mixture of **16A**[14a] (50 mg, 0.14 mmol), (azidomethyl)benzene **6e** (54 μL, 0.42 mmol), and Bu_4NF (1.0 M in THF, 0.28 mL, 0.28 mmol) in THF (1.4 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Ae** (3.6:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *distal*-**11Ae** (14.9 mg, 38%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.49 (9 H, s), 5.83 (2 H, s), 7.29−7.36 (7 H, m), 7.43 (1 H, dd, J = 2.0, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.8, 52.1, 110.2, 126.6, 127.6, 128.3, 128.9, 129.3, 131.5, 133.8, 134.9, 150.4. IR ($CHCl_3$): 1724, 1597, 1497 cm^{-1}. HRMS calcd for $C_{16}H_{20}N_3Si$ (M + H)$^+$ m/z: 282.1427, found 282.1454.

1-Benzyl-7-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*proximal*-11Ae) (Table 3, entry 3). Product (5.3 mg, 14%) was obtained by column chromatography of the above-mentioned crude product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.35 (9 H, s), 6.05 (2 H, s), 6.89 (2 H, d, J = 8.0 Hz), 7.27−7.30 (3 H, m), 7.38 (1 H, t, J = 8.0 Hz), 7.68 (1 H, d, J = 8.0 Hz), 8.15 (1 H, dd, J = 2.0, 8.0 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: 1.5, 50.1, 122.6, 124.3, 126.2, 127.9, 129.7, 130.7, 137.8, 138.8, 139.6, 146.8. IR ($CHCl_3$): 2396, 1778, 1620, 1527, 1497 cm^{-1}. HRMS calcd for $C_{16}H_{20}N_3Si$ (M + H)$^+$ m/z: 282.1427, found 282.1446.

1-Benzyl-6-methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Be) (Table 3, entry 4). Following the general procedure II, a mixture of **16B**[14a] (50 mg, 0.13 mmol), (azidomethyl)benzene **6e** (50 μL, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Be** (3.3:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *distal*-**11Be** (22 mg, 57%) as a colorless oil, the regiochemistry of which was determined by NOESY spectrum. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.64 (9 H, s), 2.60 (3 H, s), 5.92 (2 H, s), 7.40−7.49 (7 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.8, 21.9, 51.8, 109.3, 127.4, 128.1, 128.8, 131.6, 132.0, 133.0, 135.1, 136.9, 148.9. IR ($CHCl_3$): 2277, 1605 cm^{-1}. HRMS calcd for $C_{17}H_{22}N_3Si$ (M + H)$^+$ m/z: 296.1583, found 296.1554.

1-Benzyl-5-methyl-7-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*proximal*-11Be) (Table 3, entry 4). Product (6.5 mg, 18%) was obtained by column chromatography of the above-mentioned crude product as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.34 (9 H, s), 2.52 (3 H, s), 6.02 (2 H, s), 6.87 (2 H, d, J = 8.0 Hz), 7.26−7.28 (3 H, m), 7.48 (1 H, brs), 7.90 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.7, 21.4, 52.4, 120.5, 121.1, 126.1, 127.8, 128.8, 133.1, 136.1, 136.3, 137.6, 145.9. IR ($CHCl_3$): 2463, 1620, cm^{-1}. HRMS calcd for $C_{17}H_{22}N_3Si$ (M + H)$^+$ m/z: 296.1583, found 296.1605.

1-Benzyl-4-(*tert*-butyldimethylsilyl)-6-methyl-1*H*-benzo[*d*]-triazole (*distal*-11Be′) (Table 3, entry 4). Following the general procedure II, a mixture of **16B′** (50 mg, 0.12 mmol), (azidomethyl)-benzene **6e** (46 μL, 0.36 mmol) and Bu_4NF (1.0 M in THF, 0.24 mL, 0.24 mmol) in THF (1.2 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Be′** (10:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *distal*-**11Be′** (27 mg, 69%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.52 (6 H, s), 0.95 (9 H, s), 2.46 (3 H, s), 5.77 (2 H, s), 7.12 (1 H, brs), 7.24 (1 H, d, J = 2.0 Hz), 7.28−7.34 (5 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.9, 17.2, 22.0, 26.9, 51.8, 109.3, 127.5, 128.2, 128.9, 130.9, 132.1, 133.2, 135.2, 136.7, 149.5. IR ($CHCl_3$): 2927, 1605, 1406 cm^{-1}. HRMS calcd for $C_{20}H_{28}N_3Si$ (M + H)$^+$ m/z: 338.2053, found 338.2066.

1-Benzyl-7-(*tert*-butyldimethylsilyl)-5-methyl-1*H*-benzo[*d*]-triazole (*proximal*-11Be′) (Table 3, entry 4). Product (3.1 mg, 8.0%) was obtained by column chromatography of the above-mentioned crude product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.37 (6 H, s), 0.88 (9 H, s), 2.53 (3 H, s), 6.00 (2 H, s), 6.83 (2 H, dd, J = 2.0, 8.0 Hz), 7.24−7.27 (3 H, m), 7.52 (1 H, d, J = 2.0 Hz), 7.91 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −2.3, 17.9, 21.4, 27.0, 52.4, 110.4, 118.6, 120.6, 126.1, 127.6, 128.7, 132.8, 136.6, 139.6, 146.0. IR ($CHCl_3$): 2929, 1606, 1566, 1497 cm^{-1}. HRMS calcd for $C_{20}H_{28}N_3Si$ (M + H)$^+$ m/z: 338.2053, found 338.2038.

1-Decyl-6-methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Bf) (Table 3, entry 5). Following the general procedure II, a mixture of **16B**[14a] (50 mg, 0.13 mmol), 1-azidodecane **6f**[35] (71 mg, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Bf** (4.0:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound *distal*-**11Bf** (24 mg, 53%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 58−59 °C. ^{1}H NMR (500 MHz, CD_3OD) δ: 0.44 (9 H, s), 0.88 (3 H, t, J = 7.5 Hz), 1.24−1.33 (14 H, m), 1.98 (2 H, quint, J = 7.5 Hz), 2.54 (3 H, s), 4.65 (2 H, t, J = 7.5 Hz), 7.33 (1 H, d, J = 2.0 Hz), 7.51 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: −0.8, 14.1, 22.0, 22.6, 26.8, 29.1, 29.2, 29.3, 29.5, 29.7, 31.8, 47.9, 109.1, 131.5, 132.2, 133.0, 136.6, 148.6. IR ($CHCl_3$): 2928, 2857, 2099, 1605, 1466 cm^{-1}. HRMS calcd for $C_{20}H_{36}N_3Si$ (M + H)$^+$ m/z: 346.2679, found 346.2684.

1-Decyl-5-methyl-7-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*proximal*-11Bf) (Table 3, entry 5). Product (9.0 mg, 20%) was obtained by column chromatography of the above-mentioned crude product as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.46 (9 H, s), 0.87 (3 H, t, J = 7.5 Hz), 1.25−1.43 (14 H, m), 2.06 (2 H, quint, J = 7.5 Hz), 2.49 (3 H, s), 4.65 (2 H, t, J = 7.5 Hz), 7.43 (1 H, d, J = 2.0 Hz), 7.82 (1 H, brs). ^{13}C NMR (125 MHz, CD_3OD) δ: 0.8, 14.1, 21.3, 22.7, 26.8, 29.3, 29.4, 29.5, 30.8, 31.6, 31.8, 49.6, 120.3, 121.0, 132.8, 135.4, 137.0, 145.7. IR ($CHCl_3$): 2928, 2857, 1717, 1601, 1466 cm^{-1}. HRMS calcd for $C_{20}H_{36}N_3Si$ (M + H)$^+$ m/z: 346.2679, found 346.2649.

Ethyl 2-(6-Methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazol-1-yl)-acetate (*distal*-11Bg) (Table 3, entry 6). Following the general procedure II, a mixture of **16B**[14a] (50 mg, 0.13 mmol), ethyl 2-azidoacetate **6g**[10c] (50 mg, 0.39 mmol) and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Bg** (3.3:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound *distal*-**11Bg** (22 mg, 58%) as a yellow solid. Mp 58−60 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.48 (9 H, s), 1.29 (3 H, t, J = 7.5 Hz), 2.52 (3 H, s), 4.26 (2 H, q, J = 7.5 Hz), 5.35 (2 H, s), 7.20 (1 H, brs), 7.28 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.8, 14.1, 22.0, 48.9, 62.2, 108.9, 131.8, 132.7, 133.3, 137.5, 148.7, 166.7. IR ($CHCl_3$): 1755, 1605 cm^{-1}. HRMS calcd for $C_{14}H_{22}N_3O_2Si$ (M + H)$^+$ m/z: 292.1481, found 292.1507.

Ethyl 2-(5-Methyl-1*H*-benzo[*d*]triazol-1-yl)acetate (Desilylated Product of *proximal*-11Bg) (Table 3, entry 6). Product (5.3 mg, 20%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 104−105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (3 H, t, J = 7.5 Hz), 2.53 (3 H, s), 4.25 (2 H, q, J = 7.5 Hz), 5.39 (2 H, s), 7.35 (2 H, brs), 7.84 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 21.5, 49.1, 62.3, 108.7, 119.1, 130.1, 131.9, 134.2, 146.6, 166.4. IR ($CHCl_3$): 1755, 1591 cm^{-1}. HRMS calcd for $C_{11}H_{14}N_3O_2$ (M + H)$^+$ m/z: 220.1086, found 220.1084.

1-Benzhydryl-6-methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]-triazole (*distal*-11Bh) (Table 3, entry 7). Following the general procedure II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), (azidomethylene)dibenzene **6h**[39] (82 mg, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 1.0 h. The ratio of *distal*- to *proximal*-**11Bh** (5.0:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 15:1) to provide the titled compound *distal*-**11Bh** (27 mg, 55%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 138−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.47 (9 H, s), 2.40 (3 H, s), 6.92 (1 H, s), 7.23−7.26 (7 H, m), 7.31−7.36 (5 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.7, 22.0, 66.7, 110.1, 128.2, 128.4, 128.7, 131.7, 132.3, 133.1, 136.8, 138.1, 148.8. IR ($CHCl_3$):

1601, 1497, 1454 cm^{-1}. HRMS calcd for $C_{23}H_{26}N_3Si$ $(M + H)^+$ m/z: 372.1896, found 372.1909.

1-Benzhydryl-5-methyl-7-(trimethylsilyl)-1*H*-benzo[*d*]-triazole (*proximal*-11Bh) (Table 3, entry 7). Product (5.1 mg, 10%) was obtained by column chromatography of the above-mentioned crude product as a colorless oil, the regiochemistry of which was determined by NOESY spectrum. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.39 (9 H, s), 2.51 (3 H, s), 4.11−4.25 (1 H, m), 7.15 (4 H, dd, J = 2.0, 8.0 Hz), 7.31 (5 H, m), 7.39 (1 H, s), 7.49 (1 H, s), 7.90 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 1.0, 21.3, 65.8, 120.6, 121.0, 128.0, 128.4, 128.5, 128.8, 133.1, 136.4, 137.7, 139.5. IR ($CHCl_3$): 1719, 1568, 1495, 1450 cm^{-1}. HRMS calcd for $C_{23}H_{26}N_3Si$ $(M + H)^+$ m/z: 372.1896, found 372.1903.

1-(3,5,7-Adamantan-1-yl)-6-methyl-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Bj) (Table 3, entry 8). Following the general procedure II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), 1-azidoadamantane **6j**[10c] (69 mg, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The crude product was purified by column chromatography (hexane/EtOAc = 30:1) to provide the titled compound *distal*-**11Bj** (25 mg, 57%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 198−199 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.47 (9 H, s), 1.86 (6 H, brs), 2.32 (3 H, s), 2.50 (6 H, d, J = 2.0 Hz), 2.53 (3 H, s), 7.23 (1 H, brs), 7.53 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.8, 22.1, 29.6, 36.2, 41.9, 61.0, 112.3, 130.8, 131.0, 133.0, 135.5, 149.6. IR ($CHCl_3$): 2855, 1730, 1597, 1456 cm^{-1}. HRMS calcd for $C_{20}H_{30}N_3Si$ $(M + H)^+$ m/z: 340.2209, found 340.2210.

5-Methyl-7-(trimethylsilyl)-1*H*-indazole (*distal*-11Bn) (Table 3, entry 9). Following the general procedure II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), (diazomethyl)trimethylsilane **6n** (2.0 M in Et_2O, 0.20 mL, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 1.0 h. The ratio of *distal*- to *proximal*-**11Bn** (1.4:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound *distal*-**11Bn** (16 mg, 59%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum after N^1-methylation using MeI and *t*-BuOK. Mp 137−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.43 (9 H, s), 2.46 (3 H, s), 7.34 (1 H, d, J = 2.0 Hz), 7.54 (1 H, brs), 8.01 (1 H, s), 10.6 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.7, 21.3, 120.2, 120.9, 122.3, 130.0, 134.4, 135.0, 142.5. IR ($CHCl_3$): 3479, 1776, 1578, 1530 cm^{-1}. HRMS calcd for $C_{11}H_{17}N_2Si$ $(M + H)^+$ m/z: 205.1161, found 205.1140.

6-Methyl-4-(trimethylsilyl)-1*H*-indazole (*proximal*-11Bn) (Table 3, entry 9). Product (10 mg, 39%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 57−58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.41 (9 H, s), 2.49 (3 H, s), 7.14 (1 H, brs), 7.28 (1 H, brs), 8.11 (1 H, brs), 10.0 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.6, 21.9, 109.9, 124.9, 129.3, 133.4, 135.5, 136.2, 139.8. IR ($CHCl_3$): 3469, 1782, 1531 cm^{-1}. HRMS calcd for $C_{11}H_{17}N_2Si$ $(M + H)^+$ m/z: 205.1161, found 205.1149.

5-Methyl-7-(*tert*-butyldimethylsilyl)-1*H*-indazole (*distal*-11Bn′) (Table 3, entry 9). Following the general procedure II, a mixture of **16B′** (85 mg, 0.20 mmol), (diazomethyl)trimethylsilane **6n** (2.0 M in Et_2O, 0.30 mL, 0.60 mmol) and Bu_4NF (1.0 M in THF, 0.40 mL, 0.40 mmol) in THF (2.0 mL) was stirred for 1 h. The ratio of *distal*- to *proximal*-**11Bn′** (3.3:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound *distal*-**11Bn′** (38 mg, 76%) as a colorless solid. Mp 199−201 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.45 (6 H, s), 0.93 (9 H, s), 2.47 (3 H, s), 7.30 (1 H, s), 7.54 (1 H, s), 7.99 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.2, 17.6, 21.3, 26.5, 117.9, 120.9, 122.4, 129.6, 134.0, 136.5, 143.1. IR ($CHCl_3$): 3483, 1722, 1600, 1463, 1257 cm^{-1}. HRMS calcd for $C_{14}H_{23}N_2Si$ $(M + H)^+$ m/z: 247.1631, found 247.1645.

6-Methyl-4-(*tert*-butyldimethylsilyl)-1*H*-indazole (*proximal*-11Bn′) (Table 3, entry 9). Product (12 mg, 24%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 145−147 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.43 (9 H, s), 0.92 (9 H, s), 2.50 (3 H, s), 7.13 (1 H,s), 7.28 (1 H, s), 8.09 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.8, 17.3, 22.0, 26.7, 109.9, 125.8, 130.9, 131.1, 135.9, 136.5, 139.7. IR ($CHCl_3$): 3469, 1602, 1251 cm^{-1}. HRMS calcd for $C_{14}H_{23}N_2Si$ $(M + H)^+$ m/z: 247.1631, found 247.1652.

2-(*tert*-Butyl)-5-methyl-3-phenyl-7-(trimethylsilyl)-2,3-dihydrobenzo[*d*]isoxazole (*distal*-11Br) (Table 3, entry 10).[10a] Following the general procedure II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), *N*-*tert*-butyl-α-phenylnitrone **6r** (69 mg, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 3.0 h. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *distal*-**11Br** (41 mg, 94%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.32 (9 H, s), 1.17 (9 H, s), 2.20 (3 H, s), 5.51 (1 H, s), 6.70 (1 H, s), 7.00 (1 H, s), 7.24 (1 H, t, J = 8.0 Hz), 7.32 (2 H, t, J = 8.0 Hz), 7.36 (2 H, d, J = 8.0 Hz) ^{13}C NMR (125 MHz, $CDCl_3$) δ: −1.2, 20.7, 25.4, 60.9, 66.7, 116.7, 125.1, 127.2, 127.4, 128.2, 128.5, 129.4, 134.2, 144.1, 159.2. IR ($CHCl_3$): 2976, 1602, 1454, 1393 cm^{-1}. HRMS calcd for $C_{21}H_{30}NOSi$ $(M + H)^+$ m/z: 340.2097, found 340.2090.

1-Benzyl-6-fluoro-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11Ce) (Table 3, entry 16). Following the general procedure II, a mixture of **16C**[14c] (50 mg, 0.13 mmol), (azidomethyl)benzene **6e** (50 μL, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Ce** (2.8:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *distal*-**11Ce** (27 mg, 56%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.48 (9 H, s), 5.77 (2 H, s), 6.91 (1 H, dd, J = 2.0, 8.0 Hz), 7.16 (1 H. dd, J = 2.0, 8.0 Hz), 7.28−7.36 (5 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.9, 52.3, 95.6 (J = 25 Hz), 118.7 (J = 25 Hz), 127.7, 128.5, 129.0, 132.2 (J = 10 Hz), 134.5, 136.8 (J = 10 Hz), 147.1, 161.7 (J = 240 Hz). IR ($CHCl_3$): 1724, 1604, 1501 cm^{-1}. HRMS calcd for $C_{16}H_{19}FN_3Si$ $(M + H)^+$ m/z: 300.1332, found 300.1336.

1-Benzyl-5-fluoro-1*H*-benzo[*d*]triazole (Desilylated Product of *proximal*-11Ce) (Table 3, entry 16). Product (8.2 mg, 28%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 101−103 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.84 (2 H, s), 7.18 (1 H, dt, J = 2.0, 8.0 Hz), 7.27−7.37 (6 H, m), 7.68 (1 H, dd, J = 2.0, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.6, 104.6 (J = 26 Hz), 110.7 (J = 10 HZ), 117.4 (J = 26 Hz), 127.6, 128.7, 129.1, 129.8, 134.3, 146.6 (J = 10 Hz), 159.7 (J = 240 Hz). IR ($CHCl_3$): 2396, 1778, 1627, 1595, 1499 cm^{-1}. HRMS calcd for $C_{13}H_{11}FN_3$ $(M + H)^+$ m/z: 228.0937, found 228.0916.

1-Benzyl-6-chloro-4-(trimethylsilyl)-1*H*-benzo[*d*]triazole (*distal*-11De) (Table 3, entry 17). Following the general procedure II, a mixture of **16D**[14c] (50 mg, 0.12 mmol), (azidomethyl)benzene **6e** (46 μL, 0.36 mmol), and Bu_4NF (1.0 M in THF, 0.24 mL, 0.24 mmol) in THF (1.2 mL) was stirred for 1.0 h. The ratio of *distal*- to *proximal*-**11De** (3.0:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound *distal*-**11De** (12 mg, 31%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.48 (9 H, s), 5.78 (2 H, s), 7.29−7.36 (7 H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.9, 52.2, 109.7, 127.6, 128.6, 129.1, 130.0, 132.3, 133.5, 134.4, 136.0, 148.8. IR ($CHCl_3$): 2959, 1750, 1593, 1497 cm^{-1}. HRMS calcd for $C_{16}H_{19}ClN_3Si$ $(M + H)^+$ m/z: 316.1037, found 316.1048.

1-Benzyl-5-chloro-1*H*-benzo[*d*]triazole (Desilylated Product of *proximal*-11De) (Table 3, entry 17). Product (3.0 mg, 12%) was obtained by column chromatography of the above-mentioned crude product as a colorless solid. Mp 148−149 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.84 (2 H, s), 7.25−7.27 (4 H, m), 7.33−7.37 (3 H, m), 8.05 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.6, 110.7, 119.5, 127.69, 128.4, 128.7, 129.1, 129.9, 131.5, 134.3, 147.0. IR ($CHCl_3$): 1732, 1583, 1497, 1479 cm^{-1}. HRMS calcd for $C_{13}H_{11}ClN_3$ $(M + H)^+$ m/z: 244.0642, found 244.0624.

Ethyl 5-Methyl-7-(trimethylsilyl)-1*H*-indazole-3-carboxylate (*distal*-11Bp) (Table 3, entry 18). Following the general procedure

II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), ethyl 2-diazoacetate **6p** (40 μL, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 0.5 h. The ratio of *distal*- to *proximal*-**11Bp** (12:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *distal*-**11Bp** (30 mg, 83%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 165−166 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.44 (9 H, s), 1.48 (3 H, t, J = 8.0 Hz), 2.50 (3 H, s), 4.51 (2 H, q, J = 8.0 Hz), 7.36 (1 H, s), 8.03 (1 H, s), 10.35 (NH, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −0.8, 14.4, 21.5, 60.9, 121.3, 121.9, 122.0, 132.6, 135.6, 136.1, 143.8, 162.7. IR ($CHCl_3$): 3466, 1715, 1601, 1452 cm^{-1}. HRMS calcd for $C_{14}H_{21}N_2O_2Si$ $(M + H)^+$ m/z: 277.1372, found 277.1351.

Ethyl 6-Methyl-4-(trimethylsilyl)-1*H*-indazole-3-carboxylate (*proximal*-11Bp) (Table 3, entry 18). Product (3.6 mg, 10%) was obtained by column chromatography of the above-mentioned crude product as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.41 (9 H, s), 1.46 (3 H, t, J = 7.5 Hz), 2.49 (3 H, s), 4.48 (2 H, q, J = 7.5 Hz), 7.34 (1 H, s), 7.39 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 1.1, 14.5, 21.8, 61.2, 110.5, 128.8, 130.1, 133.8, 134.4, 136.6, 141.6, 163.1. IR ($CHCl_3$): 3451, 1724, 1609, 1443 cm^{-1}. HRMS calcd for $C_{14}H_{21}N_2O_2Si$ $(M + H)^+$ m/z: 277.1372, found 277.1356.

5-Methyl-3,3-diphenyl-7-(trimethylsilyl)-3*H*-indazole (*distal*-11Bq) (Table 3, entry 19). Following the general procedure II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), (diazomethylene)dibenzene **6q**[42] (76 μL, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.26 mL, 0.26 mmol) in THF (1.3 mL) was stirred for 1.0 h. The ratio of *distal*- to *proximal*-**11 Bq** (3.0:1) was determined using ^{1}H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 50:1) to provide the titled compound *distal*-**11 Bq** (37 mg, 80%) as a colorless solid. Mp 122−123 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.49 (9 H, s), 2.45 (3 H, s), 7.27−7.30 (10 H, m), 7.37 (1 H, s), 7.40 (1 H, s). ^{13}C NMR (125 MHz, CD_3OD) δ: 0.6, 22.5, 102.3, 127.6, 129.6, 130.0, 130.5, 137.3, 137.9, 140.3, 142.3, 145.7, 161.7. IR ($CHCl_3$): 2959, 1591, 1493, 1466 cm^{-1}. HRMS calcd for $C_{23}H_{25}N_2Si$ $(M + H)^+$ m/z: 357.1787, found 357.1766 .

5-Methyl-3-phenyl-7-(trimethylsilyl)benzo[*d*]isoxazole (*distal*-11Bs) (Table 3, entry 20). Following the general procedure II, a mixture of **16B**[14c] (50 mg, 0.13 mmol), *N*-hydroxybenzimidoyl chloride[43] (61 mg, 0.39 mmol), and Bu_4NF (1.0 M in THF, 0.65 mL, 0.65 mmol) in THF (1.3 mL) was stirred for 24 h. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound *distal*-**11Bs** (27 mg, 73%) as a colorless solid, the regiochemistry of which was determined by NOESY spectrum. Mp 159−160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.45 (9 H, s), 2.51 (3 H, s), 7.45 (1 H, d, J = 2.0 Hz), 7.51−7.58 (3 H, m), 7.68 (1 H, brs), 7.95 (2 H, dd, J = 2.0, 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −1.2, 21.3, 119.1, 121.8, 122.2, 128.0, 129.0, 129.4, 129.9, 133.1, 136.8, 156.8, 167.1. IR ($CHCl_3$): 3059, 2361, 1595 cm^{-1}. HRMS calcd for $C_{17}H_{20}NOSi$ $(M + H)^+$ m/z: 282.1314, found 282.1323.

Synthesis of Hippadine Analogue 18 (Scheme 1a). 1-[(6-Iodobenzo[*d*][1,3]dioxol-5-yl)methyl]-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]triazole (*proximal*-10At). Following the general procedure I, a mixture of **14A** (0.30 g, 0.51 mmol), 5-(azidomethyl)-6-iodobenzo[*d*]1,3-dioxole **6t**[43] (0.46 g, 1.5 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.47 mL, 0.61 mmol) in Et_2O (5.1 mL) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound *proximal*-**10At** (178 mg, 69%) as a colorless solid. Mp 166−168 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21 (12 H, s), 5.51 (1 H, s), 5.85 (2 H, s), 6.16 (2 H, s), 7.30 (1 H, s), 7.41 (1 H, t, J = 7.5 Hz), 8.08 (1 H, d, J = 7.5 Hz), 8.24 (1 H, d, J = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.5, 58.0, 83.7, 84.4, 101.6, 106.9, 118.5, 123.6, 123.7, 133.2, 136.2, 137.8, 145.9, 147.4, 148.6. IR ($CHCl_3$): 2982, 1042 cm^{-1}. HRMS calcd for $C_{20}H_{21}BIN_3NaO_4$ $(M + Na)^+$ m/z: 528.0567, found 528.0568.

1-((6-Iodobenzo[*d*][1,3]dioxol-5-yl)methyl)-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]-triazole (*proximal*-10Bt). Following the general procedure I, a mixture of **14B** (0.20 g, 0.33 mmol), 5-(azidomethyl)-6-iodobenzo-[*d*]1,3-dioxole **6t**[43] (0.30 g, 0.99 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.31 mL, 0.39 mmol) in THF (1.0 mL) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 7:1) to provide the titled compound *proximal*-**10Bt** (115 mg, 67%) as a colorless solid. Mp 163−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21 (12 H, s), 2.53 (3 H, s), 5.49 (1 H, s), 5.85 (2 H, s), 6.13 (2 H, s), 7.30 (1 H, s), 7.90 (1 H, s), 7.99 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.5, 58.0, 83.7, 84.4, 101.6, 106.9, 118.5, 122.8, 133.3, 133.5, 134.7, 139.8, 146.6, 147.4, 148.6. IR ($CHCl_3$): 2982, 1042 cm^{-1}. HRMS calcd for $C_{21}H_{23}BIN_3NaO_4$ $(M + Na)^+$ m/z: 542.0724, found 542.0724.

7*H*-[1,3]Dioxolo[4,5-j]triazolo[4,5,1-*de*]phenanthridine (17A). An oven-dried round-bottom flask was charged with *proximal*-**10At** (50 mg, 0.096 mmol), $PdCl_2(dppf)·CH_2Cl_2$ (24 mg, 0.029 mmol), and $Ba(OH)_2·8H_2O$ (91 mg, 0.29 mmol). The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous dioxane (0.50 mL) was added via a syringe, and the mixture was stirred at 100 °C for 16 h. After the reaction, the mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and evaporated under reduced pressure. The residue was washed with acetone to provide the titled compound **17A** (10 mg, 40%) as a colorless solid. Mp >350 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 80 °C) δ: 6.02 (2 H, s), 6.12 (2 H, s), 7.05 (1 H, s), 7.34 (1 H, t, J = 7.5 Hz), 7.68 (1 H, s), 7.76 (2 H, d, J = 7.5 Hz). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 80 °C) δ: 50.5, 103.3, 104.8, 109.5, 118.4, 118.7, 121.3, 123.1, 126.8, 126.9, 132.3, 144.6, 149.4, 150.0. IR ($CHCl_3$): 3008, 1039 cm^{-1}. HRMS calcd for $C_{14}H_{10}N_3O_2$ $(M + H)^+$ m/z: 252.0773, found 252.0796.

2-Methyl-7*H*-[1,3]dioxolo[4,5-*j*]triazolo[4,5,1-*de*]-phenanthridine (17B). An oven-dried round-bottom flask was charged with *proximal*-**10Bt** (50 mg, 0.096 mmol), $PdCl_2(dppf)·CH_2Cl_2$ (24 mg, 0.029 mmol), and $Ba(OH)_2·8H_2O$ (91 mg, 0.29 mmol). The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous dioxane (0.50 mL) was added via a syringe, and the mixture was stirred at 100 °C for 16 h. After the reaction, the mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and evaporated under reduced pressure. The residue was washed with acetone to provide the titled compound **17B** (15 mg, 59%) as a colorless solid. Mp 267−269 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.53 (3 H, s), 5.92 (2 H, s), 6.07 (2 H, s), 6.79 (1 H, s), 7.32 (1 H, s), 7.35 (1 H, s), 7.55 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.2, 49.4, 101.9, 103.1, 107.7, 116.6, 118.9, 119.1, 122.2, 124.5, 129.9, 135.6, 144.2, 148.3, 148.7. IR ($CHCl_3$): 3008, 1039 cm^{-1}. HRMS calcd for $C_{15}H_{12}N_3O_2$ $(M + H)^+$ m/z: 266.0930, found 266.0921.

Preparation of 7*H*-[1,3]Dioxolo[4,5-*j*]triazolo[4,5,1-*de*]-phenanthridin-7-one (18A) from *proximal*-10At. An oven-dried round-bottom flask was charged with *proximal*-**10At** (50 mg, 0.099 mmol), $PdCl_2(dppf)·CH_2Cl_2$ (24 mg, 0.030 mmol), and $Ba(OH)_2·8H_2O$ (94 mg, 0.30 mmol). The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous dioxane (0.50 mL) was added via a syringe and the mixture was stirred for 18 h at 100 °C. After the reaction, the mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and evaporated under reduced pressure to give crude **17A**. Then, activated MnO_2 (85 mg, 0.99 mmol) was added into the crude **17A**. The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous CH_2Cl_2 (3.3 mL) was added via a syringe, and the mixture was stirred for 24 h at room temperature. After the reaction, the mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and evaporated under reduced pressure. The crude product was washed with ethanol to provide the titled compound **18A** (10 mg, 53% from *proximal*-**10At**) as a pale yellow solid. Mp >350 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 80 °C) δ: 6.32 (2 H, s), 7.77 (1 H, t, J = 7.5 Hz), 7.90 (1 H, s), 8.13 (1 H, s), 8.33 (1 H, d, J = 7.5 Hz), 8.54 (1 H, d, J = 7.5 Hz). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 80 °C) δ: 103.8, 108.5, 117.7, 121.3, 123.2, 124.9, 127.8, 129.2, 131.4, 144.2, 149.9, 154.2, 155.4. IR ($CHCl_3$): 3008, 1715, 1039 cm^{-1}. HRMS calcd for $C_{14}H_8N_3O_3$ $(M + H)^+$ m/z: 266.0566, found 266.0583.

Preparation of 2-Methyl-7*H*-[1,3]dioxolo[4,5-*j*]triazolo[4,5,1-*de*]phenanthridin-7-one (18B) from *proximal*-10Bt. An oven-dried round-bottom flask was charged with *proximal*-**10Bt** (50 mg, 0.096 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (24 mg, 0.030 mmol), and $Ba(OH)_2\cdot 8H_2O$ (91 mg, 0.30 mmol). The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous dioxane (0.50 mL) was added, and the mixture was stirred at 100 °C for 18 h. After the reaction, the mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and evaporated under reduced pressure to give crude **17B**. Then, activated MnO_2 (80 mg, 0.96 mmol) was added into the crude **17B**. The flask was capped with a rubber septum, then evacuated, and backfilled with argon. Anhydrous CH_2Cl_2 (3.3 mL) was added, and the mixture was stirred for 24 h at room temperature. After the reaction, the mixture was filtered through a short pad of Celite, washed with CH_2Cl_2, and evaporated under reduced pressure. The residue was washed with acetone to provide the titled compound **18B** (16 mg, 61% from *proximal*-**10Bt**) as a pale yellow solid. Mp 256−258 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.69 (3 H, s), 6.22 (2 H, s), 7.60 (1 H, s), 7.93 (2 H, s), 7.98 (1 H, s), 8.06 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.1, 102.2, 102.9, 109.5, 116.7, 120.7, 123.6, 124.4, 127.7, 130.9, 137.4, 144.9, 149.6, 153.8, 155.2. IR ($CHCl_3$): 3008, 1703, 1039 cm^{-1}. HRMS calcd for $C_{15}H_{10}N_3O_3$ $(M + H)^+$ m/z: 280.0722, found 280.0727.

Formal Synthesis of Vorozole 21 (Scheme 1b). 4-(*tert*-Butyldimethylsilyl)-6-(1,3-dioxolan-2-yl)-1-methyl-1*H*-benzo-[*d*]triazole (*distal*-11Eu′). Following the general procedure II, a mixture of **16E′** (100 mg, 0.158 mmol), (azidomethyl)trimethylsilane **6u** (62 mg, 0.48 mmol) (*for safety reasons, commercially available* **6u** *was used as an equivalent of the highly explosive methyl azide*), and Bu_4NF (1.0 M in THF, 0.32 mL, 0.32 mmol) in THF (1.6 mL) was stirred for 30 min at 0 °C. The ratio of *distal*- to *proximal*-**11Eu′** (15:1) was determined using ^1H NMR spectra of the crude product. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to provide the titled compound *distal*-**11Eu′** (43 mg, 84%) as a colorless solid. Mp 92−94 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.52 (6 H, s), 0.93 (9 H, s), 4.09−4.20 (4 H, m), 4.28 (3 H, s), 6.00 (1 H, s), 7.54 (1 H, d, J = 8.0 Hz), 7.68 (1 H, d, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.0, 17.2, 26.9, 34.1, 65.4, 103.5, 107.5, 129.5, 131.8, 133.2, 136.2, 151.0. IR ($CHCl_3$): 1602, 1408, 1328, 1236, 1120 cm^{-1}. HRMS calcd for $C_{16}H_{26}N_3O_2Si$ $(M + H)^+$ m/z: 320.1794, found 320.1801.

6-(1,3-Dioxolan-2-yl)-1-methyl-1*H*-benzo[*d*]triazole (24). Bu_4NF (1.0 M in THF, 0.35 mL, 350 μmol) was added into the THF solution (0.70 mL, 0.10 M) of *distal*-**11E′** (23 mg, 71 μmol) and stirred for 48 h at 70 °C. The reaction mixture was cooled to room temperature and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to provide the titled compound **24** (14 mg, 94%) as a colorless solid. Mp 97−98 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.08−4.18 (4 H, m), 4.31 (3 H, s), 5.98 (1 H, s), 7.49 (1 H, d, J = 8.0 Hz), 7.69 (1 H, s), 8.05 (1 H, d, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.3, 65.4, 103.2, 107.1, 120.0, 122.6, 133.3, 137.7, 146.4. IR ($CHCl_3$): 1600, 1193 cm^{-1}. HRMS calcd for $C_{10}H_{12}N_3O_2$ $(M + H)^+$ m/z: 206.0930, found 206.0910.

1-Methyl-1*H*-benzo[*d*]triazole-6-carbaldehyde (20). $TsOH\cdot H_2O$ (3.4 mg, 20 μmol) was added into the acetone solution (0.70 mL) of **24** (14 mg), and the mixture was stirred at room temperature for 3 h. After the reaction, a saturated aqueous $NaHCO_3$ was added into the reaction mixture, and the mixture was extracted with Et_2O. The aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to provide the titled compound **20** (10 mg, 96%) as a colorless solid. Mp 119−122 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.41 (3 H, s), 7.91 (1 H, d, J = 8.0 Hz), 8.11 (1 H, s), 8.19 (1 H, d, J = 8.0 Hz), 10.19 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.7, 112.4, 120.9, 124.0, 133.5, 135.1, 148.6, 191.3. IR ($CHCl_3$): 1703, 1616, 1602, 1236 cm^{-1}. HRMS calcd for $C_8H_8N_3O$ $(M + H)^+$ m/z: 162.0667, found 162.0692.

Synthesis of *iso*-Vorozole 23 (Scheme 1c). 5-(1,3-Dioxolan-2-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((trimethylsilyl)methyl)-1*H*-benzo[*d*]triazole (*proximal*-10Cu). Following the general procedure I, a mixture of **14C** (94 mg, 0.14 mmol), (azidomethyl)trimethylsilane **6u** (0.21 mL, 1.41 mmol), and *i*-PrMgCl·LiCl (1.3 M in THF, 0.21 mL, 0.27 mmol) in Et_2O (1.4 mL) was stirred for 30 min at 0 °C. The crude product was purified by column chromatography (hexane/EtOAc = 5:2) to provide the titled compound *proximal*-**10Cu** (33 mg, 57%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.15 (9 H, s), 1.40 (12 H, s), 4.07−4.09 (2 H, m), 4.17−4.20 (2 H, m), 4.57 (2 H, s), 5.98 (1 H, s), 8.10 (1 H, d, J = 1.5 Hz), 8.24 (1 H, d, J = 1.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −2.1, 24.9, 40.7, 65.3, 84.5, 103.5, 121.3, 132.9, 135.2, 136.9, 145.3. IR ($CHCl_3$): 1587 cm^{-1}. HRMS calcd for $C_{19}H_{30}BN_3NaO_4Si$ $(M + Na)^+$ m/z: 426.1996, found 426.1991.

5-(1,3-Dioxolan-2-yl)-1-methyl-1*H*-benzo[*d*]triazole (25). The mixture of *proximal*-**10Cu** (27 mg, 67 μmol), 10% Pd/C (3.4 mg), and KF (12 mg, 0.20 mmol) was evacuated and backfilled with argon. MeOH (0.70 mL) was added into the reaction tube, and the mixture was heated using microwave for 3 h at 150 °C.[26] The reaction mixture was filtered through a short pad of Celite and evaporated under reduced pressure. CH_2Cl_2 was added into the mixture, filtered through a short pad of Celite, concentrated under reduced pressure to provide **25** as a colorless solid (13.5 mg), and used without further purification for the next reaction.

1-Methyl-1*H*-benzo[*d*]triazole-5-carbaldehyde (22). $TsOH\cdot H_2O$ (3.8 mg, 20 μmol) was added into an acetone solution (0.70 mL) of **25** (13.5 mg). The mixture was stirred at room temperature for 9 h. After the reaction, a saturated aqueous $NaHCO_3$ was added into the reaction mixture and extracted with EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc = 2:1) to provide the titled compound **22** (9.5 mg, 88% 2 steps) as a colorless solid. Mp 165−167 °C. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.36 (3 H, s), 7.63 (1 H, d, J = 8.5 Hz), 8.09 (1 H, dd, J = 1.0, 8.5 Hz), 8.55 (1 H, brs), 10.13 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.5, 110.1, 125.6, 126.1, 133.1, 136.5, 145.7, 191.1. IR ($CHCl_3$): 1701 cm^{-1}. HRMS calcd for $C_8H_7N_3NaO$ $(M + Na)^+$ m/z: 184.0487, found 184.0481.

(4-Chlorophenyl)(1-methyl-1*H*-benzo[*d*]triazol-5-yl)-methanol (26). An oven-dried flask was charged with **22** (46 mg, 0.29 mmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with argon. Et_2O (2.8 mL, 0.10 M) was added via a syringe into the reaction mixture and cooled to −78 °C. 4-Chlorophenylmagnesiumbromide (1.0 M in Et_2O, 0.57 mL, 0.57 mmol) was added into the solution and stirred at −78 °C for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and extracted with EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 2:1) to provide the titled compound **26** (65 mg, 83%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.28 (3 H, s), 6.00 (1 H, s), 7.32 (4 H, m), 7.46 (2 H, s), 8.08 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.3, 75.3, 109.5, 117.3, 126.6, 127.9, 128.7, 133.1, 133.5, 139.9, 142.0, 145.9. IR ($CHCl_3$): 3603, 1600, 1491, 1281, 1236 cm^{-1}. HRMS calcd for $C_{14}H_{13}ClON_3$ $(M + H)^+$ m/z: 274.0747, found 274.0726.

5-((4-Chlorophenyl)(1*H*-1,2,4-triazol-1-yl)methyl)-1-methyl-1*H*-benzo[*d*]triazole (23). A mixture of **26** (65 mg, 0.23 mmol), 1,2,4-triazole (33 mg, 0.47 mmol), and $TsOH\cdot H_2O$ (13 mg, 71 μmol) in a pear-shaped flask was dissolved in toluene (5.0 mL). The flask was connected with a Dean−Stark apparatus and stirred at 150 °C for 24 h. The reaction mixture was cooled to room temperature and quenched with a saturated aqueous $NaHCO_3$. The reaction mixture was

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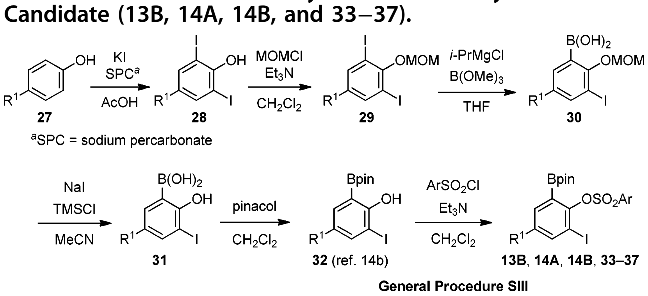
extracted with EtOAc, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. The solution was filtered through a glass filter and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 1:2) to provide the titled compound **23** (60 mg, 79%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.31 (3 H, s), 6.90 (1 H, s), 7.10 (2 H, d, J = 8.0 Hz), 7.36 (1 H, d, J = 8.0 Hz), 7.37 (2 H, d, J = 8.0 Hz), 7.55 (1 H, d, J = 8.0 Hz), 7.78 (1H, s), 8.00 (1 H, s), 8.05 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 34.4, 66.9, 110.14, 119.8, 127.6, 129.3, 129.4, 133.4, 133.8, 135.0, 143.5, 145.9, 152.5. IR ($CHCl_3$): 1732, 1597, 1492, 1274, 1238 cm^{-1}. HRMS calcd for $C_{16}H_{14}ClN_6$ (M + H)$^+$ m/z: 325.0968, found 325.0984.

General Procedure SIII: Synthesis of Benzyne Precursor Candidate (13B, 14A, 14B, and 33–37).



An oven-dried round-bottom flask was charged with **32**[14b] (crude product from **29**) (1.0 equiv), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with nitrogen. Anhydrous CH_2Cl_2 (0.30 M) was added via a syringe, and the mixture was cooled to 0 °C. Et_3N (3.0 equiv) and chlorinated benzene sulfonyl chloride (1.5 equiv) were added and stirred for several hours at room temperature. After the completion of the reaction, water was added to the reaction mixture. The mixture was extracted with CH_2Cl_2, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with a saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4, filtered through a glass filter, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to provide **13B**, **14A**, **14B**, and **33–37**.

2-Iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 4-Chlorobenzenesulfonate (13B). Following the general procedure SIII, a mixture of 2-iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **32B**[14b] (crude product from **29B**) (1.0 g, 2.8 mmol), Et_3N (0.80 mL, 5.6 mmol), and 4-chlorobenzenesulfonyl chloride (0.89 g, 4.2 mmol) in CH_2Cl_2 (5.0 mL, 0.30 M) was stirred for 5 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 11:1) to provide the titled compound **13B** (0.85 g, 59% from **29B**) as a colorless solid. Mp 165–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (12 H, s), 2.29 (3 H, s), 7.48 (2 H, d, J = 8.5 Hz), 7.55 (1 H, s) 7.57 (1 H, s), 7.74 (2 H, d, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.2, 24.9, 84.6, 89.6, 129.5, 130.5, 135.3, 136.5, 138.3, 141.1, 142.7, 150.8. IR ($CHCl_3$): 3036 cm^{-1}. HRMS calcd for $C_{19}H_{21}BClINaO_5S$ (M + Na)$^+$ m/z: 556.9834, found 556.9860.

2-Iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,5-Dichlorobenzenesulfonate (33). Following the general procedure SIII, a mixture of a mixture of **32B**[14b] (crude product from **29B**) (2.0 g, 5.6 mmol), Et_3N (1.6 mL, 11 mmol), and 2,5-dichlrobenzenesulfonyl chloride (1.6 mg, 6.7 mmol) in CH_2Cl_2 (19 mL, 0.30 M) was stirred for 5 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound **33** (2.5 g, 78% from **29B**) as a colorless solid. Mp 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (12 H, s), 2.29 (3 H, s), 7.46–7.54 (2 H, m), 7.56 (1 H, d, J = 1.5 Hz), 7.61 (1 H, d, J = 1.5 Hz), 7.88 (1 H, d, J = 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 24.8, 84.6, 88.7, 131.7, 133.0, 133.1, 133.4, 134.8, 136.7, 137.3, 138.4, 143.0, 151.5. IR ($CHCl_3$): 3036 cm^{-1}. HRMS calcd for $C_{19}H_{20}BCl_2INaO_5S$ (M + Na)$^+$ m/z: 590.9444, found 590.9447.

2-Iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,3-Dichlorobenzenesulfonate (34). Following the general procedure SIII, a mixture of a mixture of **32B**[14b] (crude product from **29B**) (101 mg, 0.28 mmol), Et_3N (0.12 mL, 0.84 mmol), and 2,3-dichlrobenzenesulfonyl chloride (103 mg, 0.42 mmol) in CH_2Cl_2 (1.0 mL, 0.30 M) was stirred for 3 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **34** (126 mg, 79% from **29B**) as a colorless solid. Mp 135–140 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (12 H, s), 2.28 (3 H, s), 7.29 (1 H, t, J = 8.0 Hz), 7.56 (1 H, s), 7.58 (1 H, s), 7.74 (1 H, d, J = 8.0 Hz), 7.78 (1 H, d, J = 8.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 24.8, 84.6, 88.5, 127.1, 130.2, 133.4, 135.6, 136.2, 136.6, 138.2, 138.3, 143.0, 151.7. IR ($CHCl_3$): 2982 cm^{-1}. HRMS calcd for $C_{19}H_{20}BCl_2INaO_5S$ (M + Na)$^+$ m/z: 590.9444, found 590.9451.

2-Iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,4-Dichlorobenzenesulfonate (35). Following the general procedure SIII, a mixture of a mixture of **32B**[14b] (crude product from **29B**) (101 mg, 0.30 mmol), Et_3N (0.12 mL, 0.84 mmol), and 2,4-dichlrobenzenesulfonyl chloride (103 mg, 0.42 mmol) in CH_2Cl_2 (1.0 mL, 0.30 M) was stirred for 20 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **35** (116 mg, 73% from **29B**) as a colorless solid. Mp 100–105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (12 H, s), 2.28 (3 H, s), 7.33 (1 H, dd, J = 2.5, 8.5 Hz), 7.55 (1 H, d, J = 1.5 Hz), 7.57 (1 H, d, J = 2.5 Hz), 7.59 (1 H, d, J = 1.5 Hz), 7.78 (1 H, d, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 24.9, 84.6, 88.7, 127.3, 132.2, 132.9, 134.7, 135.9, 136.6, 138.4, 141.0, 142.9, 151.5. IR ($CHCl_3$): 2982 cm^{-1}. HRMS calcd for $C_{19}H_{20}BCl_2INaO_5S$ (M + Na)$^+$ m/z: 590.9444, found 590.9471.

2-Iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,6-Dichlorobenzenesulfonate (36). Following the general procedure SIII, a mixture of a mixture of **32B**[14b] (crude product from **29B**) (101 mg, 0.28 mmol), Et_3N (0.12 mL, 0.84 mmol), and 2,6-dichlrobenzenesulfonyl chloride (103 mg, 0.42 mmol) in CH_2Cl_2 (1.0 mL, 0.30 M) was stirred for 5 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **36** (142 mg, 89% from **29B**) as a colorless solid. Mp 197–202 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (12 H, s), 2.29 (3 H, s), 7.38 (1 H, t, J = 8.0 Hz), 7.46 (2 H, d, J = 8.0 Hz), 7.56 (1 H, d, J = 2.0 Hz), 7.61 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 24.8, 84.6, 88.2, 131.5, 133.6, 135.1, 136.7, 137.2, 138.3, 142.9, 151.9. IR ($CHCl_3$): 3011 cm^{-1}. HRMS calcd for $C_{19}H_{20}BCl_2INaO_5S$ (M + Na)$^+$ m/z: 590.9444, found 590.9468.

2-Iodo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl 2,4,5-Trichlorobenzenesulfonate (14A). Following the general procedure SIII, a mixture of a mixture of 2-iodo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **32A**[14b] (crude product from **29A**) (2.9 mmol of **29A**), Et_3N (0.87 mL, 6.2 mmol), and 2,4,5-trichlrobenzenesulfonyl chloride (0.87 g, 3.1 mmol) in CH_2Cl_2 (7.0 mL) was stirred for 4 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **14A** (1.0 g, 75% from **29A**) as a colorless solid. Mp 106–108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (12 H, s), 7.02 (1 H, t, J = 7.5 Hz), 7.67 (1 H, s), 7.79 (1 H, dd, J = 1.5, 7.5 Hz), 7.81 (1 H, dd, J = 1.5, 7.5 Hz), 7.97 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 24.8, 84.7, 88.7, 131.6, 133.0, 133.4, 133.5, 135.6, 136.8, 138.6, 139.3, 143.0, 151.4. IR ($CHCl_3$): 3009 cm^{-1}. HRMS calcd for $C_{18}H_{17}BCl_3INaO_5S$ (M + Na)$^+$ m/z: 610.8898, found 610.8871.

2-Iodo-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,4,5-Trichlorobenzenesulfonate (14B). Following the general procedure SIII, a mixture of a mixture of **32B**[14b] (crude product from **29B**) (1.1 g, 3.0 mmol), Et_3N (1.2 mL, 8.9 mmol), and 2,4,5-trichlrobenzenesulfonyl chloride (1.2 g, 4.4 mmol) in CH_2Cl_2 (10 mL, 0.30 M) was stirred for 12 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **14B** (1.3 g, 75% from **29B**) as a colorless solid. Mp 134–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39

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(12 H, s), 2.30 (3 H, s), 7.57 (1 H, d, J = 1.5 Hz), 7.62 (1 H, d, J = 1.5 Hz), 7.67 (1 H, s), 7.97 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.1, 24.8, 84.7, 88.7, 131.6, 133.0, 133.4, 133.5, 135.6, 136.8, 138.6, 139.3, 143.0, 151.4. IR ($CHCl_3$): 3034 cm^{-1}. HRMS calcd for $C_{19}H_{19}BCl_3INaO_5S$ $(M + Na)^+$ m/z: 624.9054, found 624.9068.

Methyl 3-Iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(((2,4,5-trichlorophenyl)sulfonyl)oxy)benzoate (37). Following the general procedure SIII, a mixture of methyl 4-hydroxy-3-iodo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate **32D**[14b] (1.06 g, crude product from **29D**), Et_3N (1.1 mL, 7.9 mmol), and 2,4,5-trichlrobenzenesulfonyl chloride (1.1 g, 3.9 mmol) in CH_2Cl_2 (26 mL, 0.10 M) was stirred for 12 h at room temperature. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound **37** (1.46 g, 53% from **29D**) as a colorless solid. Mp 174−176 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.40 (12 H, s), 3.92 (3 H, s), 7.68 (1 H, brs), 7.98 (1 H, brs), 8.42 (1 H, d, J = 2.0 Hz), 8.47 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.8, 52.5, 85.0, 88.9, 129.9, 131.8, 132.9, 133.3, 133.6, 135.4, 137.4, 139.7, 143.8, 156.5, 164.6. IR ($CHCl_3$): 1705 cm^{-1}. HRMS calcd for $C_{20}H_{19}BCl_3INaO_7S$ $(M + Na)^+$ m/z: 668.8952, found 668.8944.

4-Formyl-2-iodo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,4,5-Trichlorobenzenesulfonate (38). An oven-dried round-bottom flask was charged with **37** (1.34 g, 2.1 mmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with nitrogen. CH_2Cl_2 (11 mL) was added into the flask via a syringe and cooled to −78 °C. A 1.0 M diisobutyl aluminum hydride solution in CH_2Cl_2 (2.1 mL, 2.1 mmol) was added to the mixture and stirred over 1 h. MeOH (0.50 mL) and a saturated aqueous Rochell's salt (2.0 mL) were added to the reaction mixture and stirred over 1 h at room temperature. The mixture was filtered through a pad of Celite and constructed twice by CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4, and solvent was removed under reduced pressure. Compound **38** was obtained as a colorless solid (1.26 g) and used as such without further purification for the next reaction.

4-(1,3-Dioxolan-2-yl)-2-iodo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl 2,4,5-Trichlorobenzenesulfonate (14C). A mixture of **38** (196 mg) and ethylene glycol (40 μL, 0.72 mmol) in CH_2Cl_2 (3.0 mL) was cooled to 0 °C and stirred under argon. Trimethylsilyl chloride (80 μL, 0.63 mmol) was added to the solution and slowly warmed to room temperature. After 9 h, solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 6:1) to provide the titled compound **14C** (104 mg, 49%) as a colorless solid. Mp 73−75 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.39 (12 H, s), 4.03−4.11 (4 H, m), 5.76 (1 H, s), 7.67 (1 H, brs), 7.86 (1 H, d, J = 2.0 Hz), 7.92 (1 H, d, J = 2.0 Hz), 7.96 (1 H, brs). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.8, 65.4, 84.8, 88.8, 101.8, 131.7, 133.0, 133.4, 133.5, 134.5, 135.6, 138.3, 139.4, 140.6, 153.9. IR ($CHCl_3$): 1394 cm^{-1}. HRMS calcd for $C_{21}H_{21}BCl_3INaO_7S$ $(M + Na)^+$ m/z: 682.9109, found 682.9110.

Synthesis of Silylbenzyne Precursors (16B′ and 16E′)[14c] 2-(*tert*-Butyldimethylsilyl)-4-methyl-6-(trimethylsilyl)phenol (39). An oven-dried round-bottom flask was charged with 2-bromo-6-(*tert*-butyldimethylsilyl)-4-methylphenol[14a] (3.6 g, 12 mmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with nitrogen. CH_2Cl_2 (30 mL, 0.40 M) was added into the flask via a syringe, cooled to 0 °C, and stirred for 10 min. Triethylamine (2.0 mL, 14 mmol) and trimethylsilyl chloride (1.9 mL, 14 mmol) were added into the flask, and the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure. Hexane was added to the residue, filtered through a pad of short pad of Celite, and concentrated under reduced pressure to afford (3-bromo-5-methyl-2-[(trimethylsilyl)oxy]phenyl)-(*tert*-butyl)dimethylsilane. THF (24 mL, 0.50 M) was added to the crude product, and the mixture was stirred at −78 °C for 10 min. *n*-BuLi (1.6 M in hexane, 7.4 mL, 12 mmol) was added to the mixture and stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and evaporated under reduced pressure. The residue was extracted with hexane and water. The aqueous layer was extracted twice with hexane. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous $MgSO_4$, and solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane) to provide the titled compound **39** (3.2 g, 92%) as a colorless solid. Mp 54−56 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.31 (9 H, s), 0.36 (6 H, s), 0.91 (9 H, s), 2.27 (3 H, s), 4.90 (1 H, s), 7.12 (1 H, d, J = 2.0 Hz), 7.17 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.6, −0.8, 17.6, 20.6, 26.6, 120.5, 124.6, 128.5, 137.2, 138.2, 163.5 . IR ($CHCl_3$): 3612, 1570, 1464, 1402, 1253, 1167 cm^{-1}. HRMS calcd for $C_{16}H_{29}OSi_2$ $(M{-}H^+)$ m/z: 293.1733, found 293.1757.

2-(*tert*-Butyldimethylsilyl)-4-(1,3-dioxolan-2-yl)-6-(trimethylsilyl)phenyl Trifluoromethanesulfonate (16B′). An oven-dried round-bottom flask was charged with **39** (1.0 g, 3.4 mmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with nitrogen. Et_2O (14 mL, 0.25 M) was added into the flask via a syringe, cooled to −78 °C, and stirred for 10 min. *n*-BuLi (1.62 M in hexane, 2.3 mL, 3.7 mmol) was added and stirred at −78 °C for 10 min. Then, trifluoromethanesulfonic anhydride (0.62 mL, 3.7 mmol) was added into the mixture at −78 °C. The mixture was warmed to room temperature and stirred at room temperature for 3 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and extracted with EtOAc. The aqueous layer was extracted twice by EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure (this reaction did not complete). Et_2O (13 mL, 0.25 M) was added into the flask via a syringe, cooled to −78 °C, and stirred for 10 min. *n*-BuLi (1.62 M in hexane, 0.23 mmol) was added and stirred at −78 °C for 10 min. Then, trifluoromethanesulfonic anhydride (63 μL, 0.38 mmol) was added into the mixture at −78 °C. The mixture was warmed to room temperature and stirred at room temperature for 3 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and extracted with EtOAc. The aqueous layer was extracted twice by EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound **16B′** (1.31 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, CD_3OD) δ: 0.33 (9 H, s), 0.39 (6 H, s), 0.78 (9 H, s), 2.39 (3 H, s), 7.43 (1 H, d, J = 2.0 Hz), 7.47 (1 H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.0, −0.56, 18.1, 20.8, 26.9, 118.5 (q, J = 318 Hz), 131.6, 134.8, 136.1, 138.7, 139.2, 152.7. IR ($CHCl_3$): 1566, 1463, 1392, 1367, 1253 cm^{-1}. HRMS calcd for $C_{17}H_{30}F_3O_3SSi_2$ $(M + H)^+$ m/z: 427.1406, found 427.1419.

4-(1,3-Dioxolan-2-yl)-2,6-diiodophenol (40). A mixture of 4-hydroxy-3,5-diiodobenzaldehyde (3.0 g, 8.0 mmol), ethylene glycol (0.90 mL, 16 mmol) and $TsOH{\cdot}H_2O$ (69 mg, 0.40 mmol) was dissolved in toluene. The reaction flask was connected with Dean−Stark apparatus and stirred at 150 °C for 10 h. After the reaction was completed, K_2CO_3 (0.20 g, 1.4 mmol) was added to the mixture, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 1:1) to provide the titled compound **40** (3.0 g, 89%) as a colorless solid. Mp 120−122 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.04 (4 H, m), 5.66 (1 H, s), 5.88 (1 H, s), 7.77 (2 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 65.2, 82.0, 101.4, 133.9, 137.5, 154.1. IR ($CHCl_3$): 3479, 2891, 1600, 1460, 1363, 1238 cm^{-1}. HRMS calcd for $C_9H_9I_2O_3$ $(M + H)^+$ m/z: 418.8670, found 418.8641.

(4-(1,3-Dioxolan-2-yl)-2,6-diiodophenoxy)(*tert*-butyl)-dimethylsilane (41). A mixture of **40** (1.0 g, 2.4 mmol) and imidazole (0.24 g, 3.6 mmol) was dissolved in THF (10 mL, 0.25 M). *tert*-Butyldimethylsilyl chloride was added to the mixture and stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and extracted with EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **41** (1.20 g, 95%) as a colorless solid. Mp 103−104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.46 (6 H, s), 1.07 (9 H, s), 4.05 (4 H, m), 5.65 (1 H, s), 7.86 (2 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0, 18.9, 26.5, 65.3, 88.5, 101.5, 134.4, 138.5, 155.9. IR ($CHCl_3$): 2958, 2931, 2887, 2858, 1600, 1448, 1276, 1255 cm^{-1}. HRMS calcd for $C_{15}H_{23}I_2O_3Si$ $(M + H)^+$ *m*/*z*: 532.9528, found 532.9506.

2-(*tert*-Butyldimethylsilyl)-4-(1,3-dioxolan-2-yl)-6-iodophenol (42). An oven-dried round-bottom flask was charged with **41** (0.80 g, 1.51 mmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with nitrogen. THF (15 mL, 0.10 M) was added into the flask via a syringe, cooled to −78 °C, and stirred for 10 min. *n*-BuLi (1.65 M in hexane, 1.2 mL, 2.0 mmol) was added to the solution at −78 °C, warmed to room temperature, and stirred for 2 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and extracted with EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 10:1) to provide the titled compound **42** as a colorless solid (0.53 g, 88%). Mp 112−113 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.30 (6 H, s), 0.89 (9 H, s), 0.78 (9 H, s), 4.06 (4 H, m), 5.53 (1 H, s), 5.70 (1 H, s), 7.36 (1 H, d, *J* = 2.0 Hz), 7.80 (1 H, d, *J* = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.8, 17.6, 27.0, 65.2, 87.2, 102.8, 123.5, 131.2, 135.7, 137.4, 159.4. IR ($CHCl_3$): 3489, 2955, 2928, 2886, 2856, 1589, 1560, 1413, 1359, 1248 cm^{-1}. HRMS calcd for $C_{15}H_{24}IO_3Si$ $(M + H^+)$ *m*/*z*: 407.0539, found 407.0551.

2-(*tert*-Butyldimethylsilyl)-4-(1,3-dioxolan-2-yl)-6-(trimethylsilyl)phenol (43). An oven-dried round-bottom flask was charged with **42** (63 mg, 0.15 mmol), capped with an inlet adapter with a three-way stopcock, then evacuated, and backfilled with nitrogen. CH_2Cl_2 (1.0 mL, 0.25 M) was added into the flask via a syringe, cooled to 0 °C, and stirred for 10 min. Triethylamine (26 μL, 0.19 mmol) and trimethylsilyl chloride (25 μL, 0.19 mmol) were added into the flask, and the mixture was stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure. Hexane was added to the residue, filtered through a pad of short pad of Celite and concentrated under reduced pressure to afford (5-(1,3-dioxolan-2-yl)-3-iodo-2-((trimethylsilyl)oxy)phenyl)(*tert*-butyl)-dimethylsilane. The crude product was dissolved in THF (1.0 mL, 0.25 M) and stirred at −78 °C for 10 min. *n*-BuLi (1.5 M in hexane, 0.12 mL, 0.19 mmol) was added to the mixture and stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl and evaporated under reduced pressure. The residue was extracted with hexane and water. The aqueous layer was extracted twice with hexane. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 20:1) to provide the titled compound **43** (23 mg, 42%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.32 (9 H, s), 0.39 (6 H, s), 0.92 (9 H, s), 4.08 (4 H, m), 5.16 (1 H, s), 5.74 (1 H, s), 7.41 (1 H, d, *J* = 2.0 Hz), 7.50 (1 H, d, *J* = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.6, −0.9, 17.6, 26.5, 65.2, 104.2, 120.3, 125.0, 128.6, 134.9, 136.3, 166.5. IR ($CHCl_3$): 3609, 2955, 1587, 1576, 1409, 1364, 1238 cm^{-1}. HRMS calcd for $C_{18}H_{33}O_3Si_2$ $(M + H^+)$ *m*/*z*: 353.1968, found 353.1982.

2-(*tert*-Butyldimethylsilyl)-4-methyl-6-(trimethylsilyl)phenyl 1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonate (16E′). Compound **43** (4.4 g, 12.5 mmol) and 18-crown-6 (3.3 g, 12.5 mmol) were dissolved in THF (125 mL, 0.10 M) and stirred at 0 °C for 10 min. NaH (0.75 g, 18.7 mmol) was added to the mixture and stirred at 0 °C for 30 min. Then, nonafluorobutanesulfonyl fluoride[23] (0.62 mL, 3.7 mmol) was added to the solution and stirred at 80 °C for 20 h. The reaction mixture was quenched with water and evaporated under reduced pressure. The residue was extracted with EtOAc and water, and the aqueous layer was extracted twice with hexane. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered with a glass filter, and concentrated under reduced pressure (this reaction did not complete). THF (125 mL, 0.10 M), NaH (0.25 g, 6.2 mmol) and nonafluorobutanesulfonyl fluoride (1.2 mL, 7.1 mmol) were added again to obtain a full conversion. The mixture was stirred at 80 °C for 20 h. The reaction mixture was quenched with water and evaporated under reduced pressure. The residue was extracted with EtOAc and water, and the aqueous layer was extracted twice with hexane. The combined organic layers were washed with a saturated aqueous NaCl solution. The organic layer was dried over anhydrous Na_2SO_4, filtered with a glass filter and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 5:1) to provide the titled compound **16E′** (6.1 g, 77%) as a colorless solid. Mp 67−69 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.35 (9 H, s), 0.40 (6 H, s), 0.79 (9 H, s), 4.05−4.12 (4 H, m), 5.84 (1 H, s), 7.67 (2 H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −4.0, 0.5, 18.1, 26.9, 65.3, 102.9, 108.6−120.8 (4 C, m), 132.4, 135.5, 135.9, 136.1, 136.3, 136.7, 155.2. IR ($CHCl_3$): 1603, 1396, 1352, 1238, 1194, 1146 cm^{-1}. HRMS calcd for $C_{25}H_{28}F_9O_3SSi_2$ $(M + H)^+$ *m*/*z*: 635.1154, found 635.1149.

■ ASSOCIATED CONTENT

Supporting Information

Optimization of 3-borylbenzyne precursors (Tables S1−S3), interaction of ions with silyl- and borylbenzynes **4** and **5** (Tables S4−S6), ^{1}H and ^{13}C NMR spectra for all new compounds, and Cartesian Coordinates for ground and transition state structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: akai@u-shizuoka-ken.ac.jp; tokiwa@rikkyo.ac.jp.

Notes

The authors declare no competing financial interest.

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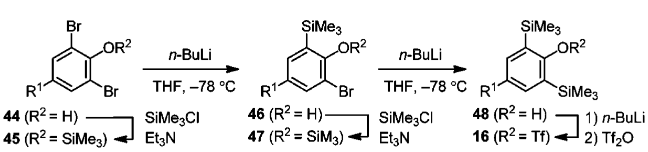
(19) According to our previous work,[14b] new borylbenzyne precuosors **14** were prepared from 2,6-diiodophenols **28**. For details, see experimental section and reference 14b.

(20) According to our previous work,[14c] silylbenzyne precursors **16** were prepared from 2,6-dibromophenols **44** as shown in the scheme below. For details, see reference 14c.



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(26) These deborylation conditions (soon to be published) were recently found in our laboratory.

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(28) The interaction of ions in the reaction mixture with benzynes (**4** and **5**) may have some influence on the regioselectivities. However, in fact, the ratios of distal- to proximal-adducts were not significantly affected by changing the conditions of preparation of **4** and **5** (see Tables S5 and S6 in Supporting Information). Therefore, we have reached the conclusion that the effects of ions were negligibly small, and they were not considered for the calculations of ground and transition state structures.

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(31) As for the (3 + 2) cycloaddition of 3-silylbenzynes, similar discussion was also reported by Houk and Garg.[12]

(32) All graphics were prepared with CYLview: *CYLview, 1.0b*; Legault, C. Y. Université de Sherbrooke, 2009 (http://www.cylview.org).

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