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Generation of 3-borylbenzynes, their regioselective Diels–Alder reactions, and theoretical analysis

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ABSTRACT

3-Borylbenzynes were generated in situ from 6-boryl-2-iodophenyl trifluoromethanesulfonates using *i*-PrMgCl·LiCl and applied to Diels–Alder reactions with substituted furans and pyrroles. The reactions allowed good functional group compatibility and produced the cycloadducts in high yields with high distal selectivities. Effective conversion of the boryl group of the products was achieved. A series of these reactions provides a new method for producing multifunctionalized benzo-fused aromatic compounds. Additionally, the regioselectivities of these Diels–Alder reactions were theoretically analyzed by DFT calculations to find that the reactions were mainly controlled by the electrostatic effect and aryne distortion caused by the boryl group.

1. Introduction

Arylboronic acid derivatives are among the most useful building blocks in organic synthesis, because they are extensively used in the C–C, C–N, and C–O bond-forming reactions.[1] They have also found wide applications in saccharide sensing,[2] medicinal chemistry,[3] and boron neutron capture therapy.[4] Therefore, the development of an efficient synthesis of boronic acid derivatives is an important research topic these days. The arylboronic acid derivatives have generally been synthesized by the borylation of boron-free compounds in the last stage of the synthesis.[5] The construction of carbon frameworks under mild reaction conditions using reactive species with suitably protected boryl groups has been developed recently,[6] which produces different kinds of arylboronic acid derivatives, some of whose yields are very poor by the existing synthetic methods.

Benzynes are strained and highly reactive intermediates that have been applied to various bond-forming reactions, such as cycloadditions, nucleophilic additions, transition metal-catalyzed coupling reactions, and noncatalyzed multicomponent coupling reactions.[7] Among them, the Diels–Alder (DA) reactions of benzynes with furans are some of the most intensively studied ones, and they have found extensive applications in synthesizing multisubstituted naphthalene derivatives, for example, in the effective total synthesis of fused aromatic natural products.[7d,8] However, the reactions with unsymmetrically substituted benzynes with substituted furans generally produce mixtures of two possible regioisomers. For example, the DA reactions of benzynes containing an alkyl,[9a] carbamoyl,[9b] or nitro[9c] group at the C3 position, provided mixtures of the distal and proximal adducts in varying ratios, some of which were hardly separable, and their regioselectivities were barely predictable. The steric bulkiness of the substituents were less effective, and even the reactions of 3-phenyl-**7**[10] or 3-(*tert*-butyl)benzyne **8A**[9d] with 2-(*tert*-butyl)furan **6a** resulted in low regioselectivities (Table 1, entries 1 and 2). On the other hand, benzynes bearing inductively electron-withdrawing groups, such as fluoro[9e] and alkoxy[9f] groups produced cycloadducts, such as **14a** (entry 3), with good-to-excellent proximal selectivities.

We recently reported that 3-silylbenzynes (**10A** and **10B**) underwent DA reactions with a variety of 2-substituted furans to give distal cycloadducts (**15A** and **15B**) with high selectivities (some typical examples are shown in entries 4 and 5, Table 1).[10] This was the first example of highly distal selective DA reactions between substituted benzynes and furans, which are opposite to those of 3-fluoro- and 3-alkoxybenzynes and were thought to mainly caused by the inductively electron-donating effect of the silyl group, arising from the lower electronegativity of silicon relative to carbon.

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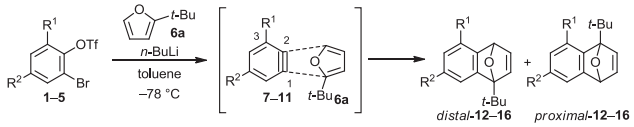
Table 1
Diels–Alder reactions of 3-substituted benzynes **7**–**11** with 2-(*tert*-butyl)furan **6a**



Entry	R^1	R^2	Precursor, benzyne	**12**–**16**	*d*:*p*[a]	Ref.
1	Ph	H	**1**, **7**	**12a**	43:57	10
2	*t*-Bu	*t*-Bu	**2**, **8A**	**13Aa**	63:37	9d
3	OMe	H	**3**, **9**	**14a**	15:85	9f
4	$SiMe_3$	H	**4A**, **10A**	**15Aa**	97:3	10
5	Si(*t*-Bu)Me_2	H	**4B**, **10B**	**15Ba**	>98:2	10
6	Bpin[b]	Me	**5A**, **11A**	**16Aa**	93:7	12

[a] The ratio of distal (*d*) to proximal (*p*) adducts.
[b] Bpin=(pinacol)boryl.

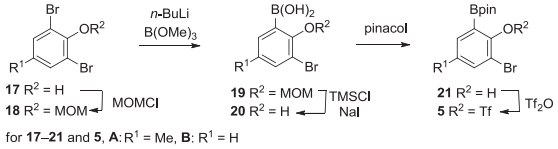
Given that boron and silicon have electronegativities similar to that of carbon (Allred–Rochow electronegativities: B, 2.0; Si, 1.7; C, 2.5),[11] we expected that the similar DA reactions of 3-borylbenzynes with furans would selectively produce distal cycloadducts. Furthermore, the C–B bonds of the products were expected to be convertible into C–C, C–N, and C–O bonds.

Therefore, the DA reaction of 3-borylbenzynes appeared to undergo regioselective synthesis of not only phenylboronic acid derivatives but also multisubstituted benzo-fused compounds. However, there were no reports on the generation and reaction of benzynes containing boryl groups. Very recently, we have succeeded in preparing 3-[(pinacol)boryl]benzynes **11** and found that their DA reactions with furans **6** or pyrroles **41** proceeded with high distal selectivities and produced highly functionalized arylboronic acid derivatives (for a typical example, see Table 1, entry 6).[12,13] We also discovered that the regioselectivities of the DA reactions of **11** resembled those of 3-silylbenzynes **10**, but the boryl groups exerted effects different from the silyl groups. We describe herein a full account on the generation of 3-borylbenzynes **11** and their regioselective DA reactions. We also analyzed the transition states (TSs) of these reactions by density functional theory (DFT) calculations to disclose the origin of the unique regioselectivities of **11**.

2. Results and discussion

2.1. The first generation of 3-borylbenzynes and their regioselective DA reactions

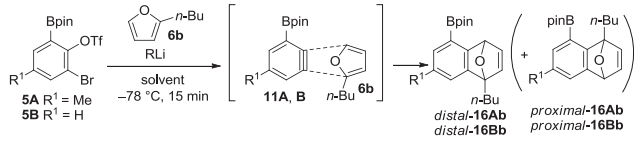
Given that the treatment of 2-bromophenyl trifluoromethanesulfonates with BuLi[14] has been well known to generate benzynes at low temperature, 2-bromo-6-[(pinacol)boryl]phenyl trifluoromethanesulfonates (**5A** and **5B**) were selected as some of the most promising precursors of 3-borylbenzynes **11**.[15] The precursors (**5A** and **5B**) were synthesized from the dibromophenol derivatives **17** in six steps; viz., MOM protection of the hydroxyl group of **17**, halogen–lithium exchange followed by the reaction with trimethyl borate, deprotection of the MOM group, esterification of boronic acid with pinacol, and triflation of the hydroxyl group (Scheme 1). This sequence required only two chromatographic separations and gave **5A** and **5B**, each in 73% overall yield, from **17A** and **17B**, respectively.[16]



Scheme 1. Preparation of 3-borylbenzyne precursors **5**.

Next, we preliminarily examined the generation of borylbenzyne **11** by the reaction of the precursor **5** with alkyl lithiums. Due to the high instability of benzynes, the benzyne-generation reaction was conducted in the presence of 2-(*n*-butyl)furan **6b** to immediately and effectively trap **11** as a DA adduct. First, according to the generation of silylbenzynes,[10] the reaction of **5A** with *n*-BuLi was conducted in toluene at −78 °C to obtain 9% yield of **16Ab** (Table 2, entry 1), which can be improved by conducting the reaction in THF (entry 2) and further increased by using bulkier and more reactive alkyl lithiums, such as *s*-BuLi and *t*-BuLi (entries 3 and 4). More importantly, the reactions under different conditions (entries 2–4) produced the distal adduct *distal*-**16Ab**, in which the boryl and *n*-butyl groups were located away from each other as the major products with the same distal-to-proximal ratios.[17] The use of **5B** also provided a mixture of the corresponding *distal*- and *proximal*-**16Bb** in similar yield with the same ratio (entry 5). Notably, a similar reaction using an alternative precursor **5B′**, in which the positions of the bromo and sulfonyloxy groups were interchanged (entry 6), gave a mixture of *distal*- and *proximal*-**16Bb** in the same ratio and similar yield to that of entry 5. These results strongly suggested that borylbenzynes (**11A** and **11B**) were certainly generated under these conditions.

Table 2
Optimization of the reaction conditions for the generation of benzyne **11**[a]



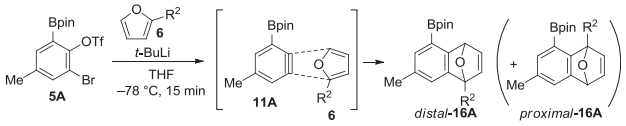
Entry	**5**	RLi	Solvent	Product		
					d:*p*[b]	Yield[c] (%)
1	**5A**	*n*-BuLi	Toluene	**16Ab**	ND[d]	9
2	**5A**	*n*-BuLi	THF	**16Ab**	91:9	34
3	**5A**	*s*-BuLi	THF	**16Ab**	92:8	47
4	**5A**	*t*-BuLi[e]	THF	**16Ab**	92:8	67
5	**5B**	*t*-BuLi[e]	THF	**16Bb**	92:8	63
6	**5B′**[f]	*t*-BuLi[e]	THF	**16Bb**	91:9	51

[a] Conditions: A mixture of **5** (1.0 equiv), **6b** (10 equiv), BuLi (1.2 equiv) in a solvent (0.10 M) was stirred at −78 °C for 15 min.
[b] The ratio of distal (*d*) to proximal (*p*) adducts determined by 500 MHz ^{1}H NMR analysis of the crude reaction products and also by the yield of the isolated products.
[c] Total yield of the isolated *distal*- and *proximal*-**16**.
[d] Not determined.
[e] With 2.2 equiv of *t*-BuLi.
[f] The precursor **5B′** was used instead of **5B**.

We then investigated the DA reactions of **11A** with selected 2-substituted furans **6** under the reaction conditions similar to the entry 4 of Table 2. All reactions gave *distal*-**16** with high selectivities, and the bulkiness of the furan substituent (R^2) was found to have relatively small effect on the regioselectivities (Table 3, entries 1–4). A similar reaction of **11A** with 2-methoxyfuran **6f** also proceeded with exclusive distal selectivity; however, the 1,4-epoxide moiety of the product **16Af** opened immediately to yield 8-boryl-1-naphthol derivative. Because of its high sorption on silica gel, silica gel chromatography was performed after the acetylation of naphthol to give the acetate *distal*-**22Af** (Table 3, entry 5).

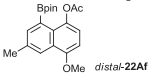
As already described, we succeeded in generating borylbenzynes **11** for the first time, and also found that their DA reactions with 2-substituted furans **6** preferentially produced *distal*-**16** with high selectivities. However, the use of very strong bases,

Table 3
Diels–Alder reactions of borylbenzyne **11A** with 2-substituted furans **6**[a]



Entry	R^2	6	Product		
				d:*p*[b]	Yield (%)[c]
1	*t*-Bu	**6a**	**16Aa**	93: 7	63
2	Me	**6c**	**16Ac**	89:11	53
3	$SiMe_3$	**6d**	**16Ad**	94: 6	57
4	$SnBu_3$	**6e**	**16Ae**	>98:2	56
5	OMe	**6f**	**22Af**	>98:2	66[d]

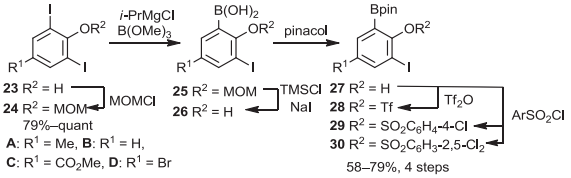
[a] Conditions: A mixture of **5A** (1.0 equiv), **6** (10 equiv), and *t*-BuLi (2.2 equiv) in THF (0.10 M) was stirred at −78 °C for 15 min.
[b] The ratio of distal (*d*) to proximal (*p*) adducts determined by 500 MHz ^{1}H NMR analysis of the crude reaction products and also by the yield of the isolated products.
[c] Total yield of the isolated *distal*- and *proximal*-**16A**.
[d] Isolated as 8-boryl-1-naphthyl acetate *distal*-**22Af** after the acetylation of the crude reaction products with Ac_2O and pyridine.



such as *t*-BuLi hampered the application of the method to benzynes and furans bearing wider range of functional groups.

2.2. Generation of borylbenzynes under milder reaction conditions

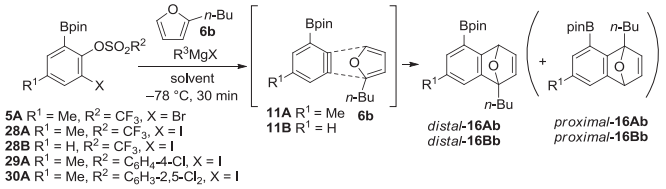
The synthetic utility of 2-(trimethylsilyl)phenyl triflates as another versatile precursors has been well recognized because they generate benzynes under mild conditions using a fluoride ion;[18] however, BuLi is still needed in their preparation. Inspired by a report by Knochel, in which benzynes possessing various functional groups were generated from the corresponding 2-iodophenyl (4-chlorobenzene)sulfonates by the use of Grignard reagents at low temperature,[19] we suggest that 6-boryl-2-iodophenyl trifluoromethanesulfonates **28** would serve as new promising precursors for 3-borylbenzynes **11**. We prepared **28A**–**D** from the corresponding 2,6-diiodophenols **23A**–**D** in good overall yields. In particular, the incorporation of Bpin group was successfully attained by iodo–magnesium exchange reaction of **24** using *i*-PrMgCl at −78 °C followed by the removal of MOM group and the esterification of boronic acid moiety with pinacol, while maintaining the ester and bromo groups intact under these conditions (Scheme 2).



Scheme 2. Synthesis of the borylbenzyne precursors **28**–**30** from 2,6-diiodophenols **23**.

Then, the optimization of the reaction conditions for generating 3-borylbenzyne **11A** from **28A** was investigated using Grignard reagents in the presence of 2-butylfuran **6b**. A preliminary trial using *i*-PrMgCl at −78 °C for 30 min successfully generated **11A**, which was supported by the formation of 88:12 mixture of *distal*- and *proximal*-**16Ab** in 82% total yield (Table 4, entry 2). In contrast, a similar reaction of the corresponding bromide **5A** did not proceed within the range −78 °C to room temperature, and **5A** was recovered almost quantitatively (entry 1). The use of more active Grignard reagent *i*-PrMgCl·LiCl[20] slightly improved the yield of

Table 4
Optimization of the reaction conditions for generating benzyne **11** using Grignard reagents[a]



Entry	R^2	Precursor	R^3MgX	Solvent	Product		
						d:*p*[b]	Yield[c] (%)
1	CF_3	**5A**	*i*-PrMgCl	THF	**16Ab**	—	Trace
2	CF_3	**28A**	*i*-PrMgCl	THF	**16Ab**	88:12	82
3	CF_3	**28A**	*i*-PrMgCl·LiCl	THF	**16Ab**	88:12	88
4[d]	C_6H_4-4-Cl	**29A**	*i*-PrMgCl·LiCl	THF	**16Ab**	87:13	74[e]
5[d]	C_6H_3-2,5-Cl_2	**30A**	*i*-PrMgCl·LiCl	THF	**16Ab**	89:11	62
6	CF_3	**28A**	*i*-PrMgCl	Et_2O	**16Ab**	92: 8	59
7[f]	CF_3	**28A**	*i*-PrMgBr	Et_2O	**16Ab**	86:14	59
8[f]	CF_3	**28A**	*t*-BuMgCl	Et_2O	**16Ab**	—	Trace
9[f]	CF_3	**28A**	*i*-PrMgCl·LiCl	Et_2O	**16Ab**	90:10	82
10	CF_3	**28A**	*i*-PrMgCl·LiCl	Et_2O	**16Ab**	92: 8	93
11	CF_3	**28B**	*i*-PrMgCl·LiCl	Et_2O	**16Bb**	90:10	88
12[g]	CF_3	**28B′**	*i*-PrMgCl·LiCl	Et_2O	**16Bb**	91:9	24

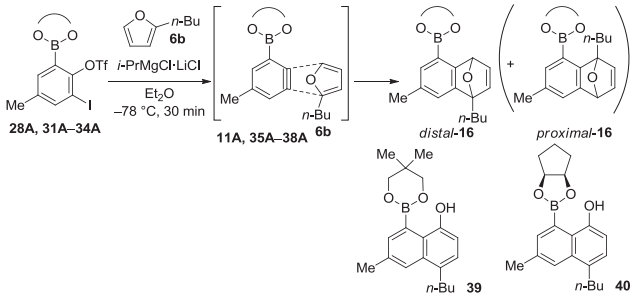
[a] Conditions: A mixture of precursor **5** or **28**–**30** (1.0 equiv), **6b** (3.0 equiv), R^3MgX (1.2 equiv) in a solvent (0.10 M) was stirred at −78 °C for 30 min.
[b] The ratio of distal (*d*) to proximal (*p*) adducts determined by 500 MHz ^{1}H NMR analysis of the crude products and also by the yield of the isolated products.
[c] Total yield of the isolated *distal*- and *proximal*-**16**.
[d] Reaction was run at −78 to 0 °C.
[e] NMR yield with 1,4-dimethoxybenzene as the internal standard.
[f] Reaction was run at 0 °C.
[g] The precursor **28B′** was used.

16Ab while maintaining the regioselectivity (entry 3). These results showed that **28A** was highly reactive in generating **11A** even at −78 °C, whereas (chlorobenzene)sulfonates[18] required higher temperature to generate **11A** and produced **16Ab** in lower yields (entries 4 and 5). We also found that Et_2O was a slightly better solvent than THF as far as regioselectivity was concerned, though the yield reduced (entry 6). Finally, the reaction of **28A** with *i*-PrMgCl·LiCl in Et_2O at −78 °C was found to be the best reaction conditions to produce **16Ab** in 93% yield with 92:8 regioselectivity (entry 10),[21] whose selectivity was exactly the same as that using *t*-BuLi (Table 2, entry 4). In addition, the use of other Grignard reagents (Table 4, entries 7 and 8) and/or the reaction at higher temperature (entry 9) were less effective. The comparison of the reaction of **28B** with that of its regioisomer **28B′** under the same conditions also proved the generation of benzyne **11B**, because both reactions gave a mixture of *distal*- and *proximal*-**16Ab** in the same ratio, albeit the yields were different (entries 11 and 12).

2.3. Effect of the boryl group on the generation of borylbenzyne and its DA reaction

Next, we examined the effect of the boryl group of benzyne precursors on the generation of benzynes **11** and their DA reactions with **6b**. The borates **31A**–**33A** were prepared by the esterification of phenylboronic acid **34A** with the corresponding diols (for details, see SI). Under the same reaction conditions as those of Table 4, entry 10, the precursor **31A**, possessing a (1,3-dimethylpropanediol)boryl group, reacted with *i*-PrMgCl·LiCl to directly give a borylnaphthol **39** (49% NMR yield) as a single detectable product (Table 5, entry 2). It was thought that **39** was generated from the adduct *distal*-**16** via the

Table 5
Diels–Alder reaction of 3-borylbenzynes (**11A**, **35A**–**38A**), generated from **28A**, **31A**–**34A**, with **6b**[a]



Entry		Precursor, benzyne	Product		
				d:*p*[b]	Yield[c] (%)
1[d]		**28A**, **11A**	**16Ab**	92:8	93
2		**31A**, **35A**	**39**	—[e]	49[f]
3		**32A**, **36A**	**40**	—[e]	49[g]
4		**33A**, **37A**	**16Ab**[h]	>98:2	38
5[i]	$B(OH)_2$	**34A**, **38A**	**16Ab**[h]	>98:2	39

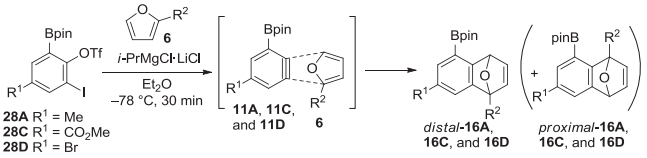
[a] Conditions: A mixture of a precursor **28**, **31**–**34** (1.0 equiv), **6b** (3.0 equiv), *i*-PrMgCl·LiCl (1.2 equiv) in Et_2O (0.10 M) was stirred at −78 °C for 30 min.
[b] The ratio of distal (*d*) to proximal (*p*) adducts were determined by 500 MHz ^1H NMR analysis of the crude products and also by the yield of the isolated products.
[c] Total yield of the isolated distal and proximal adducts.
[d] Cited from Table 4, entry 10.
[e] The regioisomer and other cycloadducts were not detected by 500 MHz ^1H NMR analysis of the crude products.
[f] Borylnaphtol **39** was obtained, and its yield was determined by NMR analysis with 1,4-dimethoxybenzene as the internal standard.
[g] Borylnaphtol **40** was obtained, and its yield was determined by NMR analysis with 1,4-dimethoxybenzene as the internal standard.
[h] **16Ab** was obtained after the treatment of the crude products with pinacol.
[i] *i*-PrMgCl·LiCl (3.1 equiv) was used.

spontaneous epoxide ring opening. Similar reaction of (*cis*-cyclopentane-1,2-diol)boryl precursor **32A** also gave naphthol **40** as a single product (entry 3). In contrast, the benzyne precursor **33A** possessing a small (ethyleneglycol)boryl group exclusively gave a distal adduct, albeit in lower yield (entry 4). (Because the borate moiety of the adduct partly hydrolyzed during the aqueous workup and silica gel chromatography, the product was isolated as pinacol borate *distal*-**16Ab** after transesterification with pinacol.) Similar reaction of phenylboronic acid **34A** also gave *distal*-**16Ab** (39% yield) exclusively after the esterification (entry 5). Thus, the benzyne-generation and the DA reaction with **6b** were generally available for the precursors possessing a range of boryl groups; the pinacol borate **28A** was found to be the best in terms of the stability and yield of the cycloadducts.

2.4. Substrate scope of the DA reaction of borylbenzynes 11 generated from triflates 28 using *i*-PrMgCl·LiCl

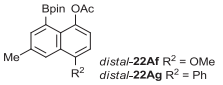
The DA reaction of a variety of borylbenzynes **11**, generated from **28** using *i*-PrMgCl·LiCl, with 2-substituted furans **6** gave the corresponding products **16** with high distal selectivities (Table 6). The

Table 6
Regioselective Diels–Alder reactions of **11**, generated from **28**, with 2-substituted furans **6**[a]



Entry	R^1	**28, 11**	R^2	**6**	Product		
						d:*p*[b]	Yield (%)[c]
1	Me	**28A**, **11A**	*t*-Bu	**6a**	**16Aa**	94:6 (93:7)[d]	Quant (63)[d]
2	Me	**28A**, **11A**	Me	**6c**	**16Ac**	88:12 (89:11)[d]	85 (53)[d]
3	Me	**28A**, **11A**	$SiMe_3$	**6d**	**16Ad**	>98:2 (94:6)[d]	91 (57)[d]
4	Me	**28A**, **11A**	$SnBu_3$	**6e**	**16Ae**	>98:2 (>98:2)[d]	79 (56)[d]
5	Me	**28A**, **11A**	OMe	**6f**	**22Af**[e]	>98:2 (>98:2)[d]	68 (66)[d]
6	Me	**28A**, **11A**	Ph	**6g**	**22Ag**[f]	>98:2	40[e]
7	Me	**28A**, **11A**	CO_2Me	**6h**	**16Ah**	93:17	57
8	Me	**28A**, **11A**	Ac	**6i**	**16Ai**	87:13	51
9	Me	**28A**, **11A**	CN	**6j**[g]	**16Aj**	>98:2	46
10[h]	CO_2Me	**28C**, **11C**	*n*-Bu	**6b**[i]	**16Cb**	83:17	68
11	Br	**28D**, **11D**	*n*-Bu	**6b**	**16Db**	84:16	64

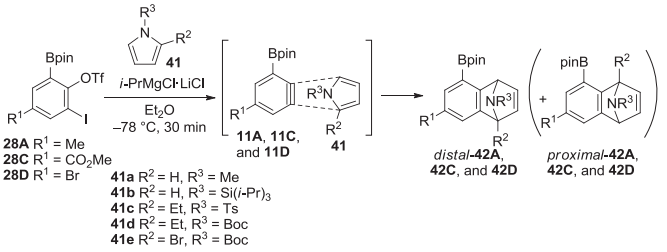
[a] Conditions: A mixture of a precursor **28** (1.0 equiv), **6** (3.0 equiv), and *i*-PrMgCl·LiCl (1.2 equiv) in Et_2O (0.10 M) was stirred at −78 °C for 30 min.
[b] The ratio of distal (*d*) to proximal (*p*) adducts determined by 500 MHz ^1H NMR analysis of the crude products and also by the yield of the isolated products.
[c] Total yield of isolated distal and proximal adducts.
[d] The results of the corresponding reactions of Tables 2 and 3 are shown in the parentheses.
[e] Isolated as 8-boryl-1-naphthyl acetate **22Af** after the acetylation of the crude reaction products with Ac_2O and pyridine.
[f] Isolated as 8-boryl-1-naphthyl acetate **22Ag** after the acetylation of the crude reaction products with Ac_2O and pyridine.
[g] **6j** (10 equiv) was used.
[h] *i*-PrMgBr (2.1 equiv) was applied instead of *i*-PrMgCl·LiCl.
[i] **6b** (10 equiv) was used at 0 °C.



yields of **16** were significantly improved compared to the results of Tables 2 and 3, while the selectivities were the same (Table 6, entries 1–5). Various reactive functional groups, such as ester (entries 7 and 10), acetyl (entry 8), nitrile (entry 9), and bromo (entry 11) groups were tolerant to the reaction conditions. All these reactions produced *distal*-**16** with high selectivities, although the ester and bromo group at the C5 position of **11** caused a slight decrease in the selectivities (entries 10 and 11). Importantly, the reactions with furans possessing either electron-donating (entry 5) or electron-withdrawing groups (entries 7–9) at the C2 position produced similar distal selectivity.

The applicability of **11** to the DA reaction with substituted pyrroles **41** was also of interest because the cycloadditions of benzynes with pyrroles have been extensively studied to synthesize biologically active compounds.[22] We found that the selection of the *N*-protective group of **41** was one of the most important factors to achieve the reaction. Thus, whereas the reactions of **11A** with *N*-methyl and *N*-silyl pyrroles (**41a** and **41b**) did not provide any cycloadducts (Table 7, entries 1 and 2), similar reactions with *N*-tosyl (Ts) and *N*-(*tert*-butoxy)carbonyl (Boc)-pyrroles (**41c**–**e**) gave mixtures of two regioisomers of cycloadducts (*distal*- and *proximal*-**42**) (entries 3–7). The Boc group was preferred to the Ts group in producing better regioselectivity (entries 3 and 4), and the regioselectivities were higher than those of the DA reactions with furans **6** possessing same or similar substituents (entries 4, 6, and 7). These results represent the first examples of highly regioselective DA reactions between the substituted benzynes and pyrroles.[23]

Table 7
Regioselective Diels–Alder reactions of **11**, generated from **28**, with 2-substituted pyrroles **41**[a]



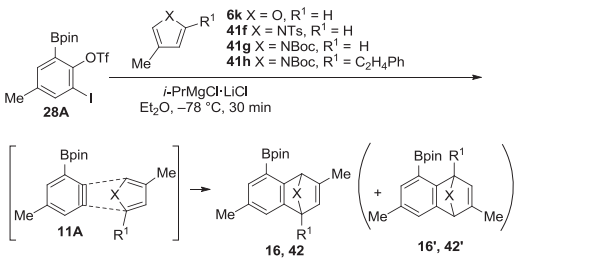
Entry	R^1	**28**, **11**	R^2	R^3	**41**	**42**	*d*:*p*[b]	Yield[c] (%)
1	Me	**28A**, **11A**	H	Me	**41a**	**42Aa**	—	0
2	Me	**28A**, **11A**	H	Si(*i*-Pr)$_3$	**41b**	**42Ab**	—	0
3	Me	**28A**, **11A**	Et	Ts	**41c**	**42Ac**	87:13	63
4	Me	**28A**, **11A**	Et	Boc	**41d**	**42Ad**	>98:2	70
5	Me	**28A**, **11A**	Br	Boc	**41e**	**42Ae**	>98:2	58
6	CO_2Me	**28C**, **11C**	Et	Boc	**41d**	**42Cd**	88:12	61
7	Br	**28D**, **11D**	Et	Boc	**41d**	**42Dd**	95:5	72

[a] Conditions: A mixture of **28** (1.0 equiv), **41** (3.0 equiv), and *i*-PrMgCl·LiCl (1.2 equiv) in Et_2O (0.10 M) was stirred at −78 °C for 30 min.
[b] The ratio of distal (*d*) to proximal (*p*) adducts determined by 500 MHz ^{1}H NMR analysis of the crude products and also by the yield of the isolated products.
[c] Total yield of the isolated *distal*- and *proximal*-**42**.

In addition, halogen (entries 5 and 7) and ester (entry 6) groups were tolerant to these reaction conditions.

In this study, we found that the DA reaction of **11A** with 3-methylfuran **6k** and with 3-methylpyrroles (**41f** and **41g**) predominantly gave adducts (**16** and **42**) with at least 86:14 selectivity, in which the methyl groups derived from the furan and pyrroles were located close to the boryl group (Table 8, entries 1–3). In particular, the *N*-Boc group again displayed its ability to produce high regioselectivity, and the reaction with *N*-Boc-2,4-disubstituted pyrrole **41h** exclusively provided **42Ah** (entry 4). These high levels of regioselectivity are outstanding among the existing DA reactions of the substituted benzynes and 3-substituted furans. Therefore, it is worth noting that the boryl group has strong effect in controlling the orientation in DA reactions even with dienes that have a small methyl group at the position distant from the reactive site.

Table 8
Diels–Alder reaction of **11A** with 3-methylfuran **6k** and with 3-methylpyrroles **41f**–**h**[a]



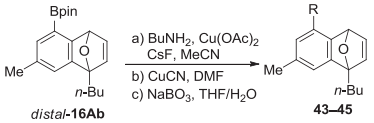
Entry	X	R^1	Diene	Product		
				16:**16**′ or **42**:**42**′[b]		Yield[c] (%)
1	O	H	**6k**	**16Ak**	87:13	Quant
2	NTs	H	**41f**	**42Af**	86:14	87
3	NBoc	H	**41g**	**42Ag**	92:8	95
4	NBoc	C_2H_4Ph	**41h**	**42Ah**	>98:2	81

[a] Conditions: A mixture of **28A** (1.0 equiv), diene **6** or **41** (3.0 equiv), and *i*-PrMgCl·LiCl (1.2 equiv) in Et_2O (0.10 M) was stirred −78 °C for 30 min.
[b] The ratio of **16** (or **42**) to **16**′ (or **42**′) determined by 500 MHz ^{1}H NMR analysis of the crude products and also by the yield of the isolated products.
[c] Total yield of the isolated adducts.

2.5. Transformation of the boryl group of the DA products

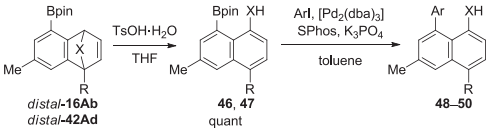
The boryl group of the DA product *distal*-**16Ab** was converted into amino group (Table 9, entry 1)[24] or cyano group (entry 2)[25] by the treatment with copper reagents, or also into hydroxyl group by the oxidation with $NaBO_3$ (entry 3).[26] The epoxide ring was intact under these reaction conditions. However, the Suzuki–Miyaura cross-coupling reaction of *distal*-**16Ab** gave a complex mixture, probably because of the reactivity of its 1,4-epoxy-1,4-dihydronaphthalene frame under the palladium-catalyzed conditions.[27] On the other hand, after the TsOH-catalyzed epoxide ring opening, the corresponding naphthol derivatives (**46** and **47**) were subjected to the Suzuki–Miyaura cross-coupling reaction with aryliodides to give biaryl compounds (**48**–**50**) in high overall yields (Table 10).[28] Because the boryl group may be easily eliminated by protodeboronation,[29] it additionally serves as a regio-directing auxiliary. Thus, the regioselective DA reaction of borylbenzynes **11** followed by the transformation of the boryl group provides a reliable and alternative method for synthesizing multisubstituted fused aromatic compounds.

Table 9
Conversion of the boryl group of *distal*-**16Ab**



Entry	Conditions	R	Product	Yield (%)
1	a	NHBu	**43**	71
2	b	CN	**44**	53
3	c	OH	**45**	85

Table 10
Epoxide ring opening of *distal*-**16Ab** and -**42Ad** and successive Suzuki–Miyaura cross-coupling reactions



Entry	R	X	**16**, **42**	**46**, **47**	Ar	Product	Yield (%)
1	*n*-Bu	O	**16Ab**	**46**	Ph	**48**	94
2	*n*-Bu	O	**16Ab**	**46**	1-Np	**49**	99
3	Et	NBoc	**42Ad**	**47**	Ph	**50**	82

2.6. Mechanistic consideration of regioselectivity in the DA reaction of borylbenzynes

Herein, we discuss why the boryl group strongly affected the regioselective DA reaction of benzynes.

It has been considered that the methoxy group at the C3 position of benzyne exhibited electron-withdrawing inductive effect on the triple bond of benzyne to make the C1 electron-deficient ($\delta+$) and C2 electron rich ($\delta-$).[30] Due to the lower electronegativity of boron in respect to carbon, the electron-donating inductive effect of the boryl group at the C3 position of benzyne was thought to exhibit the opposite trend at these carbons and result in regioselectivities contrasting with those of 3-methoxybenzynes. We also considered that the possible coordination of anion, such as alkyl anion and halide ion to the Lewis acidic boron atom might enhance the electron-donating inductive effect on the triple bond of **11**; however, the fact that the regioselectivities of the DA reactions of **11**

with 2-substituted furans **6** were scarcely influenced by the benzyne-generation conditions (Tables 2 and 4) probably means that such coordination to the vacant orbital of the boron of **11** is very weak or almost negligible.

We then aimed to quantitatively elucidate the influence of the boryl group of 3-borylbenzynes on the regioselectivity of their DA reactions based on DFT calculation. We adopted standard 6-31G(d) basis sets for C, H, O, N, S, Si, and Br, and the Hay–Wadt valence double-ζ (LANL2DZ) basis set, which includes the influence of the inner-shell electrons on the valence shell using effective core potentials (ECP), for Sn with B3LYP functionals. All calculations were performed using the Gaussian 09 program package.[31] In particular, we focused our attention to the orbital of the triple bonds of benzynes that deal with the bond formation in the benzyne reactions in order to evaluate in detail the electrostatic character of the benzynes, whereas the theoretical studies had been reported based on HOMO and LUMO coefficients of 1 and 2 carbons of benzynes.[30]

First, the orbitals of the triple bond of benzyne were divided into sp hybrid orbital (σ_{sp}) and two π-bond orbitals (π_1 and π_2) by a natural bond orbital (NBO) method[32,33] (Fig. 1), and the electron density of the π_1 orbital, which is involved in the bond formation of benzyne reactions, was analyzed. The electron densities of the π_1 orbitals of C1 and C2 of the selected 3-substituted benzynes (**7**–**9**, **11A**, **11B**) and unsubstituted benzyne **51** are summarized in Table 11. In the cases of 3-phenylbenzyne **7** and 3-(*tert*-butyl)benzyne **8B**, no extensive differences between the C1 and C2 atoms were observed (entries 1 and 2). The electron density at the C2 position of 3-methoxybenzyne **9** was higher than at the corresponding C1 position, whereas those of 3-borylbenzynes (**11A** and **11B**) exhibited the opposite trend, and the substituents (H and Me) at the C5 position had little influence on the electron densities.

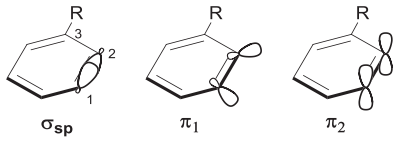
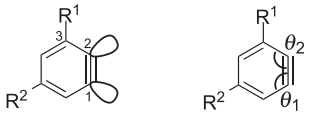


Fig. 1. Three divided bonding orbitals of the triple bond of benzyne.

Table 11
Electron densities of π_1 orbital and internal angles at C1 and C2 positions of 3-substituted benzynes (**7**–**9**, **11A**, **11B**) and **51** analyzed by the natural bond orbital method

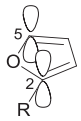


Entry	R^1	R^2		Electron density (π_1)			Internal angle	
				C1	C2	C1–C2	θ_1	θ_2
1	Ph	H	**7**	0.95	0.98	−0.03	128°	128°
2	*t*-Bu	Me	**8B**	0.98	0.95	+0.03	126°	129°
3	OMe	H	**9**	0.77	1.05	−0.28	135°	119°
4	Bpin	Me	**11A**	1.03	0.85	+0.18	122°	132°
5	Bpin	H	**11B**	1.06	0.87	+0.18	122°	133°
6	H	H	**51**	0.96	0.96	±0.00	127°	127°

We also analyzed the internal angles of geometry-optimized 3-substituted benzynes (**7**–**9**, **11A**, **11B**) and also **51** at C1 and C2 to evaluate the contribution of distortion energy[34] (Table 11) and found similar tendency. That is, C1 of **9** as well as C2s of **11A** and **11B** are more electrophilic.

The electron densities of π orbital at C2 and C5 of 2-substituted furans **6** were calculated similarly (Table 12). We found that alkyl and alkoxy groups at the C2 position of **6** enhanced the electron density at the C5 position as compared to C2 (entries 1–3), and the presence of electron-withdrawing groups, such as methoxycarbonyl, acetyl, and cyano groups (**6h**–**j**) made C5 more electron-deficient (entries 4–6).[35]

Table 12
Electron density of π orbital at C2 and C5 positions of 2-substituted furans **6** analyzed by the natural bond orbital method



Entry	R		Electron density		
			C2	C5	C2–C5
1	*t*-Bu	**6a**	0.89	0.94	−0.05
2	Me	**6c**	0.89	0.94	−0.05
3	OMe	**6f**	0.84	0.98	−0.14
4	CO_2Me	**6h**	0.92	0.86	+0.06
5	Ac	**6i**	0.94	0.87	+0.07
6	CN	**6j**	0.98	0.89	+0.09

Based on the electron density of each π orbital and benzyne distortion, we concluded that the electrostatic interactions between benzyne **11A** and furans (**6c** and **6f**) roughly accounted for the experimentally favorable orientation of their DA reactions (Fig. 2). However, similar interactions between **11A** and **6h**–**j** were inadequate to explain the preferential formation of *distal*-**16Ah**–**Aj** (as a typical example, the DA reaction of **11A** and **6h** is shown in Fig. 2). The DA reaction of **11A** and **6h** was theoretically analyzed based on the frontier orbital theory;[29] however, the HOMO–LUMO interaction of these reactants did not provide an adequate platform for understanding its anomalous orientation. These results clearly indicated that the electrostatic and orbital interactions of the reactants as well as the benzyne distortion were not always sufficient for a global and quantitative explanation of the experimental regioselectivities.[36]

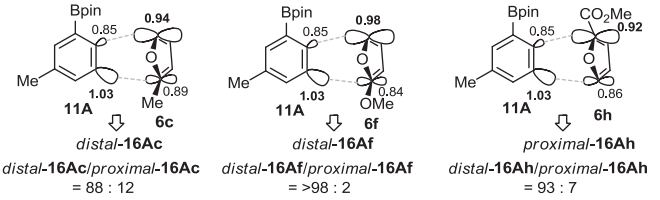
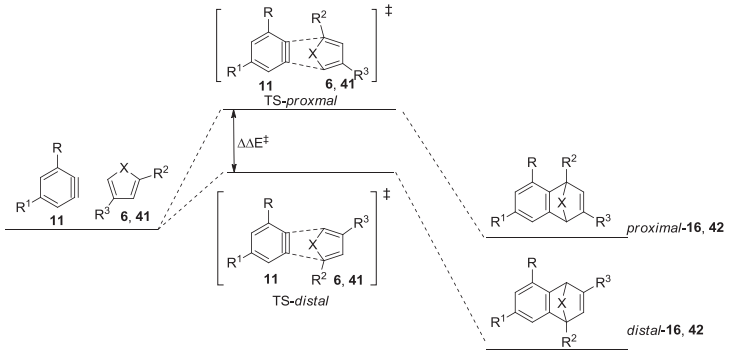


Fig. 2. Electrostatic interaction between borylbenzyne **11A** and furans (**6c**, **6f**, and **6h**) by natural bond orbital (NBO) analysis. The numbers next to the orbital lobes indicate the electron density of NBO. The distal-to-proximal ratio of each reaction indicates the experimental result.

In order to quantitatively rationalize the origin of the regioselectivities of the DA reactions, reaction pathway analysis, including a pair of transition states (TSs) leading to distal and proximal adducts, respectively,[37] was subsequently executed. We determined twelve pairs of TSs of the DA reactions of **11** and furans **6** (Table 13, entries 1–12) and four pairs of TSs of the DA reactions of **11** and pyrroles **41** (entries 13–16). For example, **TS*d*2** leading to *distal*-**16Ab** is 1.42 kcal/mol lower than **TS*p*2** leading to *proximal*-**16Ab**, which theoretically indicates a 92:8 distal selectivity and is in excellent agreement with the experimental result (*distal*-**16Ab**/*proximal*-**16Ab**=92:8, Table 13, entry 2). Similarly, the distal-to-proximal ratios based on the activation energy difference between two TSs were compared to the experimentally determined ratios (Table 13). For reference, the TSs of the DA reaction of 3-(*tert*-butyl)benzyne **8A** and 2-(*n*-butyl)furan **6b**, leading to *distal*- and *proximal*-**13b**, were also determined, and the theoretical and experimental ratios were compared with each other (entry 17). Significantly, all theoretical ratios were in excellent agreement with

Table 13
Theoretical and experimental ratios of the DA reactions of borylbenzynes **11** with furans **6** or pyrroles **41**.



Entry	R	R^1	11	X	R^2	R^3	Diene	Product	TS	ΔΔE‡ (kcal/mol)	Theoretical *d*:*p*	Experimental *d*:*p*
1	Bpin	Me	**11A**	O	*t*-Bu	H	**6a**	**16Aa**	**TS*d*1**, **TS*p*1**	1.63	94: 6	94: 6
2	Bpin	Me	**11A**	O	*n*-Bu	H	**6b**	**16Ab**	**TS*d*2**, **TS*p*2**	1.42	92: 8	92: 8
3	Bpin	Me	**11A**	O	Me	H	**6c**	**16Ac**	**TS*d*3**, **TS*p*3**	1.50	93: 7	88:12
4	Bpin	Me	**11A**	O	$SiMe_3$	H	**6d**	**16Ad**	**TS*d*4**, **TS*p*4**	1.58	93: 7	>98: 2
5	Bpin	Me	**11A**	O	$SnBu_3$	H	**6e**	**16Ae**	**TS*d*5**, **TS*p*5**	2.39	>98: 2	>98: 2
6	Bpin	Me	**11A**	O	OMe	H	**6f**	**16Af**	**TS*d*6**, **TS*p*6**	1.85	96: 2	>98: 2
7	Bpin	Me	**11A**	O	Ph	H	**6g**	**16Ag**	**TS*d*7**, **TS*p*7**	2.48	>98: 2	>98: 2
8	Bpin	Me	**11A**	O	CO_2Me	H	**6h**	**16Ah**	**TS*d*8**, **TS*p*8**	1.46	92: 8	93: 7
9	Bpin	Me	**11A**	O	Ac	H	**6i**	**16Ai**	**TS*d*9**, **TS*p*9**	1.15	88:12	87:13
10	Bpin	Me	**11A**	O	CN	H	**6j**	**16Aj**	**TS*d*10**, **TS*p*10**	1.81	95: 5	>98: 2
11	Bpin	Me	**11A**	O	H	Me	**6k**	**16Ak**	**TS*d*11**, **TS*p*11**	0.63	74:26	87:13
12	Bpin	H	**11B**	O	*n*-Bu	H	**6b**	**16Bb**	**TS*d*12**, **TS*p*12**	1.39	91: 9	91: 9
13	Bpin	Me	**11A**	NTs	Et	H	**41c**	**42Ac**	**TS*d*13**, **TS*p*13**	1.42	92: 8	87:13
14	Bpin	Me	**11A**	NBoc	Et	H	**41d**	**42Ad**	**TS*d*14**, **TS*p*14**	2.68	>98: 2	>98: 2
15	Bpin	Br	**11C**	NBoc	Et	H	**41d**	**42Cd**	**TS*d*15**, **TS*p*15**	2.07	97: 3	95: 5
16	Bpin	CO_2Me	**11D**	NBoc	Et	H	**41d**	**42Dd**	**TS*d*16**, **TS*p*16**	1.38	91: 9	88:12
17	*t*-Bu	Me	**8B**	O	*n*-Bu	H	**6b**	**13Bb**	**TS*d*17**, **TS*p*17**	0.026	51:49	52:48

the experimental ratios. Thus, the reliability of the theoretically determined TSs was deemed acceptable. These results also suggested that the regioselectivities of DA reactions were critically controlled by the TSs. To further evaluate the origin of the regioselectivities, the structures of these TSs were characterized. They were also compared with the TSs of the DA reactions of either **11** or 3-(*tert*-butyl)benzyne **8B** with furan itself **6l**, that of benzyne itself **51** with **6b**, and that of **8B** with **6b** as standard references. The following findings are noteworthy:

First, the TS (**TS18**) of the DA reaction of **11B** with **6l** showed that the C2 atom of **11B** was closer to the carbon atom of furan than the C1 atom of **11B** (Fig. 3A). The similarity of **TS19** to **TS18** indicates that the C5 methyl group had little effect on the TS (Fig. 3B). On the other hand, the TS (**TS20**) of the DA reaction of **8B** with **6l** showed that the C1 atom of benzyne was closer to the carbon atom of furan than the C2 atom of benzyne (Fig. 3C). TS (**TS21**) of the DA reaction of **51** with **6b** showed that the C5 atom of **6b** was closer to the carbon atom of benzyne (Fig. 3D). These results indicate that the reactions proceeded via non-synchronous concerted mechanism. Because the electron densities of C1 of **11A** and **11B** are higher than those of C2 (Table 11), the electrostatic interaction was found to have precedence. In addition, the steric hindrance between the boryl group of **11** and the hydrogen of furan was very small. On the other hand, the alkyl substituent of either benzyne **8B** or furan **6b** had a considerable steric effect to distance its neighboring carbon from its reaction partner.

Second, we compared two TS structures (**TS*d*2** and **TS*p*2**) of the DA reaction of **11A** with **6b** (Fig. 4A). In the case of electrostatically more favorable **TS*d*2**, the distance between the more electron-deficient C2 of **11A** and the electron-sufficient C5 of **6b** (2.42 Å) is shorter than that between C1 of **11A** and C2 of **6b** (2.90 Å). On the other hand, in **TS*p*2**, the distance between C2 of **11A** and C2 of **6b** (2.65 Å) is longer than that between C1 of **11A** and C5 of **6b** (2.48 Å) but is shorter than the

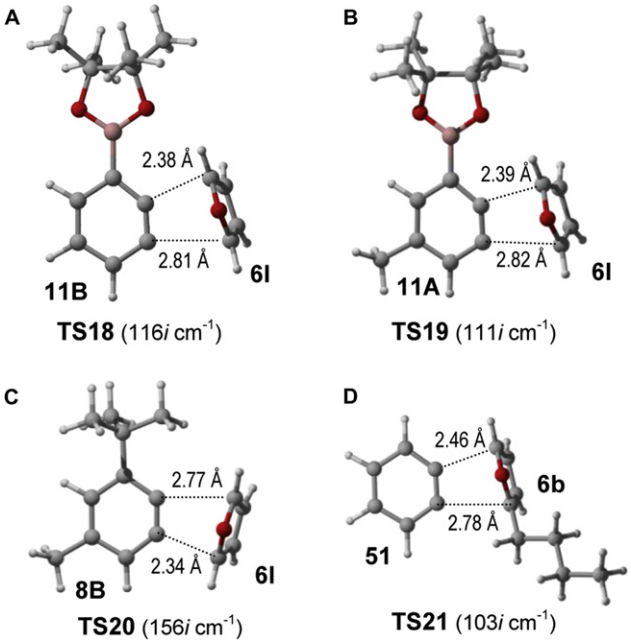


Fig. 3. The transition state (TS) structures of the Diels–Alder reaction of 3-borylbenzyne **11B** with furan **6l** (A), that of 3-boryl-5-methylbenzyne **11A** with **6l** (B), that of 3-(*tert*-butyl)benzyne **8B** with **6l** (C), and that of benzyne **51** with 2-*n*-butylfuran **6b** (D).[37]

distance of **51** and C2 of **6b** (2.78 Å, Fig. 3D). These results show that the TS structures clearly reflect the inherent electrostatic nature of **11A** and also that the steric hindrance between the boryl group and the *n*-butyl group is small. The TS structures of the DA reactions of **11A**

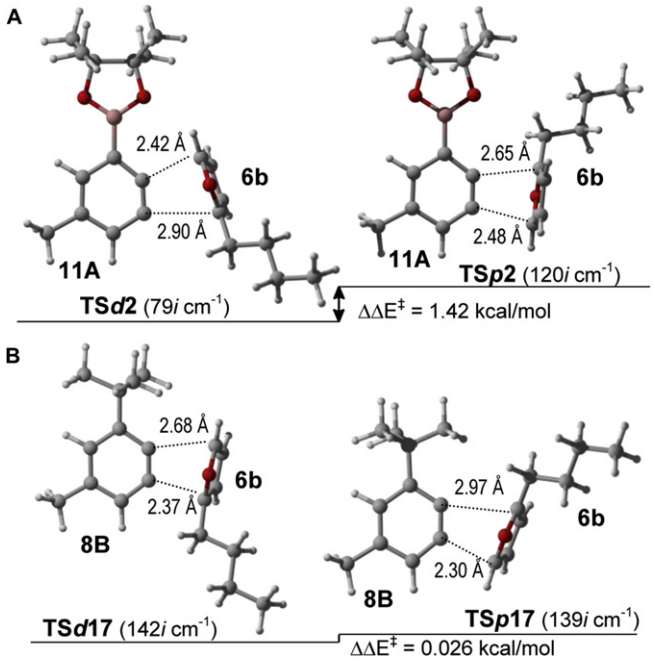


Fig. 4. Transition state (TS) structures of the Diels–Alder reactions of borylbenzyne **11A** and 2-(*n*-butyl)furan **6b** (A) and those of 3-(*tert*-butyl)benzyne **8B** and **6b** (B).[37]

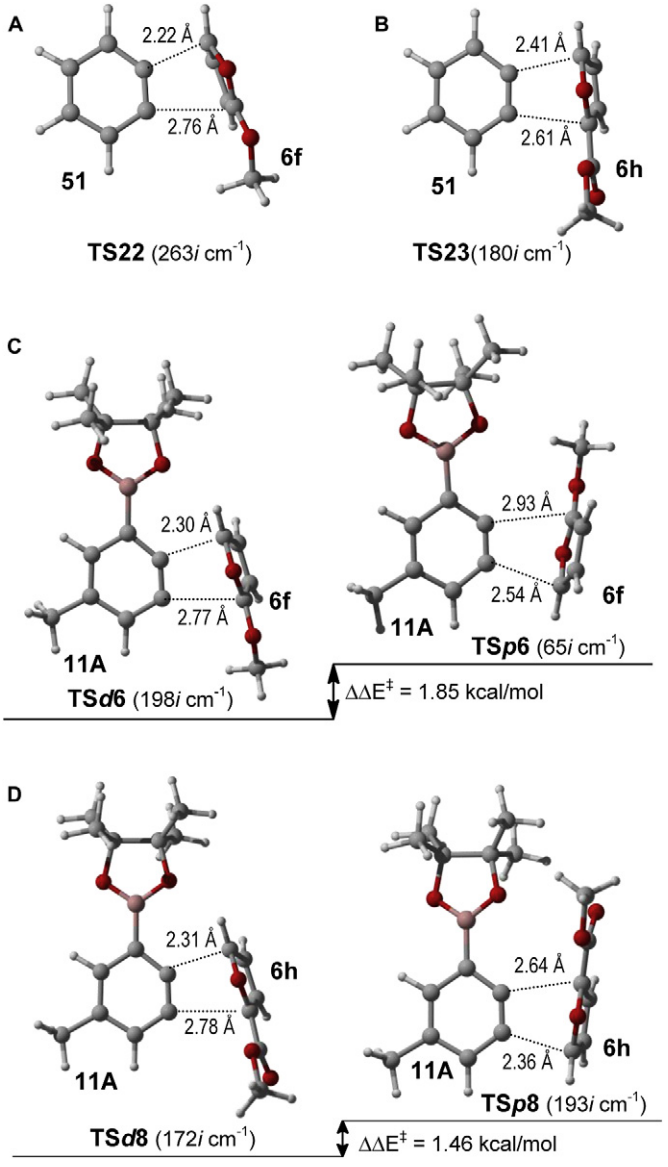


Fig. 5. Transition state (TS) structures of the Diels–Alder reaction of benzyne with 2-methoxyfuran **6f** (A), that of benzyne with methyl furan-2-carboxylate **6h** (B), that of **11A** with **6f** (C), and that of **11A** with **6h** (D).[37]

with 2-(*tert*-butyl)furan **6a** and those with 2-methylfuran **6c** were also examined to find very close tendencies (for details, see Supplementary data). Thus, the DA reactions of borylbenzynes **11** seem to be determined mainly by their electrostatic interactions with furans as well as by a small steric effect.

Third, in the electrostatically more favorable TS (**TS*d*17**) of the DA reaction of 3-(*tert*-butyl)benzyne **8B** with **6b** (Fig. 4B), the distance between C2 of **8B** and C5 of **6b** was supposed to be shorter than that between C1 of **8B** and C2 of **6b** because C2 of **8B** is slightly more electrophilic than C1 (see Table 11, entry 2); however, it is actually longer. This means that there is much bigger steric hindrance between the *tert*-butyl group of **8B** and the hydrogen of **6b** than that between the hydrogen of **8B** and the *n*-butyl group of **6b**, and such steric hindrance makes the electrostatically favorable **TS*d*17** considerably unstable. As a result, the energy difference $\Delta\Delta E^{\ddagger}$ between **TS*d*17** and **TS*p*17** is thought to be small (0.026 kcal/mol). The comparison of Fig. 4A and B also shows that the steric hindrance of the boryl group of **11A** is smaller than that of the *tert*-butyl group.

Fourth, the origins of regioselectivities of the DA reactions of borylbenzyne **11A** with furans (**6h**–**j**), possessing an electron-withdrawing group at the C2 position (Table 6, entries 7–9) were investigated based on the TS structures, given that the theoretical distal-to-proximal ratios for the DA reactions with **6h**–**j** were in good agreement with the experimental ratios (Table 13, entries 8–10). For reference, the TS structure (**TS22**) of the DA reaction of benzyne itself **51** with 2-methoxyfuran **6f** and TS structures (**TS*d*6** and **TS*p*6**) of the DA reaction of **11A** and **6f** were also analyzed to show that C5 of **6f** was closer (2.22 Å) to the carbon of benzyne than C2 of **6f** (2.76 Å) (Fig. 5A) and that the corresponding distances of the electrostatically more favorable **TS*d*6** (Fig. 5C) were similar to those of **TS22**. On the other hand, another reference TS (**TS23**) of the DA reaction between **51** and methyl furan-2-carboxylate **6h** showed that the more electron-deficient C5 of **6h** was closer (2.41 Å) to the carbon of benzyne than the more electron-sufficient C2 of **6h** (2.61 Å) (Fig. 5B), which might be accounted for by the steric hindrance between the methoxycarbonyl group of **6h** and the benzyne hydrogen. The favorable electrostatic interaction of C2 of **11A** and C2 of **6h** in **TS*p*8** probably brought them closer. However, this made **TS*p*8** extensively unstable because of the large steric hindrance between the boryl and the methoxycarbonyl groups (the planer structure of **6h** forced these two groups even closer).[35] Consequently, the alternative electrostatically less favorable **TS*d*8** became relatively more stable (Fig. 5D).

Thus, it has been revealed that the electrostatic interaction between the reactants (**6** and **11**) is a primary factor that determines the regioselectivities, which makes the distal TSs more stable in most cases. In some other cases, such as the DA reactions involving **6h**–**j** possessing electron-withdrawing groups, the steric hindrance between the substituents works as the dominant factor and may override the electrostatic interaction to make the electrostatically favorable TSs less stable.

3. Conclusion

We have developed a new method for the regiocontrol of the DA reaction of the substituted benzynes by installing a boryl group at C3 position. The generation of the previously unknown borylbenzynes **11** was effectively achieved by reacting the precursors, 6-boryl-2-

iodophenyl trifluoromethanesulfonates **28**, with *i*-PrMgCl·LiCl, while **11** immediately reacted with the substituted furans **6** and pyrroles **41** to produce multisubstituted fused aromatic boronates (**16** and **42**) in good-to-excellent yields with high distal regioselectivities. Given that the boryl groups of the DA adducts are convertible into carbon, nitrogen, and oxygen substituents, the developed method serves as a useful strategy to prepare variously functionalized naphthalene derivatives. Additionally, the regioselectivities of these reactions were quantitatively interpreted based on the theoretical analysis of the TS structures obtained from the DFT calculations, revealing that the boryl group mainly controlled regioselectivity by electrostatic effects.

Thus, this study provides an insight into certain longstanding problems related to the regioselectivity of the benzyne reactions. The investigations on the further application of borylbenzynes are currently underway in our laboratory.

4. Experimental section

4.1. General considerations

4.1.1. Reagents. Test tubes with ground joint capped with rubber septa (containing a stir-bar) were used for the copper and palladium-catalyzed reaction. All other reactions were carried out under an argon or nitrogen atmosphere in a round bottom flask or a pear-shaped flask containing a stir-bar with an inlet adapter with a three-way stopcock. 1.6 M *n*-BuLi in *n*-hexane and 1.6 M *t*-BuLi in *n*-pentane was purchased from Kanto Chemical Co. 2.0 M *i*-PrMgCl in tetrahydrofuran (THF) and 1.3 M *i*-PrMgCl·LiCl in THF were obtained from Aldrich Chemical Co. and used as they were. Anhydrous THF, CH_2Cl_2 and diethyl ether (Et_2O) were purchased from Wako Pure Chemical Industries and used without further purification. 2-(Trimethylsilyl)furan **6d**,[38] 2-phenylfuran **6g**,[39] *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **41e**,[40] 3-methyl-1-tosyl-1*H*-pyrrole **41f**,[39] 4-methyl-2-phenethyl-1-tosyl-1*H*-pyrrole **41h**,[39] 2,6-diiodophenol,[41] and 2,6-diiodo-4-methylphenol[42] were prepared according to the literature. All other reagents were purchased from Tokyo Chemical Industry Co., Aldrich Chemical Co., Kishida Chemical Co. or Nacalai Tesque and used without further purification. Flash chromatography[43] was performed with Silica gel 60N, spherical (40–50 μm) purchased from Kanto Chemical Co.[16]

4.1.2. Analytical methods. IR spectra were obtained on a JASCO WS/IR-8000. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JMN-A500 or ECA-500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) instrument with chemical shifts reported in parts per million relative to the residual deuterated solvent or the internal standard tetramethylsilane. The mass spectra were measured on a Bruker micrOTOF, JEOL JMS-700 MStation or JMS-T100TD spectrometer. Elemental analyzes were performed by YANACO CHN CORDER MT-5 instrument. 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 in references. All new products were further characterized by HRMS.

4.2. General procedure for the generation of borylbenzyne 11 followed by its Diels–Alder reaction with furan 6 or pyrrol 41 (Tables 4–8)

An oven-dried pear-shaped flask was charged with a borylbenzyne precursor **28** (1.0 equiv) and capped with an inlet adapter with a three-way stopcock and then evacuated and back-filled with argon. Anhydrous Et_2O (0.10 M) was added, and the reaction mixture was cooled to −78 °C. Furan **6** or pyrrol **41** (3.0 equiv) was added, and then a 1.3 M solutions of *i*-PrMgCl·LiCl (1.2 equiv) in THF was slowly added over 5 min. After being stirred at −78 °C for 30 min, the reaction mixture was quenched by a saturated aqueous NH_4Cl solution. The reaction mixture was extracted with EtOAc. Aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with a saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel. Most of major regioisomers (*distal*-**16** and *distal*-**42**) were isolated, while minor regioisomers (*proximal*-**16** and *proximal*-**42**) could be hardly isolated because both distal and proximal adducts were slightly prone to be adsorbed on silica gel. The structures of the minor regioisomers were determined by similarity of their characteristic ^{1}H NMR data to those of *proximal*-**16Ab**, whose structure was determined by NOESY spectra.

*4.2.1. 2-(1-Butyl-7-methyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane distal-**16Ab**.* Following the general procedure, a mixture of **28A** (74 mg, 0.15 mmol), 2-*n*-butylfuran **6b** (64 μL, 0.45 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.14 mL, 0.18 mmol)] in Et_2O (1.5 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=92:8, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=12:1) to provide a mixture of *distal*- and *proximal*-**16Ab** (47 mg, 93%). Pure *distal*-**16Ab** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless solid; mp 118–121 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, t, *J*=7.5 Hz), 1.33 (12H, s), 1.45–1.50 (2H, m), 1.56–1.63 (2H, m), 2.23–2.39 (2H, m), 2.28 (3H, s), 6.05 (1H, d, *J*=2.0 Hz), 6.73 (1H, d, *J*=5.5 Hz), 7.02 (1H, dd, *J*=2.0, 5.5 Hz), 7.04 (1H, s), 7.13 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 21.2, 23.2, 24.8, 25.0, 26.8, 29.0, 82.0, 83.6, 92.3, 123.0, 129.9, 133.5, 144.5, 144.7, 150.1, 156.1; IR ($CHCl_3$, cm^{-1}) 3007; HRMS *m*/*z* (FAB$^+$) calcd for $C_{21}H_3BO_3$ [(M+H)$^+$] 341.2292, found. 341.2303.

*4.2.2. 2-(4-Butyl-7-methyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane proximal-**16Ab**.* Regiochemistry was determined by NOESY spectra of the mixture of *distal*- and *proximal*-**16Ab**. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J*=7.5 Hz), 1.38–1.41 (2H, m), 2.19–2.34 (2H, m), 2.27 (3H, s), 2.55–2.63 (2H, m), 5.56 (1H, d, *J*=2.0 Hz), 6.82 (1H, d, *J*=5.5 Hz), 6.96 (1H, dd, *J*=2.0, 5.5 Hz), 7.09 (1H, br s), 7.15 (1H, br s).

*4.2.3. 2-(1-(tert-Butyl)-7-methyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane distal-**16Aa**.* Following the general procedure, a mixture of **28A** (56 mg, 0.12 mmol), 2-*tert*-butylfuran **6a** (50 μL, 0.35 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.11 mL, 0.14 mmol)] in Et_2O (1.2 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=94:6, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=15:1) to provide a mixture of *distal*- and *proximal*-**16Aa** (40 mg, >99%). Pure *distal*-**16Aa** was isolable from the reaction mixture by the same column chromatography (hexane/EtOAc=15:1). A colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (9H, s), 1.32 (12H, s), 2.29 (3H, s), 6.09 (1H, d, *J*=1.5 Hz), 6.90 (1H, d, *J*=5.5 Hz) 7.01 (1H, dd, *J*=1.5, 5.5 Hz), 7.13 (1H, br s), 7.28 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.3, 24.8, 25.0, 26.6, 81.7, 83.6, 99.0, 125.4, 129.7, 142.5, 144.8, 148.7, 157.3; IR ($CHCl_3$, cm^{-1}) 3009; HRMS *m*/*z* (FAB$^+$) calcd for $C_{21}H_{30}BO_3$ [(M+H)$^+$] 341.2288, found. 341.2292.

*4.2.4. 2-(4-(tert-Butyl)-7-methyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane proximal-**16Aa**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.30 (9H, s), 1.37 (12H, s), 2.25 (3H, s), 5.53 (1H, br s), 6.80 (1H, s), 6.93 (2H, br s), 7.01 (1H, br s).

*4.2.5. 2-(1,7-Dimethyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane distal-**16Ac**.* Following the general procedure, a mixture of **28A** (57 mg, 0.12 mmol), 2-

methylfuran **6c** (31 μL, 0.34 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.11 mL, 0.14 mmol)] in Et_2O (1.2 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=88:12, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=10:1) to provide a mixture of *distal*- and *proximal*-**16Ac** (29 mg, 85%). Pure *distal*-**16Ac** was isolable from the reaction mixture by the same column chromatography (hexane/EtOAc=10:1). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (12H, d, J=2.5 Hz), 1.90 (3H, s), 2.30 (3H, s), 6.02 (1H, d, J=2.0 Hz), 6.72 (1H, d, J=5.5 Hz), 7.04 (1H, dd, J=2.0, 5.5 Hz), 7.06 (1H, s), 7.14 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 21.1, 24.8, 25.0, 82.1, 83.6, 88.8, 122.5, 130.0, 133.6, 144.8, 145.3, 150.8, 155.6; IR ($CHCl_3$, cm^{-1}) 3011; HRMS m/z (FAB^+) calcd for $C_{18}H_{24}BO_3$ [$(M+H)^+$] 299.1819, found. 299.1818.

*4.2.6. 2-(4,7-Dimethyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane proximal-**16Ac**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (12H, d, J=8.0 Hz), 2.07 (3H, s), 2.27 (3H, s), 5.53 (1H, s, br s), 6.83 (1H, d, J=5.0 Hz), 6.97 (1H, d, J=5.0 Hz), 7.08 (1H, br s), 7.14 (1H, br s).

*4.2.7. Trimethyl(7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalen-1-yl)silane distal-**16Ad**.* Following the general procedure, a mixture of **28A** (48 mg, 0.10 mmol), 2-trimethylsilylfuran **6d** (46 μL, 0.29 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.090 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=12:1) to provide a mixture of *distal*- and *proximal*-**16Ad** (31 mg, 91%). Pure *distal*-**16Ad** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.30 (9H, s), 1.33 (12H, s), 2.28 (3H, s), 6.14 (1H, d, J=1.5 Hz), 6.92 (1H, d, J=5.5 Hz), 7.03 (1H, dd, J=1.5, 5.5 Hz) 7.06 (1H, br s), 7.12 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: −3.1, 21.2, 24.8, 25.0, 83.5, 85.4, 124.0, 129.6, 133.2, 143.5, 145.4, 151.9, 155.8; IR ($CHCl_3$, cm^{-1}) 3017; HRMS m/z (FAB^+) calcd for $C_{20}H_{30}BO_3$ [$(M+H)^+$] 357.2057, found. 357.2061.

*4.2.8. Tributyl(7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalen-1-yl)stannane distal-**16Ae**.* Following the general procedure, a mixture of **28A** (49 mg, 0.10 mmol), 2-tributylstannylfuran **6e** (94 μL, 0.30 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.090 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=18:1) to provide a mixture of *distal*- and *proximal*-**16Ae** (45 mg, 79%). Pure *distal*-**16Ae** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.89 (9H, t, J=7.0 Hz), 1.11 (6H, t, J=8.0 Hz), 1.32 (12H, s), 1.33–1.36 (6H, m), 1.53–1.59 (6H, m), 2.27 (3H, s), 6.09 (1H, d, J=1.5 Hz), 6.94 (1H, br s), 6.95 (1H, d, J=6.0 Hz), 7.01 (1H, dd, J=1.5, 6.0 Hz), 7.09 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.1, 13.6, 21.2, 24.8, 25.0, 27.4, 29.0, 29.1, 82.8, 83.5, 87.0, 124.0, 129.4, 133.2, 142.2, 148.7, 154.5, 155.4; IR ($CHCl_3$, cm^{-1}) 3005; HRMS m/z (ESI) calcd for $C_{29}H_{47}BNaO_3Sn$ [$(M+Na)^+$] 597.2532, found. 597.2553.

*4.2.9. 4-Methoxy-6-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl acetate distal-**22Af**.* Following the general procedure, a mixture of **28A** (51 mg, 0.11 mmol), 2-methoxyfuran **6f** (30 μL, 0.33 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.10 mL, 0.13 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. To the crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) were added 1.0 mL of pyridine and 0.10 mL of acetic anhydride. After 6.5 h, the reaction mixture was quenched by water, and the product was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc=6:1) to provide *distal*-**22Af** (26 mg, 68%), the regiochemistry of which was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (12H, s), 2.35 (3H, s), 2.50 (3H, s), 3.98 (3H, s), 6.74 (1H, d, J=8.5 Hz), 6.99 (1H, d, J=8.5 Hz), 7.60 (1H, d, J=1.5 Hz), 8.12 (1H, d, J=1.5 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ: 20.4, 20.9, 24.0, 54.9, 84.0, 103.1, 117.8, 122.7, 126.2, 127.6, 134.3, 135.3, 141.3, 153.2, 171.3; IR ($CHCl_3$, cm^{-1}) 1763, 3017, 3021; HRMS m/z (ESI) calcd for $C_{20}H_{25}BNaO_5$ [$(M+Na)^+$] 379.1687, found. 379.1687.

*4.2.10. 6-Methyl-4-phenyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl acetate distal-**22Ag**.* Following the general procedure, a mixture of **28A** (56 mg, 0.12 mmol), 2-phenylfuran **6g** (49 mg, 0.34 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.11 mL, 0.14 mmol)] in Et_2O (1.2 mL) was stirred for 30 min at −78 °C. To the crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) were added 1.0 mL of pyridine and 0.10 mL of acetic anhydride. After 3.0 h, the reaction mixture was quenched by water, and the product was extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc=8:1) to provide *distal*-**22Ag** (18 mg, 40%), the regiochemistry of which was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (12H, s), 2.40 (3H, s), 2.43 (3H, s), 7.15 (1H, d, J=8.0 Hz), 7.35 (1H, d, J=8.0 Hz), 7.41–7.50 (5H, m), 7.60 (1H, br s), 7.67 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.6, 22.1, 24.9, 83.9, 117.6, 126.5, 127.1, 127.2, 128.2, 130.2, 133.2, 135.2, 135.4, 138.1, 140.7, 147.1, 170.3; IR ($CHCl_3$, cm^{-1}) 1759, 3007; HRMS m/z (ESI) calcd for $C_{25}H_{27}BNaO_4$ [$(M+Na)^+$] 425.1895, found. 425.1886.

*4.2.11. Methyl 7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalene-1-carboxylate distal-**16Ah**.* Following the general procedure, a mixture of **28A** (58 mg, 0.12 mmol), methyl furan-2-carboxylate **6h** (38 μL, 0.36 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.11 mL, 0.14 mmol)] in Et_2O (1.2 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=93:7, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=5:1) to provide a mixture of *distal*- and *proximal*-**16Ah** (23 mg, 57%). Pure *distal*-**16Ah** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless solid; mp 95–97 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (12H, s), 2.29 (3H, s), 3.98 (3H, s), 6.02 (1H, d, J=2.0 Hz), 7.04 (1H, d, J=5.5 Hz), 7.07 (1H, dd, J=2.0, 5.5 Hz), 7.21 (1H, br s), 7.25 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.8, 25.0, 52.7, 82.9, 83.8, 90.0, 123.5, 131.1, 134.1, 142.2, 144.0, 146.8, 152.6, 168.6; IR ($CHCl_3$, cm^{-1}): 1742, 3022; HRMS m/z (ESI) calcd for $C_{19}H_{23}BNaO_5$ [$(M+Na)^+$] 365.1531, found. 365.1531.

*4.2.12. Methyl 6-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalene-1-carboxylate proximal-**16Ah**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (12H, s), 2.29 (3H, s), 3.90 (3H, s), 5.72 (1H, d, J=1.5 Hz), 7.00 (1H, dd, J=1.5, 5.0 Hz), 7.15 (1H, br s), 7.18 (1H, d, J=5.0 Hz), 7.21 (1H, br s).

*4.2.13. 1-(7-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalen-1-yl)ethanone distal-**16Ai**.* Following the general procedure, a mixture of **28A** (64 mg, 0.13 mmol), 2-acetylfuran **6i** (40 μL, 0.40 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.12 mL, 0.16 mmol)] in Et_2O (1.3 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=87:13, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=10:1) to provide a mixture of *distal*- and *proximal*-**16Ai** (22 mg, 51%). Pure *distal*-**16Ai** was isolable from the reaction

mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless solid; mp 104–106 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (6H, s), 1.35 (6H, s), 2.28 (3H, s), 2.40 (3H, s), 6.21 (1H, d, J=1.0 Hz), 7.02–7.04 (2H, m), 7.14 (1H, br s), 7.20 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.8, 25.0, 26.8, 82.7, 83.8, 95.4, 123.1, 130.9, 134.1, 141.9, 143.8, 147.1, 153.0, 205.8; IR ($CHCl_3$, cm^{-1}) 1717, 3017; HRMS m/z (ESI) calcd for $C_{19}H_{23}BNaO_4$ [$(M+Na)^+$] 349.1582, found. 349.1601.

*4.2.14. 1-(6-Methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalen-1-yl)ethanone proximal-**16Ai**.* Characteristic ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30 (3H, s), 2.37 (3H, s), 5.73 (1H, d, J=2.0 Hz), 6.98 (1H, dd, J=2.0, 5.0 Hz).

*4.2.15. 7-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalene-1-carbonitrile distal-**16Aj**.* Following the general procedure, a mixture of **28A** (53 mg, 0.11 mmol), 2-furancarbonitrile **6j** (95 μL, 1.1 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 −78 °C. The crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=12:1) to provide a mixture of *distal*- and *proximal*-**16Aj** (16 mg, 46%). Pure *distal*-**16Aj** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless solid; mp 111–112 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (6H, s), 1.35 (6H, s), 2.34 (3H, s), 6.18 (1H, d, J=2.0 Hz), 6.97 (1H, d, J=5.5 Hz), 7.14 (1H, dd, J=2.0, 5.5 Hz), 7.25 (1H, s), 7.34 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.9, 25.0, 79.0, 83.5, 84.0, 115.5, 123.2, 131.9, 134.9, 141.1, 144.5, 145.8, 151.1; IR ($CHCl_3$, cm^{-1}) 1599, 3019; HRMS m/z (ESI) calcd for $C_{18}H_{20}BNNaO_3$ [$(M+Na)^+$] 332.1428, found. 332.1442.

*4.2.16. 2-(3,7-Dimethyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane distal-**16Ak** and its regioisomer proximal-**16Ak**.* Following the general procedure, a mixture of **28A** (54 mg, 0.11 mmol), 3-methylfuran **6k** (30 μL, 0.34 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 −78 °C. The crude product (*distal*/*proximal*=87:13, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=10:1) to provide a hardly separable mixture of *proximal*- and *distal*-**16Ak** (33 mg, quant), the regiochemistries of which were determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (6/6H, s), 1.34 (36/6H, s), 1.36 (30/6H, s), 1.89 (3/6H, d, J=1.5 Hz), 1.91 (15/6H, J=1.5 Hz, d), 2.30 (18/6H, br s), 5.28 (1/6H, br s), 5.61 (5/6H, br s), 5.80 (5/6H, br s), 6.06 (1/6H, br s), 6.38–6.39 (5/6H, m), 6.44–6.46 (1/6H, m), 7.12 (5/6H, br s), 7.16 (5/6H, br s), 7.19 (2/6H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 14.1, 15.3, 23.1, 23.3, 24.6, 24.7, 24.78, 24.83, 25.0, 26.7, 27.2, 28.8, 29.7, 65.8, 80.7, 81.8, 84.0, 84.2, 85.0, 92.3, 94.9, 118.1, 118.4, 121.8, 122.8, 125.0, 125.1, 132.3, 133.4, 135.7, 139.8, 143.9, 144.3, 144.6, 145.3, 152.7, 152.9, 153.4, 155.7, 157.7; IR ($CHCl_3$, cm^{-1}) 3009; HRMS m/z (ESI) calcd for $C_{18}H_{23}BNaO_3$ [$(M+Na)^+$] 321.1632, found. 321.1638.

*4.2.17. 2-(1-Butyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane distal-**16Bb**. From **28B**:* Following the general procedure, a mixture of **28B** (52 mg, 0.11 mmol), 2-*n*-butylfuran **6b** (47 μL, 0.33 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 −78 °C. The crude product (*distal*/*proximal*=90:10, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=13:1) to provide a mixture of *distal*- and *proximal*-**16Bb** (31 mg, 88%). Pure *distal*-**16Bb** was isolable from the reaction mixture by the same column chromatography (hexane/EtOAc=13:1).

From **28B′**: Following the general procedure, a mixture of **28B′** (31 mg, 64 μmol), 2-*n*-butylfuran **6b** (30 μL, 0.21 mmol), *i*-PrMgCl·LiCl [1.3 M in THF (0.060 mL, 0.080 mmol)] in Et_2O (0.70 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=91:9, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=13:1) to provide a mixture of *distal*- and *proximal*-**16Bb** (5.1 mg, 24%). Pure *distal*-**16Bb** was isolable from the reaction mixture by the same column chromatography (hexane/EtOAc=13:1). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.5 Hz), 1.33 (12H, s), 1.43–1.51 (2H, m), 1.53–1.64 (2H, m), 2.22–2.36 (2H, m), 6.09 (1H, d, J=2.0 Hz), 6.75 (1H, d, J=5.5 Hz), 6.96 (1H, t, J=7.5 Hz), 7.04 (1H, dd, J=2.0, 5.5 Hz), 7.21 (1H, d, J=7.5 Hz), 7.33 (1H, d, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 23.2, 24.75, 24.80, 25.0, 26.9, 28.9, 82.1, 83.7, 92.3, 121.5, 123.9, 130.1, 144.5, 144.7, 149.6, 158.9; IR ($CHCl_3$, cm^{-1}) 3007; HRMS m/z (FAB^+) calcd for $C_{20}H_{28}BO_3$ [$(M+H)^+$] 327.2132, found. 327.2118.

*4.2.18. 2-(4-Butyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane proximal-**16Bb**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (3H, t, J=7.5 Hz), 1.37 (12H, s), 1.41–1.49 (2H, m), 1.54–1.64 (2H, m), 2.53–2.64 (2H, m), 5.61 (1H, d, J=2.0 Hz), 6.83 (1H, d, J=5.0 Hz), 6.93 (1H, t, J=7.5 Hz), 6.99 (1H, dd, J=2.0, 5.0 Hz), 7.25 (1H, d, J=7.5 Hz), 7.34 (1H, d, J=7.5 Hz).

*4.2.19. Methyl 4-butyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalene-6-carboxylate distal-**16Cb**.* Following the general procedure, a mixture of **28C** (59 mg, 0.11 mmol), 2-*n*-butylfuran **6b** (0.15 mL, 1.1 mmol), and *i*-PrMgBr [0.77 M in THF (0.30 mL, 0.23 mmol)] in Et_2O (1.1 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=83:17, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=12:1) to provide a mixture of *distal*- and *proximal*-**16Cb** (29 mg, 68%). Pure *distal*-**16Cb** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.0 Hz), 1.34 (12H, s), 1.47 (2H, sext, J=7.0 Hz), 1.51–1.62 (2H, m), 2.24–2.39 (2H, m), 3.89 (3H, s), 6.10 (1H, d, J=1.5 Hz), 6.76 (1H, d, J=5.0 Hz), 7.00 (1H, dd, J=1.5, 5.0 Hz), 7.80 (1H, d, J=1.5 Hz), 8.09 (1H, d, J=1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 23.1, 24.7, 24.8, 25.0, 26.8, 28.8, 52.0, 82.0, 84.0, 92.3, 121.7, 126.2, 133.2, 143.8, 145.0, 150.4, 164.1, 167.2; IR ($CHCl_3$, cm^{-1}) 1715, 3026; HRMS m/z (ESI) calcd for $C_{22}H_{29}BNaO_5$ [$(M+Na)^+$] 407.2000, found. 407.2022.

*4.2.20. Methyl 1-butyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epoxynaphthalene-6-carboxylate proximal-**16Cb**.* ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (3H, t, J=7.5 Hz), 1.38 (12H, s), 1.43–1.62 (4H, m), 2.52–2.64 (2H, m), 3.88 (3H, s), 5.64 (1H, d, J=1.5 Hz), 6.80 (1H, d, J=5.5 Hz), 6.99–7.02 (1H, m), 7.83 (1H, d, J=1.5 Hz), 8.09 (1H, d, J=1.5 Hz).

*4.2.21. 2-(7-Bromo-1-butyl-1,4-dihydro-1,4-epoxynaphthalen-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane distal-**16Db** and its regioisomer proximal-**16Db**.* Following the general procedure, a mixture of **28D** (56 mg, 0.10 mmol), 2-*n*-butylfuran **6b** (50 μL, 0.35 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.10 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=84:16, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=12:1) to provide a hardly separable mixture of *distal*- and *proximal*-**16Db** (29 mg, 64%), the regiochemistries of which were determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.93 (3/5H, t, J=7.5 Hz), 0.97 (12/5H, t, J=7.5 Hz), 1.33 (48/5H, s), 13.6 (12/5H, s), 1.41–1.50 (8/5H, m), 1.51–1.61 (8/5H, m), 2.18–2.32 (8/5H, m), 2.32–2.35 (2/5H, m), 2.50–2.59 (2/5H, m), 3.48 (1/5H, q, J=7.5 Hz), 5.56 (1/5H, d, J=1.5 Hz), 6.03 (4/5H, d, J=1.5 Hz), 6.73 (4/5H, d, J=7.5 Hz), 6.82 (1/5H, d, J=7.5 Hz), 6.96 (1/5H, dd, J=1.5,

7.5 Hz), 7.02 (4/5H, dd, *J*=1.5, 7.5 Hz), 7.30 (4/5H, d, *J*=1.5 Hz), 7.35 (1/5H, d, *J*=1.5 Hz), 7.46 (4/5H, d, *J*=1.5 Hz), 7.47 (1/5H, d, *J*=1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 14.1, 21.0, 21.1, 24.8, 24.9, 25.0, 82.5, 83.3, 83.58, 83.62, 85.2, 85.8, 123.2, 123.6, 129.8, 130.3, 133.2, 133.8, 134.5, 135.1, 148.2, 149.4, 153.6, 154.1, 154.6, 154.9; IR ($CHCl_3$, cm^{-1}) 3019; HRMS *m*/*z* (ESI) calcd for $C_{20}H_{26}BBrNaO_3$ [$(M+Na)^+$] 427.1051, found. 427.1057.

*4.2.22. 1-Ethyl-7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-tosyl-1,4-dihydro-1,4-epiminonaphthalene distal-**42Ac**.* Following the general procedure, a mixture of **28A** (52 mg, 0.11 mmol), 2-ethyl-1-tosyl-1*H*-pyrrole **41c** (77 mg, 0.31 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 −78 °C. The crude product (*distal*/*proximal*=87:13, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=9:1) to provide a mixture of *distal*- and *proximal*-**42Ac** (31 mg, 63%). Pure *distal*-**42Ac** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.349 (3H, t, *J*=7.0 Hz), 1.354 (6H, s), 1.37 (6H, s), 2.09 (3H, s), 2.27 (3H, s), 2.40 (1H, qd, *J*=7.0, 15.0 Hz), 2.58 (1H, qd, *J*=7.0, 15.0 Hz), 5.85 (1H, d, *J*=3.0 Hz), 6.70 (1H, s), 6.72 (1H, d, *J*=6.0 Hz), 6.78 (1H, s), 6.89 (2H, d, *J*=8.0 Hz), 7.02 (1H, dd, *J*=3.0, 6.0 Hz), 7.26 (2H, d, *J*=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.6, 20.4, 20.8, 21.3, 24.8, 25.0, 68.2, 79.6, 83.7, 123.7, 128.5, 129.9, 133.5, 134.8, 142.5, 143.7, 146.1, 147.9, 154.2; IR ($CHCl_3$, cm^{-1}) 1597, 3015; HRMS *m*/*z* (ESI) calcd for $C_{26}H_{32}BNNaO_4S$ [$(M+Na)^+$] 488.2037, found. 488.2037.

*4.2.23. 1-Ethyl-6-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-tosyl-1,4-dihydro-1,4-epiminonaphthalene proximal-**42Ac**.* ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.27 (3H, t, *J*=7.5 Hz), 1.35 (12H, d, *J*=7.5 Hz), 2.06 (3H, s), 2.29 (3H, s), 2.65–2.72 (1H, m), 2.83–2.90 (1H, m), 5.26 (1H, d, *J*=3.0 Hz), 6.67 (1H, br s), 6.70 (1H, d, *J*=5.5 Hz), 6.75 (1H, br s), 6.91 (1H, dd, *J*=3.0, 5.5 Hz), 6.95 (2H, d, *J*=8.0 Hz), 7.30 (2H, d, *J*=8.0 Hz).

*4.2.24. tert-Butyl 1-ethyl-7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate distal-**42Ad**.* Following the general procedure, a mixture of **28A** (52 mg, 0.11 mmol), *tert*-butyl 2-ethyl-1*H*-pyrrole-1-carboxylate **41d** (0.54 g, 1.1 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (1.0 mL, 1.3 mmol)] in Et_2O (11 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=13:1) to provide *distal*-**42Ad** (0.32 g, 70%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.22 (3H, t, *J*=7.5 Hz), 1.336 (12H, s), 1.344 (9H, s), 2.28 (3H, s), 2.49 (1H, qd, *J*=7.5, 14.0 Hz), 2.59–2.72 (1H, br m), 5.93 (1H, br s), 6.62 (2H, d, *J*=6.0 Hz), 6.97 (1H, br s), 7.05 (1H, br s), 7.13 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.6, 21.1, 21.2, 24.9, 25.0, 28.2, 67.3, 77.9, 83.6, 123.6, 130.1, 133.4, 145.9, 150.4, 155.1; IR ($CHCl_3$, cm^{-1}) 1701, 3021; HRMS *m*/*z* (ESI) calcd for $C_{24}H_{34}BNNaO_4$ [$(M+Na)^+$] 434.2473, found. 434.2473.

*4.2.25. tert-Butyl 1-bromo-7-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate distal-**42Ae**.* Following the general procedure, a mixture of **28A** (50 mg, 0.10 mmol), *tert*-butyl 2-bromo-1*H*-pyrrole-1-carboxylate **41e** (86 mg, 0.35 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.10 mL, 0.13 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=11:1) to provide a mixture of *distal*- and *proximal*-**42Ae** (27 mg, 58%). Pure *distal*-**42Ae** was isolable from the reaction mixture by the same column chromatography, and its regiochemistry was determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (15H, s), 1.35 (6H, s), 2.31 (3H, s), 5.93 (1H, d, *J*=3.0 Hz), 6.80 (1H, d, *J*=6.0 Hz), 6.96 (1H, dd, *J*=3.0, 6.0 Hz), 7.20 (1H, br s), 7.33 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.1, 24.9, 25.0, 28.0, 67.4, 76.5, 81.3, 83.8, 125.1, 131.5, 134.5, 142.9, 147.4, 148.4, 151.2, 155.4; IR ($CHCl_3$, cm^{-1}) 1724, 3007; HRMS *m*/*z* (ESI) calcd for $C_{22}H_{29}BBrNNaO_4$ [$(M+Na)^+$] 484.1265, found. 484.1268.

*4.2.26. 9-tert-Butyl 6-methyl 4-ethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-6,9-dicarboxylate distal-**42Cd**.* Following the general procedure, a mixture of **28C** (53 mg, 0.10 mmol), *tert*-butyl 2-ethyl-1*H*-pyrrole-1-carboxylate **41d** (58 mg, 0.30 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.090 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=88:12, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=7:1) to provide a mixture of *distal*- and *proximal*-**42Cd** (29 mg, 61%). Pure *distal*-**42Cd** was isolable from the reaction mixture by the same column chromatography. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.23 (3H, t, *J*=7.0 Hz), 1.32 (9H, s), 1.35 (12H, s), 2.52 (1H, qd, *J*=7.0, 14.0 Hz), 2.64–2.78 (1H, m), 3.88 (3H, s), 5.99 (1H, d, *J*=1.5 Hz), 6.65 (1H, d, *J*=6.0 Hz), 6.95 (1H, br s), 7.82 (1H, br s), 8.09 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.6, 21.0, 24.9, 25.0, 28.1, 28.2, 52.0, 67.4, 77.9, 84.0, 122.2, 126.1, 133.2, 146.4, 150.7, 154.9, 163.2, 167.2; IR ($CHCl_3$, cm^{-1}) 1708, 3019; HRMS *m*/*z* (ESI) calcd for $C_{25}H_{34}BNNaO_6$ [$(M+Na)^+$] 478.2371, found. 478.2373.

*4.2.27. 9-tert-Butyl 6-methyl 1-ethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-6,9-dicarboxylate proximal-**42Cd**.* Characteristic ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.43 (1H, d, *J*=3.0 Hz).

*4.2.28. tert-Butyl 7-bromo-1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate distal-**42Dd**.* Following the general procedure, a mixture of **28D** (54 mg, 0.10 mmol), *tert*-butyl 2-ethyl-1*H*-pyrrole-1-carboxylate **41d** (60 mg, 0.31 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.090 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=95:5, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=13:1) to provide a mixture of *distal*- and *proximal*-**42Dd** (33 mg, 72%). Pure *distal*-**42Dd** was isolable from the reaction mixture by the same column chromatography. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.21 (3H, t, *J*=7.5 Hz), 1.33 (15H, s), 1.34 (6H, s), 2.44 (1H, qd, *J*=7.5, 14.0 Hz), 2.54–2.70 (1H, m), 5.91 (1H, d, *J*=2.0 Hz), 6.62 (1H, d, *J*=5.0 Hz), 6.96 (1H, dd, *J*=2.0, 5.0 Hz), 7.31 (1H, d, *J*=2.0 Hz), 7.46 (1H, d, *J*=2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.5, 21.0, 24.9, 25.0, 28.1, 67.1, 77.9, 80.3, 84.0, 118.3, 125.6, 132.4, 145.8, 152.9, 154.8, 156.7; IR ($CHCl_3$, cm^{-1}) 1703, 3019; HRMS *m*/*z* (ESI) calcd for $C_{23}H_{31}BBrNNaO_4$ [$(M+Na)^+$] 498.1422, found. 498.1440.

*4.2.29. tert-Butyl 6-bromo-1-ethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate proximal-**42Dd**.* Characteristic ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.35 (1H, d, *J*=3.0 Hz), 6.69 (1H, d, *J*=5.5 Hz), 6.88 (1H, dd, *J*=3.0, 5.5 Hz).

*4.2.30. 2,6-Dimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-tosyl-1,4-dihydro-1,4-epiminonaphthalene distal-**42Af** and its regioisomer proximal-**42Af**.* Following the general procedure, a mixture of **28A** (50 mg, 0.10 mmol), 3-methyl-1-tosyl-1*H*-pyrrole **41f** (72 mg, 0.31 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.10 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=86:14, determined by 500 MHz ^{1}H

NMR analysis) was purified by column chromatography (hexane/EtOAc=5:1) to provide a hardly separable mixture of *distal*- and *proximal*-**42Af** (40 mg, 87%), the regiochemistries of which were determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (42/7H, s), 1.35 (6/7H, s), 1.36 (36/7H, s), 1.76 (3/7H, d, J=1.5 Hz), 1.77 (18/7H, d, J=1.5 Hz), 2.13 (21/7H, br s), 2.30 (21/7H, br s), 4.94 (1/7H, br s), 5.29–5.32 (6/7H, m), 5.57 (6/7H, br s), 5.82 (1/7H, br s), 6.23–6.27 (6/7H, m), 6.31–6.34 (1/7H, m), 6.82 (6/7H, br s), 6.86 (6/7H, br s), 6.88 (1/7H, br s), 6.89 (1/7H, br s), 6.98 (14/7H, d, J=8.0 Hz), 7.35 (14/7H, d, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.0, 20.75, 20.84, 21.4, 24.7, 24.8, 24.9, 25.1, 68.0, 68.2, 70.8, 70.9, 83.6, 83.7, 124.2, 124.7, 127.1, 128.3, 128.8, 129.8, 130.3, 133.3, 133.8, 134.7, 134.9, 135.3, 142.7, 147.1, 152.0, 153.7, 154.5; IR ($CHCl_3$, cm^{-1}) 1597, 3026; HRMS m/z (ESI) calcd for $C_{25}H_{30}BNNaO_4S$ [(M+Na)$^+$] 474.1881, found. 474.1875.

*4.2.31. tert-Butyl 2,6-dimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate distal-**42Ag** and its regioisomer proximal-**42Ag**.* Following the general procedure, a mixture of **28A** (50 mg, 0.10 mmol), *tert*-butyl 3-methyl-1*H*-pyrrole-1-carboxylate **41g** (54 mg, 0.30 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.10 mL, 0.12 mmol)] in Et_2O (1.0 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=92:8, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=11:1) to provide a hardly separable mixture of *distal*-**42Ag** and its regioisomer *proximal*-**42Ag** (38 mg, 95%), the regiochemistries of which were determined by NOESY spectra. A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (60/10H, s), 1.36 (150/10H, s), 1.89 (30/10H, br s), 2.27 (30/10H, br s), 5.05 (1/10H, br s), 5.35 (9/10H, br s), 5.60 (10/10H, br s), 6.34 (10/10H, br s), 7.13 (20/10H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.1, 15.2, 21.0, 21.1, 24.8, 24.9, 28.1, 66.1, 66.7, 69.6, 70.4, 80.0, 83.6, 123.4, 124.3, 129.8, 133.1, 133.4, 134.2, 148.7, 149.3, 153.0, 153.3, 154.1, 155.0, 155.7, 155.9; IR ($CHCl_3$, cm^{-1}) 1701, 3007; HRMS m/z (ESI) calcd for $C_{23}H_{32}BNNaO_4$ [(M+Na)$^+$] 420.2317, found. 420.2304.

*4.2.32. tert-Butyl 3,7-dimethyl-1-phenethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate distal-**42Ah**.* Following the general procedure, a mixture of **28A** (60 mg, 0.12 mmol), *tert*-butyl 4-methyl-2-phenethyl-1*H*-pyrrole-1-carboxylate **41h** (0.10 g, 0.36 mmol), and *i*-PrMgCl·LiCl [1.3 M in THF (0.11 mL, 0.14 mmol)] in Et_2O (1.2 mL) was stirred for 30 min at −78 °C. The crude product (*distal*/*proximal*=>98:2, determined by 500 MHz ^{1}H NMR analysis) was purified by column chromatography (hexane/EtOAc=13:1) to provide *distal*-**42Ah** (49 mg, 81%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.34 (9H, s), 1.37 (6H, s), 1.38 (6H, s), 1.91 (3H, br s), 2.29 (3H, s), 2.62–2.69 (1H, m), 2.88–3.05 (2H, m), 3.05–3.12 (1H, m), 5.68 (1H, br s), 6.11 (1H, br s), 7.04 (1H, br s), 7.15 (1H, br s), 7.22 (1H, t, J=7.5 Hz), 7.31–7.37 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.2, 21.2, 24.8, 25.0, 28.2, 30.0, 31.4, 71.1, 77.4, 79.8, 83.5, 84.2, 122.8, 125.7, 128.3, 128.4, 129.7, 133.6, 137.6, 142.7, 151.2, 155.0, 155.4; IR ($CHCl_3$, cm^{-1}) 1699, 3020; HRMS m/z (ESI) calcd for $C_{31}H_{40}BNNaO_4$ [(M+Na)$^+$] 524.2943, found. 524.2945.

4.3. Copper catalyzed amination of the boryl group of *distal*-16Ab (Table 9, entry 1)

*4.3.1. N,1-Dibutyl-7-methyl-1,4-dihydro-1,4-epoxynaphthalen-5-amine **43**.* A suspension of *distal*-**16Ab** (21 mg, 60 μmol), copper(II) acetate (0.60 mg, 3.3 μmol), and cesium fluoride (4.6 mg, 30 μmol) in acetonitrile (1.0 mL) was stirred at room temperature for 5–10 min. *n*-Butylamine (3.0 μL, 30 μmol) was added, and the reaction mixture was stirred at room temperature under an oxygen atmosphere for 12 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc=10:1) to provide **43** (8.7 mg, 71%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.95–0.98 (6H, m), 1.39–1.51 (4H, m), 1.51–1.65 (4H, m), 2.16–2.31 (2H, m), 2.25 (3H, s), 3.08–3.19 (2H, m), 3.37 (1H, br s), 5.72 (1H, d, J=1.5 Hz), 6.15 (1H, s), 6.48 (1H, s), 6.75 (1H, d, J=5.5 Hz), 7.02 (1H, dd, J=1.5, 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 14.0, 20.2, 21.5, 23.2, 26.8, 29.1, 32.0, 44.5, 79.3, 93.0, 111.4, 130.7, 136.3, 141.3, 144.0, 144.3, 152.1; IR ($CHCl_3$, cm^{-1}) 3005, 3422; HRMS m/z (ESI) calcd for $C_{19}H_{28}NO$ [(M+H)$^+$] 286.2165, found. 286.2179.

4.4. Cyanidation of the boryl group of *distal*-16Ab (Table 9, entry 2)

*4.4.1. 1-Butyl-7-methyl-1,4-dihydro-1,4-epoxynaphthalene-5-carbonitrile **44**.* A suspension of *distal*-**16Ab** (24 mg, 69 μmol), copper(I) cyanide (9.3 mg, 0.10 mmol), and potassium carbonate (29 mg, 0.21 mmol) in DMF (1.4 mL) was stirred at 60 °C for 12 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc=15:1) to provide **44** (8.7 mg, 53%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.5 Hz), 1.45–1.60 (4H, m), 2.20–2.34 (2H, m), 2.32 (3H, s), 5.83 (1H, d, J=1.5 Hz), 6.79 (1H, d, J=5.5 Hz), 6.95 (1H, br s), 7.05 (1H, dd, J=1.5, 5.5 Hz), 7.13 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.9, 21.1, 23.1, 26.7, 28.7, 80.6, 93.3, 104.2, 117.0, 124.3, 126.3, 136.2, 143.7, 145.0, 152.6, 153.4; IR ($CHCl_3$, cm^{-1}) 1548, 2232, 3009; HRMS m/z (ESI) calcd for $C_{16}H_{17}NNaO$ [(M+Na)$^+$] 262.1202, found. 262.1191.

4.5. Oxidation of the boryl group of *distal*-16Ab (Table 9, entry 3)

*4.5.1. 1-Butyl-7-methyl-1,4-dihydro-1,4-epoxynaphthalen-5-ol **45**.* A round bottom flask was charged with *distal*-**16Ab** (27 mg, 80 μmol) and sodium perborate tetrahydrate (62 mg, 0.40 mmol). THF/H_2O (1:1, 1.0 mL) was added. The reaction mixture was stirred for 3.0 h at room temperature. H_2O was added to the reaction mixture. The reaction mixture was extracted with EtOAc. Aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc=3:1) to provide **45** (16 mg, 85%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.5 Hz), 1.42–1.50 (2H, m), 1.62–1.52 (2H, m), 2.25 (3H, s), 2.17–2.33 (2H, m), 4.71 (1H, s), 5.83 (1H, d, J=2.0 Hz), 6.23 (1H, s), 6.63 (1H, s), 6.75 (1H, d, J=5.5 Hz), 7.03 (1H, dd, J=2.0, 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 21.2, 23.2, 26.8, 29.0, 78.8, 93.2, 114.1, 114.5, 131.8, 137.1, 144.0, 144.1, 148.0, 153.3; IR ($CHCl_3$, cm^{-1}) 1616, 3017; HRMS (FAB$^+$) calcd for $C_{15}H_{18}O_2$ (M$^+$): 230.1307, found: 230.1318.

4.6. General procedure for the ring opening of 1,4-epoxy ring and Suzuki–Miyaura cross-coupling reactions of cycloadducts (16Ab and 42Ad) (Table 10)

A round bottom flask was charged with **16Ab** [or **42Ad** (1.1 equiv)] and *p*-TsOH·H_2O (1.0 equiv) and then evacuated and back-filled with nitrogen. Anhydrous THF (0.05 M) was added via syringe, and the reaction mixture was stirred at room temperature. After 12 h, the second portion of *p*-TsOH·H_2O (1.0 equiv) was added, and the reaction mixture was stirred for another 12 h. The reaction mixture was separated, and the aqueous layer was extracted twice with EtOAc. The combined organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. A suspension of crude

product **46** [or **47** (1.1 equiv)], $Pd_2(dba)_3$ (0.05 equiv), SPhos (0.10 equiv), and K_3PO_4 (3.0 equiv) in toluene (0.20 M) was stirred under ambient conditions for 5–10 min. Aryl iodide (1.0 equiv) was added, and the reaction mixture was heated at 100 °C under an argon atmosphere for 12 h. The reaction mixture was diluted with Et_2O (1.0 mL) and filtered through a pad of Celite, and the filtrated was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to provide the product.

*4.6.1. 4-Butyl-6-methyl-8-phenylnaphthalen-1-ol **48**.* Following the general procedure, a mixture of *distal*-**16Ab** (0.33 g, 0.97 mmol), *p*-TsOH·H_2O (0.19 g, 0.98 mmol) in THF (10 mL) was stirred at room temperature for 12 h. *p*-TsOH·H_2O (0.19 g, 0.98 mmol) was added, and the reaction mixture was stirred for another 12 h. A solution of the crude product **46** (34 mg), $Pd_2(dba)_3$ (3.9 mg, 4.6 μmol), SPhos (3.5 mg, 8.5 μmol), K_3PO_4 (54 mg, 0.25 mmol), and iodobenzene (9.4 μL, 84 μmol) in toluene was stirred at 100 °C for 7.0 h. The crude product was purified by column chromatography (hexane/EtOAc=10:1) to give **48** (22 mg, 94% 2 steps). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.99 (3H, t, J=7.5 Hz), 1.47 (2H, sext, J=7.5 Hz), 1.74 (2H, q, J=7.5 Hz), 2.54 (3H, s), 3.01 (2H, t, J=7.5 Hz), 5.22 (1H, s), 6.76 (1H, d, J=7.5 Hz), 7.06 (1H, br s), 7.22 (1H, d, J=7.5 Hz), 7.46–7.55 (5H, br s), 7.83 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 21.7, 22.9, 33.00, 33.04, 110.4, 119.9, 123.7, 127.1, 128.4, 128.9, 129.4, 130.4, 130.5, 133.8, 134.0, 136.6, 141.7, 151.4; IR ($CHCl_3$, cm^{-1}) 3019, 3514; HRMS *m*/*z* (FAB^+) calcd for $C_{21}H_{23}O$ [$(M+H)^+$] 291.1743, found. 291.1767.

*4.6.2. 5-Butyl-3-methyl-[1,1′-binaphthalen]-8-ol **49**.* Similarly to the preparation of **48**, a mixture of *distal*-**16Ab** (82 mg, 0.24 mmol), *p*-TsOH·H_2O (46 mg, 0.24 mmol) in THF (2.4 mL) was stirred at room temperature for 12 h. *p*-TsOH·H_2O (46 mg, 0.24 mmol) was added, and the reaction mixture was stirred for 3.0 h. A solution of **46** (42 mg), $Pd_2(dba)_3$ (3.7 mg, 4.0 μmol), SPhos (3.3 mg, 8.0 μmol), K_3PO_4 (52 mg, 0.24 mmol), and 1-iodonaphthalene (12 μL, 82 μmol) in toluene was stirred at 100 °C for 2.0 h. The crude product was purified by column chromatography (hexane/EtOAc=10:1) to give **49** (30 mg, 99%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.04 (3H, t, J=7.5 Hz), 1.53 (2H, sext, J=7.5 Hz), 1.80 (2H quint, J=7.5 Hz), 2.57 (3H, s), 3.02–3.12 (2H, m), 5.19 (1H, s), 6.69 (1H, d, J=8.0 Hz), 7.13 (1H, d, J=1.5 Hz), 7.23 (1H, d, J=7.5 Hz), 7.36–7.39 (1H, m), 7.45 (1H, d, J=7.5 Hz), 7.51–7.54 (1H, m), 7.59 (1H, d, J=2.5 Hz), 7.60 (1H, br s), 7.93 (1H, d, J=2.5 Hz), 7.95 (1H, br s), 7.98–8.01 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1, 21.7, 22.9, 33.0, 33.1, 110.2, 121.2, 123.9, 125.2, 126.4, 126.6, 126.9, 127.0, 127.3, 128.2, 129.0, 130.5, 130.8, 132.6, 133.5, 133.8, 134.2, 134.4, 139.0, 151.5; IR ($CHCl_3$, cm^{-1}) 3006, 3510; HRMS *m*/*z* (ESI) calcd for $C_{25}H_{24}NaO$ [$(M+Na)^+$] 363.1719, found. 363.1712.

*4.6.3. tert-Butyl (4-ethyl-6-methyl-8-phenylnaphthalen-1-yl)carbamate **50**.* Similarly to the preparation of **48**, a mixture of *distal*-**42Ad** (24 mg, 59 μmol), *p*-TsOH·H_2O (12 mg, 59 μmol) in THF (1.0 mL) was stirred at room temperature for 3.0 h. *p*-TsOH·H_2O (12 mg, 59 μmol) was added, and the reaction mixture was stirred for 3.0 h to give a crude product **47**. A solution of **47** (21 mg), $Pd_2(dba)_3$ (2.0 mg, 2.2 μmol), SPhos (2.1 mg, 5.1 μmol), K_3PO_4 (33 mg, 0.15 mmol), and iodobenzene (4.8 μL, 43 μmol) in toluene was stirred at 100 °C for 12 h. The crude product was purified by column chromatography (hexane/EtOAc=12:1) to give **50** (13 mg, 82%). A colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (9H, s), 1.38 (3H, t, J=7.5 Hz), 2.53 (3H, s), 3.09 (2H, q, J=7.5 Hz), 6.10 (1H, br s), 7.12 (1H, d, J=1.5 Hz), 7.32 (1H, d, J=7.5 Hz), 7.37–7.48 (5H, m), 7.65 (1H, d, J=7.5 Hz), 7.86 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.1, 21.6, 26.4, 28.1, 28.4, 79.3, 119.8, 123.0, 123.4, 125.4, 127.3, 128.6, 131.3, 131.8, 133.4, 133.8, 136.0, 137.6, 143.8, 152.9; IR ($CHCl_3$, cm^{-1}) 1721, 3009, 3428; HRMS *m*/*z* (ESI) calcd for $C_{24}H_{27}NNaO_2$ [$(M+Na)^+$] 384.1934, found. 384.1953.

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Supplementary data

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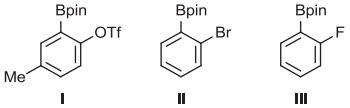
15. The generation of borylbenzyne **11** from the substrates (**I**–**III**) was also examined using LDA. Only **I** gave Diels–Alder adduct **16Ab** in low yield (for detail, see Supplementary data).



I II III

16. Because phenylboronic acids were prone to the adsorption on the silica gel, the flash SiO_2-chromatography purification was conducted after converting the acids into their corresponding pinacol esters, which were in general relatively

stable during the flash chromatography. However, it would be better if it is conducted under slightly acidic conditions (pH 6.5–6.8).
17. The regiochemistries of the products, *distal*-**16Ab** and *proximal*-**16Ab**, were determined by NOESY NMR experiment.
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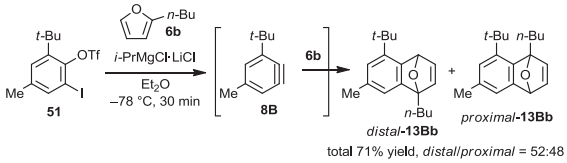
21. The reaction of 3-(*tert*-butyl)benzyne **8B**, generated from **26** under similar reaction conditions, with **6b** gave 52:48 mixture of *distal*- and *proximal*-**13Bb**, which reaffirmed the powerful effect of the boryl group on the regiocontrol of the DA reaction.



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Entry	R		Natural charge	
			C2	C5
1	*t*-Bu	**6a**	0.31	0.09
2	Me	**6c**	0.30	0.09
3	OMe	**6f**	0.63	0.06
4	CO_2Me	**6h**	0.17	0.13
5	Ac	**6i**	0.19	0.13
6	CN	**6j**	0.17	0.13

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