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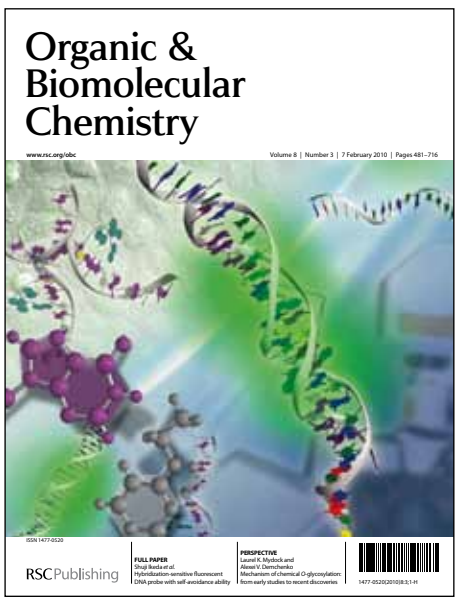

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PAPER

ortho-Selective nucleophilic addition of amines to 3-borylbenzynes: Synthesis of multisubstituted anilines by triple role of boryl group

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Nucleophilic addition of amines to 3-[(dan)boryl]benzynes (dan = 1,8-diaminonaphthalene), generated by a fluoride ion, proceeded with high *ortho*-selectivity to give 2-borylaniline derivatives, under conditions that are tolerant to various functional groups. The (dan)boryl group of the adduct was hydrolyzed into a boronic acid under acidic conditions, which could further serve for various C–C, C–O, C–N, and C–H bond-formation reactions. The overall process provides a promising entry for preparing multisubstituted aniline derivatives.

Introduction

Anilines are abundant in the core structures of natural and/or biologically active compounds,[1] and synthesis of aniline moieties has constantly been drawing attention during the last several decades.[2] In addition to the classical aniline syntheses, which include electrophilic nitration of arenes followed by reduction of the nitro groups[3] and copper-mediated arylation of amines (Ullmann condensation),[4] Buchwald and Hartwig independently developed a highly efficient synthesis of anilines by the palladium-catalyzed cross-coupling reaction of aryl halides (or pseudohalides) and amines.[5] This reaction has become one of the most useful methods for synthesizing various types of aniline derivatives.[6]

On the other hand, benzynes are highly reactive intermediates, and amines react with benzynes to produce anilines.[7,8] Further, the regiochemistry of these reactions with unsymmetrically substituted benzynes has been a longstanding interest. It is known that these reactions predominantly take place at the C1-position of the benzynes that possess a fluorine or an oxygen substituent at the C3-position, which is because the C1-positions of such benzynes are more electrophilic than the C2-positions due to the distortion and polarization caused by these substituents.[8c,9] The benzynes with a sterically bulky substituent at the C3-position also undergo the addition reactions at the C1-position owing to the steric repulsion between the substituent and the incoming amine.[10]

In addition to rare examples of the *ortho*-selective nucleophilic addition of organolithiums to 3-(oxazolin-2-yl)benzyne via the coordination of lithium to oxygen,[11] we recently reported another *ortho*-selective nucleophilic addition of primary amines to 3-(trialkylsilyl)benzynes.[12,13] This is more unique and intriguing because the reactions occurred at the vicinal position of the bulky trialkylsilyl group without any attractive interaction between the silyl group and the nucleophiles, whose regiochemistry is thought to be caused by the electron-donating inductive effect of the silyl substituent. We expected a similar *ortho*-selective nucleophilic addition of amines to 3-borylbenzynes,[14–18] which would provide another useful method for synthesizing various functionalized 2-substituted anilines[19] after the well-known conversion of the boryl group into carbon-, nitrogen-, or oxygen-substituents.[20] In this study, we validate this idea by the fluoride-mediated generation of 3-[(dan)boryl]benzynes **1** (dan = 1,8-diaminonaphthalene) from 2-[(dan)boryl]-6-(trimethylsilyl)phenyl triflates **2**, which upon reaction with amines provide 2-[(dan)boryl]anilines **6** in high yields and excellent *ortho*-selectivities.

Results

At first, we examined the fluoride-mediated generation[21] of 3-[(pin)boryl]benzyne **1A** (pin = pinacol) from 2-[(pin)boryl]-6-(trimethylsilyl)phenyl triflate **2A** as a test case. In the presence of *n*-butylamine **3a**, the reaction of **2A** and CsF proceeded in MeCN at 60 °C to produce a mixture of aniline derivatives.[22] However, the expected borylanilines were not observed at all, and silylanilines (*ortho*- and *meta*-**5Aa**) were instead obtained in 57% total yield (Scheme 1). Some other trials by changing solvents, reaction temperatures, and fluoride sources did not produce any improvement. These results indicated that the fluoride ion exclusively attacked the boron of **2A** to generate 3-silylbenzyne **4A**, with the silyl group remaining intact.[23,24] Next, we synthesized a new benzyne precursor **2B**[25] with dan as the protective group for the boronic acid[26] and used it to prepare the corresponding benzyne followed by nucleophilic amination. We found that the borylanilines (*ortho*- and *meta*-**6Ba**) were obtained under similar reaction conditions, albeit in low yield (26%), and that the silylanilines were not observed. The precursor **2C**, with *N*-methyliminodiacetic acid (MIDA)[27] as the protective group for

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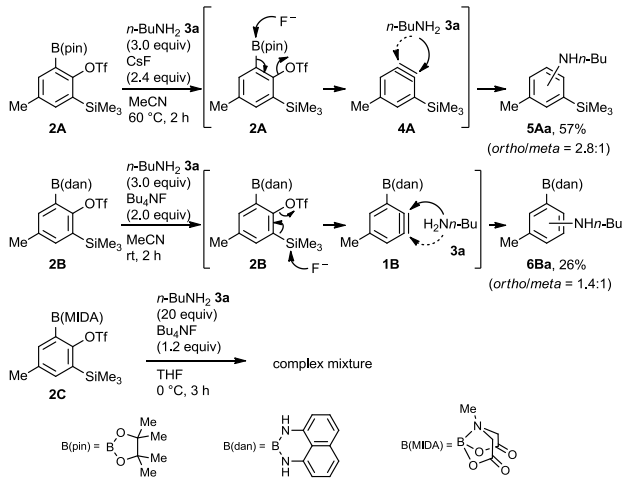
the boronic acid, was another promising candidate; however, a similar reaction of **2C** resulted in the formation of a complex mixture (Scheme 1).

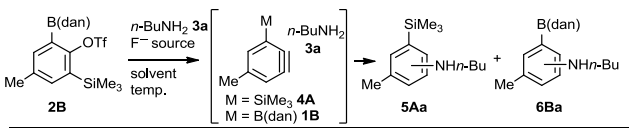


Scheme 1 Fluoride-mediated generation of benzyne (from precursors **2A**–**2C**) followed by nucleophilic amination.

With the potential results of the chemoselective generation of 3-borylbenzyne **1B** and its *ortho*-selective amination in hand, we proceeded to optimize the reaction conditions by varying the fluoride sources, solvents, and temperature (Table 1). A significant amount of silylaniline **5Aa** was generated in less polar solvents (entries 1 and 2). In contrast, *ortho*-**6Ba** was obtained as the major product in polar solvents, such as THF, DMF, NMP, DMPU, and DMSO, although the *ortho*/*meta*-selectivities were moderate (*ortho*/*meta* = 2.4–3.8:1) (entries 4–9). Very interestingly, HMPA dramatically improved both the yield and selectivity (entry 10). After further optimization, it was concluded that the use of CsF and 18-crown-6 (18-c-6) in a 1:1 mixture of THF and HMPA at 0 °C was the best reaction conditions to produce high regioselectivity (*ortho*/*meta* = 9.2:1), product yield (99%), and reproducibility (entry 12). To our surprise, the use of 2,6-lutidine as a solvent reversed the selectivity of this reaction to predominantly produce *meta*-**6Ba** (entry 13).

Under the optimized reaction conditions obtained above, the nucleophilic addition of various amines **3** to 3-[(dan)boryl]benzynes **1**, generated from **2**, were carried out to provide mixtures of *ortho*-**6** and *meta*-**6** (Table 2). The following observations are worth noting: (i) All the reactions preferentially provided *ortho*-**6**, and the total yields were very high (85–99%) in most cases. (ii) The reactions with α-unbranched aliphatic primary amines (**3a**, **3b**, **3c**, and **3f**–**3i**) proceeded with good regioselectivities (*ortho*/*meta* = 9.2–20:1) (entries 1–3, and 6–9). (iii) Even the reactions of α-branched aliphatic primary amines such as *c*-hexylamine **3d** and *t*-butylamine **3e** and those of secondary amines (**3k**–**3m**) predominantly afforded *ortho*-**6**,

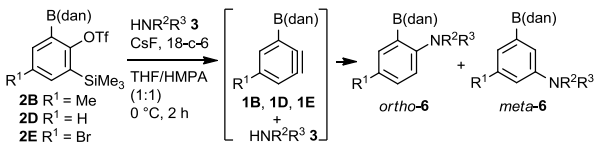
Table 1 Optimization of reaction conditions[a]

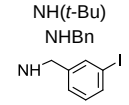
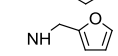
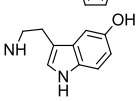
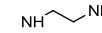
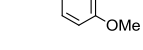


entry	fluoride source	solvent	temp. (°C)	5Aa yield (%)[b]	6Ba *ortho*/*meta*[b]	6Ba yield (%)[b]
1	Bu_4NF	toluene	rt	55	2.0:1	33
2	Bu_4NF	CH_2Cl_2	rt	27	1 :1.4	31
3	Bu_4NF	MeCN	rt	2	1.4:1	26
4	Bu_4NF	THF	rt	4	2.7:1	73
5	Bu_4NF	DMF	rt	0	3.8:1	87
6	KF/18-c-6[c]	DMF	40	0	2.8:1	95
7	KF/18-c-6[c]	NMP	rt	0	2.4:1	92
8	KF/18-c-6[c]	DMPU	rt	0	2.4:1	65
9	KF/18-c-6[c]	DMSO	rt	0	2.4:1	71
10	KF/18-c-6[c]	HMPA	rt	0	10 :1	90[d]
11	KF/18-c-6[c]	THF/HMPA[e]	0	0	9.0:1	96[d]
12	CsF/18-c-6[c]	THF/HMPA[e]	0	0	9.2:1	99[d]
13	CsF/18-c-6[c]	2,6-lutidine	rt	0	1 :2.0	73

[a] Conditions: A mixture of **2B** (1.0 equiv), **3a** (3.0 equiv), a fluoride source (2.0 equiv) in a solvent (0.1 M) was stirred at the given temperature for 2 h. [b] Total yield of **5Aa**, that of **6Ba**, and the *ortho*/*meta* ratio of **6Ba** were based on the ^{1}H NMR analysis of the crude product using 1,4-dimethoxybenzene as the internal standard. [c] 18-crown-6 (18-c-6) (2.0 equiv) was used as an additive. [d] Isolated yield by chromatography on silica gel. [e] A 1:1 mixture of THF/HMPA was used as the solvent. NMP = *N*-methyl-2-pyrrolidinone, DMPU = *N*,*N*-dimethyl propylene urea.

Table 2 Nucleophilic addition of various amines **3** to 3-borylbenzynes **1**, generated from **2**[a]



entry	R^1 (**2**)	NR^2R^3	**3**	**6**	*ortho*/*meta*[b]	yield (%)[c]
1	Me (**2B**)	NH(*n*-$C_{10}H_{21}$)	**3b**	**6Bb**	9.2:1	99
2	H (**2D**)	NH(*n*-Bu)	**3a**	**6Da**	14 :1	99
3	H (**2D**)		**3c**	**6Dc**	>20 :1	87
4	H (**2D**)	NH(*c*-Hex)	**3d**	**6Dd**	10 :1	99
5	H (**2D**)	NH(*t*-Bu)	**3e**	**6De**	2.5:1	94
6	H (**2D**)	NHBn	**3f**	**6Df**	12 :1	97
7	H (**2D**)		**3g**	**6Dg**	10 :1	85[d]
8	H (**2D**)		**3h**	**6Dh**	15 :1	93
9	H (**2D**)		**3i**	**6Di**	13 :1	98
10	H (**2D**)	NHC_6H_4-(4-Me)	**3j**	**6Dj**	2.9:1	86
11	H (**2D**)	NEt_2	**3k**	**6Dk**	1.6:1	>99
12	H (**2D**)		**3l**	**6Dl**	6.7:1	>99
13	H (**2D**)		**3m**	**6Dm**	5.7:1	99
14	H (**2D**)	NHNHBoc	**3n**	**6Dn**	>20 :1	81
15	H (**2D**)		**3o**	**6Do**	>20 :1	76[d]
16	Br (**2E**)	NH(*n*-Bu)	**3a**	**6Ea**	>20 :1	89
17[e]	Br (**2E**)		**3m**	**6Em**	2.2:1	86
18	Br (**2E**)		**3p**	**6Ep**	8.0:1	85

[a] Conditions: A mixture of **2** (1.0 equiv), **3** (3.0 equiv), CsF (2.0 equiv), and 18-c-6 (2.0 equiv) in THF/HMPA (1:1, 0.10 M) was stirred for 2 h at 0 °C. [b] Determined by ^{1}H NMR analysis of a mixture of two regioisomers obtained by short column chromatography on silica gel. [c] Total isolated yield of *ortho*-**6** and *meta*-**6**. [d] Total ^{1}H NMR yield of *ortho*-**6** and *meta*-**6**. [e] In THF/HMPA (1:4, 0.10 M).

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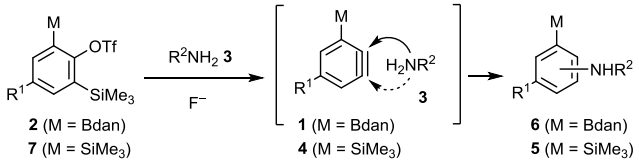
although with lower regioselectivities (*ortho*/*meta* = 1.6–10:1) (entries 4, 5, and 11–13).

From the perspective of synthetic application, the following results present some advantages of this method: (i) In the reaction of furfurylamine **3h**, only *N*-arylfurylamine **6Dh** was obtained, leaving the furyl moiety unreacted, which indicated that the nucleophilic addition was significantly faster than the Diels–Alder reaction[17] (Table 2, entry 8). (ii) A range of functional groups such as bromo, iodo, hydroxyl, *t*-butoxycarbonyl, allyl, furyl, and indolyl groups were perfectly tolerant under these conditions to produce highly functionalized aniline derivatives (**6Dc**, **6Dg**–**6Di**, **6Dn**, **6Ea**, **6Em**, and **6Ep**) (entries 3, 7–9, 14, and 16–18). In particular, the reactions of halogen-containing substrates produced valuable aniline derivatives possessing both boryl and halogen groups, which were hardly available by the transition-metal-catalyzed coupling reaction of multihalogen-containing substrates. (iii) The reaction of unprotected 5-hydroxytryptamine **3i** is of particular interest (entry 9) because the complete arylation of its primary amino group was achieved while two other heteroatom nucleophilic sites remained intact. (iv) The reaction of ethylenediamine **3o** with **1D** showed another important feature of this reaction, viz., the exclusive formation of a mono *N*-arylation product **6Do** while another reactive alkyl amino group remained intact (entry 15). The lower isolated yield was because of the high polarity of **6Do** that made it difficult to isolate.

It should also be noted that the amination reactions of **1** generally exhibited better *ortho*-selectivities than those of 3-(trimethylsilyl)benzynes[12] (Table 3). For example, while the addition of α-unbranched aliphatic primary amines to 3-(trimethylsilyl)benzynes **4** provided mixtures of *ortho*- and *meta*-adducts **5** in 4.1–8.5:1 ratios, similar reactions of **1** gave the corresponding adducts **6** in 9.2–20:1 ratios. The reaction of **4** with *tert*-butylamine **3e** exclusively afforded *meta*-**5e**, whereas that of **1D** with **3e** preferentially produced *ortho*/*meta*-**6De** in a 2.5:1 ratio (Table 2, entry 5 and Table 3). The addition of the aromatic primary amine **3j** to **1D** preferentially provided *N*,*N*-diarylamine *ortho*-**6Dj** with a moderate selectivity (*ortho*/*meta* = 2.9:1) (Table 2, entry 10), whereas a similar reaction of **3j** and **4** provided a 1:1.6 mixture of *ortho*- and *meta*-**5j**.

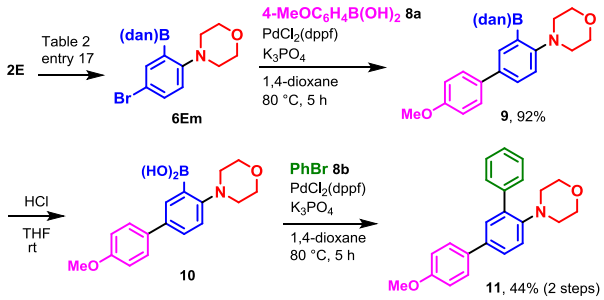
Table 3 Selectivity comparison between borylbezynes **1** and silylbenzynes **4**[a]



M	R^2	*ortho*-**6**/*meta*-**6**		M	R^2	*ortho*-**5**/*meta*-**5**	
Bdan	1° alkyl	9.2–20:1		$SiMe_3$	1° alkyl	4.1–8.5:1	
Bdan	*tert*-Bu (**3e**)	**6De**	2.5:1	$SiMe_3$	*tert*-Bu (**3e**)	**5e**	1:>50
Bdan	tolyl (**3j**)	**6Dj**	2.9:1	$SiMe_3$	tolyl (**3j**)	**5j**	1:1.6

[a]All data were cited from Table 2 and ref 12.

As reported by Suginome et al.,[26] the products (**6Ea**, **6Em**, and **6Ep**), possessing both (dan)boryl and bromo groups, have outstanding potential to install different aryl groups on the starting benzene scaffold **2E** (Scheme 2). Thus, the Suzuki–Miyaura coupling of **6Em** and **8a** provided **9** (92% yield), which was then subjected to the acidic hydrolysis of the (dan)boryl moiety to produce **10**. The second coupling reaction with **8b** under the same reaction conditions produced the 2,4-diarylaniline derivative **11** (44% yield over two steps) (the reaction conditions were not optimized).



Scheme 2 Stepwise Suzuki–Miyaura cross coupling reactions of the nucleophilic adduct **6Em**.

The overall process in this study could be achieved for the first time owing to a triple role of the (dan)boryl group: (i) the chemoselective generation of 3-borylbenzyne, (ii) the regiocontrol for the nucleophilic *ortho*-amination reaction, and (iii) the masked boryl group that can be arbitrarily reactivated to a boronic acid group for further coupling reactions. These results were also attributed to the excellent stability of the (dan)boryl group under various conditions, including benzyne generation, coupling reactions, and silica gel chromatography.

Discussion

In this study, we have found that the solvents have significant effects on the reactions. We think that the solvent affects two steps of the reactions, viz., the benzyne generation and the nucleophilic attack to benzyne, and each effect should be separately discussed. In the first benzyne generation step, the reversible coordination of polar solvents such as DMF, DMSO and HMPA to the boron atom protects the boron against the fluoride-ion attack and makes the fluoride hit the silicon atom instead. On the other hand, in less polar solvents such as toluene and CH_2Cl_2, the fluoride ion preferentially attacked the boron atom to form significant amounts of silylbenzyne **4A** (Table 1, entries 1 and 2), which unambiguously supports the above-mentioned explanation. In the second nucleophilic addition step, the stronger reversible coordination of HMPA to the boron atom makes the borylbenzynes more distorted and polarized. As a result, the yield and the selectivity of these overall reactions became much better in HMPA (Table 1, entry 10). However, we cannot account for the reverse selectivity when using 2,6-lutidine as a solvent.

The possibility of the fluoride ion coordination to the boron atom is another very important issue, and we have concluded that the fluoride ion hardly coordinated to the boron atom based on the following three results: Firstly, the use of 1.5 equivalents of a fluoride source did not change the regioselectivity, but slightly

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lowered the yield, in which a small amount of the starting material was recovered. We have found that the use of two equivalents of the fluoride ion is necessary to obtain the addition products **6** in high yields (almost quantitative in many cases) (Table 2). Secondly, if the excess fluoride ion coordinated to the boron atom of the generated benzyne to form a boron-ate complex (that is 3-[(dan)FB]benzyne), the complex would never get back to the (dan)B group again. The fact that we obtained almost quantitative yields of **6** that possessed the (dan)B group clearly denied the formation of the boron-ate complexes. Thirdly, because the nitrogen generally has a strongly electron-donating effect, the vacant p-orbital of the boron atom should be filled with lone pair electrons of the diaminonaphthalene's nitrogens in some degree.[28] Therefore, a fluoride ion selectively attacked the $SiMe_3$ group in the presence of the B(dan) group at the first benzyne generation step.

Next, we analyzed the origin of the *ortho*-selectivities of 3-[(dan)boryl]benzynes **1** based on theoretical calculations. The structure of **1D**[29] was optimized by the B3LYP/6-31G(d) level,[30] and the internal angles at its C1 and C2 positions were analyzed to evaluate the contribution of distortion energy.[8c,9c] The electron densities of the π orbitals of benzyne located in the same plane with the aromatic ring were also calculated by a natural bond orbital (NBO) method[30] (Figure 1). These two sets of results showed that the C2 position was more electrophilic than the C1 position. Therefore, both the aryne distortion and the electrostatic effect caused by the (dan)boryl group overcame the steric disadvantage of the bulky boryl group, resulting in the preferential nucleophilic attacks at the C2 position.

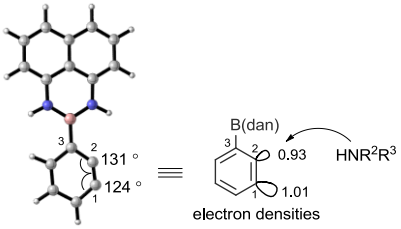

Fig. 1 Internal angles of 3-[(dan)boryl]benzyne **1D** optimized by B3LYP/6-31G(d) and its electron densities analyzed by an NBO method.[30]

Conclusions

In conclusion, highly *ortho*-selective nucleophilic addition of amines to 3-borylbenzynes **1** has been achieved for the first time by using the (dan)boryl group as a multifunctional directing group. The fluoride-mediated benzyne generation under mild conditions enabled excellent tolerance of various reactive functional groups such as bromo, iodo, hydroxyl, *t*-butoxycarbonyl, allyl, furyl, and indolyl groups; thus, the highly functionalized 2-borylaniline derivatives *ortho*-**6** were produced. The adducts possessing both the (dan)boryl and bromo groups serve as useful intermediates for the consecutive Suzuki–Miyaura cross-coupling reactions. The overall process provides a new entry for the synthesis of the multisubstituted aniline derivatives. Further applications of these reactions with other nucleophiles and to the synthesis of biologically active compounds are currently under investigation in our laboratory.

Experimental section

General procedure for nucleophilic addition of amines to 3-borylbenzynes (Table 2)

An oven-dried round-bottomed flask was evacuated and back-filled with argon after cooling to room temperature. The flask was charged with a borylbenzyne precursor **2** (1.0 equiv) and 18-crown-6 (2.0 equiv), and then capped with a rubber septum. Anhydrous THF/HMPA (THF/HMPA = 1:1, 0.10 M) and amine **3** (3.0 equiv) were successively added to the flask via syringes. After the mixture was stirred at 0 ºC for 5 min, CsF (2.0 equiv) was added. The reaction mixture was stirred at 0 ºC for 2 h, quenched by a saturated aqueous NH_4Cl solution and extracted with EtOAc. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and then filtrated. The filtrate was evaporated under reduced pressure. The resultant residue, containing a significant amount of HMPA, was filtered through a short pad of silica gel to afford a mixture of *ortho*-**6** and *meta*-**6**, and the ratio of these two regioisomers was determined by the ^1H NMR analyses. Further purification of the mixture by flash column chromatography on silica gel provided pure *ortho*-**6**.

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Notes and references

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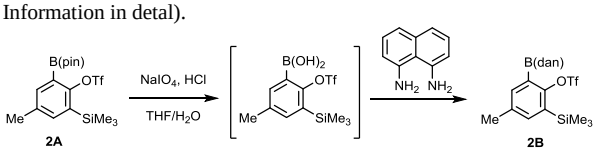

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30 For details, see the Electronic Supplementary Information.