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Regioselective Stepwise Bromination of Boron Dipyrromethene (BODIPY) Dyes

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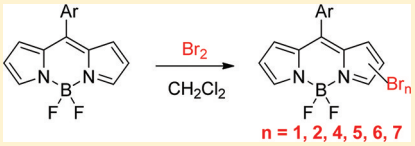
Supporting Information

ABSTRACT: Halogenated BODIPYs are important synthetic precursors and potential sensitizers for photodynamic therapy (PDT). Electrophilic bromination of pyrrolic-unsubstituted BODIPYs using bromine regioselectively generated mono- to heptabromoBODIPYs in a stepwise fashion in good to excellent yields. These resultant bromoBODIPYs were applied for regioselective substitution and Suzuki coupling reaction to generate BODIPYs **4**, **5**, **6**, and **7** in good to excellent yields. According to NMR and X-ray analysis results, the stepwise bromination first takes place at 2,6-, then at 3,5-, and eventually at 1,7-positions, whereas the regioselective substitution occurs first at 3,5- then at 1,7-positions of the chromophore. The spectroscopic properties of these resultant BODIPYs were studied, which shows the potential application of these bromoBODIPYs as sensitizers for PDT.



INTRODUCTION

The wide application of fluorescent dyes has led to the increased research interest in these molecules lately, especially 4,4-difluoro-4-bora-3a,4a-diaza-s-indacenes, also known as BODIPYs.[1−6] BODIPYs have found wide applications in diverse fields, for example, as labeling reagents,[7,8] chemosensors,[9−11] and energy transfer cassettes,[12−15] due to their remarkable properties, including large molar absorption coefficient, sharp fluorescence emissions, high fluorescence quantum yields, and high photophysical stability.

Postmodification[16−23] of some ready-made BODIPY frameworks (such as halogenated BODIPYs **A** and **B** shown in Figure 1) is a convenient avenue for the facile functionalization of BODIPYs. Among those, 3,5-chlorinated BODIPYs (**A** with X = Cl), first developed by Boens et. al[24] via total synthesis, have been used for S_NAr and palladium-catalyzed cross-coupling reactions to generate the corresponding mono- and disubstituted BODIPYs.[25−34] As complementary to Dehaen and Boens's chlorinated BODIPYs, our group[35−37] recently has developed 3-chloro- and 3,5-diiodoBODIPYs from the BF_3 complexation of the corresponding halogenated dipyrromethenes. 2,6-Halogenated BODIPYs **B**[38] are potential sensitizers for photodynamic therapy (PDT) using the heavy atom effect of these halogen atoms[39−45] and have also found wide applications in the construction of many interesting molecules,[46−52] including long wavelength fluorescent dyes. However, it is hard to control the halogen regiochemistry in these halogenated BODIPYs. It is achieved either through the halogenation of the key synthetic precursor of BODIPY (dipyrromethanes) during the course of BODIPY total synthesis, or through the blocking effects of 1,3,5,7-tetraalkyl-substituents. No direct regioselective halogenation on BODIPY has been achieved until the recent disclosure of tetra- and hexabromoBODIPYs by Churchill and co-workers[53] and of 2,6-dibromoBODIPYs by Shinokubo and co-workers.[54] The first case is achieved from the bromination of *meso*-thienyl BODIPY using bromine, and the second one is obtained using *N*-bromosuccinimide (NBS) at −78 °C. Therefore, the regioselective halogenation of pyrrolic-unsubstituted BODIPYs like **1a** (Scheme 1) remains a challenge.

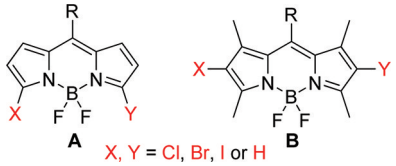


Figure 1. Chemical structures of halogenated BODIPYs **A** and **B**.

Inspired by recent reports of the iridium-catalyzed regioselective *β*-borylation of BODIPY **1a** by Osuka[55] and regioselective nucleophilic substitution of BODIPY **1a** by Dehaen and Boens,[56,57] respectively, herein we report the preparation of mono- to heptabromoBODIPYs from the regioselective stepwise bromination of pyrrolic-unsubstituted BODIPYs **1** using bromine and the subsequent application of these resultant bromoBODIPYs for the regioselective nucleophilic substitution and Suzuki coupling reactions. The stepwise bromination was achieved through the variation of the amount of bromine and the reaction time. As shown by NMR and X-ray analysis results, this stepwise bromination first took place at 2,6-, then at 3,5-, and eventually at 1,7-positions, whereas the regioselective nucleophilic substitution occurred first at 3,5- then at 1,7-positions of the chromophore.

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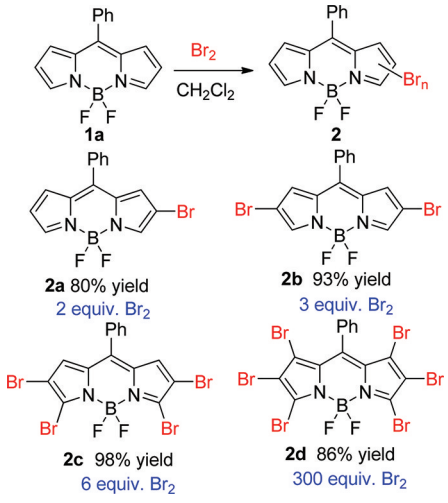
Scheme 1. Syntheses of BODIPYs 2a−d



RESULTS AND DISCUSSION

Synthesis. As an electrophilic substitution reaction, bromination would prefer to occur at the least positively charged positions of the BODIPY core. According to the mesomeric structures[1] of the BODIPY core, 2,6-(*β*-)positions bear the least positive charge. Therefore, they should be most susceptible to electrophilic attack. Thus 2- or 2,6-brominated BODIPYs would be the major products by carefully controlling the amount of bromine. Treatment of BODIPY **1a** with 1 equiv of bromine (dropwise addition) in dichloromethane at room temperature gave mono bromoBODIPY **2a**. The monobromination occurred exclusively at the 2,6-position. No other monobrominated BODIPY was obtained under this reaction condition. Increasing the amount of bromine up to 2 equiv still gave BODIPY **2a** as the major product (Scheme 1). When the amount of bromine was increased to 3 equiv, dibromoBODIPY **2b** became the major product with a 93% isolated yield. Only negligible amount of **2a** or other brominated products were obtained. The assignment of bromine regiochemistry in BODIPYs **2a** and **2b** was based on ^{1}H NMR results. Hydrogens at different pyrrolic positions on BODIPY core show different chemical shifts on the ^{1}H NMR spectra, with the largest chemical shift for 3,5-positional hydrogens and the smallest chemical shift for 2,6-positional ones, as shown in a recent report.[58] The comparison of the ^{1}H NMR spectra before and after the bromination reaction clearly showed the disappearance of 2,6-protons on the BODIPY core. Thus, the bromine(s) were present at 2- and 2,6-positions for BODIPYs **2a** and **2b**, respectively.

Further increasing the amount of bromine to 6 equiv resulted only in tetrabromoBODIPY **2c** in a 98% isolated yield. As shown in the X-ray structure (Figure 2), the four bromine-

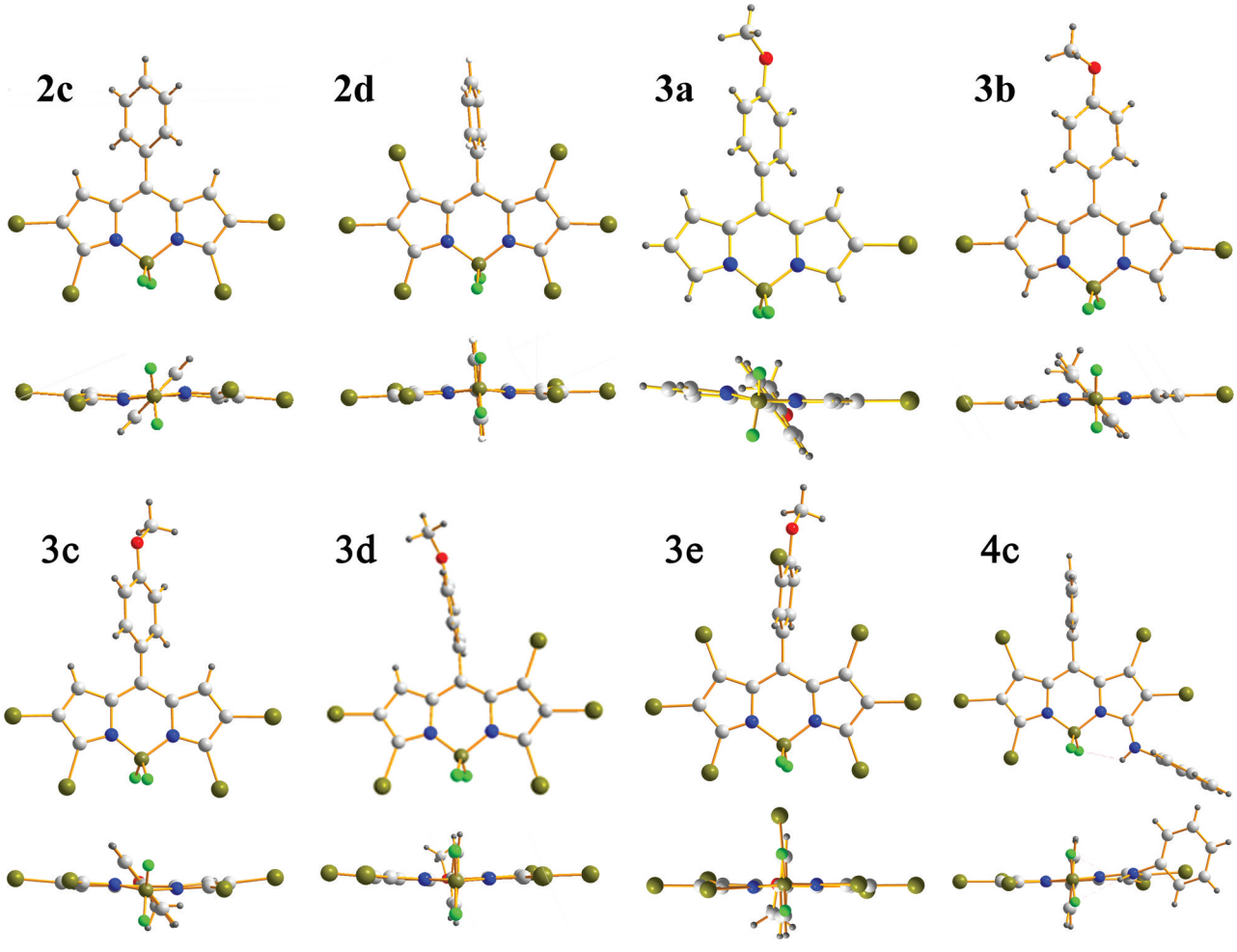


Figure 2. X-ray structures of BODIPYs **2c,d**, **3a−e**, and **4c**.

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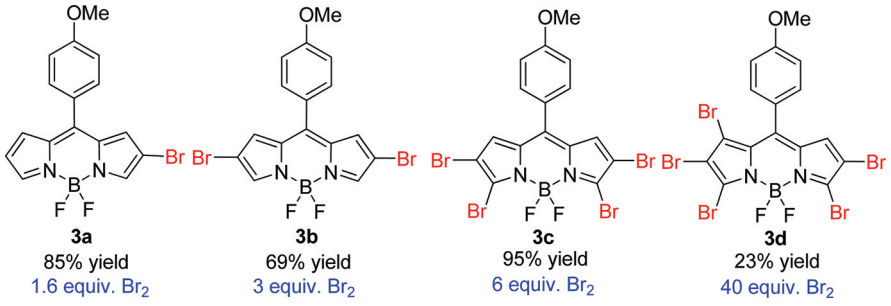


Figure 3. Chemical structures and isolated yields of bromoBODIPYs **3a–d**.

substituents were present at the 2,3,5- and 6-positions of the BODIPY core. Although the formation of tribromoBODIPY could be detected on TLC during the reaction process, it was difficult to isolate in a pure form because of the similar polarities of these bromoBODIPYs. In addition, because of the similar reactivity between 3- and 5-positions of the BODIPY core, we were unable to get it as a major product.

The further bromination at 1,7-positions of BODIPY **1a** required a large excess amount (300 equiv) of bromine and gave hexabromoBODIPY **2d** in an 86% isolated yield. The regiochemistry of bromine was confirmed by X-ray analysis as shown in Figure 2. The requirement of a large excess amount of bromine indicates that 1,7-positions are the least reactive sites toward electrophilic substitution reaction. This may be attributed to both the electronic and the steric hindrance effects: among the six pyrrolic positions, these two positions bear the most positive charge and have a *meso*-substituent in their adjacent position. During the course of the reaction, the formation of pentabromoBODIPY was detected on TLC and confirmed by mass spectra (MALDI-TOF) with a $[M - F]^+$ peak at 642.3 (calcd. 642.3). Because of the similar reactivity between 1- and 7-positions, we were unable to get the pentabromoBODIPY as the major product. The attempt to isolate it in a pure form also failed because of the close polarity of these bromoBODIPYs. Our experiment showed that these bromoBODIPYs were formed in a stepwise manner and that the bromination first occurred at the 2,6- instead of the 3,5-positions proposed by the literature.[53]

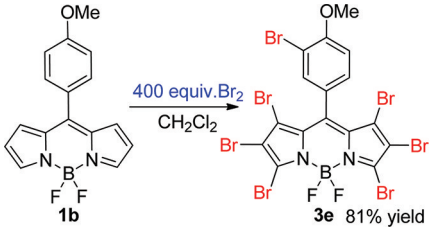
That the bromination occurs in a stepwise manner was consistent with ^{1}H NMR results, in which there is a stepwise disappearance of pyrrolic protons in the order of 2,6-, 3,5-, and 1,7-protons. Interestingly, our stepwise bromination occurs in a similar order to that of Knoevenagel condensations[18,22] on 1,3,5,7-tetramethylBODIPYs using aromatic aldehydes (first at 3,5- then at 1,7-positional methyl-substituents).

Although the electronic effect on pyrrolic positions of the BODIPY core plays a crucial role, solvent is also important in this regioselective stepwise bromination reaction. Among the solvents studied, dichloromethane gave the best result. Carbon tetrachloride is a poor solvent for this reaction because it requires longer reaction time and gives poor regioselectivity, especially for the generation of mono- and dibromoBODIPYs. For example, in order to generate the desired tetra- and hexabromoBODIPYs **2c** and **2d** in a comparative yield to that in dichloromethane, a longer reaction time and larger amount of bromine were required. Also, in the preparation of mono- and dibromoBODIPYs **2a** and **2b**, it gave a poor selectivity, which made it difficult to get them in a pure form. Other common organic solvents, such as *N*,*N*-dimethylmethanamide, carbon disulfide, and tetrahydrofuran, were also not suitable for this reaction because of the poor solubility of BODIPYs in these solvents.

This stepwise bromination reaction was further applied to *meso*-(4-methoxyphenyl) BODIPY **1b**, and gave a similarly high regioselectivity. In comparison with *meso*-phenyl BODIPY **1a**, BODIPY **1b** showed an enhanced reactivity in this regioselective stepwise bromination reaction and generally required a shorter reaction time. This may be attributed to the higher electron density in the BODIPY core of BODIPY **1b** due to the existence of methoxy-substituent at the *meso*-aryl position. By varying the amount of bromine, the desired mono-, di-, and tetrabromoBODIPYs **3a–c** were obtained in good to excellent yields (Figure 3). The structures of these bromoBODIPYs were confirmed by NMR and X-ray analysis results (Figure 2). The disappearance of the proton signals for BODIPYs **3a** and **3b** followed a similar order to that of BODIPYs **2a** and **2b**, which supports our previous assignment of the bromine regiochemistry in BODIPYs **2a** and **2b** based on ^{1}H NMR results.

Unlike that of the *meso*-phenyl BODIPY **1a**, at varying amounts of bromine, *meso*-(4-methoxyphenyl)BODIPY **1b** failed to generate the desired hexabromoBODIPY. With 40 equiv of bromine, tetrabromoBODIPY **3c** was still obtained as the major product plus pentabromoBODIPY **3d** (Figure 3), which was obtained in a 23% isolated yield. Further increasing the amount of bromine leads to the yield decrease of **3c** and increase of **3d** and to the appearance of heptabromoBODIPY **3e**. However, it is difficult to isolate **3d** in pure form because of the similar polarity of **3d** and **3e**. When the amount of bromine was increased to 400 equiv, only **3e** was obtained in an 81% yield (Scheme 2). On the other hand, Lakshmi and Ravikanth

Scheme 2. Synthesis of HeptabromoBODIPY 3e



recently have disclosed the preparation of the corresponding hexabromoBODIPY in 24% yield via the BF_3 complexation of hexabromodipyrromethene, which was generated through NBS bromination of suitable dipyrromethane in THF and the subsequent oxidation with DDQ.[59] The structures of BODIPYs **3d** and **3e** were confirmed by NMR and X-ray analysis results (Figure 2). *meso*-Aryl groups in BODIPYs **3d** and **3e** are nearly

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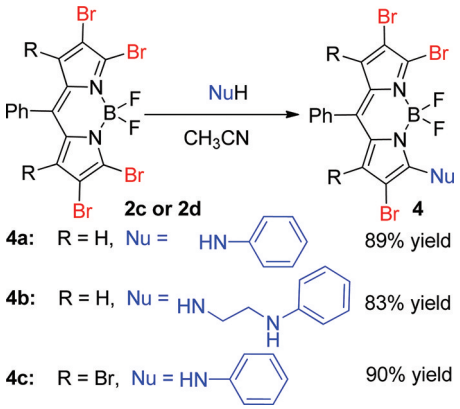
perpendicular to the planes of the BODIPY core (87° for BODIPY **3d** and 90° for BODIPY **3e**), consistent with that of the hexabromoBODIPY (88°) reported in the literature.[59]

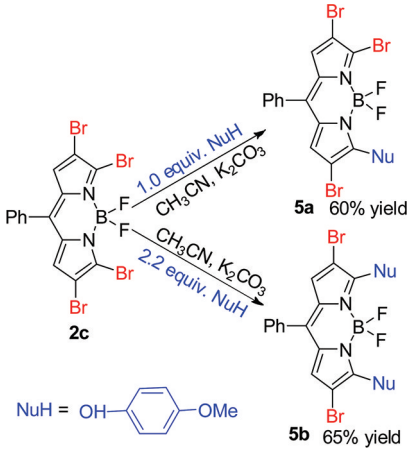
Nucleophilic Substitution and Suzuki Coupling of BromoBODIPYs. S_NAr reactions on 3-chloro- or 3,5-dichloroBODIPYs **A** have been used as an efficient method for the functionalization of the BODIPY core with various functionalities for various applications. With these bromoBODIPYs in hand, we then studied their applications in the nucleophilic substitution reactions. Our bromoBODIPYs **2c** and **2d** showed a similar reactivity to that of 3,5-dihalogenated BODIPYs **A**[26] in this nucleophilic substitution reaction. As shown in Schemes 3 and 4, treatment of tetra- and hexabromoBODIPYs **2c** and **2d** with various nucleophiles smoothly generated BODIPYs **4** and **5** in good yields under mild reaction conditions.

Similar to that of the 3,5-positions in 3,5-dihalogenated BODIPY dyes, the electron density at 1,7-positions are rather poor for hexabromoBODIPY **2d**. Thus, we rationalized that 1,7-positions would show similar reactivity to that for 3,5-positions. However, all attempts to substitute 1,7-positional bromines of BODIPYs **2d** failed, even using a large excess amount of oxygen and nitrogen nucleophiles. In contrast, a strongly nucleophilic thiolate anion was able to participate in this 1,7-disubstitution reaction with hexabormoBODIPY **2d** to generate the corresponding tetrathioether **6b** in excellent yield (Scheme 5). Our result is consistent with a recent report of the disubstitution of 1,7-dichloroBODIPY by Dehaen and Boens, in which the authors attributed this lowering of the reactivity of the 1,7-compared to the 3,5-positions to their smaller HOMO coefficients.[60]

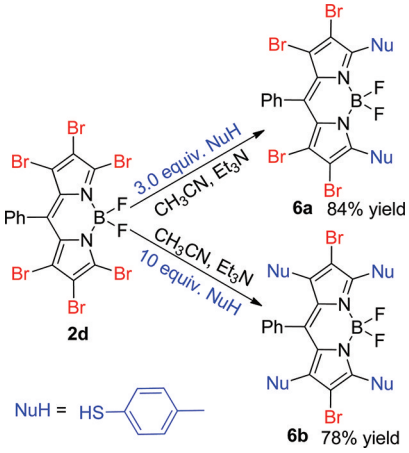
Scheme 3. Syntheses of BODIPYs 4a–c



Scheme 4. Syntheses of BODIPYs 5a–b



Scheme 5. Syntheses of BODIPYs 6a–b



By carefully controlling the amount of thiol nucleophile and the reaction time, we were also able to synthesize the corresponding 3,5-disubstituted product **6a** in high yield. On the other hand, all attempts to introduce substitutions at 2,6-positions of BODIPYs **2c** and **2d** failed, even using a large excess amount of thiol nucleophilies with extended reaction time. Substitution positions for BODIPYs **4c**, **6a**, and **6b** were confirmed by X-ray analysis results (Figures 2 and 4), whereas substitution positions for BODIPYs **4a**, **4b**, **5a**, and **5b** were based on the ^{1}H NMR results in light of X-ray structures for these mono-, di-, and tetrasubstitutedBODIPYs **4c**, **6a**, and **6b**.

TetrabromoBODIPY **2c** was used as an example to study the performance of our bromoBODIPYs in Suzuki coupling reaction. BODIPY **2c** showed a similarly excellent reactivity in Suzuki coupling reaction in comparison to that of hexabromoBODIPY reported in the literature.[59] This Pd-catalyzed cross-coupling reaction of tetrabromoBODIPY **2c** with benzene boronic acid was proceeded in refluxing toluene using $Pd(PPh_3)_4$ as a catalyst in the presence of aqueous Na_2CO_3, from which tetra-coupling BODIPY **7** was generated in high yield (Scheme 6). In contrast to that of nucleophilic substitution reactions, the 2,6-positions of BODIPY **2c** showed a good reactivity in this Pd-catalyzed reaction.

X-ray Structure Analysis. Crystals suitable for X-ray analysis were obtained via slow diffusion of hexane into dichloromethane solutions of bromoBODIPYs under atmospheric pressure. Most of these BODIPYs (Figures 2 and 4) show an almost planar structure for the BODIPY core (the central six-membered ring with two adjacent five-membered rings). The plane defined by F–B–F atoms for these BODIPY molecules is perpendicular to that of BODIPY core as usual. The B–N distance for these BODIPYs is within 1.54–1.60 Å, which indicates the usual delocalization of the positive charge.

The average dihedral angles between *meso*-aryl-substituents and the BODIPY core are 45°, 51°, 50°, and 51° for BODIPYs **2c** and **3a–c**, respectively. In contrast, larger dihedral angles are observed for BODIPYs **2d** (85°), **3d** (87°), **3e** (90°), **4c** (84°), **6a** (77°), and **6b** (76°). This may be attributed to the steric hindrance effect from 1,7-dibromo-substituents of the BODIPY

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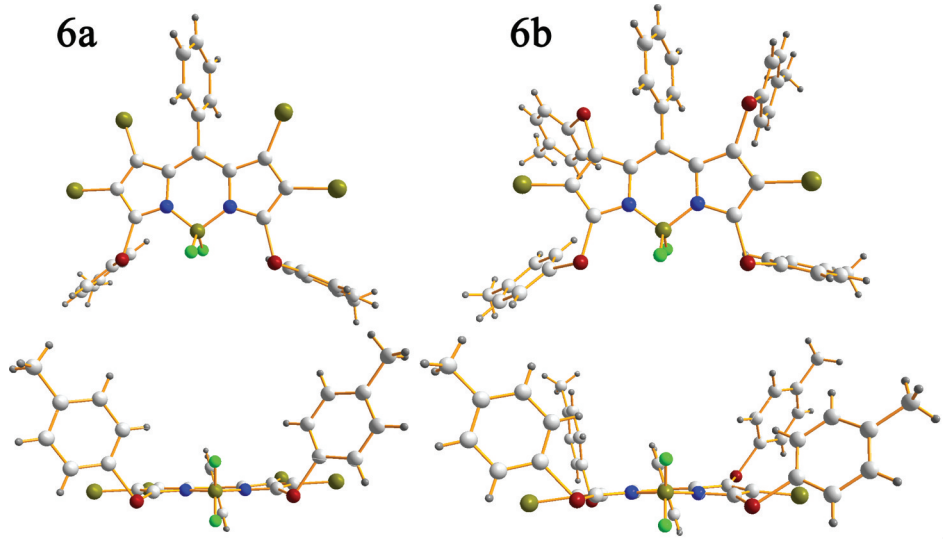
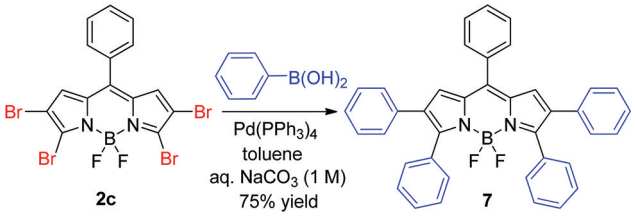


Figure 4. X-ray structures of BODIPYs **6a** and **6b**.

Scheme 6. Synthesis of BODIPY 7 via Suzuki Coupling Reaction



core. Interestingly, in BODIPY **4c**, the intermolecular hydrogen bonding between two F atoms and the NH proton (2.42 and 2.53 Å) makes the aniline ring almost perpendicular to the BODIPY core, with a dihedral angle of 78°.

In the solid state, most of these bromoBODIPYs form multiple C−H···F intermolecular hydrogen bonds due to the strong electron negativity of the F atom.[61−63] Multiple intermolecular hydrogen bonds between F atoms and various hydrogen atoms (phenyl, pyrrolic, and methyl hydrogens) are formed with the H···F hydrogen bond distance in the range of 2.31−2.77 Å (Supporting Information, Figures S1−S10).

This strong intermolecular hydrogen bonding helps the establishment of the crystal packing structure and leads to the formation of various interesting hydrogen bonding networks (Supporting Information, Figures S1−S10). In these crystal packing structures, most of bromoBODIPYs are nearly parallel to each other in a head-to-tail orientation except BODIPYs **3a** and **4c** as shown in Figure 5, which show unusual partially parallel packing in a head-to-head orientation.

Photophysical Properties. The photophysical properties of these resultant BODIPYs are summarized in Table 1. Most of BODIPY analogues showed strong absorption bands at 530 ± 30 nm and weaker absorption bands at around 350 nm, whereas longer wavelength absorption and emission were observed for BODIPYs **6a**, **6b**, and **7**. In comparison to the starting BODIPYs, the installation of bromo-substituent(s) onto the BODIPY core lead to an up to 56 nm red-shift of the absorption maximum and an up to 52 nm red-shift of the emission maximum as shown in Figure 5, similar to those reported bromoBODIPYs.[26,53,59,60]

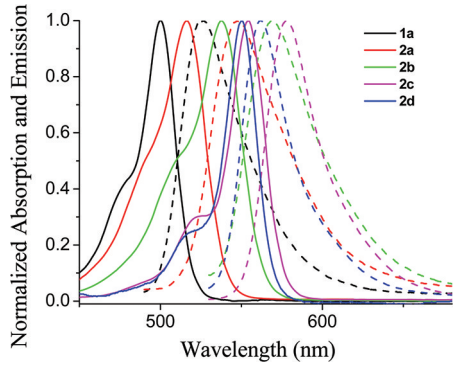


Figure 5. Normalized absorption (solid lines) and emission (dashed lines) spectra of BODIPYs **1a** (black), **2a** (red), **2b** (green), **2c** (pink), and **2d** (blue) in dichloromethane.

Similar to literature results,[24−26,30,31,60,64] the installation of new substituents on the BODIPY core greatly affects the spectroscopic characteristics of the chromophore. Among those, oxygen and nitrogen nucleophiles cause an up to 53 nm blue-shift of the absorption with little effect on the emission spectra. In addition, nitrogen nucleophiles generally gave broad spectra. In contrast, thiol nucleophile shows an up to 74 and 72 nm red-shift of the absorption and emission spectra, respectively. Interestingly, the installation of benzene rings on the BODIPY core in BODIPY **7** not only results in a 30 and 50 nm red-shift of the absorption and emission spectra respectively, but also causes a restore of fluorescence of the chromophore.

Consistent with the literature,[65,66] BODIPYs **1a** and **1b** gave low fluorescent quantum yields. These low emission yields found in these two aryl-substituted BODIPYs bearing no internal steric hindrance may be attributed to a facile S_1-excited-state nonradiative decay channel that is restricted when internal steric constraints are imposed or in the absence of a *meso*-aryl-substituent. On the other hand, the low fluorescence quantum yields of bromoBODIPYs **2**−**5** could be partially attributed to the heavy atom effect, which facilitates the $S_1 \rightarrow T_1$ intersystem crossing process. This heavy atom effect indicates the potential application of these resultant bromoBODIPYs as sensitizers for PDT.[39−45]

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Table 1. Photophysical Properties of BODIPYs 1−7 in Dichloromethane at Room Temperature

					Stokes shift	
BODIPY	λ_{max} (nm)	log ε_{max}	λ_{em} (nm)	Φ^a	(cm^{-1})	(nm)
1a	500	4.52	527	0.03	1025	27
2a	516	4.53	547	0.08	1098	31
2b	538	4.14	569	0.08	1013	31
2c	554	4.99	578	0.03	750	24
2d	551	4.83	562	0.13	355	11
1b	498	4.68	521	0.05	886	23
3a	514	4.61	542	0.10	1005	28
3b	533	4.92	562	0.07	968	29
3c	550	5.08	572	0.13	699	22
3d	551	5.00	573	0.03	697	22
3e	554	4.52	567	0.04	414	13
4a	534	4.53	580	0.01	1485	46
4b	501	4.53	565	0.02	2261	64
4c	534	4.79	561	0.02	901	27
5a	549	4.94	573	0.02	763	24
5b	549	5.01	576	0.02	854	27
6a	606	4.83	634	0.001	729	28
6b	625	4.47	630	0.003	127	5
7	584	4.77	628	0.40	1200	44

[a]The fluorescence quantum yields (Φ) were calculated using Rhodamine B in anhydrous ethanol (Φ = 0.49) for **2b−d**, **3b−e**, **5a,b**, and **7**; fluorescein in 0.1 N NaOH aqueous solution (Φ = 0.90) for **1a,b**, **2a**, **3a**, and **4a−c**; or cresyl violet perchlorate in anhydrous methanol (Φ = 0.54) for **6a,b** as the standard.

To demonstrate their potential application as sensitizers for PDT, a photooxidation study was performed for bromoBODIPYs **2c** and **2d** using methylene blue as a comparative reference.[44] This was achieved by monitoring the light-induced degradation of 1,3-diphenylisobenzofuran (DPBF) with reactive oxygen species (ROS) generated by sensitizers (bromoBODIPYs **2c** and **2d** or methylene blue). Following a literature procedure,[67] the toluene solution of each of these sensitizers (1×10^{-7} M) and DPBF (initial concentration of 5×10^{-5} M) was irradiated, and the disappearance of the absorbance band of DPBF at 415 nm over a period of time was recorded. The comparison of DPBF degradation profiles of these sensitizers clearly shows that bromoBODIPYs **2c** and **2d** can efficiently generate ROS with a DPBF degradation profile comparable to that of methylene blue (Supporting Information, Figure S30).

CONCLUSIONS

In summary, we have developed a highly regioselective stepwise electrophilic bromination of BODIPYs, from which a series of mono- to heptabromoBODIPYs have been prepared in good to excellent yields. These resultant bromoBODIPYs have been applied for further functionalization via nucleophilic substitution and Suzuki coupling reactions. The regiochemistry has been confirmed by NMR and X-ray analysis results. This regioselective stepwise bromination and its applications for the regioselectively nucleophilic substitution reaction presented in this work provide another dimension for the regioselective functionalization of BODIPY derivatives.

EXPERIMENTAL SECTION

General Methods. Reagents were purchased as reagent-grade and used without further purification unless otherwise stated. Solvents were used as received from commercial suppliers unless noted otherwise. All reactions were performed in oven-dried or flame-dried glassware unless otherwise stated and were monitored by TLC using 0.25 mm silica gel plates with UV indicator (60F-254). ^{1}H and ^{13}C NMR were obtained on a 300 MHz NMR spectrometer at room temperature. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm for ^{1}H and 77 ppm for ^{13}C) or to internal TMS (0 ppm for ^{1}H). High-resolution mass spectra were obtained using EI-TOF in positive mode. MALDI-TOF mass spectra were obtained in positive mode using cyano-4-hydroxycinnamic acid as matrix.

UV−vis absorption spectra and fluorescence emission spectra were recorded on a commercial spectrophotometer (190−1100 nm scan range). The slit width was set at 2.5 nm for excitation and 5.0 nm for emission. Relative quantum efficiencies of fluorescence of BODIPY derivatives were obtained by comparing the areas under the corrected emission spectrum of the test sample with fluorescein (0.95 in 0.1 M NaOH aqueous solution) and Rhodamin B (0.49 in EtOH),[68] respectively. Non-degassed, spectroscopic-grade solvents and a 10 mm quartz cuvette were used. Dilute solutions ($0.01 < A < 0.05$) were used to minimize the reabsorption effects. Quantum yields were determined using the following equation:[69]

$$\Phi_X = \Phi_S(I_X/I_S)(A_S/A_X)(n_X/n_S)^2$$

where Φ_S stands for the reported quantum yield of the standard, I stands for the integrated emission spectra, A stands for the absorbance at the excitation wavelength, and n stands for the refractive index of the solvent being used ($n = 1$ when the same solvent was used for both the test sample and the standard). X subscript stands for the test sample, and S subscript stands for the standard.

Crystals of BODIPYs **2c−d**, **3a−e**, **4c**, and **6a−b** suitable for X-ray analysis were obtained by slow diffusion of hexane into their dichloromethane solutions. The vial containing this solution was placed, loosely capped, to promote the crystallization upon hexane diffusion. The structure was solved by the direct method using the SHELXS-974 program and refined by the least-squares method on F^2, SHELXL-97,[70] incorporated in SHELXTL V5.10.[71]

Syntheses and Characterizations of Compounds. *BODIPY **2a**.* To BODIPY **1a** (29 mg, 0.11 mmol) in 40 mL of dry CH_2Cl_2 was slowly added liquid bromine (13 μL, 0.24 mmol) in dry CH_2Cl_2 (10 mL) over a period of 6 h. This reaction was tracked by TLC. The reaction mixture was washed with an aqueous solution of sodium thiosulfate. Organic layers were combined, extracted by CH_2Cl_2, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (6:1, v/v) as eluent, from which the desired product **2a** was obtained as a red solid in 80% yield (30 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.80 (s, 1H), 7.56 (s, 5H), 7.02 (s, 1H), 6.89 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 146.2, 144.1, 142.2, 135.4, 134.3, 133.2, 131.1, 130.4, 130.3, 128.6, 119.6, 105.9; HRMS (EI) Calcd. for $C_{15}H_{10}B^{79}BrF_2N_2$ [M^+] 346.0088, found 346.0094; HRMS (EI) Calcd. For $C_{15}H_{10}B^{81}BrF_2N_2$ [M^+] 348.0068, found 348.0067.

*BODIPY **2b**.* To BODIPY **1a** (30 mg, 0.11 mmol) in 40 mL of dry CH_2Cl_2 was added dropwise liquid bromine (18 μL, 0.34 mmol) in CH_2Cl_2 (5 mL) over a period of 1 h. The mixture was left stirring for an additional 2 h, washed with an aqueous solution of sodium thiosulfate, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (7:1, v/v) as eluent, from which the desired product **2b** was obtained as red solid in 93% yield (44 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.64−7.53 (m, 5H), 6.96 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 144.2, 134.6, 132.8, 131.7, 131.5, 130.3, 128.8, 107.2; HRMS (EI) Calcd. for $C_{15}H_9B^{79}Br_2F_2N_2$ [M^+] 423.9294, found 423.9189; HRMS (EI) Calcd. for $C_{15}H_9B^{81}Br_2F_2N_2$ [M^+] 427.9153, found 427.9117.

*BODIPY **2c**.* To BODIPY **1a** (27 mg, 0.1 mmol) in 16 mL of dry CH_2Cl_2 was added liquid bromine (35 μL, 0.6 mmol) in CH_2Cl_2 (4 mL). The mixture was left stirring for 2 h at room temperature, washed with an aqueous solution of sodium thiosulfate, and extracted

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by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using CH_2Cl_2 as eluent, from which the desired product **2c** was obtained as red solid in 98% yield (57 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64−7.47 (m, 5H), 6.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 135.1, 134.7, 131.6, 131.5, 131.4, 130.3, 128.9, 112.0; MALDI-TOF Calcd. for $C_{15}H_7BBr_4F_2N_2$ [M^+] 583.73, found 583.43. Anal. Calcd. for $C_{15}H_7BBr_4F_2N_2$: C, 30.87; H, 1.21; N, 4.80. Found: C, 30.62; H, 1.31; N, 4.81.

BODIPY ***2d***. To BODIPY **1a** (31 mg, 0.11 mmol) in 16 mL of dry CH_2Cl_2 was added liquid bromine (2 mL, 36 mmol) in CH_2Cl_2 (4 mL). The mixture was left stirring for 2 h at room temperature, washed with an aqueous solution of sodium hydroxide, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using CH_2Cl_2 as eluent, from which the desired product **2d** was obtained as red solid in 86% yield (73 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (br, 3H), 7.26 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 135.2, 131.4, 130.5, 129.6, 129.5, 128.5, 123.9, 117.7; MALDI-TOF Calcd. for $C_{15}H_5BBr_6FN_2$ [$M - F$]$^+$ 720.56, found 720.24. Anal. Calcd. for $C_{15}H_5BBr_6F_2N_2$: C, 24.30; H, 0.68; N, 3.78. Found: C, 24.03; H, 0.74; N, 4.01.

BODIPY ***3a***. To BODIPY **1b** (31 mg, 0.10 mmol) in 40 mL of dry CH_2Cl_2 was slowly added liquid bromine (9 μL, 165 μmol) in dry CH_2Cl_2 (6 mL) over a period of 4 h at 0 °C. TLC was used to track this reaction. The mixture was washed with an aqueous solution of sodium thiosulfate and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (7:1, v/v) as eluent, from which the desired product **3a** was obtained as a red solid in 85% yield (33 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.77 (s, 1H), 7.54 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.4 Hz, 3H), 6.93 (s, 1H), 6.61 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 146.2, 144.3, 140.4, 134.2, 133.2, 131.9, 131.5, 129.1, 124.8, 118.3, 113.3, 104.7, 54.6; MALDI-TOF Calcd. for $C_{16}H_{12}BBrF_2N_2O$ [M^+] 378.01, found 377.97. Anal. Calcd. for $C_{16}H_{12}BBrF_2N_2O$: C, 50.97; H, 3.21; N, 7.43. Found: C, 51.08; H, 3.04; N, 7.17.

BODIPY ***3b***. To BODIPY **1b** (33 mg, 0.11 mmol) in 50 mL of dry CH_2Cl_2 was added dropwise liquid bromine (17 μL, 325 μmol) in CH_2Cl_2 (6 mL) over a period of 2 h at 0 °C. The mixture was left stirring until most of the starting material had been converted to the desired product, washed with an aqueous solution of sodium thiosulfate, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (7:1, v/v) as eluent, from which the desired product **3b** was obtained as metallic brown solid in 69% yield (35 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.7 Hz, 2H), 6.99 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 147.1, 143.4, 134.5, 132.6, 131.5, 125.4, 114.5, 106.9, 54.7; MALDI-TOF Calcd. for $C_{16}H_{11}BBr_2F_2N_2O$ [M^+] 455.93, found 455.79. Anal. Calcd. for $C_{16}H_{11}BBr_2F_2N_2O$: C, 42.15; H, 2.43; N, 6.14. Found: C, 41.96; H, 2.28; N, 6.04.

BODIPY ***3c***. To BODIPY **1b** (31 mg, 0.10 mmol) in 16 mL of dry CH_2Cl_2 was added liquid bromine (37 μL, 0.63 mmol) in CH_2Cl_2 (4 mL). The mixture was left stirring for 1.5 h at room temperature, washed with an aqueous solution of sodium thiosulfate, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (2:1, v/v) as eluent, from which the desired product **3c** was obtained as red solid in 95% yield (60 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 6.95 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 142.0, 133.7, 133.1, 131.3, 130.4, 123.1, 113.6, 110.7, 54.6; MALDI-TOF Calcd. for $C_{16}H_9BBr_4F_2N_2O$ [M^+] 613.75, found 613.56. Anal. Calcd. for $C_{16}H_9BBr_4F_2N_2O$: C, 31.31; H, 1.48; N, 4.56. Found: C, 31.56; H, 1.57; N, 4.73.

BODIPY ***3d***. To BODIPY **1b** (31 mg, 0.10 mmol) in 16 mL of dry CH_2Cl_2 was added liquid bromine (242 μL, 4.1 mmol) in CH_2Cl_2 (4 mL). The mixture was left stirring at room temperature for 4.5 h, washed with an aqueous solution of sodium thiosulfate, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (8:1, v/v) as eluent, from which the desired product **3d** was obtained as red solid in 25% yield (18 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 2H), 7.03 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 143.1, 136.5, 135.7, 133.9, 132.7, 132.2, 131.3, 122.5, 122.3, 116.6, 114.3, 112.4, 55.5; MALDI-TOF Calcd. for $C_{16}H_8BBr_5FN_2O$ [$M - F$]$^+$ 670.66, found 670.07. Anal. Calcd. for $C_{16}H_8BBr_5F_2N_2O$: C, 27.75; H, 1.16; N, 4.04. Found: C, 27.92; H, 1.37; N, 4.22.

BODIPY ***3e***. To BODIPY **1b** (31 mg, 0.10 mmol) in 16 mL of dry CH_2Cl_2 was added liquid bromine (2.23 mL, 0.04 mol) in CH_2Cl_2 (4 mL). The mixture was left stirring at room temperature for 30 min, washed with an aqueous solution of sodium hydroxide, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness under vacuum. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (2:1, v/v) as eluent, from which the desired product **3e** was obtained as red solid in 81% yield (71 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 140.7, 135.5, 133.6, 131.5, 129.3, 123.8, 122.6, 117.8, 112.7, 112.5, 56.4; MALDI-TOF Calcd. for $C_{16}H_6BBr_7FN_2O$ [$M - F$]$^+$ 828.48, found 828.04. Anal. Calcd. for $C_{16}H_6BBr_7F_2N_2O$: C, 22.60; H, 0.71; N, 3.29. Found: C, 22.83; H, 0.87; N, 3.43.

BODIPY ***4a***. To BODIPY **2c** (30 mg, 0.05 mmol) in 50 mL of CH_3CN was added aniline (10 μL, 0.1 mmol). The mixture was left stirring at room temperature for 3 h and evaporated to dryness under vacuum. The crude product was further purified by column chromatography on silica gel using hexane/ethyl acetate (8:1, v/v) as eluent, from which **4a** was obtained as a green solid in 89% yield (28 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.51−7.26 (m, 10H), 7.01 (s, 1H), 6.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 137.5, 135.4, 133.0, 132.8, 131.8, 130.2, 130.1, 129.2, 128.6, 127.6, 126.0, 123.2, 119.3, 116.4, 105.8, 101.8; HRMS (EI) Calcd. for $C_{21}H_{13}B^{79}Br_3F_2N_3$ [M^+] 592.8721, found 592.8723.

BODIPY ***4b***. To BODIPY **2c** (31 mg, 0.05 mmol) in 50 mL of CH_3CN was added *N*-phenylethylenediamine (15 μL, 0.11 mmol) in CH_3CN (1 mL). The mixture was left stirring at room temperature for 2 h and evaporated to dryness under vacuum. The crude product was further purified by column chromatography on silica gel using hexane/CH_2Cl_2 (1:1, v/v) as eluent, from which **4b** was obtained as a pink solid in 83% yield (28 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.38 (m, 6H), 7.26−7.20 (m, 2H), 6.93 (s, 1H), 6.80 (t, J = 7.2 Hz, 1H), 6.73 (d, J = 6.9 Hz, 2H), 6.60 (s, 1H), 6.40 (s, 1H), 4.20 (q, 2H), 3.57 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 147.2, 135.5, 133.1, 132.7, 132.5, 130.5, 130.2, 129.7, 129.5, 128.5, 121.1, 118.9, 116.8, 113.7, 105.1, 103.8, 43.9, 43.7; HRMS (EI) Calcd. for $C_{23}H_{18}B^{79}Br_3F_2N_4$ [M^+] 635.9143, found 635.9150.

BODIPY ***4c***. To BODIPY **2d** (26 mg, 0.03 mmol) in 50 mL of CH_3CN was added aniline (8 μL, 0.08 mmol). The mixture was left stirring at room temperature for 30 min and evaporated to dryness under vacuum. The crude product was further purified by column chromatography on silica gel using CH_2Cl_2 as eluent, from which **4c** was obtained as a red solid in 90% yield (23 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.50−7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 135.2, 133.2, 131.0, 130.7, 130.0, 129.7, 129.3, 129.0, 128.7, 128.0, 126.4, 119.6, 119.3, 113.5, 111.8, 107.1; MALDI-TOF Calcd. for $C_{21}H_{11}BBr_5F_2N_3$ [M^+] 754.69, found 754.42. Anal. Calcd. for $C_{21}H_{11}BBr_5F_2N_3$: C, 33.47; H, 1.47; N, 5.58. Found: C, 33.62; H, 1.31; N, 5.81.

BODIPY ***5a***. To BODIPY **2c** (32 mg, 0.06 mmol) in 50 mL of CH_3CN was added 4-methoxyphenol (6 mg, 0.05 mmol). The mixture was left stirring at room temperature for 5 min in the presence of K_2CO_3, filtrated to remove excess amount of K_2CO_3, and washed with CH_3CN. Organic layer was washed with brine and evaporated to dryness under vacuum. The crude product was further purified by

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column chromatography on silica gel using hexane/ethyl acetate (6:1, v/v) as eluent, from which **5a** was obtained as a red solid in 60% yield (21 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 6.6 Hz, 5H), 7.13 (s, 2H), 7.00 (s, 1H), 6.89 (s, 2H), 6.76 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 156.2, 147.5, 140.3, 137.0, 134.2, 132.7, 131.0, 129.9, 129.3, 127.8, 127.6, 127.5, 118.9, 113.7, 108.1, 97.3, 54.6; MALDI-TOF Calcd. for $C_{22}H_{14}BBr_3FN_2O_2$ $[M - F]^+$ 606.87, found 606.59. Anal. Calcd. for $C_{22}H_{14}BBr_3F_2N_2O_2$: C, 42.15; H, 2.25; N, 4.47. Found: C, 41.90; H, 2.13; N, 4.21.

BODIPY ***5b***. To BODIPY **2c** (29 mg, 0.05 mmol) in 50 mL of CH_3CN was added 4-methoxyphenol (14 mg, 0.11 mmol). The mixture was left stirring at room temperature for 30 min in the presence of K_2CO_3, filtrated to remove excess amount of K_2CO_3, and washed with CH_3CN. Organic layer was evaporated to dryness under vacuum and the crude product was further purified by column chromatography on silica gel using CH_2Cl_2 as eluent, from which **5b** was obtained as a red solid in 65% yield (22 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, J = 10.2 Hz, 5H), 7.07 (d, J = 9.0 Hz, 4H), 6.87−6.83 (t, 6H), 3.78 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.4, 149.3, 141.4, 132.1, 131.9, 130.6, 130.2, 128.6, 127.2, 119.0, 114.5, 95.3, 55.5; HRMS (EI) Calcd. for $C_{29}H_{21}B^{79}Br^{81}BrF_2N_2O_4$ $[M^+]$ 669.9910, found 669.9940.

BODIPY ***6a***. To a solution of BODIPY **2d** (32 mg, 0.04 mmol) in acetonitrile (20 mL) were added triethylamine (14 mg, 0.14 mmol) and *p*-thiocresol (16 mg, 0.13 mmol). This mixture was left stirring for 5 min at room temperature, washed with brine, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (7:1, v/v) as eluent, from which the desired product **6a** was obtained in 84% yield (30 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (br, 3H), 7.41 (d, J = 7.4 Hz, 4H), 7.29 (br, 2H), 7.13 (d, J = 7.5 Hz, 4H), 2.34 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 141.1, 138.7, 132.4, 131.3, 130.6, 130.1, 129.3, 129.0, 128.0, 123.9, 119.3, 21.3; HRMS (EI) Calcd. for $C_{29}H_{19}B^{79}Br_4BrF_2N_2S_2$ $[M - F]^+$ 804.7795, found 806.7799; HRMS (EI) Calcd. for $C_{29}H_{19}B^{79}Br_3{}^{81}BrF_2N_2S_2$ $[M - F]^+$ 806.7774, found 806.7771; HRMS (EI) Calcd. for $C_{29}H_{19}B^{79}Br_2{}^{81}Br_2F_2N_2S_2$ $[M - F]^+$ 808.7754, found 808.7746; HRMS (EI) Calcd. for $C_{29}H_{19}B^{79}Br_2{}^{81}Br_2F_2N_2S_2$ $[M - F]^+$ 810.7733, found 810.7720.

BODIPY ***6b***. To a solution of BODIPY **2d** (33 mg, 0.05 mmol) in acetonitrile (2 mL) were added triethylamine (47 mg, 0.46 mmol) and *p*-thiocresol (58 mg, 0.47 mmol). The mixture was left stirring for 5 h at 70 °C, washed with brine, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (6:1, v/v) as eluent, from which the desired product **6b** was obtained in 78% yield (32 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 7.4 Hz, 4H), 7.22 (br, 3H), 7.09 (d, J = 7.3 Hz, 6H), 6.93 (d, J = 7.3 Hz, 4H), 6.68 (d, J = 7.4 Hz, 4H), 2.31 (s, 6H), 2.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6, 140.9, 138.1, 137.7, 136.1, 135.5, 132.2, 132.1, 131.6, 130.0, 129.9, 129.5, 129.0, 128.8, 128.7, 128.1, 123.1, 21.2, 21.0; HRMS (EI) Calcd. for $C_{44}H_{34}B^{79}Br^{81}BrF_2N_2S_4$ $[M + H]^+$ 915.0007, found 914.9981; HRMS (EI) Calcd. for $C_{44}H_{33}B^{79}Br^{81}BrFN_2S_4$ $[M - F]^+$ 894.9945, found 894.9936; HRMS (EI) Calcd. for $C_{44}H_{33}B^{79}Br_2FN_2S_4$ $[M - F]^+$ 892.9959, found 892.9965.

BODIPY ***7***. BODIPY **2c** (60 mg, 0.1 mmol) was dissolved in toluene (2 mL), followed by the addition of benzene boronic acid (57 mg, 0.47 mmol), $Pd(PPh_3)_4$ (11 mg, 0.01 mmol, 10%), and aqueous Na_2CO_3 (1 mL of a 1 M solution). The resulting mixture was refluxed under argon for 4 h, washed with brine, and extracted by CH_2Cl_2. Organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. Purification was performed by column chromatography on silica gel using hexane/ethyl acetate (6:1, v/v) as eluent, from which the desired product **7** was obtained in 75% yield (44 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 6.4 Hz, 2H), 7.59 (d, J = 6.8 Hz, 3H), 7.49 (d, J = 6.4 Hz, 4H), 7.32 (d, J = 6.8 Hz, 6H), 7.16 (s, 6H), 7.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 143.8, 134.6, 134.3, 133.7, 131.6, 130.6, 130.3, 129.0, 128.5, 128.3, 128.2, 128.0, 127.7, 126.8, 125.4, 116.8; HRMS (EI) Calcd. for $C_{39}H_{28}BF_2N_2$ $[M + H]^+$ 573.2308, found 573.2291; HRMS (EI) Calcd. for $C_{39}H_{27}BFN_2$ $[M - F]^+$ 553.2246, found 553.2235;

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR, UV−vis, and fluorescence spectra for all new compounds and crystallographic information files (CIFs) for compounds **2c−d**, **3a−e**, **4c**, and **6a−b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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