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Stepwise Polychlorination of 8-Chloro-BODIPY and Regioselective Functionalization of 2,3,5,6,8-Pentachloro-BODIPY

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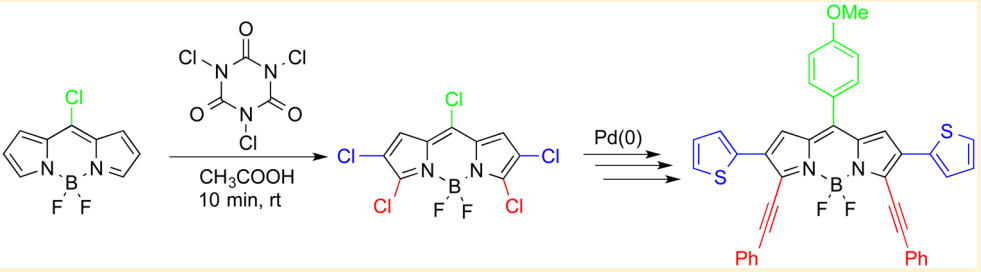
Supporting Information



ABSTRACT: An effective, stepwise methodology for polychlorination of BODIPY using trichloroisocyanuric acid (TCCA) in acetic acid was developed. In this way, selectively substituted di-, tri-, tetra-, and pentachloro-BODIPYs **2**–**5** were prepared. The pentachloro-BODIPY is shown to undergo regioselective Pd(0)-catalyzed Stille and Suzuki coupling reactions, first at the 8-position followed by the 3,5- and then the 2,6-positions; nucleophilic substitution reactions occur first at the 8- followed by the 3,5-positions, while the 2,6 are unreactive.

Because of their unique properties that include high photostability, strong absorptions in the UV–vis range, and sharp fluorescence emissions with high quantum yields, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene dyes (known as BODIPYs) are very promising for a variety of imaging, theranostics, sensing, and analytical applications.[1] Therefore, the development of efficient synthetic methodologies to functionalized BODIPYs has been the subject of intense research in recent years. Among these, core-halogenated BODIPYs are particularly attractive synthetic targets, since they allow the introduction of a variety of functionalities to the BODIPY core via both nucleophilic substitutions and metal-catalyzed cross-coupling reactions. Furthermore, halogenated BODIPYs are promising photosensitizers for photodynamic therapy (PDT) of cancer,[2] due to enhancement of intersystem crossing as a result of the heavy atom effect. The regioselective electrophilic bromination of the 1,2,3,5,6,7-positions of BODIPY has recently been reported using either bromine or *N*-bromosuccinimide (NBS) at room temperature or below.[3] On the other hand, the direct chlorination of the BODIPY core using *N*-chlorosuccinimide (NCS) can lead to mixtures of polychlorinated products that are difficult to purify. In order to better control the regioselectivity of the reaction, chlorination has been performed on the dipyrromethane or pyrrole precursors, and a variety of chlorinated derivatives have been reported using these methodologies.[4] Such chlorinated BODIPYs show higher stability than the corresponding brominated analogues and are versatile starting materials for the preparation of functionalized BODIPYs via Pd(0)-catalyzed cross-coupling reactions (Stille, Heck, Suzuki, and Sonogashira)[4b,f] and nucleophilic substitution reactions[4c,d,g] using N-, O-, S-, and C-centered nucleophiles. In particular, 3- and/or 5-chloro-BODIPYs are very useful intermediates in the preparation of aryl-, alkenyl-, and alkynyl-functionalized BODIPYs, which typically show red-shifted absorption and emission bands. Recently, the synthesis of *meso*-8-halogenated-BODIPYs from dipyrroketones and their reactivities toward both Pd(0)-catalyzed cross-couplings and nucleophilic substitutions were investigated.[5] The introduction of functionality at the 8-position was shown to greatly influence the fluorescence quantum yields, and therefore, this strategy can be used to fine-tune the fluorescence properties of this type of dye. We have also recently reported that the 8-chloro group of 3,8-di- and 3,5,8-trichloro-substituted BODIPYs is the most reactive in Pd(0)-catalyzed Stille coupling reactions and nucleophilic addition–eliminations, allowing for regioselective functionalizations at the *meso*-8 and α-3,5-positions.[6] Herein, we report an efficient new methodology for the stepwise chlorination of the BODIPY core at the 8- followed by the 2,6- and then the 3,5-positions and investigate the site-selective functionalization of pentachloro-BODIPY **5** at the 2,3,5,6,8-positions using two types of cross-coupling reactions and nucleophilic substitution reactions.

The 8-chloro-BODIPY **1** was synthesized in four steps from pyrrole following the reported procedures,[5,7] involving thiophosgenation followed by oxidative hydrolysis, chlorination, and boron complexation. Treatment of **1** with 10 equiv of NCS in THF at room temperature for 24 h[4e] afforded the 2,8-dichloro-BODIPY **2** as the major product, in only 52% yield.

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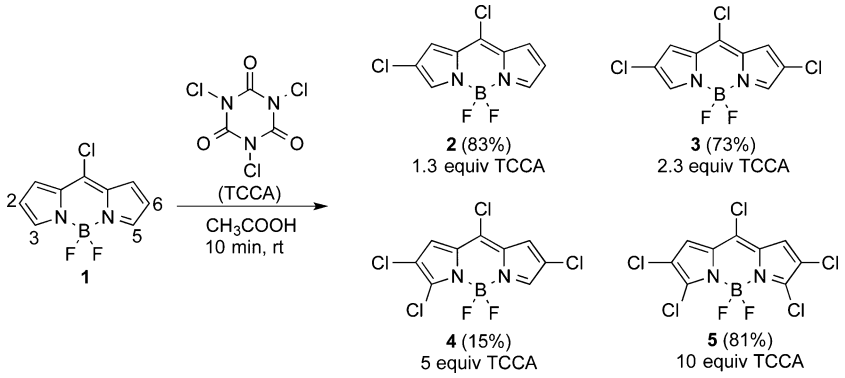
Scheme 1. Regioselective Chlorination of BODIPY 1



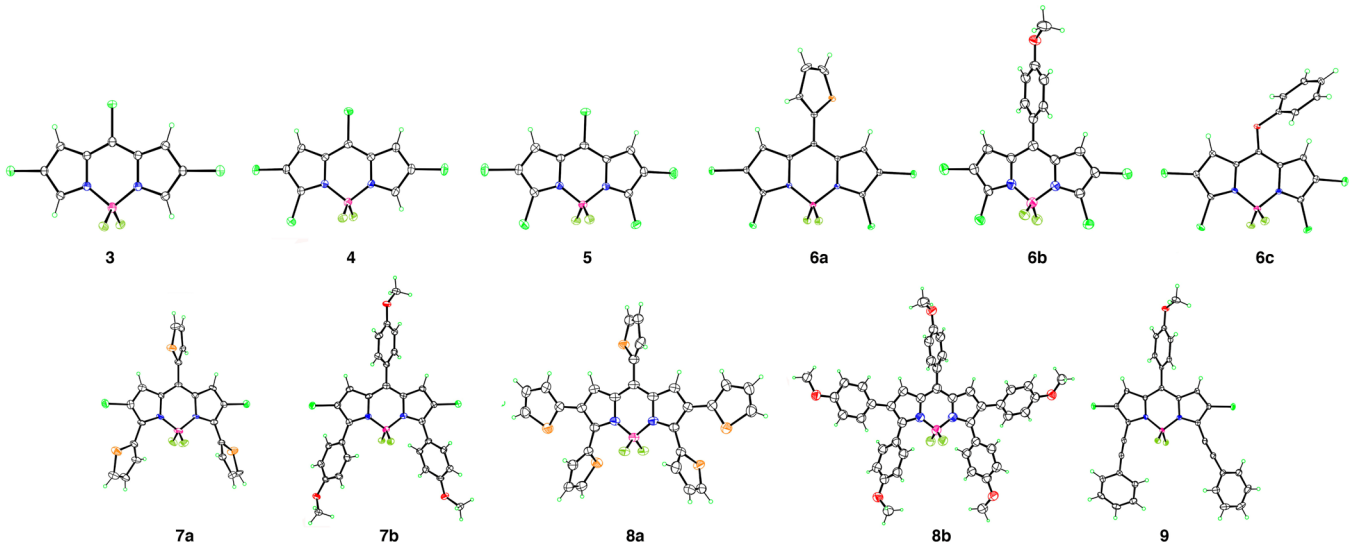


Figure 1. X-ray crystal structures of functionalized BODIPYs with ellipsoids drawn at the 50% probability level.

Increasing the temperature, reaction time, or the amount of NCS gave complex mixtures of products in low yields, probably as a result of the low reactivity of **1** under these chlorinating conditions. Therefore, alternative methodologies for the regioselective polychlorination of BODIPY **1** were investigated using more reactive sources of electrophilic chlorine compared with NCS, which is ineffective for chlorination of BODIPYs (such as **1**) bearing electron-withdrawing substituent(s). Among the chlorinating reagents considered, trichloroisocyanuric acid (TCCA) is a stable and convenient reagent that has been previously used for the chlorination of a variety of substrates, including deactivated benzenes (e.g., nitrobenzene) in good yields.[8] Inspired by these reports, we investigated the reactivity of BODIPY **1** in the presence of TCCA, at room temperature in different solvents. Our optimized conditions involved the treatment of BODIPY **1** with increasing amounts of TCCA in acetic acid, for 10 min at room temperature, as shown in Scheme 1; this methodology is significantly faster, cheaper, greener, and more efficient than previously reported methods for halogenation of BODIPYs.

When 1.3 equiv of TCCA was used, the only product formed was 2,8-dichloro-BODIPY **2**, isolated in 83% yield. Therefore, the monochlorination of **1** occurred regioselectively at the 2-position under these conditions, with no additional chlorinated byproducts being formed. When the amount of TCCA was increased to 2.3 equiv, the 2,6,8-trichloro-BODIPY **3** was the major product formed, isolated in 73% yield. This site-selectivity is due to the higher negative charge at the 2,6-positions, as previously observed.[4e] Further increasing the amount of TCCA to 3−5 equiv gave a mixture of BODIPYs **3**−**5**, as monitored by TLC, from which the 2,3,6,8-tetrachloro-BODIPY **4** could be isolated in 15% yield. On the other hand, when BODIPY **1** was treated with 10 equiv of TCCA for 10 min, 2,3,5,6,8-penta-BODIPY **5** was the major product, isolated in 81% yield. Further increasing the amount of TCCA to 50 equiv, and extending the reaction time to 72 h, did not result in further chlorination of the BODIPY at the 1,7-positions. On the other hand, increasing the temperature to reflux and using a stronger acid (H_2SO_4) in place of acetic acid led only to BODIPY decomposition. Nevertheless, BODIPY **5** can be further functionalized at the 1,7-positions under more vigorous conditions, for example, using a large excess of bromine,[3a] and these reactions are currently under investigation.

The stepwise chlorination of BODIPY **1** was verified by ^{1}H NMR spectroscopy, since BODIPY **1** shows characteristic resonance peaks at 7.8, 7.4, and 6.6 ppm, attributed to the 3,5-, 1,7-, and 2,6-hydrogens, respectively. The formation of **2**, **3**, **4**, and **5** was clearly indicated by the gradual disappearance of the peaks at 6.6 ppm, followed by those at 7.8 ppm. X-ray crystallography further confirmed the regioselectivity of the chlorination reaction. Structures of **3**−**5** are shown in Figure 1 and in the Supporting Information (for **1**). Our structure of **1**

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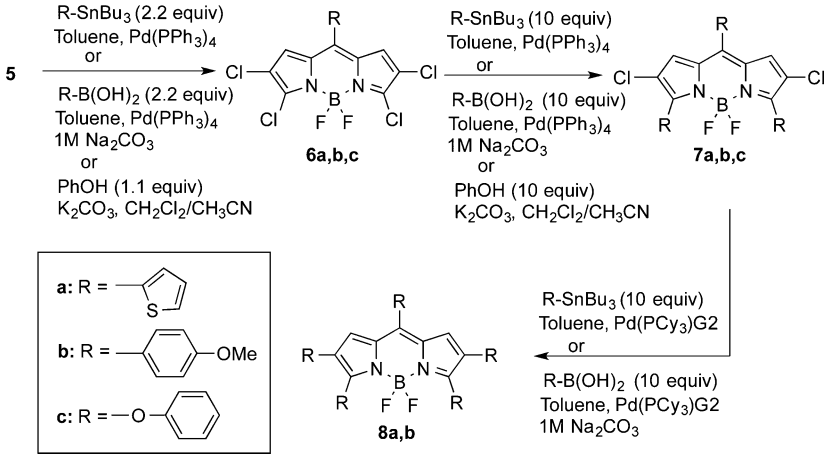
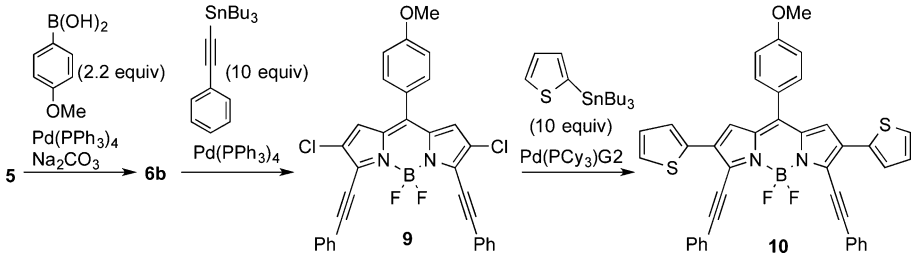
Scheme 2. Regioselective Reactions of BODIPY 5



Scheme 3. Multifunctionalization of BODIPY 5



agrees well with the published 150 K structure.[9] BODIPY **3** is disordered on a C_{2h} site, so the C_9BN_2 core is exactly planar. The mean deviation from coplanarity is slightly larger, 0.015 Å, in **4**. BODIPY **5** has two independent molecules that are less planar, one having a slightly bowed conformation with mean deviation 0.064 Å, and the other having the B atom lying 0.110 Å out of the best plane of the other 11 atoms.

Among the Pd(0)-catalyzed cross-coupling reactions investigated using chloro-BODIPYs, the Stille coupling conditions are particularly attractive since no base is required, and the products are generally obtained in high yields.[4b,5,6] We recently showed that Stille coupling occurs first at the most reactive 8-chloro site, followed by the 3(5)-chloro groups,[6] but no studies have been conducted on more highly chlorinated BODIPYs. Under similar reaction conditions, 2,3,5,6,8-pentachloro-BODIPY **5** reacted with 2.2 equiv of 2-(tributylstannyl)-thiophene and 3 mol % of $Pd(PPh_3)_4$ in refluxing toluene to regioselectively produce the 8-thienyl-2,3,5,6-tetrachloro-BODIPY **6a** in 84% yield (Scheme 2). Increasing the amount of organostannane to 10 equiv gave exclusively the 2,6-dichloro-BODIPY **7a** in 77% yield. Further increasing the amount of organotin (up to 300 equiv), the reaction temperature (up to 130 °C), and the reaction time (up to 72 h) did not produce the pentathienyl-BODIPY **8a**. However, the globally coupled BODIPY **8a** was obtained as the major product in 57% from **7a**, using chloro[(tricyclohexylphosphine-2-(2′-aminobiphenyl)-palladium $[Pd(PCy_3)G_2]$ as the catalyst,[10] in the presence of 10 equiv of 2-(tributylstannyl)thiophene.

The Suzuki cross-coupling reactions on BODIPY **5** were also investigated, since no previous studies are reported on the 8 vs 3,5 vs 2,6-regioselectivity of this type of reaction in polyhalogenated BODIPYs. The reaction of 2.2 equiv of (4-methoxyphenyl)boronic acid and BODIPY **5** in the presence of $Pd(PPh_3)_4$, toluene, and 1 M Na_2CO_3 (aq) afforded the 8-aryl BODIPY **6b** in 81% yield. Treatment with 10 equiv of boronic acid (portionwise) gave BODIPY **7b** in 74% yield. As with the Stille reaction, increasing the amount of boronic acid, the reaction temperature, and time did not produce the globally coupled product. However, in the presence of $Pd(PCy_3)G_2$[10] and 10 equiv of (4-methoxyphenyl)boronic acid, BODIPY **8b** was obtained in 56% yield from **7b**.

The regioselectivity of nucleophilic substitution reactions on polyhalogenated BODIPYs has been reported to first take place at the 8- followed by the 3(5)-position[6b] and at the 3,5- before the 1,7- and 2,6-positions.[3a,11] In agreement with these studies, BODIPY **5** reacted at room temperature with 1.1 equiv of phenol in the presence of potassium carbonate to give the 8-phenoxy-BODIPY **6c** in 85% yield. Increasing the amount of phenol to 10 equiv gave the 3,5,8-triphenoxy-BODIPY **7c** in 91% yield, as confirmed by ^{1}H NMR (see the Supporting Information). Further increasing the amount of phenol, the reaction time, and temperature did not produce the pentasubstituted product.

The regioselectivity of the cross-coupling and nucleophilic reactions was confirmed by X-ray crystallography, as shown in Figure 1. BODIPY **6a** lies on a crystallographic 2-fold axis, necessitating disorder of the 8-thienyl group, and the thiophene plane forms a dihedral angle of 37.7° with the C_3N_2B ring. In **6b**, the central ring forms a dihedral angle of 49.6° with the 8-phenyl ring. In **6c**, the 8-phenyl ring forms a dihedral angle of 75.9° with the C_3N_2B plane. BODIPY **7a**, as the hemitoluene solvate, has four independent molecules with similar conformations. The planes of the 8-thienyl groups form dihedral angles in the range 47.1−52.9° with the central ring. Thiophenes at the other positions form more variable dihedral angles with the core, in the range 38.6−55.1°. Compound **7b**

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has two independent molecules, and the 8-phenyl planes form dihedral angles of 49.5 and 50.2° with the central core planes, while the 3,5-phenyl groups form dihedral angles with them in the range 57.1−87.6°. BODIPY **8a** lies on a crystallographic 2-fold axis. Similar to **6a** and **7a**, its 8-thienyl forms a dihedral angle of 40.9° with the core. However, unlike **7a**, the 3,5-thienyl groups in **8a** are nearly orthogonal to the core (84.0° dihedral), while those at the 2,6-positions are nearly coplanar (18.5° dihedral). In **8b**, the 8-phenyl forms a dihedral angle of 50.1° with the core plane, the 2,6-phenyls form dihedral angles of 20.7 and 33.5° with it, and the 3,5-phenyls form dihedral angles of 59.4 and 69.8° with it.

To illustrate the versatility of the above regioselective reaction sequences, the multifunctionalization of BODIPY **5** was performed, as shown in Scheme 3. First, reaction with 2.2 equiv of (4-methoxyphenyl)boronic acid under Suzuki conditions gave **6b**, which then reacted with 10 equiv of tributyl(phenylethynyl)tin under Stille conditions to give the 3,5,8-trisubstituted BODIPY **9** in 77% yield. The crystal structure of **9** is shown in Figure 1. Its 8-phenyl group forms a dihedral angle of 52.0° with the C_3N_2B core, and the phenyl planes of the 3,5-substituents form dihedral angles of 13.7 and 48.7° with it. Treatment of **9** with 10 equiv of 2-(tributylstannyl)thiophene in the presence of $Pd(PCy_3)G_2$ gave BODIPY **10** in 49% yield.

The spectroscopic properties of the new BODIPYs were measured in THF for all compounds except for **8a**, due to its poor solubility in THF, and the results are summarized in Table 1.

Table 1. Spectroscopic Properties of BODIPYs in THF at Room Temperature

BODIPY	absorption λ_{max} (nm)	log ε ($M^{-1}cm^{-1}$)	emission λ_{em} (nm)	Φ_f[a]	Stokes shift (nm)
2	510	4.73	538	0.71	28
3	530	4.10	558	0.80	28
4	535	4.47	561	0.51	26
5	540	4.56	562	0.94	22
6a	543	4.29	571	0.07	28
6b	529	4.50	554	0.57	25
6c	496	4.25	542	0.94	46
7a	622	4.06	673	0.03	51
7b	574	4.35	622	0.09	48
7c	500	4.68	541	0.64	41
8a[b]	638[b]	3.89[b]	704[b]	0.003[b]	66[b]
8b	615	4.78	647	0.33	32
9	637	4.88	648	0.68	11
10	700	4.53	738	0.03	38

[a]Rhodamine 6G (0.88 in ethanol) was used as standard for **2**, **6c**, and **7c**, rhodamine B (0.49 in ethanol) for **3**−**5** and **6a**,**b**, crystal violet perchlorate (0.54 in methanol) for **7b**, and methylene blue (0.04 in ethanol) for **7a**, **8a**,**b**, **9**, and **10**.[12] [b]Data obtained in dichloromethane.

All BODIPYs show characteristically strong absorption bands (log ε = 3.9−4.9) and emission bands Stokes shifted by 22−66 nm. As previously observed,[6,13] the largest Stokes shifts were measured for the 3,5- and 2,3,5,6-thienyl-functionalized BODIPYs **7a**, **8a**, and **10** due to increased geometry relaxation in these molecules.[14] The introduction of chloro groups into the BODIPY core induced moderate red-shifts in the absorption and emission bands of **1**,[4e] while substitution with phenoxy groups caused pronounced blue-shifts due to the increase in the HOMO−LUMO gap.[6,15] On the other hand, the functionalization at the 3,5-positions with thienyl or ethynylphenyl groups and the 2,6-positions with thienyl groups decrease the HOMO−LUMO gap, producing the largest bathochromic shifts. As a result, BODIPY **10** showed the most red-shifted absorption and emission of all compounds synthesized. However, thienyl functionalization dramatically decreased the fluorescence quantum yields due to increased energy lost to nonradiative deactivation processes resulting from free motion of the thienyl groups. On the other hand, the pentachlorinated BODIPY **5** and the 8-phenoxy-BODIPY **6c** showed the largest quantum yield of all BODIPYs synthesized.

In summary, a new and convenient method for the stepwise chlorination of the 2,3,5,6-positions of "deactivated" BODIPYs that cannot be regioselectively polychlorinated using NCS was developed; the method uses TCCA in acetic acid at room temperature. The pentachloro-BODIPY **5** is a versatile platform, shown to undergo regioselective Pd(0)-catalyzed Stille and Suzuki cross-coupling reactions first at the *meso*-8-, followed by the α-3,5-, and finally the β-2,6-chloro groups. Nucleophilic substitutions occurred first at the 8-position followed by the 3,5-positions, while the 2,6-chloro groups were unreactive under these conditions. The regioselectivities of both the chlorination and coupling reactions were confirmed by X-ray crystallography. These results also showed that pentathienyl-BODIPY **8a** has the largest dihedral angles (84.0°) for the 3,5-thienyls and the smallest (18.5°) for the 2,6-thienyls. The methodologies developed were applied to the preparation of a multifunctionalized BODIPY **10**, via stepwise functionalizations at the 8-position with a *p*-methoxyphenyl group, followed by the 3,5-positions with ethylenephenyl groups and finally the 2,6-sites with thienyl groups. This BODIPY showed the most red-shifted absorption (λ_{max} 700 nm) and emission (λ_{max} 738 nm) of all compounds synthesized, while substitution at the 3,5- and/or 2,6-positions with thienyls gave the largest Stokes shifts and functionalization with a 8-phenoxy group induced a large fluorescence quantum yield.

EXPERIMENTAL SECTION

Synthesis and Spectroscopic Characterization. Reactions were monitored using 0.2 mm silica gel plates (with indicator, polyester backed, 60 Å, precoated) and UV lamp. Liquid chromatography was performed on preparative TLC plates or via silica gel column chromatography (60 Å, 230−400 mesh). NMR spectra were obtained on 400 or 500 MHz spectrometers at room temperature. Chemical shifts (δ) are given in parts per million (ppm) in CD_2Cl_2 (5.32 ppm for ^{1}H NMR, 53.4 ppm for ^{13}C NMR) or $CDCl_3$ (7.27 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR); coupling constants (J) are given in hertz. High-resolution mass spectra were performed on an ESI-TOF mass spectrometer in negative or positive modes. UV−vis and emission spectra were recorded at room temperature. Spectroscopic-grade solvents and quartz cuvettes (10 mm path length) were used. For the determination of the optical density (ε), solutions with absorbance at λ_{max} between 0.5 and 1 were used. For the determination of quantum yields, dilute solutions with absorbance between 0.03 and 0.05 at the particular excitation wavelength were used.[16] 8-Chloro-BODIPY **1** was synthesized according to a published procedure.[5a]

General Procedure for Chlorination of BODIPY 1. 8-Chloro-BODIPY **1** (22.6 mg, 0.100 mmol) was dissolved in acetic acid (2 mL). TCCA was added portionwise to the solution, and the final mixture was stirred at room temperature for 10 min. TLC was used to monitor the reactions. The mixture was poured into water (200 mL) and extracted with CH_2Cl_2 (15 mL × 3). The organic layers were combined, washed with aqueous saturated $NaHCO_3$ and water, and

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then dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the resulting residue was purified by preparative TLC and column chromatography using CH_2Cl_2/hexanes (1:8) or ethyl acetate/hexanes (1:10) for elution.

2,8-Dichloro-BODIPY ***2***. This compound was prepared using TCCA (30.9 mg, 0.133 mmol), yielding 21.6 mg, 82.8% of **2** (yellow solid): mp (°C) 143−144; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.95 (s, 1H), 7.73 (s, 1H), 7.47 (s, 1H), 7.26 (s, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 147.1, 141.1, 141.0, 134.6, 132.3, 130.6, 125.1, 122.4, 120.0; HRMS (ESI-TOF) m/z 258.9919 $[M]^-$, calcd for $C_9H_5BCl_2F_2N_2$ 258.9927.

2,6,8-Trichloro-BODIPY ***3***. This compound was prepared using TCCA (54.1 mg, 0.233 mmol), yielding 21.6 mg, 73.1% of **3** (red solid): mp (°C) 212−213; ^{1} H NMR ($CDCl_3$, 400 MHz) δ = 7.78 (s, 2H), 7.31 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 143.2, 140.9, 132.9, 126.2, 123.5; HRMS (ESI-TOF) m/z 293.9502 $[M]^-$, calcd for $C_9H_5BCl_3F_2N_2$ 293.9501.

2,3,6,8-Tetrachloro-BODIPY ***4***. This compound was prepared using TCCA (93.0 mg, 0.400 mmol), yielding 4.9 mg, 14.9% of **4** (red solid): mp (°C) 208−209; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ = 7.78 (s, 1H), 7.41 (s, 1H); 7.32 (s, 1H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ = 143.7, 143.1, 139.4, 132.7, 131.0, 126.5, 126.0, 123.7, 122.3; HRMS (ESI-TOF) m/z 329.9094 $[M]^-$, calcd for $C_9H_3BCl_4F_2N_2$ 329.9082.

2,3,5,6,8-Pentachloro-BODIPY ***5***. This compound was prepared using TCCA (0.232 g, 1.00 mmol) yielding 29.5 mg, 81.0% of **5** (red solid): mp (°C) 218−219; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.34 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 144.0, 136.7, 130.4, 125.8, 122.7; HRMS (ESI-TOF) m/z 360.8754 $[M]^-$, calcd for $C_9H_2BCl_5F_2N_2$ 360.8758.

General Procedure for Stille Cross-Couplings of BODIPYs. To a 15 mL round-bottomed flask were added the starting BODIPY, organotin reagent, and 3% mol of either $Pd(PPh_3)_4$ (for **6a**, **7a**, **9**) or $Pd(PCy_3)G2$ (for **8a**, **10**). The flask was evacuated and refilled with nitrogen four times. Toluene (5 mL) was added, and the final mixture was stirred and refluxed for about 5 h under N_2. TLC was used to monitor the reactions. The toluene was removed under reduced pressure, and the resulting residue was purified by preparative TLC and column chromatography using CH_2Cl_2/hexanes (1:1) or ethyl acetate/hexanes (1:2) for elution.

8-Thienyl-2,3,5,6-tetrachloro-BODIPY ***6a***. This compound was prepared from BODIPY **5** (18.2 mg, 0.0500 mmol) and 2-(tributylstannyl)thiophene (41.1 mg, 0.110 mmol), yielding 17.2 mg, 83.5% of **6a** (red solid): mp (°C) 298−300; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.77−7.79 (q, 1H, $^3J_{(H,H)}$ = 4.0 Hz, $^4J_{(H,H)}$ = 1.1 Hz), 7.51−7.52 (q, 1H, $^3J_{(H,H)}$ = 2.6 Hz, $^4J_{(H,H)}$ = 1.1 Hz), 7.30−7.32 (q, 1H, $^3J_{(H,H)}$ = 3.7 Hz, $^4J_{(H,H)}$ = 1.3 Hz), 7.19 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 142.7, 136.2, 133.5, 132.4, 132.3, 130.9, 128.7, 128.2, 121.8; HRMS (ESI-TOF) m/z 411.8959 $[M]^-$, calcd for $C_{13}H_5BCl_4F_2N_2S$ 411.8959.

3,5,8-Trithienyl-2,6-dichloro-BODIPY ***7a***. This compound was prepared from BODIPY **6a** (20.5 mg, 0.0500 mmol) and 2-(tributylstannyl)thiophene (187 mg, 0.500 mmol), yielding 19.5 mg, 76.9% of **7a** (dark blue solid): mp (°C) 255−257; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.94−7.95 (m, 2H), 7.71−7.72 (m, 1H), 7.63−7.64 (m, 2H), 7.51−7.52 (m, 1H), 7.28−7.30 (m, 1H), 7.19−7.21 (m, overlap, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 147.4, 134.4, 134.0, 133.5(t), 133.1, 132.7, 131.0, 130.8, 129.5, 128.5, 128.3, 127.6, 123.4; HRMS (ESI-TOF) m/z 504.9535 $[M]^-$, calcd for $C_{21}H_{11}BCl_2F_2N_2S_3$ 504.9564.

2,3,5,6,8-Pentathienyl-BODIPY ***8a***. This compound was prepared from BODIPY **7a** (15.2 mg, 0.0300 mmol) and 2-(tributylstannyl)-thiophene (112 mg, 0.300 mmol), yielding 10.3 mg, 57.0% of **8a** (dark green solid): mp (°C) 255−257; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.73−7.74 (m, 1H), 7.60−7.61 (m, 1H), 7.54−7.55 (m, 2H), 7.51−7.52 (m, 2H), 7.30−7.32 (m, overlap, 3H), 7.23−7.24 (m, 2H), 7.10−7.12 (m, 2H), 6.94−6.96 (m, 2H), 6.80−6.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 149.0, 135.6, 135.2, 134.7, 134.6, 132.6, 132.4, 130.9, 130.8, 129.7, 129.1, 128.2, 128.1, 127.3, 127.2, 126.4, 125.6; HRMS (ESI-TOF) m/z 601.0086 $[M]^-$, calcd for $C_{29}H_{17}BF_2N_2S_5$ 601.0093.

8-(p-Methoxyphenyl)-3,5-diphenylethynyl-2,6-dichloro-BODIPY ***9***. This compound was prepared from BODIPY **6b** (21.8 mg, 0.0500 mmol) and tributyl(phenylethynyl)tin (184 mg, 0.500 mmol), yielding 21.8 mg, 76.9% of **9** (dark-green solid): mp (°C) 248−250; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.74−7.76 (q, 4H, $^3J_{(H,H)}$ = 5.7 Hz, $^3J_{(H,H)}$ = 1.6 Hz), 7.48−7.50 (d, 2H, $^3J_{(H,H)}$ = 8.7 Hz), 7.40−7.45 (m, overlap, 6H), 7.06−7.08 (d, 2H, $^3J_{(H,H)}$ = 8.7 Hz), 6.86 (s, 2H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 162.3, 141.9, 135.7, 134.4, 132.6, 132.4, 130.0, 128.5, 126.9, 126.7, 125.6, 121.9, 114.4, 107.2, 80.7, 55.6; HRMS (ESI-TOF) m/z 565.0969 $[M]^-$, calcd for $C_{32}H_{19}BCl_2F_2N_2O$ 565.0972.

8-(p-Methoxyphenyl)-3,5-diphenylethynyl-2,6-dithienyl-BODIPY ***10***. This compound was prepared from BODIPY **9** (17.0 mg, 0.0300 mmol) and 2-(tributylstannyl)thiophene (112 mg, 0.300 mmol), yielding 9.7 mg, 48.8% of **10** (dark-green solid): mp (°C) 292−293; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.78−7.81 (m, 4H), 7.59−7.61 (m, 4H), 7.44−7.46 (m, overlap, 6H), 7.31−7.33 (m, 2H) 7.10−7.14 (m, 4H), 7.00 (s, 2H), 3.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 162.0, 141.3, 136.3, 135.1, 134.7, 132.5, 132.2, 131.2, 129.8, 128.5, 127.5, 126.3, 125.1, 125.0, 124.7, 122.5, 114.3, 106.4, 83.6, 55.6; HRMS (ESI-TOF) m/z 661.1493 $[M]^-$, calcd for $C_{40}H_{25}BF_2N_2OS_2$ 661.1506.

General Procedure for Suzuki Cross-Couplings of BODIPYs. To a 15 mL round-bottomed flask were added the starting BODIPY and either 3 mol % of $Pd(PPh_3)_4$ (for **6b**, **7b**) or 3 mol % of $Pd(PCy_3)G2$ (for **8b**). Toluene (4 mL) and 1 M Na_2CO_3 (aq) (1 mL) were added under N_2. (4-Methoxyphenyl)boronic acid was added portionwise, and the final mixture was stirred and refluxed under N_2. TLC was used to monitor the reactions. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic layers were combined, washed with aqueous saturated brine and water, and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure and the resulting residue was purified by column chromatography using CH_2Cl_2/hexanes (1:2) or ethyl acetate/hexanes (1:6) for elution.

8-(p-Methoxyphenyl)-2,3,5,6-tetrachloro-BODIPY ***6b***. This compound was prepared from BODIPY **5** (18.2 mg, 0.0500 mmol) and (4-methoxyphenyl)boronic acid (16.7 mg, 0.110 mmol), yielding 17.7 mg, 81.2% of **6b** (orange-red solid): mp (°C) 234−236; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.64−7.67 (d, 2H, $^3J_{(H,H)}$ = 8.1 Hz), 7.07−7.09 (d, 2H, $^3J_{(H,H)}$ = 8.1 Hz), 6.94 (s, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 162.9, 144.7, 141.5, 132.6, 131.4, 128.3, 124.0, 121.2, 114.5, 55.7; HRMS (ESI-TOF) m/z 432.9574 $[M - H]^-$ calcd for $C_{16}H_9BCl_4F_2N_2O$ 432.9572.

3,5,8-Tri(p-methoxyphenyl)-2,6-dichloro-BODIPY ***7b***. This compound was prepared from BODIPY **6b** (21.8 mg, 0.0500 mmol) and (4-methoxyphenyl)boronic acid (76.0 mg, 0.500 mmol), yielding 21.4 mg, 73.9% of **7b** (dark blue): mp (°C) 315−316; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.64−7.67 (d, 4H, $^3J_{(H,H)}$ = 8.6 Hz), 7.53−7.56 (d, 2H, $^3J_{(H,H)}$ = 8.6 Hz), 7.08−7.10 (d, 2H, $^3J_{(H,H)}$ = 8.5 Hz), 6.95−6.98 (d, 4H, $^3J_{(H,H)}$ = 8.7 Hz), 6.91 (s, 2H), 3.94 (s, 3H), 3.85 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 161.9, 160.8, 154.0, 143.3, 132.8, 132.3, 131.9, 128.1, 126.0, 122.5, 121.7, 114.2, 113.5, 55.6, 55.2; HRMS (ESI-TOF) m/z 577.1182 $[M]^-$, calcd for $C_{30}H_{23}BCl_2F_2N_2O_3$ 577.1183.

2,3,5,6,8-Penta(p-methoxyphenyl)-BODIPY ***8b***. This compound was prepared from BODIPY **7b** (17.4 mg, 0.0300 mmol) and (4-methoxyphenyl)boronic acid (45.6 mg, 0.300 mmol) yielding 12.1 mg, 55.8% of **8b** (dark blue solid): mp (°C) 252−254; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.62−7.64 (d, 2H, $^3J_{(H,H)}$ = 8.5 Hz), 7.43−7.45 (d, 4H, $^3J_{(H,H)}$ = 8.5 Hz), 7.07−7.09 (d, 2H, $^3J_{(H,H)}$ = 8.5 Hz), 6.96−6.98 (overlap, 6H), 6.84−6.86 (d, 4H, $^3J_{(H,H)}$ = 8.6 Hz), 6.72−6.74 (d, 4H, $^3J_{(H,H)}$ = 8.6 Hz), 3.93 (s, 3H), 3.82 (s, 6H), 3.76 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 161.4, 160.1, 158.5, 155.5, 142.3, 134.5, 133.9, 132.4, 132.0, 129.5, 127.7, 127.1, 126.8, 124.4, 113.9, 113.7, 113.4, 55.5, 55.2, 55.1; HRMS (ESI-TOF) m/z 721.2802 $[M]^+$, calcd for $C_{44}H_{37}BF_2N_2O_5$ 721.2800.

General Procedure for Nucleophilic Substitution of BODIPYs. The starting BODIPY was dissolved in CH_2Cl_2 (1 mL) and CH_3CN (1 mL). Phenol and Na_2CO_3 (1 equiv) were added, and the solution was stirred at room temperature. TLC was used to monitor

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the reactions. The mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic layers were combined, washed with aqueous saturated brine and water, and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the resulting residue was purified by column chromatography using ethyl acetate/hexanes (1:6) for elution.

8-Phenoxy-2,3,5,6-tetrachloro-BODIPY ***6c***. This compound was prepared from BODIPY **5** (18.2 mg, 0.0500 mmol) and phenol (5.2 mg, 0.055 mmol), yielding 17.9 mg, 84.9% of **6c** (orange-red solid): mp (°C) 198−199; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.51−7.55 (m, 2H), 7.42−7.45 (m, 1H), 7.20−7.22 (d, 2H, $^3J_{(H,H)}$ = 8.4 Hz), 6.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 155.5, 155.4, 139.2, 130.9, 127.5, 123.9, 123.6, 120.0, 119.4; HRMS (ESI-TOF) m/z 418.9413 $[M]^-$, calcd for $C_{15}H_7BCl_4F_2N_2O$ 418.9410.

3,5,8-Triphenoxy-2,6-dichloro-BODIPY ***7c***. This compound was prepared from BODIPY **6c** (12.6 mg, 0.0300 mmol) and phenol (29.1 mg, 0.300 mmol), yielding 14.7 mg, 91.2% of **7c** (orange-red solid): mp (°C) 180−181; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ = 7.50−7.54 (t, 2H, $^3J_{(H,H)}$ = 7.4 Hz), 7.33−7.41 (m, overlap, 6H), 7.28−7.30 (d, 2H, $^3J_{(H,H)}$ = 7.9 Hz), 7.14−7.17 (t, 2H, $^3J_{(H,H)}$ = 7.5 Hz), 7.04−7.06 (d, 4H, $^3J_{(H,H)}$ = 8.0 Hz), 6.60 (s, 2H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ = 156.1, 155.8, 154.4, 153.8, 130.7, 129.7, 126.8, 124.3, 119.4, 118.7, 117.0, 109.4; HRMS (ESI-TOF) m/z 535.0713 $[M]^-$, calcd for $C_{27}H_{17}BCl_2F_2N_2O_3$ 535.0714.

Crystal Data. Crystal structures were determined at low temperature (90 K except 160 K for **5**) with Mo Kα data (for **1**, **3**−**5**, **6a**−**c**, **7a**,**b**, **8a**, and **9**) or with Cu Kα radiation (for **8b**). For all structures, H atoms were located from difference maps but constrained in calculated positions during refinement. Refinement was by SHELXL-97.[17] For **3**, the molecule is disordered on a 2/m (C_{2h}) site. For **5**, Z' = 2, and the data were collected at T = 160 K, since a crystal-destroying phase change occurs around 150 K. For **6a**, Z' = 1/2 with the molecule on a 2-fold axis and the thiophene disordered. For **7a**, Z' = 4, and 5 of the 12 independent thiophenes are disordered, as is one of the two independent toluene solvent molecules. For **7b**, Z' = 2. In **8a**, Z' = 1/2 with the molecule on a 2-fold axis, and two of the three independent thiophenes disordered. CCDC 1053715−1053721 and CCDC 1401007−1401011 contain the supplementary X-ray data for this paper. These data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystal structure of **1**, UV−vis, emission, and ^{1}H-, ^{13}C NMR spectra for BODIPYS and X-ray data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01147.

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Notes

The authors declare no competing financial interest.

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