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Synthesis and Regioselective Functionalization of Perhalogenated BODIPYs

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Abstract

Three perhalogenated BODIPYs (1b–3b), bearing chloro and bromo groups at all carbon positions, were synthesized and characterized. The reactivity of BODIPY 3b was investigated under Stille cross-coupling reactions, and single crystal X-ray analysis was used to confirm the regioselectivity of the reactions. Further substitution at the boron atom produced nona-functionalized BODIPYs 7a,b, which show 676 and 739 nm emissions with 91 and 100 nm Stokes shifts, respectively.

4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene (known as boron-dipyrromethene or BODIPY) dyes have attracted growing interest both in the academic and industrial fields. This is due to their remarkable properties, including strong absorptions and sharp emissions in the UV/Vis region, relatively high photostability and solubility, and ease of tunability of their physicochemical properties. Over the past three decades, a large number of new BODIPYs were synthesized, characterized and investigated as fluorescent labelling agents for proteins or DNA, as biological imaging probes, in dye-sensitized solar cells (DSSCs), and as photodynamic therapy (PDT) sensitizers.

To have access to a variety of BODIPYs, efficient synthetic methodologies toward halogenated BODIPY platforms for subsequent functionalization through diverse reactions, are of great interest. Since the first halogenated (2,6-dibromo) BODIPY was synthesized by using Br₂ in dichloromethane, a number of versatile halogenated BODIPYs were reported over the last two decades. These can be prepared by direct halogenation at the BODIPY core, or by introducing the halogen group in pyrrole or dipyrromethane precursors. Such halogenated derivatives can be the precursors of a wide range of functionalized BODIPY dyes for various applications, via Pd(0) catalyzed cross-coupling reactions (e.g., the Suzuki, Stille, Heck or Sonogashira reactions) and/or substitution reactions with C-, N-, O-, or S-nucleophiles. On the other hand, halogen groups can be selectively introduced into the 3,5-positions, the 2,6-, 1,7-, and 8-position, allowing the subsequent introduction of various functional groups to specific positions by subsequent Pd(0) cross-coupling reactions or/and

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† Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

substitution reactions. The platforms with 3,5-halogens or/and 8-halogens have attracted considerable interest due to the large distribution of the HOMO and LUMO at the 3,5-positions and 8-position, respectively. The first 3,5-dichloro-BODIPY was reported in 2005 and 8-halogenated BODIPYs were reported recently, prepared by treating dipyrroketones with POCl₃ (POBr₃) or COCl₂. Such platforms provide a facile way for the functionalization of the 3,5- α positions and the 8-*meso* position, which significantly affect the properties of BODIPYs, including quantum yield, absorption, and fluorescence, by changing their HOMO and LUMO characteristics.

Including the boron atom, the BODIPY core can accommodate 9 halogen atoms. Previously, we reported a series of carbon-polychlorinated BODIPYs (di-, tri-, tetra-, and penta-) prepared by direct chlorination of the BODIPY core using trichloroisocyanuric acid (TCCA)/acetic acid. The polychlorinated BODIPYs can also be obtained from a dipyrromethane precursor by reaction with COCl₂/CHCl₃. The chlorinated BODIPYs show high reactivity and regioselectivity in nucleophilic substitutions and Pd(0)-catalyzed Stille and/or Suzuki cross-coupling reactions. The reactivity of the chloro groups on the different positions of BODIPYs was investigated, and shown to decrease in the order 8-*meso*-Cl > 3,5- α -Cl > 2,6- β -Cl, which allows the stepwise functionalization of BODIPYs at the 8 position, 3,5 positions, and 2,6 positions.

To the best of our knowledge, *perhalogenated* BODIPYs have not so far been reported. Extending our previous work, herein we now report the synthesis of three nona-halogenated BODIPYs, **1b**, **2b**, and **3b** starting from 8-chloro-BODIPY **1a**, 2,6,8-trichloro-BODIPY **2a** and 2,3,5,6,8-pentachloro-BODIPY **3a**, respectively. The reactivity and selectivity of BODIPY **3b** was investigated by using Stille cross-couplings at the carbon positions and substitution reactions at the boron center. Our studies show that the reactivity order of the halogens under these conditions is: 8-Cl $\approx$ 1,7-Br > 3,5-Cl > 2,6-Cl > 4,4'-F.

Perhalogenated BODIPYs **1b–3b** were synthesized by bromination of the corresponding chloro-BODIPYs, as shown in Scheme 1. The starting 8-chloro-BODIPY (**1a**) was chlorinated using TCCA in acetic acid to give **2a** and **3a** in 73 and 81% yields, respectively. Further chlorination at the 1,7-positions was unsuccessful under a variety of conditions, including NCS/THF and TCCA/acetic acid. Therefore, Br₂/CH₂Cl₂ was selected for the bromination of the unsubstituted BODIPY positions of **1a–3a**. Treatment of BODIPYs **1a–3a** with a large excess of Br₂ in CH₂Cl₂ (up to 200 equivalents) at room temperature overnight, afforded the corresponding nonahalogenated BODIPYs **1b–3b** as the only products, in 78–84% yields. The ¹H NMR spectra of **1b–3b** showed complete disappearance of all the pyrrolic protons. Furthermore, significant differences were observed in the absorption spectra of **1b–3b** relative to the starting BODIPYs **1a–3a** in CH₂Cl₂. While **1b** and **2b** showed absorptions red-shifted by 52 and 15 nm, respectively, the absorption of **3b** showed a 9 nm blue-shift in agreement with previous results. The molecular structures of **1b–3b** were further confirmed by X-ray analysis, as shown in Figure 1. In all three cases, the 11-atom dipyrrole unit is nearly planar, having mean deviation 0.016 Å in **1b**, 0.035 Å in **2b** and 0.035 Å in **3b**. The boron atom lies slightly out of this plane by 0.171 Å, 0.195 Å and 0.175 Å for **1b**, **2b**, and **3b**, respectively. The C-Br distances in **1b–3b** are within the range 1.842(2) – 1.862(3) Å, with a mean value of 1.853 Å, while the C-Cl bonds are in the range

1.695(4) – 1.712(4) Å with mean 1.703 Å. The longer C-Br bonds are expected to be more reactive and less selective in the oxidative addition of Pd(0) compared with the C-Cl bonds, therefore platform **3b** was chosen for studies of regioselectivity in Pd(0)-catalyzed cross-coupling reactions.

Due to the mild base-free reaction conditions and general scope, the Stille reaction is particularly attractive among the palladium-catalyzed cross-coupling reactions for investigation of the selectivity of different halogen groups on BODIPY **3b**. Upon treating BODIPY **3b** with 1 equivalent of 2-(tributylstannyl)thiophene or tributylphenyltin in the presence of Pd(PPh₃)₄ (3 mol%) in refluxing toluene, TLC and MS both indicated a tri-coupled molecule as the major product, along with a large amount of starting BODIPY. This result suggested similar reactivity of three halogenated positions, potentially the 1,7,8-positions, based on previous studies on the reactivity of **3a**. When 4 equivalents of tin reagent were used and the mixture was refluxed overnight, the tri-coupled BODIPYs **4a,b** were obtained as the major products (Scheme 2) via regioselective coupling at the 1,7,8-positions, and isolated in 57–71% yields.

The structures of these products were confirmed by X-ray analysis, as shown in Figure 2. In the structure of **4a**, the 12-atom BODIPY core is nearly planar, with mean deviation 0.021 Å. The three phenyl planes form dihedral angles in the range 63.5–66.6° with it. BODIPY **4b** has a very similar structure, with the 12 atoms of the BODIPY core exhibiting mean deviation 0.049 Å and the three disordered thiophene rings forming dihedral angles in the range 60.3–64.0° with it.

The 1,3,5,7,8-pentaphenyl-(pentathienyl)-2,6-dichloro-BODIPYs **5a–b** were obtained regioselectively in 75–92% yields by treating BODIPYs **4a–b** with 10 equivalents of tin reagent under similar conditions, as shown in Scheme 2. This result is in agreement with previous investigations showing that Stille coupling occurs preferentially at the most reactive 3,5-chloro groups rather than at the 2,6-chloros. X-ray crystallography was used to confirm the regioselectivity of these reactions (Figure 2). The core of BODIPY **5a** has a conformation similar to those of **1b**, **2b**, and **3b**, with the B atom lying 0.183 Å (average of two independent molecules) out of the plane of the other 11 atoms. The phenyl groups are ordered in one molecule and disordered in the other, and in the ordered one they form dihedral angles in the range 52.5–72.1° with the core. BODIPY **5b** has a core conformation similar to **5a**, but with the B atom having a smaller out-of-plane deviation, 0.106 Å. Four of the five thiophene rings are disordered, with the ordered one at an α position and forming a small dihedral angle (27.4°) with the BODIPY core. The disordered thiophene substituents have variable conformations, forming dihedral angles in the range 52.2–73.2° with the core.

The global C-C coupling reactions were accomplished by using chloro[(tricyclohexylphosphine-2-(2'-aminobiphenyl) palladium [Pd(PCy₃)G₂]] as the catalyst, in the presence of 10 equivalents of 2-(tributylstannyl)thiophene to provide the corresponding 1,2,3,5,6,7,8-heptacoupled products **6a,b** in good to excellent yields (76%–95%), as shown in Scheme 3. The structures of these BODIPYs were confirmed by NMR and MS (see Supporting Information). Further functionalization of BODIPYs **6a,b** at the boron center using an excess of trimethylsilyl cyanide in the presence of BF₃•OEt₂ as

catalyst produced the corresponding nona-functionalized BODIPYs **7a,b** in 92–93% yields, as shown in Scheme 4. The formation of **7a,b** was clearly indicated by ^{11}B -NMR which showed disappearance of the BF_2 triplet at ca. δ 0.9 ppm and the appearance of a characteristic singlet at ca. δ -16 ppm for the $\text{B}(\text{CN})_2$ group.

The spectroscopic properties of the newly generated BODIPYs, including the UV-Vis absorption, emission, molar extinction coefficient and quantum yield, were investigated in dichloromethane solution and the results are summarized in Table 1 (see also Supporting Information). All BODIPYs show typical strong absorption bands ($\log \varepsilon = 4.48\text{--}5.02$) corresponding to the $S_0\text{--}S_1$ transition. The Stokes shifts vary significantly (8–100 nm) depending on the substituent groups on the BODIPY platform, and were largest for the $\text{B}(\text{CN})_2$ -functionalized BODIPYs bearing 2,6-thienyl groups. Similar enhancement of Stokes shifts have been reported for $\text{B}(\text{CN})_2$ -functionalized-BODIPYs and for thienyl-functionalized BODIPYs. From **1b** to **3b**, the decreasing number of bromo substituents induced slight blue-shifts (3–12 nm) in the absorption and emission spectra. The introduction of phenyl or thienyl groups at positions 1,7,8 of BODIPY **3b** caused small red-shifts in the absorption and emission bands (3–26 nm), in part due to the large dihedral angles of the aryl groups at these positions, in the order of 60–67°, as seen in the crystal structures (Figure 2). On the other hand, functionalization at the 3,5-positions caused larger red-shifts (up to 121 nm for **5b**), as previously observed, particularly for the thienyl-substituted BODIPYs. In addition, the 3,5- and 2,3,5,6-thienyl functionalized BODIPYs typically show larger Stokes shifts than the phenyl analogues, due to increased geometry relaxation. However, the thienyl groups also greatly decreased the quantum yields of the functionalized BODIPYs (< 0.1) due to their greater freedom of rotation compared with phenyl, which increases the amount of energy lost to non-radiative decay to the ground state.

In summary, perhalogenated BODIPYs **1b–3b** bearing chloro or bromo groups at all carbon-positions of the BODIPY platform were synthesized in good yields, via bromination of regioselectively chlorinated BODIPYs. The regioselective nonafunctionalization of BODIPY **3b** was investigated and confirmed by X-ray crystallography and/or NMR spectroscopy and MS spectrometry. Using $\text{Pd}(0)$ -catalyzed Stille reactions, excellent regioselectivity was observed for the 1,7-dibromo-8-chloro groups over the 3,5-dichloro with formation of **4a,b** and **5a,b**, and also for the 3,5-dichloro over the 2,6-dichloro groups with formation of **6a,b**. Under the Stille coupling conditions the BF_2 moiety was unreactive; however in the presence of $\text{TMSCN}/\text{BF}_3\cdot\text{OEt}_2$ it was converted into the corresponding $\text{B}(\text{CN})_2$ -functionalized BODIPYs in high yields.

The phenyl-functionalized BODIPYs show moderate quantum yields (0.57 and 0.39 for **4a** and **5a**, respectively) while the thienyl-substituted BODIPYs showed the largest red-shifted absorptions and emissions, with large Stokes shifts and low quantum yields (< 0.1). The nona-functionalized BODIPYs had the largest Stokes shifts (91–100 nm) and slightly reduced quantum yields relative to the BF_2 derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
X-ray structures of perhalogenated BODIPYs **1b–3b**, with 50% ellipsoids.

Figure 2.

X-ray structures of BODIPYs **4a,b** and **5a,b** with 50% ellipsoids. Only one orientation of the disordered substituents is shown.

Scheme 1.
Synthesis of perhalogenated BODIPYs **1b–3b**.

Scheme 2.
Regioselective cross-coupling reactions of BODIPY **3b**.

Scheme 3.
Stille cross-coupling reactions of BODIPYs **5a,b**.

Scheme 4.
Boron-substitution reactions of BODIPYs **6a,b**.

Table 1

Spectroscopic properties of BODIPYs in dichloromethane at room temperature.

BODIPY	Absorption λ_{max} (nm)	Log ϵ ($\text{M}^{-1}\text{cm}^{-1}$)	Emission λ_{max} (nm)	Φ_f^a	Stokes shift (nm)
1b	556	5.02	572	0.17	16
2b	553	5.01	568	0.14	15
3b	546	4.87	560	0.18	14
4a	549	4.77	563	0.57	14
5a	564	4.85	596	0.39	32
6a	581	4.66	666	0.08	85
7a	585	4.48	676	0.06	91
4b	572	4.72	580	<0.003	8
5b	633	4.56	681	0.02	48
6b	643	4.74	713	0.007	70
7b	639	4.48	739	0.005	100

^a[Φ_f] Rhodamine B (0.4 in methanol) for **1b–3b** and **4a**; cresyl violet (0.55 in methanol) was used as standard for **4b** and **5a–7a**, and methylene blue (0.03 in methanol) for **5b–7b**.