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Synthesis of 3,8-Dichloro-6-ethyl-1,2,5,7-tetramethyl–BODIPY from an Asymmetric Dipyrroketone and Reactivity Studies at the 3,5,8-Positions**

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Abstract

The asymmetric BODIPY **1a** (BODIPY=4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene), containing two chloro substituents at the 3,8-positions and a reactive 5-methyl group, was synthesized from the asymmetric dipyrroketone **3**, which was readily obtained from available pyrrole **2a**. The reactivity of 3,8-dichloro-6-ethyl-1,2,5,7-tetramethyl-BODIPY **1a** was investigated by using four types of reactions. This versatile BODIPY undergoes regioselective Pd^0-catalyzed Stille coupling reactions and/or regioselective nucleophilic addition/elimination reactions, first at the 8-chloro and then at the 3-chloro group, using a variety of organostannanes and N-, O-, and S-centered nucleophiles. On the other hand, the more reactive 5-methyl group undergoes regioselective Knoevenagel condensation with an aryl aldehyde to produce a monostyryl-BODIPY, and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gives the corresponding 5-formyl-BODIPY. Investigation of the reactivity of asymmetric BODIPY **1a** led to the preparation of a variety of functionalized BODIPYs with λ_{max} of absorption and emission in the ranges 487–587 and 521–617 nm, respectively. The longest absorbing/emitting compound was the monostyryl-BODIPY **16**, and the largest Stokes shift (49 nm) and fluorescence quantum yield (0.94) were measured for 5-thienyl-8-phenoxy-BODIPY **15**. The structural properties (including 16 X-ray structures) of the new series of BODIPYs were investigated.

Keywords

addition/elimination; BODIPY; fluorescence; Pd^0-catalyzed coupling; oxidation; substitution

Introduction

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene dyes, known generically as borondipyrromethenes or BODIPYs, are very versatile compounds that have attracted much attention since they were first reported in 1968.[1] Due to their remarkable properties,

**BODIPY=4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene.

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including high extinction coefficients, and generally high fluorescence quantum yields, low molecular weights, and high thermal and photochemical stabilities,[2] BODIPYs have been actively investigated in protein[3] and DNA-labeling,[3a, 4] drug delivery,[3a, 5] light-harvesting arrays,[6] fluorescent switches,[7] and in medical imaging and theranostics.[8]

A traditional approach to the synthesis of BODIPY scaffolds involves the condensation reaction between excess α-free pyrroles and aldehydes[9] in the presence of a Lewis acid, followed by DDQ oxidation to dipyrromethene, and then boron complexation, using boron trifluoride diethyl etherate under basic conditions. Alternatively, α-free pyrroles react with acid chlorides[10] or anhydrides[11] to directly yield dipyrromethenes. Another efficient methodology for the preparation of both symmetric and asymmetric *meso*-free BODIPYs is by condensation of a 2-formylpyrrole with an α-free pyrrole by using $POCl_3$ as a catalyst, followed by boron complexation.[12] Similarly, *meso*-aryl BODIPYs can be prepared from the reaction of 2-ketopyrrole[13] with an α-free pyrrole fragment.[14] Alternatively, the synthesis of symmetric 8-functionalized BODIPYs has been reported via a dipyrrothioketone[15] or dipyrroketone[16] intermediate; this route offers expeditious access to 8-thio or 8-halo-BODIPYs, respectively.

Using the above methods, a number of BODIPY platforms, such as those in Figure 1, have been synthesized and their reactivity investigated.[2] For example, the α-methyl groups on BODIPY platform **a** undergo Knoevenagel condensations with various aldehydes, to produce the corresponding styryl-BODIPYs that display significant redshifted absorption and emission spectra.[17] On the other hand, BODIPY platform **b** bearing 3,5-chloro groups undergoes milder Pd^0-catalyzed cross-coupling reactions and nucleophilic substitution reactions at these positions, producing a variety of functionalized BODIPYs for various applications.[18] Functionalizations at the 8-position of BODIPYs are reported for platform **c**,[15, 19] which undergoes nucleophilic addition/elimination and Liebeskind–Srogl cross-coupling reactions, and also for platform **d** bearing an 8-chloro group.[16] Compared with the 8-methylthio-BODIPY **c**, platform **d** is more versatile, reacting with a variety of N-, O-, and S-centered nucleophiles, as well as under a variety of Pd^0-catalyzed Stille, Suzuki, and Sonogashira coupling conditions, producing the corresponding functionalized BODIPYs in good to quantitative yields.

We have recently synthesized a symmetric 3,5,8-trichloro-BODIPY dye and explored its regioselectivity in Stille cross-coupling conditions.[20] Herein we report the synthesis of a versatile, asymmetric BODIPY **1a** bearing two chloro substituents at positions 3 and 8, as well as a reactive 5-methyl group, starting from an asymmetric dipyrroketone. We show that BODIPY **1a** can be regioselectively functionalized using four types of reactions, at positions 3, 5 and 8, to produce new conjugated BODIPYs. The nucleophilic addition/elimination and cross-coupling reactions both occur regioselectively at the 8-chloro followed by the 3-chloro position, allowing stepwise functionalization using various organometallic reagents and N-, O-, and S-centered nucleophiles. This is the first report on the *meso*-versus α-position regioselectivity of BODIPY nucleophilic reactions. Furthermore, the 5-methyl group undergoes regioselective Knoevenagel and oxidation reactions, providing access to additional functionalized BODIPY platforms. The structural and spectroscopic properties of the new BODIPYs were investigated.

Results and Discussion

Synthesis and structural characterization

The synthetic route to asymmetric 3,8-dichloro-BODIPY **1a** is outlined in Scheme 1. The conversion of the α-methyl group of readily available pyrrole **2a**[21] to a carboxylic acid produced **2b**,[22] which was acylated with thionyl chloride followed by reaction with dimethylamine gas[22b] affording 5-(*N*,*N*-dimethylamido) pyrrole **2c** in 85% yield. The asymmetric dipyrroketone **3** was prepared by reaction of pyrrole **2c** with phosphoryl chloride, followed by addition of commercially available 3-ethyl-2,4-dimethylpyrrole and subsequent hydrolysis using aqueous sodium acetate[23] in 86% overall yield. When excess phosgene was used to convert dipyrroketone **3** to the corresponding 5-chlorodipyrrin salt, the dipyrryl salt **4** was obtained instead by chlorination of the the α-methyl group of **3**, probably due to the presence of the electron-withdrawing benzyl ester.[20] Therefore, the benzyl ester was converted to an iodide by debenzylation followed by decarboxylative iodination[24] producing dipyrroketone **5** in 84% overall yield. The reaction of **5** with excess phosgene (15% in toluene) was accompanied by a color change from yellow to dark red, along with a down-field shift of the NH protons in the ^{1}H NMR spectrum. Subsequent boron complexation using excess $BF_3{\cdot}OEt_2$ and *N*,*N*-diisopropylethylamine (DIEA) produced BODIPY **1a** in 78% overall yield. The trans-chlorination of the 1-iododipyrroketone has been previously observed under these reaction conditions;[20] in addition, the 8-monochloro-BODIPY **1b** was obtained as a minor product from the reaction, in 6% yield.

The structures of BODIPYs **1a**,**b**, dipyrroketones **3** and **5** and dipyrrin **4** were confirmed by ^{1}H, ^{13}C NMR spectroscopy, HRMS (ESI-TOF) and, in the case of **1a**,**b**, **3**, and **4** also by X-ray crystallography (Figure 2). The structure of **1a** has two independent molecules and a disordered chloroform solvent molecule. The two molecules are almost identical with mean deviations from planarity of their 12-atom BODIPY cores of 0.027 and 0.036 Å, and a 9.8° torsional difference in the conformation of the ethyl group. BODIPY **1b** has four independent molecules, and mean deviations of their BODIPY cores are in the range of 0.023–0.054 Å. As in BODIPY **1a**, the conformations of the ethyl groups are essentially perpendicular to the BODIPY planes, with C-C-C-C torsion angles differing from 90° by 0.3–1.7°.

The conformation of dipyrroketone **3** is such that one pyrrole NH group is *syn* to the central carbonyl (N-C-C-O torsion angle 15.5°), while the other is *syn* to the benzyl ester carbonyl (torsion angle 6.0°). Both form intermolecular hydrogen bond dimers. On the other hand, dipyrrin **4** is the hydrochloride salt, with both N atoms protonated, forming hydrogen bonds to the chloride. The C_9N_2 dipyrryl group is planar to within a mean deviation of 0.017 Å.

Previous work has shown that symmetric 8-chloro-,[16] 3,5-dichloro-[18c,d], and 3,5,8-trichloro-BODIPYs[20] undergo Pd^0-catalyzed cross-coupling reactions, including Suzuki, Sonogashira, Heck, and Stille reactions to produce the corresponding aryl-, alkyl-, alkenyl- and alkynyl-BODIPYs. Among these, the mild Stille cross-couplings generally give high yields of the targeted functionalized BODIPYs. Under similar conditions, BODIPY **1a** reacted in the presence of one or three equivalents of aryltin reagent and 10 mol% of $[Pd(PPh_3)_4]$ in toluene, to produce the corresponding 8-aryl-3-chloro- and 3,8-diaryl-

BODIPYs, as shown in Scheme 2. The 3,8-diaryl-BODIPYs **6a**–**c** were produced in 63–86% yields when an excess of organotin reagent was used, whereas the reaction occurred regioselectively at the most reactive 8-chloride when only one equivalent of organotin was used in a twice diluted solution (ca. 10^{-3}M) to produce BODIPYs **7a**–**c** in 77–84% yields.

The regioselectivity of these Stille reactions was confirmed by X-ray crystallography, as shown in Figure 3. Crystals of BODIPYs **6a**–**c** and **7c** were grown from slow diffusion of hexane into a solution of BODIPY in dichloromethane. Except for BODIPY **7c**, all structures exhibit disorder, with the thiophene at the 8-position in **6a** having two conformations, as do both furans in **6b** and the ethyl group in **6c**. Mean deviations from planarity of the C_9BN_2 BODIPY cores are 0.072 Å for **6a**, 0.087 for **6b**, 0.054 for **6c**, and 0.013 Å for **7c**. The substituents at the 8-positions deviate by varying amounts from being perpendicular to the BODIPY cores, forming dihedral angles of 87.7° for **6a**, 83.0° for **6b**, 79.7° for **6c**, and 75.6° for **7c**, to minimize steric interactions with the 1,7-methyl groups. On the other hand, the aryl substituents at the 3-position deviate much more from orthogonality with the BODIPY core, forming dihedral angles of 41.7° for the thiophene in **6a**, 36.9° for the furan in **6b**, and 42.7° for the phenyl group in **6c**.

We took advantage of the regioselectivity observed in the Stille cross-coupling reactions to prepare BODIPYs **8**–**10** containing two different aryl groups at the 3- and 8-positions, by performing two consecutive Stille couplings using two different organotin reagents (Scheme 3). Therefore, BODIPY **1a** reacted with one equivalent of either 2-(tributylstannyl)thiophene or 2-(tributylstannyl)furan under Stille conditions to pro- duce the 3-monochloro-BODIPYs **7a** and **7b** respectively; these BODIPYs were subjected to a second Stille coupling with a different organotin producing BODIPYs **8**–**10** in 58–91% yields. While BODIPY **7a** bearing a 8-thienyl group readily reacted with 2-(tributylstannyl)furan producing **8** in high yield, BODIPY **7b** reacted slower and required three equivalents of organotin and a more concentrated reaction mixture (ca. 10^{-2}M) to produce BODIPYs **9** and **10** in moderate to high yields.

Crystals suitable for X-ray analysis were obtained for all three BODIPYs **8**–**10** and their structures are shown in Figure 4. In BODIPY **8**, both the furan and thiophene rings exhibit rotational disorder. In these three structures, the planarity of the BODIPY core and the dihedral angles formed by the planar substituents at the 3- and 8-positions closely resemble the features in compounds **6a**–**c** and **7c**. Mean deviations for the C_9BN_2 cores are 0.082 Å for **8**, 0.071 Å for **9**, and 0.018 Å for **10**. In BODIPY **8**, the thiophene at the 8-position forms an 87.2° angle with the core, and the 8-furyl groups form slightly lower corresponding dihedral angles of 84.8° in **9** and 78.0° in **10**. On the other hand the 3-furyl forms a dihedral angle of 38.6° with the BODIPY core plane in **8**, and the 3-thienyl forms an angle of 39.6° in **9**.

Nucleophilic addition/elimination reactions of BODIPY **1a** were also investigated using N-, O-, and S-centered nucleophiles, as shown in Scheme 4. Such reactions have been previously reported on 8-chloro-BODIPYs,[16a,b] and on 3,5-dichloro-BODIPYs,[18a,b] although the regioselectivity (i.e. *meso* vs. α-pyrrolic position) of these reactions has never been investigated. BODIPY **1a** reacted at room temperature, in the presence of potassium

carbonate, with up to 10 equivalents of either phenol or aniline as the nucleophile, regioselectively affording the 3-chloro-BODIPYs **11** and **12**, respectively, in high yields (87–95%). Similar conditions but using *p*-methylthiophenol as the nucleophile produced both the mono- and disubstituted products, showing the higher reactivity of the sulphur-centered nucleophile in these reactions. When 10 equivalents of *p*-methylthiophenol were used, the disubstituted product **13** was the major product, isolated in 93% yield. With 1.5 equivalents of thiol, the nucleophilic substitution reaction proceeded with regioselectivity at only the *meso*-position. These results illustrate the higher reactivity of the 8-chloro versus the 3-chloro group towards nucleophilic reactions.

X-ray crystallography confirmed the regioselectivity of these reactions; Figure 5 shows the structures of BODIPYs **11** and **12**. In both, there is a disorder in which the methyl and chloro substituents at the 3- and 5-positions are swapped, the minor component being present with about 8% population in both cases. Mean deviations from coplanarity of the C_9BN_2 core atoms are 0.033 Å for **11** and 0.061 Å for **12**. Interestingly, the plane of the 8-phenoxy group forms a dihedral angle of 86.7° with the BODIPY core in **11**, whereas the aniline plane forms an angle of 68.6° with the core in **12**.

Additionally, we investigated sucessive Stille cross-coupling followed by nucleophilic substitution reactions, and vice-versa, of BODIPY **1a**, as shown in Scheme 5. Using this approach and using similar conditions as described above for the two types of reactions, BODIPYs **14** and **15** were synthesized in 67 and 91% overall yields, respectively. The first reaction always occurs regioselectively at the most reactive 8-chloro, followed by the second reaction at the 3-chloro group.

The X-ray structure for BODIPY **14** was also obtained to confirm the regioselectivity of these reactions, and it is shown in Figure 5. The BODIPY core atoms are coplanar to within a mean deviation of 0.019 Å, and it forms a dihedral angle of 77.9° with the 8-phenyl group plane.

The 5-methyl group of BODIPY **1a** was unreactive under the Stille cross-coupling and nucleophilic addition/elimination reactions described above. However, it is known that the α-methyl groups of BODIPYs can react with aldehydes under Knoevenagel condensation conditions,[17] providing an additional reactive site for functionalization of BODIPY **1a**. Furthermore, we anticipated that this methyl group could be regioselectively oxidized under mild conditions, providing functionality for further derivatization and/or conjugation of the BODIPY.[25] To illustrate these reactions, BODIPY **6c** reacted with 4-formylanisole in the presence of *p*-toluenesulfonic acid and piperidine, in refluxing toluene for 72 h, regioselectively affording monostyryl-BODIPY **16** in 52% yield (Scheme 6). The monostyryl-BODIPY displays further redshifted absorbance and emission spectra (see below, Table 1 and Figure 7) and potential applications as a fluorescent sensor and photosensitizer.[17]

The 3-methyl group of BODIPY **6c** was also regioselectively oxidized in the presence of DDQ[26] giving formyl-BODIPY **17** in 26% yield. Formyl-BODIPYs are useful materials with potential applications as fluorescent sensors,[27] and have been shown to undergo

Wittig reactions with alkyl or aryl ylides,[28a] as well as condensations with malononitrile, methyl acetoacetate,[28b] and pyrrole[28c] to produce further functionalized compounds.

BODIPYs **16** and **17** were characterized by X-ray crystallography, as shown in Figure 6. BODIPY **16** crystallizes with two independent molecules in the asymmetric unit, and **17** as the chloroform solvate. In **16**, the BODIPY core atoms of the two molecules have mean deviations of 0.064 and 0.078 Å from co-planarity. The 8-phenyl group forms dihedral angles of 84.0 and 75.0° with the BODIPY core, the 3-phenyl group forms dihedral angles of 59.8 and 65.9° with the BODIPY core, and the styryl group forms angles of 26.2 and 22.7° with the BODIPY core. In BODIPY **17**, the core atoms have mean deviation of 0.075 Å from coplanarity, the 8-phenyl group forms a dihedral angle of 72.7° with the BODIPY core and the formyl C–C=O group forms a small dihedral angle of 6.2° with the BODIPY core.

Spectroscopic properties

The spectroscopic properties of BODIPYs **1**, **6a**–**c**, **7a**–**c**, and **8**–**17** in dichloromethane, namely their maximum absorption and fluorescence wavelengths, Stokes shifts, molar extinction coefficients and fluorescence quantum yields, are summarized in Table 1. Figure 7 shows the normalized absorption and fluorescence spectra of four representative BODIPYs (see the Supporting Information for additional BODIPY spectra). The BODIPYs have characteristic absorption and emission spectra, showing high molar absorption coefficients (logε=4.22–4.95) and Stokes-shifted fluorescence emission bands. Relative to BODIPY **1a** bearing 3,8-chloro groups, slight blueshifts (1–5 nm) were observed in the absorption and emission bands of BODIPYs **7c** and **14** bearing 8-phenyl groups, due to the large dihedral angles between this group and the BODIPY core (see Figures 3 and 5) as a result of 1,7-dimethyl substitution.[20] Larger blue-shifts were observed as a result from 8-phenoxy and 8-phenylamino substitution, as previously observed for 8-aryloxy and 8-arylamino-BODIPYs.[16, 29] This is in part due to the destabilization of the LUMO as a result of the electron-donating effect of these groups, which increases the HOMO–LUMO gap. However in contrast, the 8-phenoxy-BODIPY **11** showed a high fluorescence quantum yield (Φ_f=0.89), whereas the 8-phenylamino analogue **12** was practically nonfluorescent (Φ_f<0.002), probably due to intramolecular charge transfer in the excited state. The largest quantum yield was observed for the 8-phenoxy-BODIPY **15**, bearing a 5-thienyl group (Φ_f=0.94). On the other hand, substitution at the 8-position with an arylthio group, as in BODIPY **13**, induced a low quantum yield (Φ_f=0.13), as previously observed.[16, 29, 30]

The introduction of 8-thienyl and 8-furyl groups into the BODIPY core caused redshifts in the absorption and emission bands relative to BODIPY **1a**, particularly for the furan group, due to a decrease in the HOMO–LUMO gap. The largest redshifts in the 3,8-diaryl-BODIPYs were induced by furan groups at the 3-position, as in BODIPYs **6b** and **8**. However, these compounds show low fluorescence quantum yields (Φ_f<0.1), as a result of the greater freedom of rotation of the thienyl and furyl groups in comparison with phenyl, which increases the amount of energy lost to nonradiative decay to the ground state.[20, 31] The monostyryl-BODIPY **16** showed the most redshifted fluorescence emission (λ_{max}=617 nm) of all the BODIPYs investigated, and a high quantum yield (Φ_f=0.73). On the other

hand, the significant redshift in the absorption and emission of formyl-BODIPY **17** relative to **6c** is due to the conjugation of the carbonyl group with the BODIPY π-system, as indicated by the nearly co-planarity seen in the X-ray structure (Figure 6). The lower quantum yield determined for **17** relative to **6c** is in agreement with previous reports.[26]

The Stokes shifts of the 3-, 5-, and/or 8-substituted BODIPYs were generally larger than that of the starting BODIPY **1a**, and they were the largest for the 5-thienyl-BODIPYs **6a** and **15** (44 and 49 nm, respectively), in agreement with previous studies, probably due to increased geometry relaxation upon photoexcitation of these compounds.[20, 32] The 8-phenylamino-BODIPY **12** also showed larger Stokes shift (44 nm) than other functionalized BODIPYs, in agreement with previous investigations.[29]

Conclusion

The total synthesis of 3,8-dichloro-6-ethyl-1,2,5,7-tetramethyl-BODIPY **1a** from an unsymmetric dipyrroketone was accomplished in good yield. BODIPY **1a** undergoes four types of reactions: nucleophilic addition/elimination using N-, O-, and S-centered nucleophiles and Stille cross-coupling reactions at the 3- and 8-chloro groups, as well as Knoevenagel condensation and oxidation at the most reactive 5-methyl group. Excellent selectivity for the *meso*-8- over the 3-chloro group of **1a** was observed using both nucleophilic and Stille coupling reactions. This regioselectivity is likely the result of the higher electrophilicity of the *meso*-position versus the α-pyrrolic position based on consideration of mesomeric resonance structures, and of the different mechanistic pathways: S_NAr for α-pyrrolic and addition/elimination for the *meso*-position. X-ray crystallography (16 structures were obtained) was used to confirm the regioselectivity of the reactions.

The BODIPYs with 8-phenyl, 8-phenoxy, and 8-phenylamino groups showed blueshifted absorption and emission bands relative to BODIPY **1a**. All other BODIPYs displayed redshifted bands, with the monostyryl-BODIPY **16** showing the most redshifted absorption and emission of all BODIPYs. The Stokes shifts varied between 15–49 nm, with the 5-thienyl-8-phenoxy-BODIPY **15** showing the largest Stokes shift, and also the highest fluorescence quantum yield. In contrast to the phenyl- and phenoxy-substitued BODIPYs, the compounds bearing phenylamino, methylphenylthio, thienyl, and furyl groups at the 8-position of the BODIPY core showed very low fluorescence.

Experimental Section

Syntheses

General—All reagents and solvents were purchased from Sigma–Aldrich, Fisher Scientific or Alfa Aesar as reagent grade and used without further purification. Argon was used to protect the air-sensitive reactions. Analytical TLC (polyester backed, 60 Å, 0.2 mm, precoated, Sorbent Technologies) was used to monitor the reactions. Column chromatography was performed on silica gel (60 Å, 230–400 mesh, Sorbent Technologies). All ^{1}H and ^{13}C NMR spectra were obtained using Bruker AV-400 nanobay or AV-500 spectrometers (400 or 500 MHz for ^{1}H and 100 MHz for ^{13}C NMR, and 128 MHz for ^{11}B NMR spectra) in $CDCl_3$ with tetramethylsilane as an internal standard, at room temperature.

Chemical shifts (δ) are given in parts per million (ppm) versus $CDCl_3$ (7.27 ppm for ^1H NMR, 77.0 ppm for ^{13}C NMR). All high-resolution mass spectra (ESI-TOF) were obtained using a 6210 ESI-TOF mass spectrometer (Agilent Technologies). All UV/Vis spectra were recorded on a Varian Cary 50 spectrophotometer at room temperature. Fluorescence spectra were studied on a PTI QuantaMaster4/2006SE spectrofluorimeter with the slit width set at 3 nm at room temperature. A 10 mm path length quartz cuvette and spectroscopic grade solvents were used for the measurements. The determination of optical density (ε) was used for the solutions with an absorbance of λ_{max} between 0.5–1. The dilute solutions with absorbance of particular excitation wavelength between 0.02–0.05 were used for fluorescence quantum yield measurements. Rhodamine 6G (0.95 in ethanol), rhodamine B (0.49 in ethanol) and crystal violet perchlorate (0.54 in methanol) were used as external standards for calculation of the relative fluorescence quantum yields of the BODIPYs. All fluorescence quantum yields (Φ_f) were determined using the following equation:[33]

$$\Phi_x = \Phi_s \times (F_x/F_s) \times (A_s/A_x) \times (n_x/n_s)^2$$

in which Φ_x and Φ_s are the fluorescence quantum yields of the test samples and standards; F_x and F_s are the areas under the test samples' and standards' emission peaks; A_x *is* the absorbance at which test samples were excited; A_s the absorbance at which standards were excited; n_x *and* n_s are refractive indexes of test samples and standards.

5-Benzyloxycarbonyl-3,4-dimethylpyrrole-2-carboxylic acid (2b): Benzyl-3,4,5-trimethylpyrrole-2-carboxylate (**2a**)[21] (4.34 g, 17.84 mmol) was dissolved in carbon tetrachloride (270 mL). Sulfuryl chloride (7.69 g, 57 mmol) was added dropwise and the resulting solution was stirred overnight at room temperature. The reaction was stopped when the signals for RCH_2Cl (δ=4.6 ppm) and $CHCl_2$ (δ=6.7 ppm) disappeared from the ^1H NMR spectra measured in CCl_4. Organic solvents were removed under reduced pressure to give a red oil residue. The oil residue was dissolved in dioxane (70 mL) and a solution of sodium acetate (11 g) in water (60 mL) was added. The solution was stirred at 60–65°C for 3 h. The solution was then cooled to room temperature and extracted using diethyl ether (2×70 mL). The organic layers were combined and washed with 5% Na_2CO_3 aqueous solution. All the aqueous layers were then combined and acidified by slowly adding acetic acid (10 %). A white precipitate was filtered and washed thoroughly with water. The solid was redissovled in THF and dried over anhydrous Na_2SO_4. The organic solvents were removed under reduced pressure to give the title product (3.64 g) in 74.7% yield. ^1H NMR ($CDCl_3$, 400 MHz): δ=9.48 (1 H, s), 7.40–7.44 (5 H, m), 5.36 (2 H, s), 2.30 ppm (6 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=165.7, 160.7, 135.7, 129.2, 128.7, 128.4, 128.3, 127.7, 122.5, 120.8, 66.5, 10.1 ppm; MS (ESI-TOF) *m/z*: calcd for $C_{15}H_{16}NO_4$: 274.1074; found: 274.1076 [M +H]$^+$.

Benzyl 5-*N*,*N*-dimethylamido-3,4-dimethylpyrrole-2-carboxylate (2c): 5-Benzyloxycarbonyl-3,4-dimethylpyrrole-2-carboxylic acid (**2b**) (4.6 g, 16.8 mol) was added portionwise into thionyl chloride (65 mL) over 20 min. The mixture was stirred for 30 min at 40–45°C. The solvent was removed under reduced pressure to give an oily product. The

oily residue was redissolved in anhydrous benzene (130 mL). Then, dimethylamine gas was passed into the mixture for 10 min, and the mixture was stirred for another 2 h. The reaction was monitored by TLC analysis. After the reaction was completed, the organic solution was washed with water (100 mL), dilute acetic acid (10 %), and water again (100 mL), and then dried over anhydrous Na_2SO_4. The organic solvents were removed under reduced pressure to give a yellow oil. Purification by silica gel column chromatography with CH_2Cl_2/MeOH as the eluent gave the yellow titled product (4.3 g, 85.1 %). ^{1}H NMR: ($CDCl_3$, 400 MHz): δ= 9.05 (1 H, s), 7.34–7.42 (5 H, m), 5.31 (2 H, s), 3.06 (6 H, s), 2.28 (3 H, s), 2.04 ppm (3 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=164.7, 160.9, 136.1, 128.6, 128.2, 127.2, 126.3, 120.6, 119.8, 66.0, 10.3, 10.3 ppm; MS (ESI-TOF): *m*/*z*: calcd for $C_{17}H_{21}N_2O_3$: 301.1547; found: 301.1548 $[M+H]^+$.

Benzyl 8-ethyl-2,3,7,9-tetramethyl-5-dipyrroketone-1-carboxylate (3): Benzyl 5-*N*,*N*-dimethylamido-3,4-dimethylpyrrole-2-carboxylate (**2c**) (1.808 g, 6.02 mmol) was dissolved in warm $POCl_3$ (9.23 g, 60.2 mmol) The mixture was stirred at 50°C for 5 h and then cooled to room temperature. Excess $POCl_3$ was removed by evaporation using a ethylene dibromide under reduced pressure to give a red oily product that was then redissolved in CH_2Cl_2 (4 mL). A solution of 3-ethyl-2,4-dimethylpyrrole (0.82 mL, 6.02 mmol) in CH_2Cl_2 (4 mL) was added into the mixture under argon. The mixture was then stirred at 30°C overnight. The reaction was monitored by UV/Vis (reaction was stopped when extinctions at 351/399 nm reached a maximum). A solution of sodium acetate (10 g) in water (25 mL) was added into the mixture, which was then refluxed for 2–3 h. After the mixture was cooled to room temperature, chloroform (50 mL×3) was used to extract the organic components, which were washed with water, aqueous Na_2CO_3 solution (10 %), water again, and finally dried over anhydrous Na_2SO_4. The organic solvents were removed under reduced pressure and then the residue was crystallized from Et_2O. Further purification by silica gel chromatography (CH_2Cl_2/MeOH as the eluent) gave a pale yellow product (1.95 g), in 85.7% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.20 (1 H, s), 8.78 (1 H, s), 7.35–7.44 (5 H, m), 5.33 (2 H, s), 2.38–2.42 (2 H, q, $^3J_{(H,H)}$=7.6 Hz), 2.36 (3 H, s), 2.31 (3 H, s), 2.25 (3 H, s), 2.15 (3 H, s), 1.04–1.08 ppm (3 H, t, $^3J_{(H,H)}$=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=175.6, 161.2, 136.0, 133.0, 131.4, 128.6, 128.3, 128.2, 127.8, 127.7, 127.4, 125.4, 124.3, 120.4, 66.1, 17.3, 15.0, 11.5, 10.8, 10.3, 9.9 ppm; MS (ESI-TOF): *m*/*z*: calcd for $C_{23}H_{27}N_2O_3$: 379.2016: found: 379.2017 $[M+H]^+$.

8-Ethyl-1-iodo-2,3,7,9-tetramethyl-5-dipyrroketone (5): Pd/C (165 mg, 10%) was added to a 250 mL flask equipped with a magnetic stirrer. The flask was evacuated and refilled with THF (10 mL) and then with H_2. The mixture was stirred strongly for 15 min under a H_2 atmosphere. A THF (150 mL) solution of dipyrroketone **3** (1.65 g, 4.36 mmol) was added to the flask under H_2. The mixture was stirred at room temperature for 12 h. The reaction was stopped when the starting material disappeared according to TLC analysis. The palladium catalyst was filtered through a celite cake and washed with THF (100 mL×3). The organic solutions were combined and the solvents were removed under reduced pressure to yield a white solid. The solid products were dissolved in a mixture of $NaHCO_3$ (1.87 g, 22.3 mmol)/H_2O (110 mL) and MeOH (44 mL). A solution of I_2 (1.63 g, 6.42 mmol) in MeOH (26 mL) was added dropwise into the mixture at room temperature and brown solids

precipitated out immediately. The mixture was stirred for another 2 h at room temperature after the addition was completed. The solids were filtered and washed with water, saturated $NaHCO_3$ (aq), water again, and hexanes to remove excess iodine. The solids were redissolved in CH_2Cl_2 and dried over anhydrous Na_2SO_4. The organic solvents were removed under reduced pressure to give a pure pale yellow product (1.36 g, 84.2 %). ^{1}H NMR: ($CDCl_3$, 400 MHz): δ=8.79 (1 H, s), 8.64 (1 H, s), 2.38–2.43 (2 H, q, $^3J_{(H,H)}$=6.9 Hz), 2.45 (3 H, s), 2.17 (3 H, s), 2.13 (3 H, s), 2.00 (3 H, s), 1.06–1.10 ppm (3 H, t, $^3J_{(H,H)}$=6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=174.5, 133.6, 131.1, 126.9, 126.5, 126.4, 124.9, 124.8, 73.2, 17.3, 15.1, 11.9, 11.5, 11.2, 10.8 ppm; MS (ESI-TOF): *m*/*z*: calcd for $C_{15}H_{20}IN_2O$: 371.0615; found: 371.0613 [*M*+H]$^+$.

3,8-Dichloro-6-ethyl-1,2,5,7-tetramethyl-BODIPY (1a): Iododipyrroketone **5** (1.36 g, 3.67 mmol) was dissolved in chloroform (300 mL). The flask was evacuated and refilled with argon. Phosgene solution (15% in toluene, 26 mL) was added into the mixture and then it was stirred overnight at room temperature. The reaction was stopped when the starting materials were totally consumed. N_2 was purged into the flask to remove extra phosgene into a beaker containing saturated $NaHCO_3$ solution. The organic solvents were removed under reduced pressure to obtain a red solid. The red solid was added into another 500 mL round-bottom flask equipped with a stirrer. The flask was evacuated and refilled with argon. Chloroform (300 mL) and *N*,*N*-diisopropylethylamine (3.32 g, 25.7 mmol) were added under argon. The mixture was then stirred for 30 min. $BF_3{\cdot}OEt_2$ (5.2 g, 36.7 mmol) was added into the mixture which was stirred for another 10 h. The organic solution was washed with water, saturated $NaHCO_3$ solution, and brine. After drying over anhydrous Na_2SO_4, the organic solvents were removed under reduced pressure. Further purification by silica gel column chromatography with CH_2Cl_2/hexanes as the eluent gave the titled BODIPY **1a** (0.99 g, 78.2%) and its 8-monochloro-BODIPY byproduct (68 mg, 6 %).

For BODIPY 1a: ^{1}H NMR ($CDCl_3$, 400 MHz): δ=2.54 (3 H, s), 2.40–2.45 (8 H, m, overlapped), 2.01(3 H, s), 1.05–1.09 ppm (3 H, t, $^3J_{(H,H)}$= 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=158.4, 140.4, 138.2, 137.5, 135.4, 135.2, 130.8, 127.6, 124.5, 17.1, 14.5, 14.2, 14.1, 12.9, 8.9 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.18 ppm (t, $^1J_{(B,F)}$= 30.2 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{15}H_{17}BCl_2F_2N_2$: 344.0939; 344.0937 [*M*+H]$^+$.

For the 8-monochloro-BODIPY byproduct 1b: ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.40 (1 H, s), 2.53 (3 H, s), 2.40–2.45 (8 H, m, overlapped), 2.04 (3 H, s), 1.05–1.09 ppm (3 H, t, $^3J_{(H,H)}$=7.5 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): δ=157.8, 140.6, 138.7, 137.5, 137.0, 134.6, 131.0, 129.2, 126.7, 17.1, 14.6, 14.1, 13.4, 12.9, 10.0 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.05 ppm (t, $^1J_{(B,F)}$=30.3 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{15}H_{19}BClF_2N_2$: 310.1329; found: 310.1307 [*M*+H]$^+$.

General procedure for the preparation of BODIPYs 6a–c: Into a 50 mL round-bottom flask was added 3,8-dichloro-1,2,5,7- tetramethyl-BODIPY **1a** (34.4 mg, 0.1 mmol) and [$Pd(PPh_3)_4$] (10 mol%). The flask was then evacuated and refilled with argon 3 times. Dry toluene (30 mL) and organostannane regent (0.3 mmol) were introduced into the flask. The mixture was refluxed for 6 h under an argon atmosphere. The reaction was stopped when

TLC analysis showed the disappearance of starting material. Toluene was removed under reduced pressure. A flash column chromatography (CH_2Cl_2 as the eluent) was used to separate the crude products. Further purification by using a silica gel column with CH_2Cl_2/hexanes or ethyl acetate/hexanes as the eluent gave the desired disubstituted BODIPY products.

BODIPY 6a: Yield: 37.7 mg, 85.6%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.50–7.55 (3 H, m), 7.02–7.19 (3 H, m), 2.51 (3 H, s), 2.31–2.36 (2 H, q, $^3J_{(H,H)}$=7.6 Hz), 1.97 (3 H, s), 1.53 (6 H, s), 0.99–1.03 ppm (3 H, t, $^3J_{(H,H)}$=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=158.6, 145.4, 140.4, 138.2, 135.6, 134.9, 133.5, 133.0, 132.8, 132.1, 130.6, 130.5, 128.1, 127.7, 127.7, 127.5, 127.0, 17.1, 14.4, 13.0, 11.3, 11.1, 10.4 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.66 ppm (t, $^1J_{(B,F)}$=32.3 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{23}H_{23}BF_2N_2S_2$: 440.1473; found: 440.1445 $[M+H]^+$.

BODIPY 6b: Yield: 25.8 mg, 63.2%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.49–7.64 (3 H, m), 6.44–6.59 (3 H, m), 2.57 (3 H, s), 2.32–2.38 (2 H, q, $^3J_{(H,H)}$=7.4 Hz), 2.17 (3 H, s), 1.52 (3 H, s), 1.50 (3 H, s), 1.01–1.05 ppm (3 H, t, $^3J_{(H,H)}$=7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.9, 147.3, 146.0, 143.6, 142.5, 142.4, 139.2, 138.7, 134.4, 133.8, 133.5, 127.7, 126.3, 115.2(t), 112.3, 111.7, 111.5, 17.1, 14.4, 13.0, 10.9, 10.4 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.87 ppm (t, $^1J_{(B,F)}$=32.7 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{23}H_{23}BF_2N_2O_2$: 408.193; found: 408.1905 $[M+H]^+$.

BODIPY 6c: Yield: 34.6 mg, 80.8 %; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.35–7.49 (10 H, m), 2.46 (3 H, s), 2.27–2.33 (2 H, q, $^3J_{(H,H)}$=7.4 Hz), 1.79 (3 H, s), 1.32 (3 H, s), 1.35 (3 H, s), 0.96–0.99 ppm (3 H, t, $^3J_{(H,H)}$= 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=156.8, 153.2, 141.3, 139.8, 138.2, 135.8, 134.0, 132.9, 131.8, 130.9, 130.0, 129.1, 128.9, 128.4, 128.3, 127.6, 126.4, 17.1, 14.4, 12.8, 12.1, 11.8, 9.7 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.67 ppm (t, $^1J_{(B,F)}$=32.4 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{27}H_{26}BFN_2$: 408.2282; found: 408.2284 $[M-F]^+$.

General procedure for the preparation of BODIPYs 7a–c: Into a 100 mL round-bottom flask was added BODIPY **1a** (34.4 mg, 0.1 mmol) and $[Pd(PPh_3)_4]$ (10 mol%). The flask was then evacuated and refilled with argon 3 times. Dry toluene (60 mL) and organostannane regent (0.1 mmol) were introduced into the flask. The mixture was refluxed at 80°C under Ar. The reaction was stopped when TLC analysis showed the disappearance of starting material. Toluene was removed under reduced pressure. Silica gel flash column chromatography was used for purification of the products, eluting with dichloromethane/hexanes or ethyl acetate/hexanes.

BODIPY 7a: Yield: 33 mg, 84%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.52–7.54 (1 H, q, $^3J_{(H,H)}$=4.0, $^4J_{(H,H)}$=1.1 Hz), 7.14–7.16 (1 H, q, $^3J_{(H,H)}$=3.5, $^3J_{(H,H)}$=1.5 Hz); 6.99–7.00 (1 H, q, $^3J_{(H,H)}$=2.3, $^4J_{(H,H)}$= 1.1 Hz), 2.58 (3 H, s), 2.31–2.37 (2 H, q, $^3J_{(H,H)}$=7.5 Hz), 1.92 (3 H, s), 1.52 (3 H, s), 1.48 (3 H, s), 1.00–1.03 ppm (3 H, t, $^3J_{(H,H)}$=7.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=159.4, 141.1, 139.0, 138.1, 135.1, 134.8, 133.4, 132.7, 130.2, 128.1, 127.7, 127.6, 124.3, 17.1, 14.3, 13.0, 11.3, 11.1, 8.8 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz):

δ=0.35 ppm (t, $^{1}J_{(B,F)}$=31.0 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{19}H_{20}BClF_2N_2S$: 392.1206; found: 392.1208 [*M*+H]$^{+}$.

BODIPY 7b: Yield: 29 mg, 77%; ^{1}H NMR ($CDCl_3$, 400 MHz): 7.63–7.64 (1 H, m), 6.56–6.57 (1 H, q, $^{3}J_{(H,H)}$=1.8, $^{3}J_{(H,H)}$=1.5 Hz), 6.45–6.46 (1 H, m), 2.57 (3 H, s), 2.32–2.38 (2 H, q, $^{3}J_{(H,H)}$=7.6 Hz), 1.93 (3 H, s), 1.52 (3 H, s), 1.49 (3 H, s), 1.01–1.05 ppm (3 H, t, $^{3}J_{(H,H)}$=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=160.3, 145.1, 142.8, 140.8, 139.3, 137.7, 135.1, 134.1, 130.6, 126.9, 124.3, 111.8, 111.6, 17.1, 14.3, 13.1, 10.8, 10.6, 8.8 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.32 ppm (t, $^{1}J_{(B,F)}$=30.9 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{19}H_{20}BClF_2N_2O$: 376.1434; found: 376.1410 [*M*+H]$^{+}$.

BODIPY 7c: Yield: 32.4 mg, 83.8 %; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.28–7.50 (5 H, m), 2.58(3 H, s), 2.29–2.35 (2 H, q, $^{3}J_{(H,H)}$=7.5 Hz), 1.90 (3 H, s), 1.28 (3 H, s), 1.30 (3 H, s), 0.98–1.02 ppm (3 H, t, $^{3}J_{(H,H)}$= 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=158.5, 140.8, 140.5, 138.4, 137.9, 135.1, 134.7, 132.2, 129.4, 129.2, 129.1, 128.1, 124.0, 17.1, 14.4, 12.9, 12.1, 11.9, 8.8 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ= 0.41 ppm (t, $^{1}J_{(B,F)}$=31.1 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{21}H_{22}BClFN_2$: 366.1579; 366.1567 [*M*−F]$^{+}$.

BODIPY 8: Into a 50 mL round-bottom flask was added BODIPY **7a** (19.6 mg, 0.05 mmol) and [$Pd(PPh_3)_4$] (10 mol%). The flask was then evacuated and refilled with argon 3 times. Dry toluene (20 mL) and tributyl-(2-furyl)stannane (0.1 mmol) were introduced into the flask. The mixture was refluxed for 6 h under Ar. The reaction was stopped when TLC analysis showed the disappearance of starting materials. Toluene was removed under reduced pressure. A flash column chromatography (CH_2Cl_2 as the eluent) was used to separate the crude products. Further purification by silica gel column chromatography with ethyl acetate/hexanes as the eluent gave the desired disubstituted BODIPY product. Yield: 19.3 mg, 91 %; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.61 (1 H, m), 7.52–7.53 (1 H, m), 7.46–7.47 (1 H, m), 7.15–7.17 (1 H, m), 7.00–7.01 (1 H, m), 6.59–6.60 (1 H, m), 2.57 (3 H, s), 2.30–2.37 (2 H, q, $^{3}J_{(H,H)}$=7.4 Hz), 2.15 (3 H, s), 1.52 (6 H, s), 1.00–1.04 ppm (3 H, t, $^{3}J_{(H,H)}$=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=157.2, 147.2, 143.5, 141.8, 139.7, 139.0, 135.8, 134.5, 133.1, 132.8, 128.2, 127.8, 127.6, 127.4, 114.9 (t), 112.2, 17.1, 14.4, 12.9, 11.1, 11.0, 10.9 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.84 ppm (t, $^{1}J_{(B,F)}$=32.8 Hz); MS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{23}BF_2N_2NaOS$: 446.1521; 446.1517 [*M*+Na]$^{+}$.

BODIPY 9: Into a 50 mL round bottom flask was added BODIPY **7b** (18.8 mg, 0.05 mmol) and [$Pd(PPh_3)_4$] (10 mol%). The flask was then evacuated and refilled with argon for 3 times. Dry toluene (20 mL) and 2-(tributylstannyl)thiophene (0.15 mmol) were introduced into the flask. The mixture was refluxed for 6 h under Ar. The reaction was stopped when TLC analysis showed the disappearance of starting material. Toluene was removed under reduced pressure. A flash column chromatography (CH_2Cl_2 as eluent) was used to give the crude products. Further purification by silica gel column chromatography with ethyl acetate/hexanes as the eluent gave the desired disubstituted BODIPY product. Yield: 19 mg, 89.6%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.67 (1 H, m), 7.51–7.56 (2 H, m), 7.18–7.20 (1 H, m), 6.59 (1 H, m), 6.48–6.49 (1 H, m), 2.51 (3 H, s), 2.32–2.37 (2 H, q, $^{3}J_{(H,H)}$=7.6 Hz), 1.99 (3 H, s), 1.53 (6 H, s), 1.00–1.04 ppm (3 H, t, $^{3}J_{(H,H)}$=7.5 Hz); ^{13}C NMR ($CDCl_3$, 100

MHz): δ=159.4, 146.0, 145.8, 142.6, 140.0, 137.9, 134.8, 134.1, 132.8, 132.6, 130.6 (t), 127.8, 127.6, 127.1, 127.0, 111.7, 112.5, 17.1, 14.4, 13.1, 10.7, 10.5, 10.4 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.68 ppm (t, $^1J_{(B,F)}$=32.2 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{23}H_{24}BF_2N_2OS$: 424.1701; found: 424.1674 [*M*+H]$^+$.

BODIPY 10: Into a 50 mL round-bottom flask was added *meso*-substituted BODIPY **7b** (18.8 mg, 0.05 mmol) and [$Pd(PPh_3)_4$] (10 mol%). The flask was then evacuated and refilled with argon 3 times. Dry toluene (4 mL) and trimethyl[(tributylstannyl)ethynyl]silane (0.06 mmol) were introduced into the flask. The mixture was refluxed for 6 h under an argon atmosphere. The reaction was stopped when TLC analysis showed the disappearance of starting material. Toluene was removed under reduced pressure. A flash column chromatography (CH_2Cl_2 as eluent) was used to separate the crude products. Further purification by silica gel column chromatography with ethyl acetate/hexanes as the eluent gave the desired disubstituted BODIPY product. Yield: 12.7 mg, 58%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.62 (1 H, m), 6.54–6.56 (1 H, q, $^3J_{(H,H)}$=1.7 Hz, $^3J_{(H,H)}$=1.5 Hz), 6.43–6.44 (1 H, m), 2.59 (3 H, s), 2.32–2.37 (2 H, q, $^3J_{(H,H)}$=7.5 Hz), 1.99 (3 H, s), 1.52 (3 H, s), 1.45 (3 H, s), 1.00–1.04 (3 H, t, $^3J_{(H,H)}$=7.5 Hz), 0.31 ppm (9 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 162.1, 145.8, 143.0, 141.1, 136.3, 135.8, 132.7, 132.6, 132.2, 126.9, 112.0, 111.8, 109.3, 97.3, 17.5, 14.6, 13.7, 10.9, 10.7, 10.0, 0.2 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.28 ppm (t, $^1J_{(B,F)}$=30.0 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{24}H_{30}BF_2N_2OSi$: 438.2219; found: 438.2223 [*M*+H]$^+$.

General procedure for the preparation of BODIPYs 11–13: Into a 5 mL round-bottom flask was added BODIPY **1a** (17.2 mg, 0.05 mmol), nucleophile (1–10 equiv), and K_2CO_3 (13.8 mg, 0.1 mmol). CH_2Cl_2 (0.5 mL) was added into the flask. The mixture was stirred at room temperature. The reaction was stopped when TLC analysis showed the disappearance of starting material. The crude product was subjected to a short flash column chromatography (CH_2Cl_2 as eluents) to remove polar byproducts. Further purification by silica gel column chromatography with CH_2Cl_2/hexanes or ethyl acetate/hexanes as the eluent gave the desired BODIPY products.

BODIPY 11: Yield: 19.1 mg, 94.9 %; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.99–7.34 (5 H, m), 2.57 (3 H, s), 2.34–2.38 (2 H, q, $^3J_{(H,H)}$=7.1 Hz), 2.01 (3 H, s), 1.98 (3 H, s), 1.93 (3 H, s), 1.01–1.04 ppm (3 H, t, $^3J_{(H,H)}$= 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=158.6, 157.5, 150.5, 138.2, 137.8, 135.2, 133.9, 130.5, 128.3, 125.6, 123.5, 123.0, 114.7, 16.9, 14.4, 13.0, 12.0, 11.7, 8.6 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ= 0.36 ppm (t, $^1J_{(B,F)}$=30.5 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{21}H_{23}BClF_2N_2O$: 402.1591; found: 402.1564 [*M*+H]$^+$.

BODIPY 12: Yield: 17.4 mg, 86.6%; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 6.93–7.25 (5 H, m), 6.55 (1 H, s), 2.55 (3 H, s), 2.31–2.37 (2 H, q, $^3J_{(H,H)}$=7.4 Hz), 1.98 (3 H, s), 1.91 (3 H, s), 1.89 (3 H, s), 1.00–1.03 ppm (3 H, t, $^3J_{(H,H)}$=7.6 Hz); ^{13}C (100 MHz, $CDCl_3$): δ=153.5, 143.5, 140.6, 135.3, 134.9, 133.0, 132.6, 129.8, 127.2, 125.5, 122.8, 118.0, 17.0, 14.7, 12.9, 12.8, 12.64, 8.8 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ= 0.47 ppm (t, $^1J_{(B,F)}$=31.1 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{21}H_{24}BClF_2N_3$: 401.1751; found: 401.1725 [*M*+H]$^+$.

BODIPY 13: Yield: 24.2 mg, 93%; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.05–7.22 (8 H, m), 2.60 (3 H, s), 2.36–2.41 (5 H, m, overlapped), 2.31 (6 H, s), 2.29 (3 H, s), 1.72 (3 H, s), 1.01–1.04 ppm (3 H, t, $^{3}J_{(H,H)}$= 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.4, 143.6, 141.9, 138.2, 137.2, 136.3, 135.9, 134.3, 133.0, 132.8, 132.1, 131.7, 130.3, 129.8, 129.4, 126.3, 21.1, 21.0, 17.2, 14.5, 14.4, 13.2, 10.1 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.51 ppm (t, $^{1}J_{(B,F)}$=31.5 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{29}H_{32}BF_2N_2S_2$: 520.2099; found: 520.2085 $[M+H]^+$.

BODIPY 14: Into a 5 mL round-bottom flask were added BODIPY **7c** (19.3 mg, 0.05 mmol), thiolcarborane (88 mg, 0.5 mmol), and K_2CO_3 (13.8 mg, 0.1 mmol). CH_2Cl_2 (1 mL) was added into the flask. The mixture was then stirred at room temperature. The reaction was quenched with water when TLC analysis showed the disappearance of starting material. CH_2Cl_2 (10 mL×3) was used to extract the organic components. Organic solvents were combined, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the crude product. Further purification by silica gel column chromatography with ethyl acetate/hexanes as the eluent gave the titled product (17.7 mg, 67.3 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.24–7.5 (5 H, m), 4.59 (1 H, s), 1.76–3.34 (10 H, m), 2.63 (3 H, s), 2.32–2.38 (2 H, q, $^{3}J_{(H,H)}$=7.6 Hz), 2.04 (3 H, s), 1.36 (3 H, s), 1.29 (3 H, s), 0.99–1.03 ppm (3 H, t, $^{3}J_{(H,H)}$=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.0, 143.4, 141.6, 137.3, 135.5, 134.9, 134.7, 134.2, 133.3, 132.5, 129.4(t), 128.0, 127.9, 66.3, 66.2, 17.1, 14.1, 13.6, 12.2, 12.1, 11.1 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.29 (1 B, t, $^{1}J_{(B,F)}$=31.1 Hz), −0.85 (1 B, d, $^{1}J_{(B,H)}$=142 Hz), −4.74 (1 B, d, $^{1}J_{(B,H)}$= 128 Hz), −10.1 to −12.92 ppm (8 B, m); MS (ESI-TOF): *m*/*z*: calcd for $C_{23}H_{24}B_{11}F_2N_2S$: 527.3520; found: 527.3512 $[M+H]^+$.

BODIPY 15: Into a 50 mL round-bottom flask was added *meso*-substiutued BODIPY **11** (10 mg, 0.025 mmol) and $[Pd(PPh_3)_4]$ (10 mol%). The flask was then evacuated and refilled with argon 3 times. Dry toluene (20 mL) and 2-(tributylstannyl)thiophene (0.05 mmol) were introduced into the flask. The mixture was refluxed for 6 h under an argon atmosphere. The reaction was stopped when TLC analysis showed the disappearance of starting material. Toluene was removed under reduced pressure. A flash column chromatography (CH_2Cl_2 as the eluent) was used to obtain the crude product. Further purification by silica gel column chromatography with ethyl acetate/hexanes as the eluent gave the desired product. Yield: 10.2 mg, 90.6%; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.50–7.53 (2 H, m), 7.32–7.36 (2 H, m), 7.17–7.19 (1 H, q, $^{3}J_{(H,H)}$=3.6, $^{3}J_{(H,H)}$=1.5 Hz), 7.05–7.10 (3 H, m), 2.50 (3 H, s), 2.31–2.37 (2 H, q, $^{3}J_{(H,H)}$=7.6 Hz), 2.04 (3 H, s), 2.02 (3 H, s), 1.99 (3 H, s), 0.99–1.03 ppm (3 H, t, $^{3}J_{(H,H)}$=7.6 Hz); ^{13}C (100 MHz, $CDCl_3$): δ=157.8, 157.7, 150.9, 145.4, 137.4, 135.3, 133.6, 132.7, 130.4 (t), 130.1, 128.3, 127.6, 127.0, 126.7, 123.0, 122.8, 114.9, 17.0, 14.5, 13.0, 11.9, 11.7, 10.2 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.64 ppm (t, $^{1}J_{(B,F)}$=32.0 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{25}H_{26}BF_2N_2OS$: 450.1858; found: 4*50*.1831 $[M+H]^+$.

BODIPY 16: Into a 50 mL round-bottom flask was added BODIPY **6c** (21.4 mg, 0.05 mmol), molecular sieves, and methyl 4-formylanisole (68 mg, 0.5 mmol) in toluene (10 mL). *p*-TsOH (10 mg) and piperidine (0.1 mL) were added into the mixture. The mixture was stirred and refluxed for 72 h under an argon atmosphere. The reaction was stopped when TLC analysis showed the disappearance of starting material. The mixture was cooled

to room temperature and filtered to remove the moleculer sieves. The filtrate was poured into water (20 mL) and CH_2Cl_2 (20 mL×3) was used to extract the organic components. The organic solvents were combined, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give the crude product. Further purification by silica gel column chromatography with ethyl acetate/hexanes as the eluent gave the styryl-BODIPY **16** (14.2 mg, 52 %). ^{1}H NMR (400 Hz, $CDCl_3$): δ=7.13–7.60 (14 H, m), 6.85–6.87 (2 H, d, $^3J_{(H,H)}$= 8 Hz), 3.83 (3 H, s), 2.56–2.62 (2 H, q, $^3J_{(H,H)}$=7.5 Hz), 1.80 (3 H, s), 1.36 (6 H, s), 1.13–1.16 ppm (3 H, t, $^3J_{(H,H)}$=7.3 Hz); ^{13}C NMR (400 Hz, $CDCl_3$): δ=160.3, 154.1, 152.1, 140.3, 140.1, 138.4, 136.2, 136.1, 133.9, 132.9, 132.8, 131.9, 130.0, 129.1, 128.9, 128.5, 127.7, 127.2, 117.9, 114.1, 55.4, 18.4, 14.0, 12.2, 11.6, 9.8 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.90 ppm (t, $^1J_{(B,F)}$=32.7 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{35}H_{33}BF_2N_2O$: 545.2685; found: 545.2687 $[M+H]^+$.

BODIPY 17: Into a 50 mL round-bottom flask was added BODIPY **6c** (21.4 mg, 0.05 mmol). The flask was then evacuated and refilled with argon 3 times. Dry toluene (10 mL) was added. The temperature was raised to 110°C. A solution of DDQ (56.8 mg, 0.25 mmol) in toluene (10 mL) was added slowly into the mixture, which was stirred and refluxed under an argon atmosphere. The reaction was stopped when TLC analysis showed the disappearance of starting material. Solvents were removed under reduced pressure to give the crude product. Further purification by silica gel column chromatography or preparative TLC plates with ethyl acetate/hexanes as the eluent gave BODIPY **17** (5.7 mg, 25.8% yield). ^{1}H NMR (400 Hz, $CDCl_3$): δ=10.30 (1 H, s), 7.37–7.59 (5 H, m), 2.67–2.71 (2 H, q, $^3J_{(H,H)}$=7.4 Hz), 1.84 (3 H, s), 1.44 (3 H, s), 1.31 (3 H, s), 1.00–1.03 ppm (3 H, t, $^3J_{(H,H)}$=7.1 Hz); ^{13}C NMR (400 Hz, $CDCl_3$): δ=186.3, 164.5, 144.7, 144.5, 141.2, 137.2, 136.3, 135.8, 134.9, 132.6, 131.5, 130.9, 130.0, 129.6, 129.5, 129.3, 128.1, 127.8, 17.6, 14.3, 12.9, 10.7, 10.0 ppm; ^{11}B NMR ($CDCl_3$, 128 MHz): δ=0.69 ppm (t, $^1J_{(B,F)}$= 32.1 Hz); MS (ESI-TOF): *m*/*z*: calcd for $C_{27}H_{26}BF_2N_2O$: 442.2137; found: 442.2145 $[M+H]^+$.

Crystal data

Diffraction data were collected at low temperature (90–105 K) on either a Nonius KappaCCD diffractometer equipped with $Mo_{K\alpha}$ radiation (λ=0.71073 Å) or a Bruker Kappa Apex-II DUO diffractometer equipped with Mo or $Cu_{K\alpha}$ radiation (λ=1.54184 Å). Refinement was by full-matrix least squares using SHELXL, with H atoms in idealized positions, except for those on N in **3**, **4**, and **12**, which were refined. BODIPYS **1a** and **16** have two independent molecules, and **1b** has four. **1a**, **6b**, and **16** were nonmerohedral twins, and disorder was present in **1a**, **6a**–**c**, **8**, **11**, and **12**. Compounds **1a** and **17** were chloroform solvates. The absolute structures of both noncentrosymmetric crystals **1b** and **7c** were determined. For **1a**: $C_{15}H_{17}BCl_2F_2N_2{\cdot}0.5CHCl_3$, triclinic *P*-1, *a*=8.4888(3), *b*=13.9111(6), *c*=14.8676(6) Å, α=86.609(3), β=88.646(2), γ=89.580(2)°, *Z*=4, *T*=90 K, *R*=0.067; **1b**: $C_{15}H_{18}BClF_2N_2$, monoclinic $P2_1$, *a*= 15.4384(5), *b*=11.5896(4), *c*=16.8479(5) Å, β=99.215(2)°, *Z*=8, *T*= 90 K, *R*=0.047; **3**: $C_{23}H_{26}N_2O_3$, monoclinic $P2_1/n$, *a*=7.7071(6), *b*= 12.3770(9), *c*=21.4131(17) Å, β=92.673(4)°, *Z*=4, *T*=100 K, *R*= 0.045; **4**: $[C_{23}H_{26}ClN_2O_2]Cl$, triclinic *P*-1, *a*=8.1637(4), *b*=9.5889(5), *c*=13.6082(8) Å, α=94.850(3), β=97.737(2), γ=92.855(2)°, *Z*=2, *T*=100 K, *R*=0.033; **6a**: $C_{23}H_{23}BF_2N_2S_2$, triclinic P-1, *a*=9.5771(14), *b*=10.3269(15), *c*=11.567(2) Å, α=77.851(8), β=66.885(6), γ= 79.384(7)°,

Z=2, *T*=100 K, *R*=0.041; **6b**: $C_{23}H_{23}BF_2N_2O_2$, triclinic *P*-1, *a*=9.362(2), *b*=10.155(2), *c*=11.682(3) Å, *α*=76.840(6), *β*= 66.796(6), *γ*=77.094(6)°, *Z*=2, *T*=90 K, *R*=0.089; **6c**: $C_{27}H_{27}BF_2N_2$, monoclinic $P2_1/n$, *a*=11.4039(6), *b*=7.9247(4), *c*=24.2010(12) Å, *β*=91.650(3)°, *Z*=4, *T*=90 K, *R*=0.047; **7c**: $C_{21}H_{22}BClF_2N_2$, monoclinic *Pc*, *a*=7.6918(2), *b*=8.2818(2), *c*=14.8858(4) Å, *β*= 94.762(2)°, *Z*=2, *T*=105 K, *R*=0.035; **8**: $C_{23}H_{23}BF_2N_2OS$, triclinic *P*-1, *a*=9.5378(3), *b*=10.1969(3), *c*=11.5554(4) Å, *α*=76.414(2), *β*= 66.800(2), *γ*=78.800(2)°, *Z*=2, *T*=90 K, *R*=0.040; **9**: $C_{23}H_{23}BF_2N_2OS$, triclinic *P*-1, *a*=9.4222(2), *b*=10.2488(2), *c*= 11.6233(3) Å, *α*=78.492(2), *β*=66.845(2), *γ*=77.813(2)°, *Z*=2, *T*= 90 K, *R*=0.043; **10**: $C_{24}H_{29}BF_2N_2OSi$, monoclinic $P2_1/c$, *a*=6.9871(2), *b*=22.5959(8), *c*=14.6041(6) Å, *β*=93.098(2)°, *Z*=4, *T*=90 K, *R*= 0.041; **11**: $C_{21}H_{22}BClF_2N_2O$, triclinic *P*-1, *a*=9.4115(3), *b*=10.4033(4), *c*=11.3995(4) Å, *α*=66.223(2), *β*=77.459(2), *γ*=68.527(2)°, *Z*=2, *T*=90 K, *R*=0.051; **12**: $C_{21}H_{23}BClF_2N_3$, monoclinic *C*2/*c*, *a*= 21.8367(10), *b*=8.9694(4), *c*=21.9939(8) Å, *β*=114.299(2)°, *Z*=8, *T*=90 K, *R*=0.050; **14**: $C_{23}H_{33}B_{11}F_2N_2S$, triclinic *P*-1, *a*=6.9030(7), *b*=12.0111(12), *c*=17.1906(14) Å, *α*=77.599(7), *β*=79.990(7), *γ*= 83.195(7)°, *Z*=2, *T*=90 K, *R*=0.070; **16**: $C_{35}H_{33}BF_2N_2O$, triclinic *P*-1, *a*=11.5598(5), *b*=13.2476(6), *c*=19.1537(8) Å, *α*=85.869(2), *β*= 86.135(2), *γ*=72.967(2)°, *Z*=4, *T*=90 K, *R*=0.048; **17**: $C_{27}H_{25}BF_2N_2O{\cdot}CHCl_3$, triclinic *P*-1, *a*=9.6902(5), *b*=10.7446(6), *c*= 13.9386(8) Å, *α*=68.727(3), *β*=75.951(3), *γ*=73.728(3)°, *Z*=2, *T*= 90 K, *R*=0.037;

CCDC 1038325, 1038326, 1038327, 1038328, 1038329, 1038330, 1038331, 1038332, 1038333, 1038334, 1038335, 1038336, 1038337, 1038338, 1038339, and 1038340 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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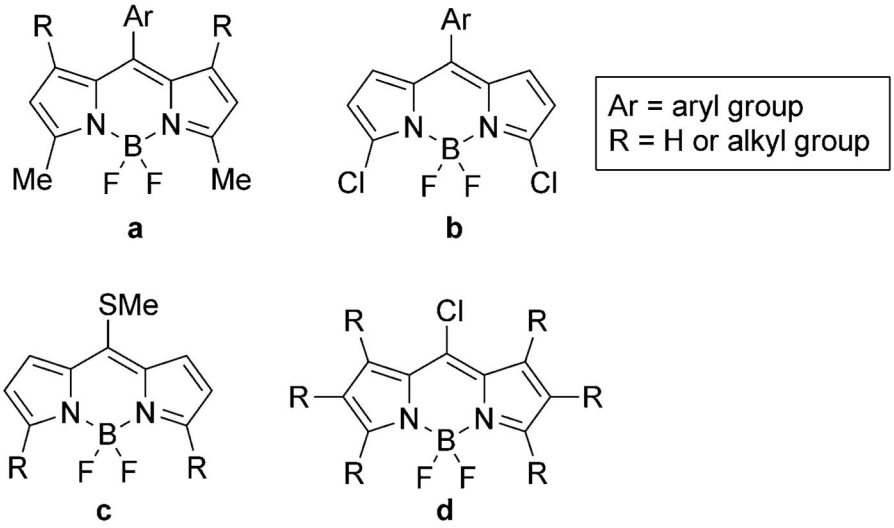


Figure 1.
Examples of reported BODIPY platforms.

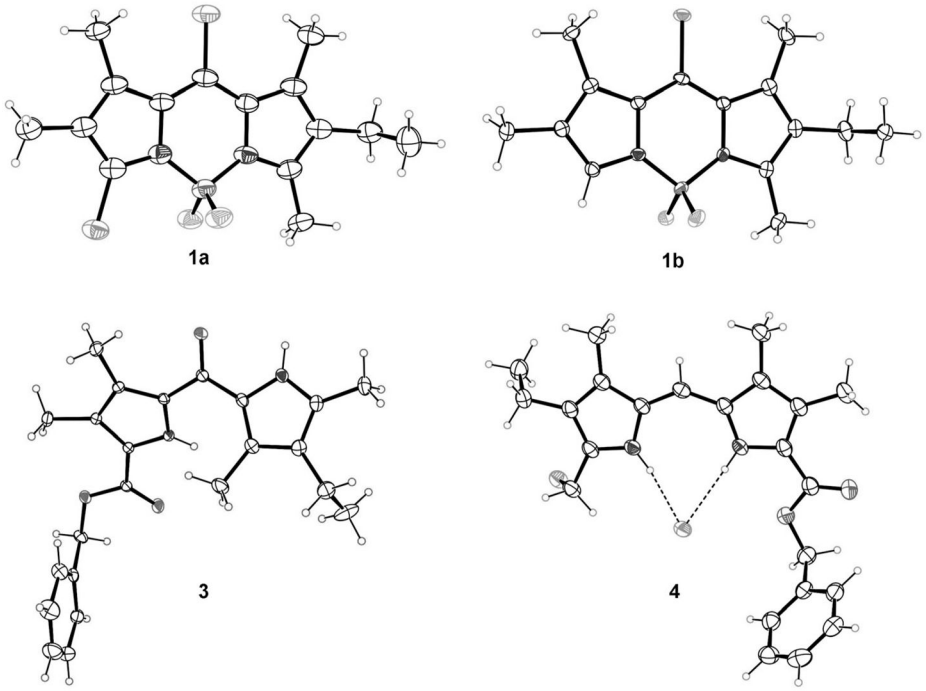


Figure 2.

X-ray crystal structures of BODIPYs **1a**,**b** dipyrroketone **3** and dipyrryl salt **4** with 50% probability ellipsoids. Only one of the independent molecules is shown for both **1a** and **1b**.

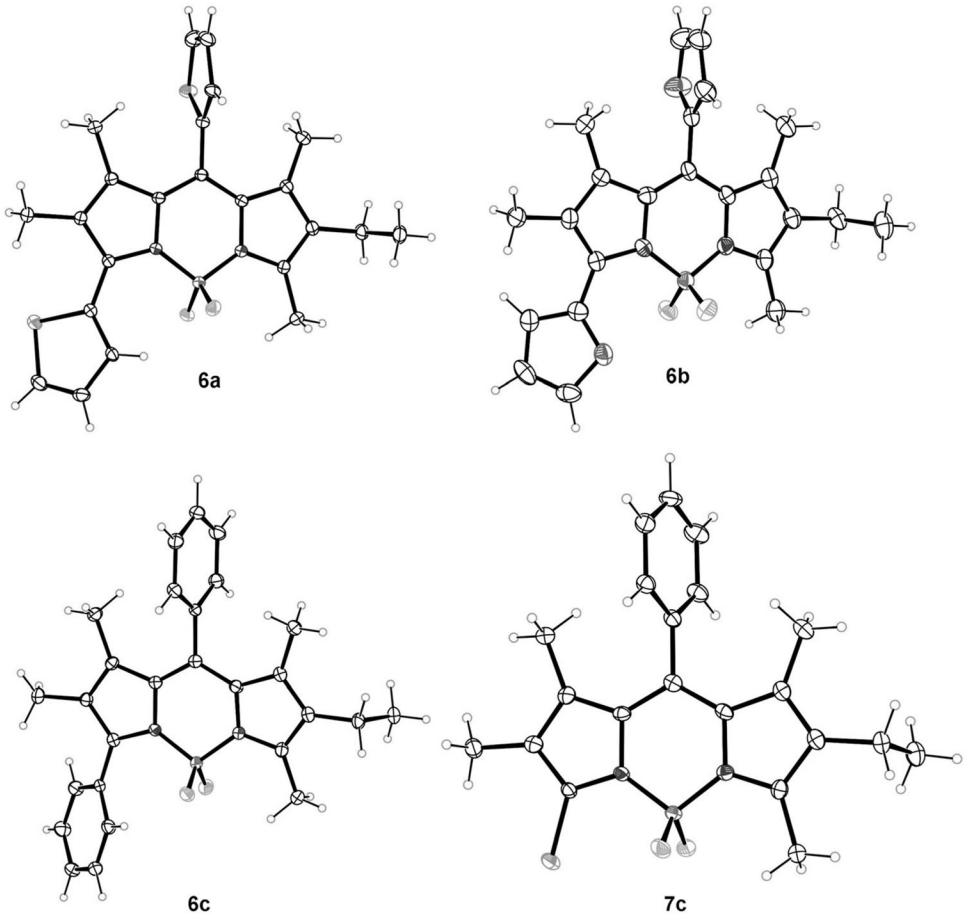


Figure 3.

X-ray crystal structures of asymmetric BODIPY dyes **6a**–**c** and **7c** (50% probability ellipsoids). Only the major conformer is shown for disordered groups.

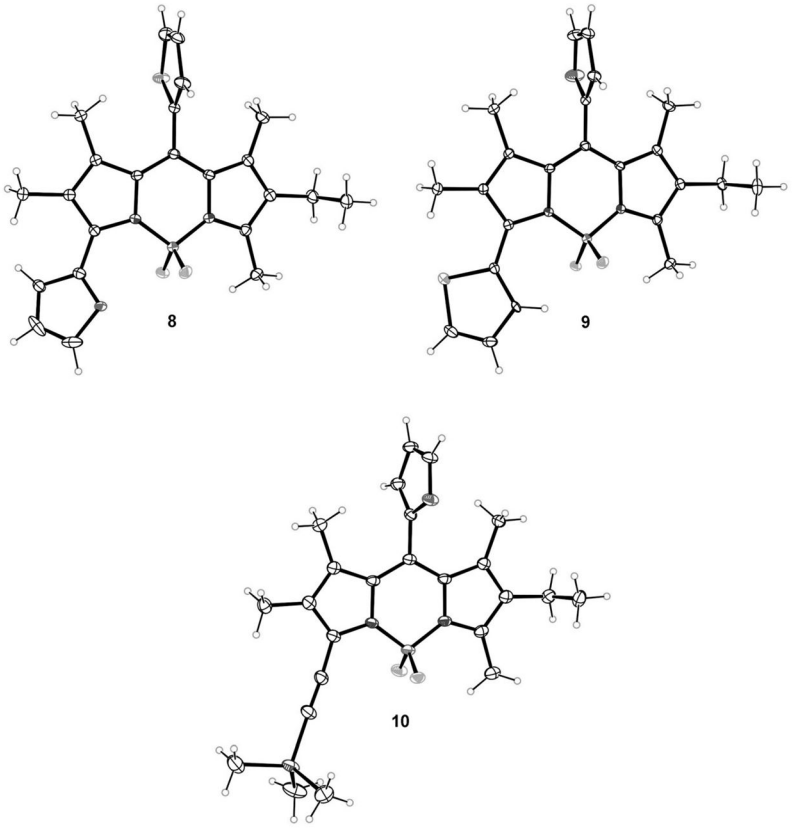


Figure 4.

X-ray crystal structures of asymmetric BODIPY dyes **8**–**10** (50% probability ellipsoids). Only the main conformers are shown for the disordered thiophene and furan in **8**.

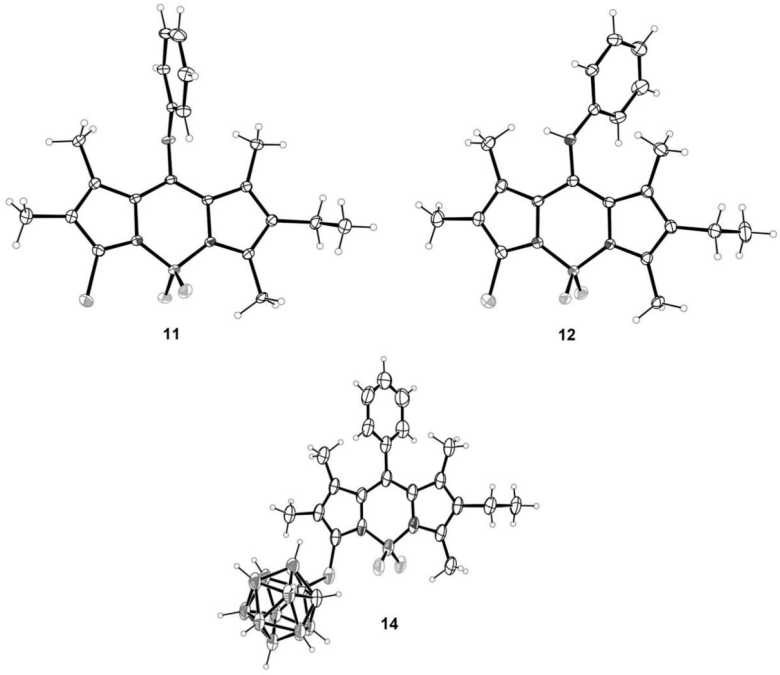


Figure 5.

X-ray crystal structures of asymmetric BODIPYS **11**, **12**, and **14** (50% probability ellipsoids). The disorder in **11** and **12** is not shown.

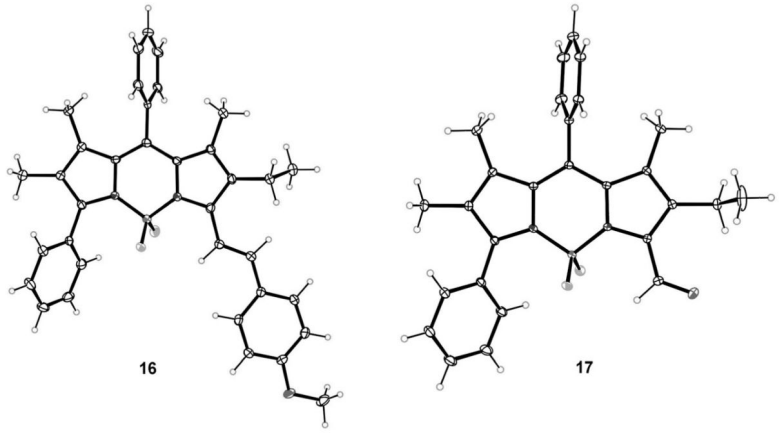


Figure 6.

X-ray crystal structures of asymmetric BODIPYS **16** and **17** (50% probability ellipsoids). Only one of the two independent molecules of **16** is shown.

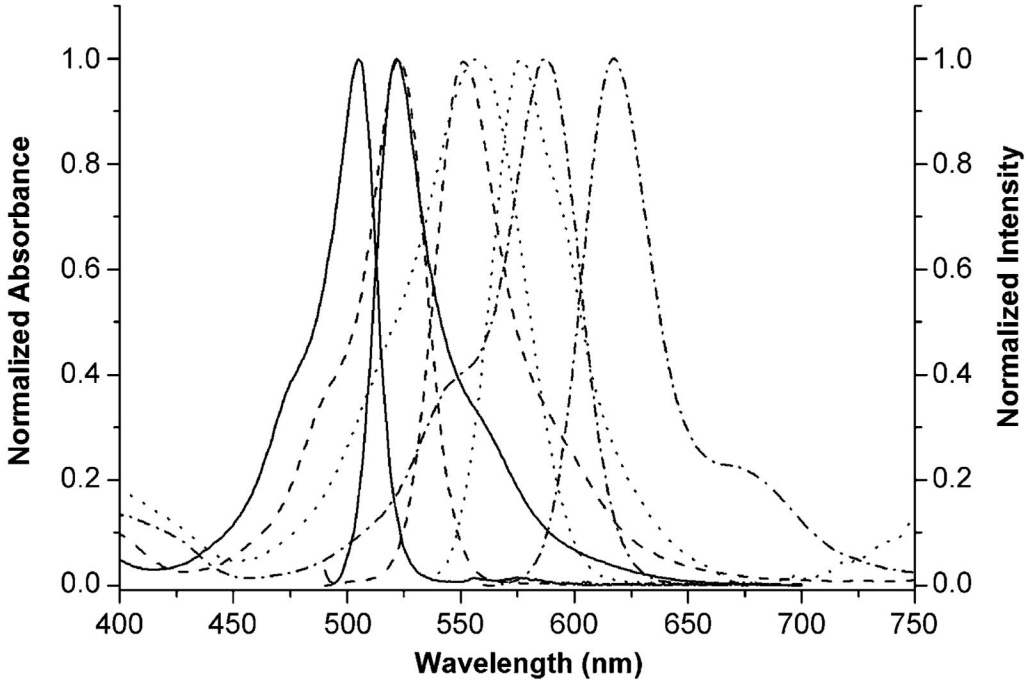
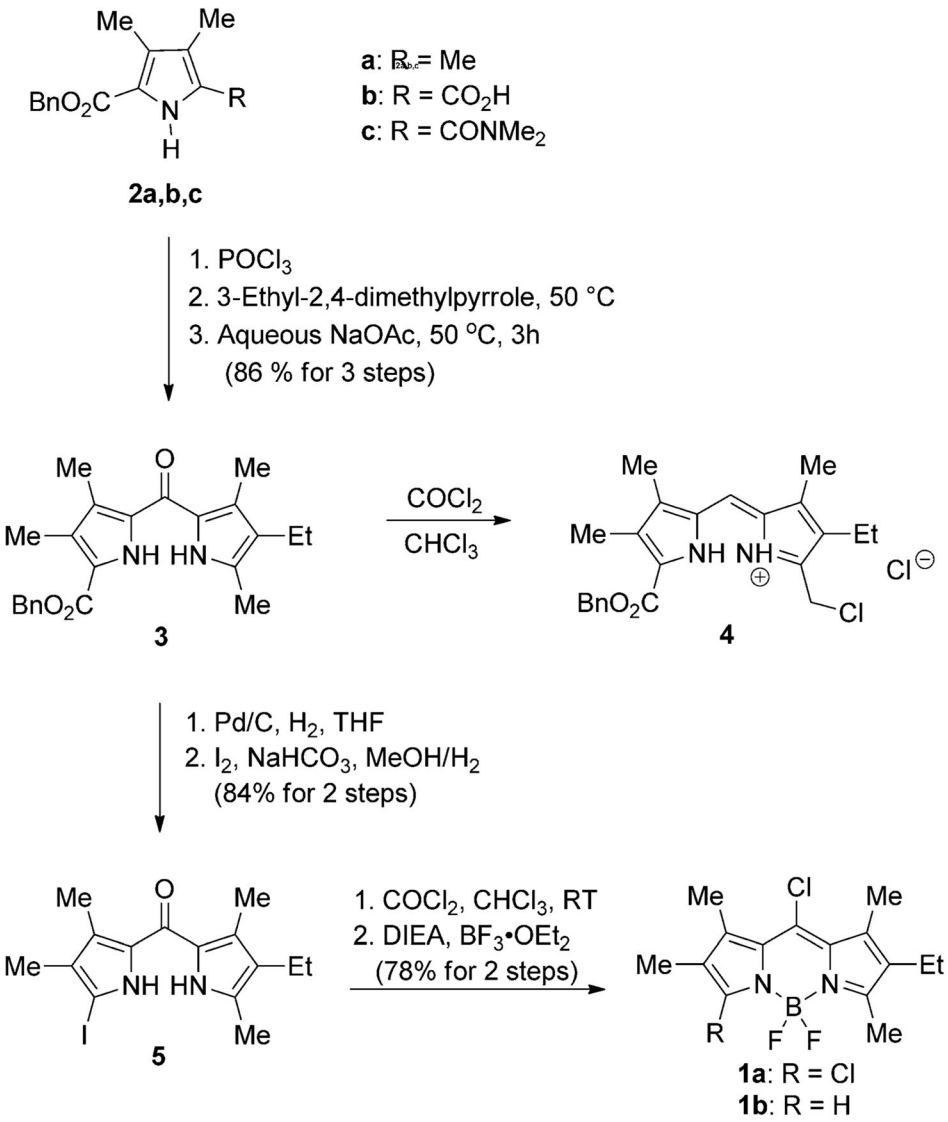
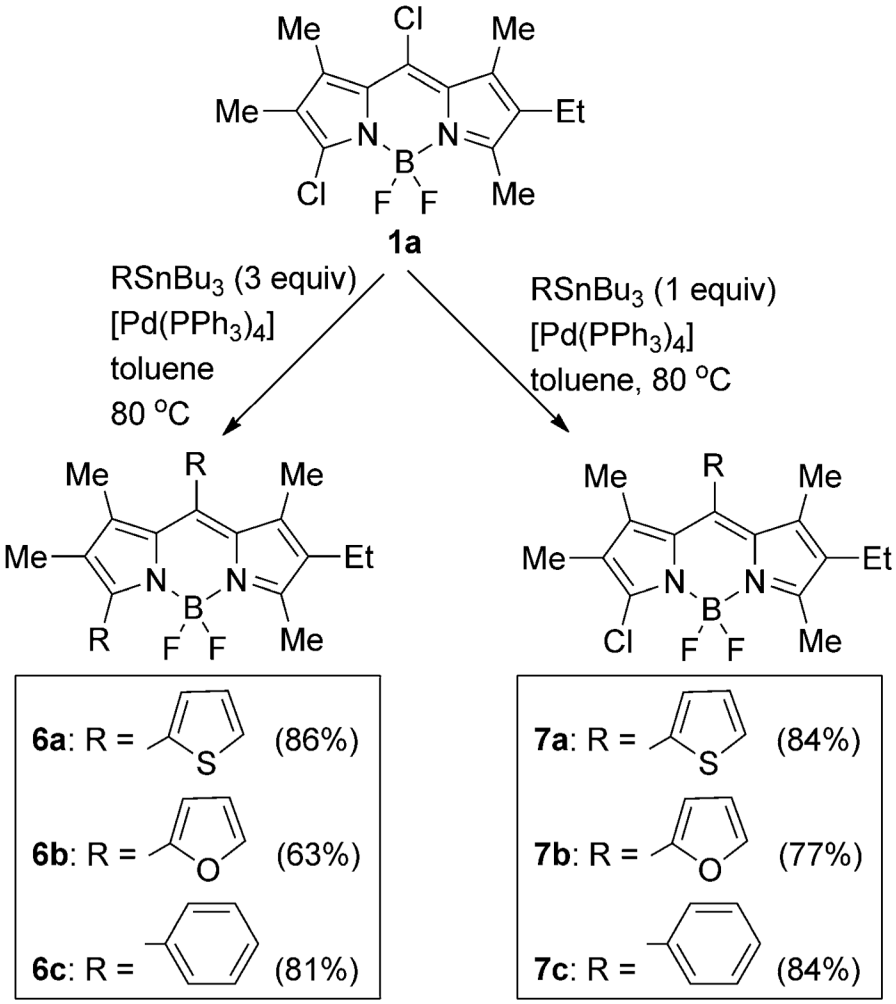


Figure 7.

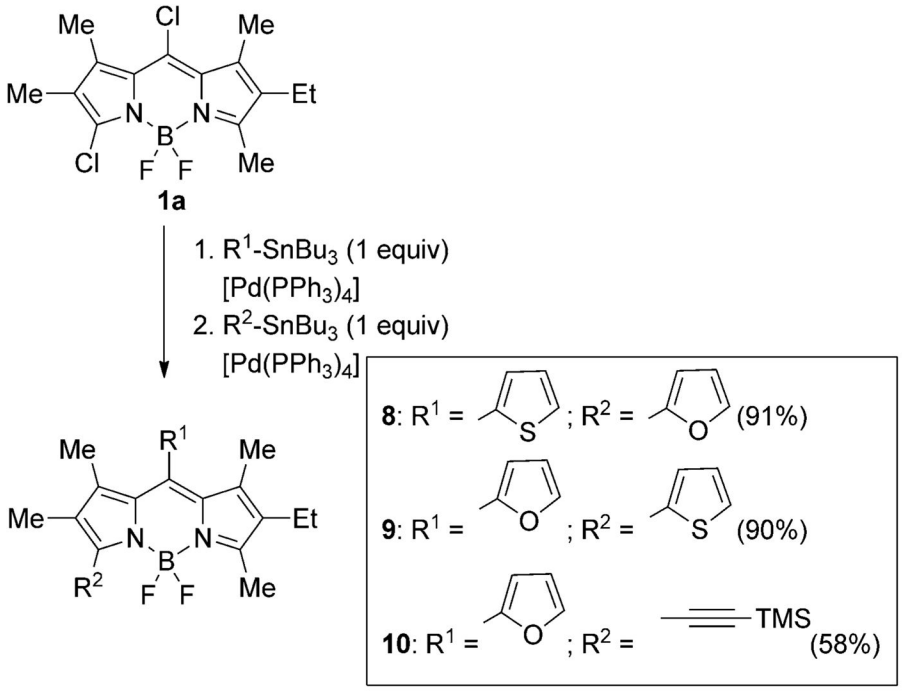
Normalized UV/Vis and fluorescence spectra of BODIPYs **6c** (dash), **9** (dot), **11** (solid) and **16** (dash dot) in dichloromethane at room temperature.



Scheme 1.
Synthesis of asymmetric 3,8-dichloro-BODIPY **1a**.

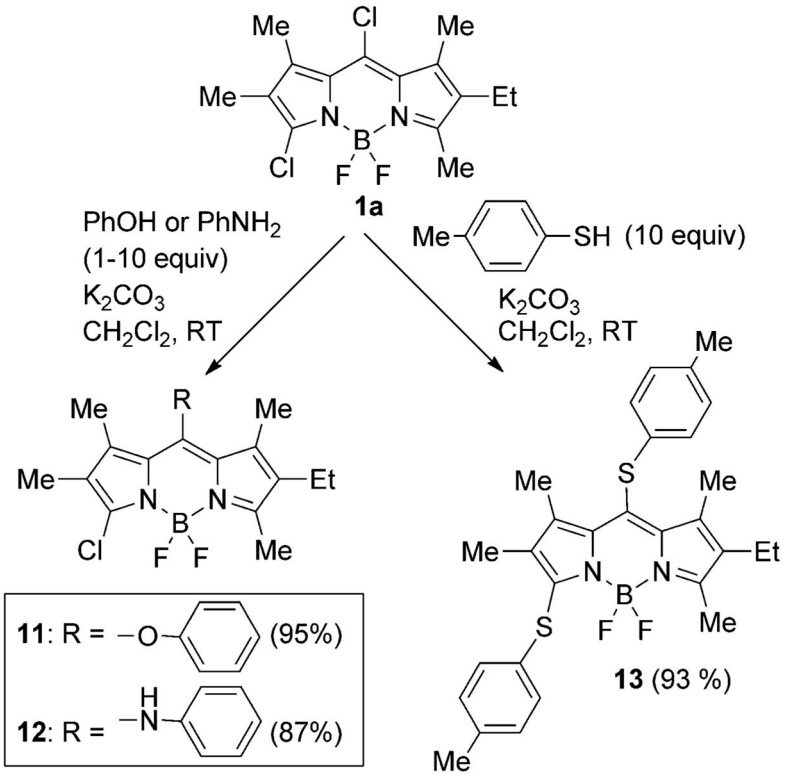


Scheme 2.
Global and regioselective Stille coupling reactions of 3,8-dichloro-BODIPY **1a**.



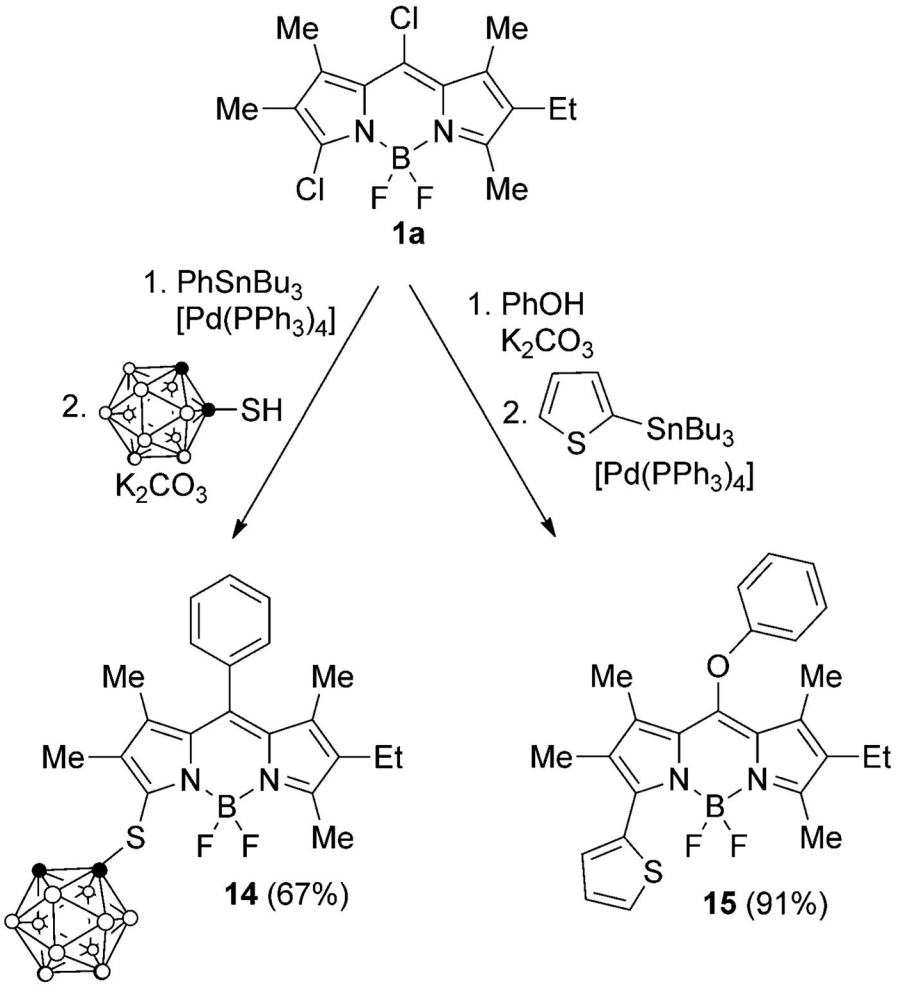
Scheme 3.

Sucessive Stille coupling reactions of 3,8-dichloro-BODIPY **1a**.



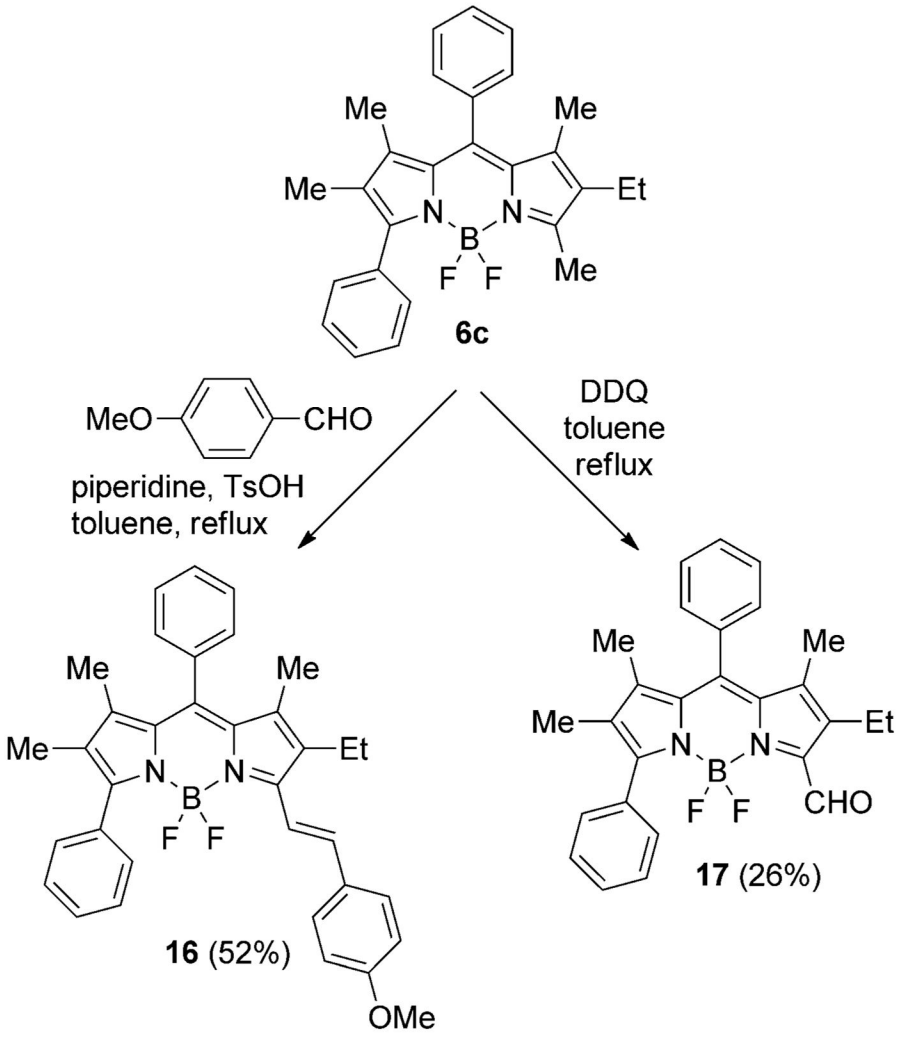
Scheme 4.

Nucleophilic additions/eliminations of BODIPY **1a**.



Scheme 5.

Sucessive Stille cross-coupling and nucleophilic reactions of BODIPY **1a**.



Scheme 6.
Knoevenagel and oxidation reactions of BODIPY **6c**.

Table 1

Spectroscopic properties of BODIPYs **1a**,**b**, **6a**–**c**, **7a**–**c**, and **8**–**17** in dichloromethane at room temperature.[a]

BODIPY	Absorption λ_{max} [nm]	log ε [$M^{-1}cm^{-1}$]	Emission λ_{max} [nm]	Φ_f	Stokes shift [nm]
1a	517	4.80	540	0.52	23
1b	513	4.95	536	0.33	23
6a	547	4.64	591	0.097	44
6b	586	4.78	611	0.022	25
6c	523	4.71	551	0.46	28
7a	529	4.73	548	0.09	19
7b	535	4.78	555	0.0097	20
7c	515	4.71	536	0.48	21
8	577	4.53	592	0.097	15
9	556	4.66	577	0.011	21
10	563	4.84	582	0.022	19
11	505	4.52	521	0.89	16
12	487	4.52	531	0.0017	44
13	582	4.35	610	0.13	28
14	512	4.41	532	0.41	20
15	521	4.62	570	0.94	49
16	587	4.22	617	0.73	30
17	538	4.46	562	0.24	24

[a]For BODIPYs **1a**,**b**, **6c**, **7a**, **7c**, **11**, **12**, **14**, and **15** the calculation of fluorescence quantum yield used rhodamine 6G in ethanol (0.95) as standard; for BODIPYs **6a**, **7b**, and **17**, rhodamine B in ethanol (0.49) was used as a standard; for BODIPYs **6b**, **8**–**10**, **13**, and **16**, crystal violet perchlorate in methanol (0.54) was used as standard.