

Steric Strain Release-Directed Regioselective Functionalization of *meso*-Methyl Bodipy Dyes

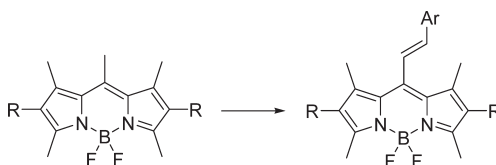
Neelam Shivran,[†] Soumyaditya Mula,[†] Tapan K. Ghanty,[‡] and
Subrata Chattopadhyay^{*,†}

Bio-Organic Division, Theoretical Chemistry Section, Bhabha Atomic Research Centre,
Mumbai-400085, India

schatt@barc.gov.in

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ABSTRACT



Starting from some *meso*-methyl Bodipy dyes, the corresponding *meso*-styryl derivatives were synthesized by regioselective Knoevenagel-type condensation with different aromatic aldehydes. The reactions were driven by the alleviation of the structural strain of the alkyl substituted Bodipys that could override the differential acidities of the methyl protons at the pyrrole ring of the Bodipy moiety.

The dipyrromethene-BF₂ (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene, Bodipy, Figure 1) compounds are valued for their optoelectronic applications.¹ Functionalization of the Bodipy core is an important synthetic goal as it helps in tuning their property to light and electron transfer induced processes, improving hydrophilicity and anchoring to various matrices for widening the scope of their applications. Most of the previous research, directed to this end, was targeted to functionalization of the pyrrole

moieties of the Bodipy core by (i) halogenation followed by organometallic coupling to introduce alkene/alkyne/arene substitutions,^{2a,b} (ii) direct nucleophilic substitution,^{2c–e} and (iii) de novo syntheses of the Bodipy core from modified pyrroles.^{2f,g} However, substitution at the pyrrole moiety may bring about undesirable changes in the physical properties, affecting the targeted function adversely. For example, the presence of electron-donating groups in the pyrrole ring would reduce the fluorescence quantum yields of the Bodipy molecules especially in polar solvents.³

Instead, *meso*-functionalization of the Bodipy moiety with an alkyl/arylalkyl moiety would provide new Bodipy-based functional molecules without perturbing the photoelectronic properties. The presence of sp²/sp²-hybridized carbon at the *meso*-position adversely affects the fluorescence and lasing efficiency of the Bodipy molecules.⁴ Earlier, Liebeskind–Srogl cross-coupling of a 8-thiomethylbodipy

[†] Bio-Organic Division.

[‡] Theoretical Chemistry Section.

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with various boronic acids has been used for *meso*-functionalization of the Bodipy moiety.⁵ However, this requires reagents that are expensive and/or have to be synthesized by multistep routes. Direct synthesis of these types of Bodipy molecules *via* the condensation of substituted pyrroles with aliphatic aldehydes/acid chlorides has inherent limitations due to the instability of the required acid chlorides and nonreactivity of the aldehydes.^{1a–c}

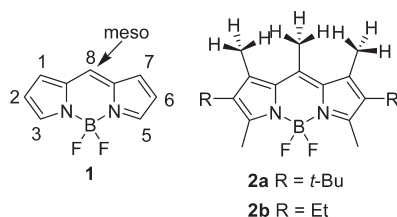


Figure 1. General structure of Bodipy core (1), structures of commercially available Bodipy dyes, PM597 (2a) and PM567 (2b).

The commercially available Bodipy dyes PM597 (2a) and PM567 (2b) (Figure 1) contain CH₃ substitutions at the pyrrole rings and at the C-8 (*meso*-) position. Mulliken-charge analysis of the 1,3,5,7,8-pentamethyl Bodipy dye showed that the electron density on the core carbon atoms follows the order C-8 > C-1/7 > C-3/5. Thus, the CH₃ groups at those positions can undergo the base-catalyzed Knoevenagel-type condensation with various aryl aldehydes according to their relative acidities C-3/5 > C-1/7 > C-8. This strategy provides another avenue for functionalization of the Bodipy moiety and has been exploited extensively to develop C-3/C-5 styryl Bodipy derivatives with red-shifted fluorescence.^{6,7} In all these studies, the chosen Bodipy substrates had an aryl substituent at the *meso*-position, ensuring the reaction to proceed regioselectively at the C-3 and C-5 methyl groups. More recently, syntheses of tri- and tetrasteryl Bodipys by this route are also reported under specific conditions.⁸ However, this strategy has never been used for *meso*-functionalization.

Our previous conformational analysis revealed that, in the planar form of 2b, the van der Waals radii of the hydrogen atoms of the C-1/C-7 and *meso*-Me groups can overlap. This makes the *meso*-site spatially crowded to force the Me groups out of the Bodipy plane. Thus, the

highly twisted *meso*-substituents are largely decoupled from the Bodipy core.⁹ Costela et al. showed that the *meso*-H analogue of 2a is planar.¹⁰ We envisaged that a Knoevenagel-type condensation of the Bodipy molecules at the *meso*-Me group would alleviate such an unfavorable steric interaction. Thus, the release of steric strain may drive the condensation selectively at the *meso*-position, overriding the least acidity of the *meso*-methyl protons. In this study, we proved the hypothesis by selective *meso*-functionalization of the Bodipy dyes 2a and 2b using readily available and inexpensive reagents (Scheme 1 and Table 1).

Scheme 1

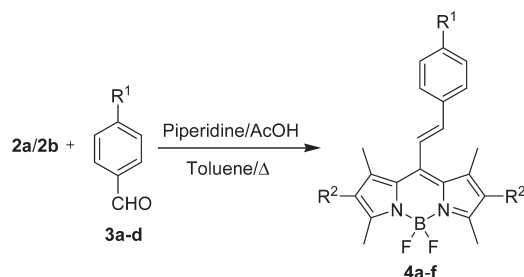


Table 1. Regioselectivity of the Reaction

Bodipy	aldehyde, R ¹	product, R ¹ , R ²	% yield ^a
2a	3a, OMe	4a, OMe, <i>t</i> -Bu	65
2a	3b, OH	4b, OH, <i>t</i> -Bu	50
2a	3c, NO ₂	4c, NO ₂ , <i>t</i> -Bu	67
2b	3a, OMe	4d, OMe, Et	10 ^b
2b	3c, NO ₂	4e, NO ₂ , Et	55
2b	3d, Br	4f, Br, Et	61

^a Based on isolation. ^b 13% 3-styryl analogue was also isolated.

Initially, we carried out the condensation between 2a and 3a in the presence of piperidine and AcOH.^{6a} The dye 2a is highly twisted due to a strong coaxial steric repulsion between the 2- (and 6-) *tert*-butyl and other methyl groups at the pyrrole moieties. The steric distortion in 2a is even more in the excited state, resulting in an uncharacteristically high Stokes shift (~1350 cm⁻¹), compared to other Bodipy dyes.¹¹ Hence, its condensation was expected to take place regioselectively at the *meso*-position to reduce the steric strain. True to our expectation, the reaction proceeded uneventfully to furnish compound 4a,¹² the

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(12) All compounds were fully characterized by NMR and mass spectroscopy, as well as elemental analyses.

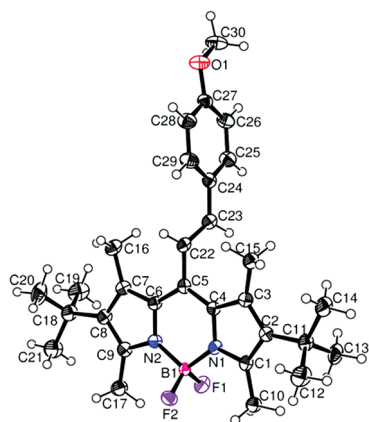


Figure 2. X-ray crystal structure of **4a**.

meso-styryl analogue of **2a** as the single product within 30 min. Earlier, condensation of **2b** with benzaldehyde, under similar conditions, furnished the 3-styryl derivative in a very low yield (<3%) along with a large number of unidentified products.¹³ Thus, our results with **2a** indicated the steric factor as the major driving force for the regioselectivity of the reaction, which was also confirmed by analyzing the X-ray crystal structure of **4a** (Figure 2). The degree of steric relaxation in forming **4a** was evident from the dihedral angle (C3–C4–C5–C6) between the two pyrrole units and the torsion angles (C1–C2–C3–C4 and C6–C7–C8–C9) of the pyrrole rings in **2a** and **4a**. The crystallographic data revealed that the torsion angles of the pyrrole rings of **4a** were significantly less than those of **2a** (3.8°),¹¹ while the C3–C4–C5–C6 dihedral angle of **4a** was much less than that of **2a** (172.8°)¹¹ (see Supporting Information). These suggested that the Bodipy chromophore of **4a** was comparatively more planar than that in **2a**. Subsequently, the synthetic strategy was extended for the condensation of **2a** with **3b** as well as **3c** to obtain the *meso*-styryl Bodipy compounds **4b** and **4c** respectively.

However, the condensation between the dye **2b** and **3a**, under the same conditions, afforded the *meso*-styryl (**4d**) and C-3 styryl analogues of **2b** in 10% and 13% yields respectively as the major isolated compounds along with some unanalyzed products (possibly polystyryl and degradation products). Based on the available X-ray crystallography data, the torsion angle (0.8°) of the pyrrole rings in **2b** is much less than that in **2a**.¹¹ Hence, the release of steric strain due to the condensation at the *meso*-position of the dye **2b** will be much less than that with **2a**. Thus, it was expected that the reaction course may be dictated by the steric factor as well as the higher acidities of the C-3/C-5 methyl protons in **2b**, resulting in the formation of a mixture of

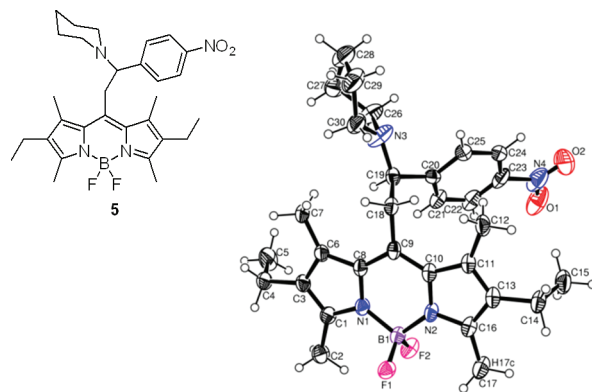


Figure 3. Chemical and X-ray crystal structure of **5**.

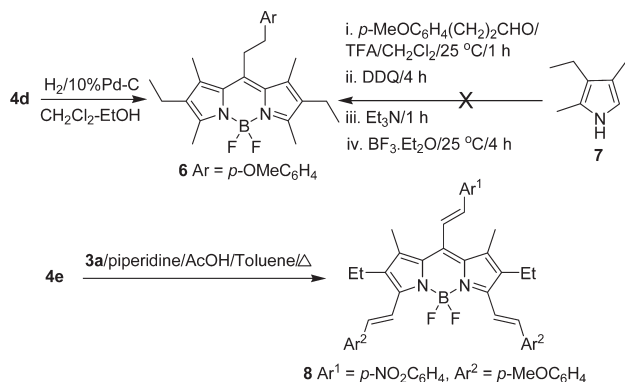
products. Nevertheless, the formation of the **4d** supported our steric factor hypothesis.

We reasoned that use of more electrophilic aldehydes might negate the acidity factor of the *meso* and pyrrole Me protons to direct the condensation at the *meso*-position even with the less strained molecule **2b**. To confirm this, **2b** was subjected to condensation with **3c**. The reaction was slow and attained an equilibrium at 4 h to furnish the *meso*-styryl analogue **4e** along with the recovered dye **2b** (40%). Formation of the C-3 and/or C-5 styryl derivatives was not noticed, despite the higher acidities of the designated Me protons. This also established that relaxation of steric strain was the major determinant of the reaction. The reaction proceeded through the intermediacy of a pink colored stable product that could be isolated (30% yield at 2 h) and characterized as **5** by spectroscopy, CHN analysis, and X-ray crystallography (Figure 3). To the best of our knowledge, this is the first report of isolation and characterization of the intermediate in a Knoevenagel type condensation with the Bodipy dyes. The intermediacy of compound **5** in the reaction was confirmed by its conversion to **4e** along with some amount of **2b** on heating in the presence of piperidine and AcOH. The partial recovery of **2b** also explained the sluggishness of the reaction and moderate yield of **4e** due to the attainment of an equilibrium. In a similar manner, the styryl derivative **4f** could also be synthesized by condensing the dye **2b** with **3d**.

As potential applications of the new method, a few new Bodipy compounds were synthesized using some of the above *meso*-styryl Bodipy compounds. For example, the highly fluorescent dye **6** was synthesized (Scheme 2) by catalytic hydrogenation of **4d** that showed a very weak fluorescence (*vide infra*). Interestingly, compound **6** could not be synthesized via the conventional route of condensing kryptopyrrole (**7**) with *p*-methoxydihydrocinnamaldehyde, due to the low reactivity of the arylalkyl aldehydes.^{1b} The polystyryl Bodipys are useful functional molecules. Previously, Akkaya et al. synthesized a tetrastyryl Bodipy (**A₄** system),^{8a} while Ziessel et al. synthesized polystyryl Bodipy dyes with AB, A₂B₂, and

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Scheme 2



ABCD systems.^{8b} In the present work, the Bodipy compound **4e** was condensed with **3a** to furnish the 3,5,8-tristyryl substituted Bodipy dye **8**, belonging to a new AB₂ system of the polystyryl Bodipy dye.

For stabilizing the radical anions the *meso*-position of the indacene framework is of crucial importance. The cyclic voltammetric results (Table S1) of some selected Bodipy compounds (**2b**, **4d**, and **8**) revealed reversible cathodic waves, assigned to the one-electron reduction of the Bodipy units.^{7b} Compound **4d** ($E_{red}^\circ = -1.36$ V) was easily reducible by ~220 mV than **2b** ($E_{red}^\circ = -1.58$ V), while reduction of the tristyryl compound **8** was even easier by ~600 mV than **2b**. These suggested better stability of the radical anions due to *meso*-styryl modification. However, this modification alone did not alter the oxidation potential, as is reflected by the same E_{ox}° value (1.02 V) of **2b** and **4d**. In the case of **8**, two anodic waves were observed; the first oxidation step ($E_{ox}^\circ = 0.75$ V) was assigned to the removal of one electron from the Bodipy core, and the higher potential ($E_{ox}^\circ = 1.23$ V) could be due to the oxidation of the styryl residue at C-3/5.^{7b}

The spectroscopic properties (Table S2) of all the compounds, recorded in CH₂Cl₂, revealed that the *meso*-styryl Bodipys (**4a–e**) were much less fluorescent ($\Phi_f < 0.01$) with reduced Stokes shifts, compared to the corresponding precursor Bodipys. The results were consistent with a previous report¹⁰ and provide direct evidence of the steric relaxation after the *meso*-styryl modification. Interestingly, saturation of the styryl double bond as in **6** augmented the fluorescence ($\Phi_f = 0.76$) significantly, offering the possibility of constructing on/off chemical sensors. The rather large red shifts (8–13 nm) of the absorption λ_{max} *vis-à-vis* the excitation λ_{max} of **4a–e** indicated complex excited state transition.

The excited state of the Bodipy core has inherent charge redistribution toward the *meso*-position.^{1d} The presence of the electron-withdrawing *meso*-styryl group would facilitate it further and may alter the localization of the HOMO and LUMO. For example, our theoretical calculations revealed that the HOMO and LUMO of **8** were mostly localized on the Bodipy and *meso*-styryl moieties respectively (Figure 4). Hence the emission process with the *meso*-styryl Bodipys is likely to be nonradiative, explaining their very weak fluorescence. However, such an excited state charge distribution would facilitate rapid electron injection into the conduction band of TiO₂.^{1d} This may be important in using the *meso*-styryl compounds as potential sensitizers for designing new dye sensitized solar cells.

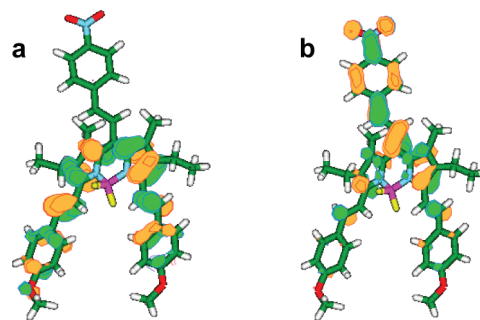


Figure 4. (a) HOMO and (b) LUMO of **8** calculated by DFT.

In short, we have tactically used the steric strain of the Bodipy moieties to functionalize them at the *meso*-position. The styryl substitutions at the *meso*-position alleviate the steric strain of the parent Bodipys. The strain release is more for **2a**, to furnish the products in high yield. For the less strained Bodipy **2b**, the *meso*-selectivity could be achieved by increasing the electrophilicity of the aldehyde. The new *meso*-styryl Bodipys could be useful for development of chemical sensors and DSSCs. Further work in this area is in progress.

Supporting Information Available. Synthetic procedures, analytical and photophysical data, and NMR spectra of all compounds; electrochemical, X-ray crystal, and computational data of selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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