**BOIMPYs: Rapid Access to a Family of Red-Emissive Fluorophores and NIR Dyes**

Lukas J. Patalag, Peter G. Jones, and Daniel B. Werz*

Dedicated to Professor Rolf Gleiter on the occasion of his 80th birthday

**Abstract:** A fundamental, highly fluorescent, and easily accessible scaffold derived from the BODIPY core is reported. The use of benzimidazole as a bridging ligand at the meso position enables the binding of two BF$_2$ units to provide sufficient rigidity and enhanced electron-withdrawing strength. Absorption and emission events thus take place in the red (λ ≈ 600 nm); the fluorescence quantum yields can reach unity (0.96) and show little dependence on solvent polarity. The synthetic route was shortened to two steps starting from commercially available precursors while the preparation is modular and tolerates various pyrrole and benzimidazole moieties. Fluoride replacement by propynyl groups, various halogenations, as well as Knoevenagel-type condensations were applied to extend the versatility of these new photostable fluorophores, which we termed BOIMPYs.

Since their first preparation in 1968,[1] BODIPY fluorophores[2] have contributed heavily to numerous research fields, such as the development of biological labels,[3] tunable laser dyes,[4] solid-state solar concentrators,[5] electroluminescence devices,[6] photodynamic therapy,[7] and diverse indicators[8] usually based on fluorescence modulation mechanisms. At the same time, various analogues have come into focus[9] as the red edge of the visible spectrum has become gradually more appealing. Aza-BODIPYs[10] filled this gap elegantly despite their restriction to redundant substitution patterns. Similarly, a range of aromatic-ring-fused and dimeric frameworks or combinations thereof were introduced[11] although synthetic efforts, also for precursor formation, often increased disproportionately with sophisticated structural complexity.[12] The ability to shift the beneficial photophysics of the BODIPY core (such as high fluorescence quantum yields, good photostability, and brightness) to longer wavelengths with the preparation is still benefiting from the synthetic repertoire available for its functionalization would greatly strengthen this vibrant field of research.

Our initial considerations about novel fluorogenic motifs arose from the idea of efficiently exploiting the crucial meso position of the parent BODIPY core. Its high LUMO coefficient can be addressed by derivatization with electron-withdrawing substituents to narrow the HOMO–LUMO gap and to achieve a red shift in absorption and emission. Even though this approach has already been applied with striking impact (aza-BODIPYs, cyano substitution),[13] no aromatic residues fully conjugated and in plane with the core structure have yet been installed at the meso position because of steric shielding by the adjacent C–H bonds at positions 1 and 7 (Figure 1).[14]

![Figure 1. Geometrical derivation of the BOIMPY motif and its modes of functionalization.](image)

Our intention was to circumvent this repulsion by transforming it into a coordination pattern, with the assistance of two BF$_2$ units and one imidazole auxochrome as a bridging ligand. As the imidazole moiety is now contributing significantly to the framework geometry, we consider the term BOIMPY (bis(borondifluoride)-8-imidazodipyrromethene) to be suitable for such motifs. Benzannulation was chosen to extend the newly accessible π system further and to enhance stability by steric encasement of the contiguous binding pockets. A mirror plane, as depicted in Figure 1, provides an alternative visualization of the structural design.

The 2-hydroxymethylbenzimidazoles 1a–i were smoothly converted into the respective carbaldehydes with orthoiodoxybenzoic acid (IBX) and condensed in situ with ethylpyrrole to furnish dipyrromethanes 2a–i in yields of up to 62% (Scheme 1). The evolving basicity of products 2a–i, additionally hampered by the very poor solubility of the carbaldehyde intermediates, was overcome with a buffering DMSO/NMP solvent system (NMP = N-methyl-2-pyrrolidinone) and an excess of trifluoroacetic acid (TFA). Extensive studies of the final step into fluorophores 3a–i revealed low...
temperatures (−78 °C) and strong, hindered bases to be prerequisites for efficient oxidation and twofold BF₂ coordination. Whereas 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) raised the yields to a level of about 20%, Schwesinger’s non-cationic phosphazene base (BEMP) established reproducible yields of up to 45% for this two-step one-pot process. The dipyrrins formed after 2,3-dichloro-5,6-dicyano-1,4-benzooquinone (DDQ) oxidation suffer from significant instability and have not yet been isolated. Surprisingly, only traces of the BODIPY congeners with a non-participating benzimidazole auxochrome were formed, which underlines its crucial role during the initial stage of the coordination process under the strongly basic reaction conditions.

Owing to its enhanced electron deficiency, the BOIMPY core can be halogenated in a controlled fashion to furnish substrates for cross-coupling reactions in high yields (Figure 2). The β-positions of the ethyl groups are strongly favored for substitution. An excess of N-bromosuccinimide (NBS) led to a triply brominated product (3n) with an increased torsion angle of 35.7° (Figure 4) whereas N-iodosuccinimide (NIS) iodination occurred far more selectively, making singly and doubly iodinated species (3o, 3p) accessible upon varying the temperature.

To demonstrate the analogy to BODIPY chemistry further, we studied the replacement of the fluorides with carbon nucleophiles to obtain so-called E-BOIMPYS (Scheme 2). Depending on the excess of 1-propynylmagnesium bromide, tetrasubstituted derivatives (5a, 5f) and their unsymmetrically disubstituted counterparts (6a, 6f) were obtained in excellent overall yields. A cooperative effect seems to promote the complete conversion of one BF₂ group before the second one is attacked. The option of addressing the boron centers sequentially sets the stage for preparing complex cascade-type dyads[15] or triads of suitable fluorophores, such as pyrenes or perylenes, attached at neighboring boron centers in a well-defined synthetic process. When acetal-protected 3-butyne-1,2-diol was employed as the Grignard reagent, the fluoride replacement can be completed with an acidic deprotection step to furnish the water-soluble variant 7 in a one-pot process. This approach constitutes a general method of converting variously derivatized fluorophores into hydrophilic congeners. As an extension to the broad portfolio of introduced water-soluble (aza-)BODIPYS (e.g., ammonium salts,[16] sulfonated species)[17,10e] fluorophore 7 is uncharged and offers eight hydroxy groups for further derivatizations or specific bioconjugation (e.g., glycosylation).

Styryl-substituted BODIPYS are known to show large bathochromic shifts in absorption and emission. When involving bulky, hydrophobic aromatic aldehydes, BOIMPY 3j proved to be ideally suited for Knoevenagel-type condensations with yields of up to 90% and very short reaction times, a feature that might be attributed to the amplified acidity at the α-methyl groups of precursor 3j (Figure 3). However, this reactivity can be tamed by replacing commonly used acetic acid with TFA to favor singly condensed NIR fluorophores, such as the fluorescent fatty acid analogue 13 or the azido-equipped congener 12 as a labeling agent for click chemistry (λ_{abs}=700 nm). Whereas these singly styryl-deriv-
atized species outpace corresponding BODIPY variants by a bathochromic shift of $\Delta l = 120$ nm in absorption, a twofold condensation with dialkoxy-substituted aromatic aldehydes leads to wavelengths of 780 nm (10, 11) and even 951 nm (9) with 2,2'-bisthiophene moieties. Compared with similar BODIPY variants, the pronounced shift of electron density to the core-centered LUMO upon excitation and the concomitantly polarized styryl double bond might be reasons for the disappointing decrease in fluorescence quantum yields for all styryl-containing NIR BOIMPYs. No significant fluorescence could be detected for NIR dye 9 (Table 1).

The exact geometry of the fluorophore was determined by single-crystal X-ray diffraction of the parent BOIMPY 3a (Figure 4). Repulsion between H2 and H6 results in an interplanar angle of 9.4° (DFT: 19.2°) between the pyrrole moieties. Thus the symmetry of the minimum-energy structure is $C_2$, which was supported by DFT calculations (B3LYP/6-311G(d,p)), even though the energy difference to a $C_{2v}$ geometry as a vibrational transition state is quite small (ca. 1 kcal mol$^{-1}$). Standard N–B bond lengths (ca. 1.55 Å) indicate a tight, symmetric mode of chelation. Unlike for the LUMO, which is partially delocalized outside the pyrrole units, the distribution of electron density in the HOMO corresponds to the pattern calculated for a typical BODIPY core (Figure 5). More remarkable, however, is the energy difference between the frontier orbitals in comparison to those of a BODIPY prototype ($\Delta E_{\text{HOMO}} = -0.76$ eV, $\Delta E_{\text{LUMO}} = -0.35$ eV) or an aza-BODIPY congener ($\Delta E_{\text{HOMO}} = -0.23$ eV, $\Delta E_{\text{LUMO}} = -0.17$ eV), rendering the chromophore highly electron-deficient. Despite its conjugation-based connectivity, the additional meso $\pi$ system is therefore not responsible for the bathochromic shift of 100 nm with respect to a comparable BODIPY variant. Instead, the second BF$_2$ unit with its strongly electron-withdrawing nature narrows the HOMO–LUMO gap down to 2.70 eV, which is somewhat smaller than that calculated for an aza-BODIPY (2.76 eV) and, to the best of our knowledge, the smallest value hitherto reported for a dipyrromethene core. Electronic saturation of the pyrroles ($\beta$-alkyl groups, 31) is consequently effective and triggers a shift of about 20 nm in absorption and a sharp increase in the extinction coefficient (Figure 6).

The Stokes shifts were small (ca. 400 cm$^{-1}$) as expected, reflecting a singlet emission event and the rigidity enforced by the two boron centers, preventing non-radiative channeling of excitation energy. This results in excellent quantum yields of up to 0.96 (3a–h, 3j–l) with slightly lower values (5–10%) in MeCN than in dichloromethane (DCM).

Distal substituents at the benzimidazole moiety (3b–h) had only a negligible effect on the maximum absorption wavelength (Table 1), which illustrates the silent role of the auxochrome with respect to the absorption and emission energies. However, a crucial influence on the emission quality was observed when the interplay of the frontier orbital energies is appropriately tuned with substituents to match

![Figure 3. Styril-containing NIR-BOIMPYs by Knoevenagel condensation.](image)

![Figure 4. X-ray crystal structure of BOIMPY 3a and calculated interplanar angles (DFT).](image)

**Table 1**: A selection of prepared compounds and their spectroscopic data at room temperature.$^\text{[a]}$

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{\text{max}}$ [nm]</th>
<th>$\lambda'_{\text{max}}$ [nm]</th>
<th>$\epsilon_\infty$ [$10^4$ M$^{-1}$ cm$^{-1}$]</th>
<th>$\Delta\rho$ [cm$^{-1}$]</th>
<th>$\Phi_\text{f}(\text{RT})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>598 (592) 602$^{23}$</td>
<td>612 (608) 618$^{23}$</td>
<td>81.4 (67.9)$^{14}$ 75.0$^{14}$</td>
<td>599 (593) 600$^{23}$</td>
<td>615 (607) 75.0 (67.7)$^{14}$</td>
</tr>
<tr>
<td>3c</td>
<td>615 (608) 607$^{23}$</td>
<td>62.5 (49.8)$^{14}$</td>
<td>–</td>
<td>3l 622 (615) 633 (627) 111 (82.4)$^{14}$</td>
<td>279 (311) 0.78 (0.72)</td>
</tr>
<tr>
<td>3d</td>
<td>600 (591) 607$^{23}$</td>
<td>57.5 (67.9)$^{14}$</td>
<td>328 (362) 0.79 (0.74)</td>
<td>3m 615 (602) 632 (627) 117</td>
<td>280 (391) 0.39 (0.36)</td>
</tr>
<tr>
<td>3d</td>
<td>615 (608) 607$^{23}$</td>
<td>72.8 (67.9)$^{14}$</td>
<td>387 (447) 0.11 (0.11)</td>
<td>3n 615 (608) 630 (625) 79.2</td>
<td>337 (397) 0.10 (0.09)</td>
</tr>
<tr>
<td>3o</td>
<td>615 (607) 628 (622)</td>
<td>72.8</td>
<td>337 (397) 0.10 (0.09)</td>
<td>3o 615 (607) 628 (622) 72.8</td>
<td>337 (397) 0.10 (0.09)</td>
</tr>
<tr>
<td>3p</td>
<td>634 (626) 649 (642)</td>
<td>92.7</td>
<td>365 (398) 0.04 (0.03)</td>
<td>3a 598 (592) 602$^{23}$ 612 (608) 618$^{23}$ 81.4 (67.9)$^{14}$ 75.0$^{14}$</td>
<td>383 (445) 430$^{23}$ 0.96 (0.83) 0.94$^{23}$</td>
</tr>
<tr>
<td>5a</td>
<td>594 (590) 607 (604)</td>
<td>59.2 (58.0)$^{14}$</td>
<td>361 (393) 0.83 (0.77)</td>
<td>7 592 (590)$^{14}$ 602 (604)$^{14}$ 51.9 (40.2)$^{14}$ 281 (393)$^{14}$ 0.65 (0.58)$^{23}$</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>803 (803)$^{14}$ 838 (828)$^{14}$</td>
<td>190 (243)$^{14}$</td>
<td>520 (376)$^{14}$ 0.05 (0.06)$^{14}$</td>
<td>9 951 (935)$^{14}$ n.d.$^{14}$ 210 (231)$^{14}$</td>
<td>– n.d.$^{14}$</td>
</tr>
<tr>
<td>10</td>
<td>784 (788)$^{14}$ 824 (816)$^{14}$</td>
<td>149 (155)$^{14}$</td>
<td>619 (435)$^{14}$ 0.04 (0.05)$^{14}$</td>
<td>11 783 (790)$^{14}$ 810 (813)$^{14}$ 174 (180)$^{14}$</td>
<td>426 (358)$^{14}$ 0.05 (0.07)$^{14}$</td>
</tr>
<tr>
<td>12</td>
<td>694 (683) 722 (715)</td>
<td>84.8 (83.9)</td>
<td>559 (655) 0.10 (0.08)</td>
<td>12 694 (683) 722 (715) 84.8 (83.9)</td>
<td>559 (655) 0.10 (0.08)</td>
</tr>
<tr>
<td>13</td>
<td>695$^{14}$ 724$^{14}$</td>
<td>91.3$^{14}$</td>
<td>576$^{14}$ 0.10$^{14}$</td>
<td>13 695$^{14}$ 724$^{14}$ 91.3$^{14}$</td>
<td>576$^{14}$ 0.10$^{14}$</td>
</tr>
</tbody>
</table>

[a] First value in DCM, second value in MeCN (brackets), unless otherwise stated. [b] Inaccurate attenuation coefficient because of poor solubility. [c] Value in toluene. [d] First value in MeOH, second value in PBS buffer (pH 7.4). [e] Value in THF. [f] n.d. = not detected, $\lambda^\prime$ = absorption wavelength, $\lambda^\prime$ = fluorescence wavelength.

__Communications__


These are not the final page numbers!
energy transfer processes. Despite its conjugation with the chromophore π system, the auxochromic moiety might still be sufficiently decoupled to allow for photoinduced electron transfer (PET). It remains controversial whether such reductive PET-like processes account for the slightly diminished fluorescence efficiencies of the electron-rich methoxy-substituted species 3c (0.79) and 3g (0.77). The total depletion of emission for 3i (meso-naphthimidazole), however, seems to be governed by the crucial interaction of the energetically raised, reshaped HOMO (ß/C0 6.07 eV), now located at the naphthimidazole moiety, with the excited chromophoric dipyrromethene system, namely the half-vacant HOMO-1 (ß/C0 6.63 eV), from which the main transition still occurs (see the Supporting Information). Considering the altered relative orbital energies, a reductive PET-like process is thus conceivable although the meso conjugation may somehow contradict the original definition of this process. In contrast to BODIPYs with distorted meso arene units, this mechanism is realized with exact coplanarity, which should turn the meso auxochrome into an equally efficient site for fluorescence modulation. Cyclic voltammetry experiments gave two quasi-reversible reduction potentials (vs. Fc+/Fc) at −390 mV and −1100 mV, respectively, without any indication of a spectral change or decomposition at slow scan rates (Figure 7). The absence of corresponding oxidation steps is in accordance with the low-energy HOMO discussed above.

To estimate the relative photostability of the BOIMPYs, a BODIPY fluorophore was used as a reference. Except for 3k, the selected BOIMPYs exhibited enhanced stabilities while the propynyl-substituted variant 5a was strikingly stable (Scheme 2); 91 % had remained intact after irradiation for 90 min with a high-intensity mercury-vapor lamp (ca. 1 W cm⁻² at the probe) in MeCN.

In conclusion, we have conducted an extensive study of a novel, red-emissive, and highly fluorescent scaffold that might be regarded as a promising structural extension to the well-established BODIPY set of fluorophores. A fully conjugated meso arene substituent bridged by two adjacent BF₂ units is an unprecedented feature of the new motif, which offers a relative bathochromic shift of 100 nm, exceptionally high quantum yields, improved photostability, a fluorescence modulation mechanism, and, furthermore, rapid synthetic access. Modes of post-functionalization known for BODIPYs are widely applicable to the new motif, as the tunable halogenations, the selective fluoride substitutions, and the variable single or twofold Knoevenagel-type condensations suggest. The latter are able to shift the absorption up to λ = 951 nm, providing easily accessible NIR dyes and fluorophores in only three linear synthetic steps.

**Acknowledgements**

L.J.P. thanks Martin Bröring, Kai Brandhorst, Sebastian Höfler, Miguel Silva Valverde, Emma Bales, Eliza Tarco-veanu, and Katharina Bossewig for kind support and the DFG (SFB 803, A05) for funding.

**Keywords:** BODIPY · dyes · fluorophores · luminescence · near-infrared
BOIMPYs: Rapid Access to a Family of Red-Emissive Fluorophores and NIR Dyes

A convenient leap into the red: Two synthetic steps provide access to a new family of highly fluorescent fluorophores termed BOIMPYs. Two BF₂ units enable the efficient exploitation of the meso position and lead to absorption at λ ≈ 600 nm. Owing to the structural similarity to well-studied BODIPY dyes, common modes of post-functionalization can be easily transferred to the new motif.