## Synthesis of 3,5-Diaryl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY®) Dyes

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**Abstract:** 2-Aryl pyrroles **2** were formed via Suzuki coupling of arylboronic acids to *N*-BOC protected 2-bromopyrrole. These pyrroles were used to produce 3,5-diaryl BODIPY<sup>®</sup> dyes **1** having red-shifted fluorescence maxima relative to comparable alkyl-substituted systems. Absorption and fluorescence spectra of the compounds **1** are discussed.

4,4-Difluoro-4-bora-3a,4a-diaza-s-indacenes<sup>1</sup> are highly fluorescent materials<sup>2</sup> that have a range of applications in such areas as biological labeling and syntheses of molecular devices.<sup>3</sup> Several of these dyes are marketed as "BODIPY<sup>®</sup> dyes", e.g. D-2190 (Molecular Probes Inc., Eugene, Oregon, USA). However, they are sold in small quantities for biological experiments, but amounts typically required for synthetic applications would be prohibitively expensive.



We required a set of BODIPY dyes that have functionality-allowing connections to other molecular fragments, and distinct fluorescence emission maxima. Consequently, a divergent route to the title compounds **1** was sought. In this structure, the aryl iodide at the dipyrromethene *meso*-position facilitates elaboration via organometallic coupling reactions,<sup>4</sup> and variation of the aryl functionality Ar allows systematic variation of the fluorescence  $\lambda_{max}$ .



None of the existing procedures for making 2-arylpyrroles seemed ideal for the divergent synthesis required in this work. The most widely used methods involve moderate yields and long purification procedures,<sup>5</sup> or the necessity of preparing specific starting materials, such as 4-aryl-1-azidobutadienes,<sup>6</sup> or a *N*-tosylarylimine,<sup>7</sup> for each product to be prepared. Suzuki couplings<sup>8,9</sup> of the boronic acid **3**, or similarly *N*-protected derivatives, were attractive insofar as this one intermediate could be reacted with several readily available aryl iodides. However, preliminary experiments indicated that the known instability of these boron-substituted pyrroles<sup>10</sup> causes problems that would not be easily overcome. Consequently, our attention shifted to Suzuki couplings of

aryl boronic acids with the bromopyrrole **4**. To the best of our knowledge, this approach has not been reported previously, although Suzuki couplings of *N-tert*-butoxycarbonyl 2,5-dibromopyrrole have been used as a route to polymeric products.<sup>11</sup>



It was found that *N*-tert-butoxycarbonyl-2-bromopyrrole<sup>12,13</sup> reacted with arylboronic acids to give the protected 2-arylpyrroles 5a - d in excellent yield. The scope of this approach is not much less than the route involving **3** because many aryl boronic acids are now commercially available (Frontier Scientific Inc. of Logan, Utah, USA is a good source). Removal of the *N*-BOC protecting group under basic conditions<sup>14</sup> gave the desired 2-aryl pyrroles 2a - d. These products decompose on standing, rapidly under acidic conditions, and are therefore best formed immediately before use in the following step.

Formation of the BODIPY products **1** via a one-pot, two-step process starting from **2** is possible, but better yields are usually obtained if the intermediate dipyrrolemethenes **6** are purified before addition of the boron source. Thus, condensation of 4-iodobenzoyl chloride with the 2-aryl pyrroles **2** gives the highly colored dipyrrolemethenes **6**; these are best isolated via chromatography on basic alumina. Finally, addition of boron trifluoride etherate gives the BODIPY's **1a** - **d**.<sup>15</sup>

The 3,5-diaryl BODIPY dyes **1** are intensely colored both in solution (e. g. in chloroform: **1a** brick red, **1b** red, **1c** violet and **1d** fuchsia) and in the solid state (dark violet crystals). Figure 1a shows the absorption spectra for the four products in chloroform and Table 1 the respective data. Compared to the alkyl substituted BODIPY system D-2190<sup>16</sup> displaying  $\lambda_{max}$  (absorption) = 495 nm and  $\varepsilon$  = 87,000 M<sup>-1</sup> cm<sup>-1</sup> (i) the wavelength for the absorption for **1a** – **1d** is red-shifted and (ii) the extinction coefficients are decreased. Fluorescence spectra for the four compounds are given in Figure 1b. Interestingly, these 3,5-diaryl BODIPY dyes exhibit larger Stokes shifts than the alkyl substituted system **1b** (> 50 nm). The fluorescence intensities are markedly lower than those of alkyl substituted BODIPYs.<sup>17</sup> This may be due to non-radiative decay of twisted biaryl conformations in the excited state.<sup>18</sup>



In summary, Suzuki coupling of arylboronic acids to *N*-BOC protected 2-bromopyrrole provides an efficient route to 2-arylpyrroles **2**. These were used as starting materials to prepare the novel 3,5-diaryl BODIPY dyes 1a - d. The absorption wavelength of compounds 1a - d is red-shifted compared with alkyl substituted BODIPY systems.

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Table 1. Spectroscopic data for compounds 1a - 1d.

compound	absorption	$\epsilon (M^{-1} cm^{-1})$	emission
	$\lambda_{_{max}}\left(nm ight)$		$\lambda_{max}\left(nm ight)$
<b>1</b> a	558	3.1 x 10 <sup>4</sup>	594
1b	551	3.5 x 10 <sup>4</sup>	608
1c	585	3.0 x 10 <sup>4</sup>	626
1d	559	3.1 x 10 <sup>4</sup>	592



Figure 1. a. Absorption spectra of compounds 1a - 1d in CHCl<sub>3</sub> (4  $\mu$ M in CHCl<sub>3</sub>). b Fluorescence spectra of compounds 1a - 1d. The compounds have been excited at  $\lambda_{max}$  Abs. (2  $\mu$ M in CHCl<sub>3</sub>).

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- (15) 5c: A Schlenk tube was charged with N-tert-butoxycarbonyl-2bromopyrrole (4) (1.20 g, 4.87 mmol), 4-methoxyphenylboronic acid (0.74)4.87 mmol). g, and tetrakis(triphenylphosphine)palladium (115 mg, 0.097 mmol). The vessel was evacuated then refilled with nitrogen three times. Freshly distilled toluene (25 mL) and degassed methanol (3 mL) were added via syringe. A degassed 2.0 M aq. solution of sodium carbonate (4.87 mL, 9.74 mmol) was added in one portion. The mixture was stirred under a nitrogen atmosphere at 80 °C (oil bath) for 14 h. The layers were separated and the organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) then evaporated. The resulting oil was purified by flash chromatography eluting with 5% ethyl acetate/ hexanes to yield 1.20 g of the desired compound 5c (90% yield) as a clear oil. R<sub>f</sub> 0.40 (10% EtOAc/hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) 1.42 (s, 9 H), 3.84 (s, 3 H), 6.17 (dd, J = 3.3 Hz, 2.1 Hz, 1 H), 6.24 (t, J = 3.3 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 2 H), 7.31 (2, J = 8.7 Hz, 2 H), 7.37 (dd, J = 3.3 Hz, 1.8 Hz, 1 H); <sup>13</sup>C NMR (CDCl<sub>2</sub>, 75 MHz) 27.5, 55.0, 83.2, 112.9, 113.3, 122.0, 130.2, 134.7, 149.2, 158.8; IR(film) (cm<sup>-1</sup>) 2980, 2933, 2836, 1735, 1314, 907, 742; HRMS (FAB, M.+) calc'd. for C16H19NO3 273.1365, found 273.1374. 2c: A suspension of sodium methoxide (625 mg, 10.99 mmol) in MeOH (3.0 mL) was added to a stirred solution of N-tert-butyloxycarbonyl-2-(4-methoxyphenyl)pyrrole (1.0 g, 3.6 mmol) in THF (15 mL) and stirred at 25 °C for 3 h. The reaction was diluted with Et<sub>2</sub>O (30 mL) and extracted with H<sub>2</sub>O (2 x 20 mL), brine (2 x 20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. The crude reaction mixture was purified by flash chromatography using hexanes to 5% EtOAc/hexanes eluant giving 2c as white plates (550 mg, 86% yield; the sample had analytical data in accord with the literature values Laatsch, H.; Pudleiner, H. Liebigs Ann. Chem. 1989, 863). Rf 0.17 (10% EtOAc/hexanes). 6c: 2-(4-Methoxyphenyl)pyrrole (100 mg, 0.58 mmol), 4-iodobenzoylchloride (354 g, 1.39 mmol), and (CH<sub>2</sub>Cl)<sub>2</sub>

(4 mL) were heated to reflux for 6 h, during which time the solution gradually acquired a purple hue. The reaction mixture was diluted with CH2Cl2 (50 mL), washed with 5% NaHCO3 (2 x 25 mL), dried (Na2SO4), filtered, and concentrated. The crude product was purified via chromatography on basic alumina using 10% CH<sub>2</sub>Cl<sub>2</sub>/hexanes as eluant giving 6c as a dark purple solid (140 mg, 87% yield). R<sub>f</sub> 0.49 (20 % EtOAc/hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) 3.39 (s, 6H), 6.67 (d, J = 4.2 Hz, 2H), 6.80 (d, J = 4.2 Hz, 2H), 7.06 (d, J = 9.0 Hz, 4H), 7.32 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 9.0 Hz, 4H);  ${}^{13}$ C NMR (CDCl<sub>3</sub>, 75 MHz) 51.0, 110.0, 110.7, 121.5, 123.1, 124.8, 128.1, 132.4, 136.8, 149.4, 155.9. 1c: Compound above (590 mg, 1.1 mmol), NEt<sub>3</sub> (0.46 g, 3.3 mmol), and PhMe (30 mL) were stirred at 25 °C for 10 min then boron trifluoride etherate (0.7 mL, 5.5 mmol) was added and heated to 80 °C for 20 min. Fluorescence first appeared 2 min after addition of BF3 · OEt2 at 25 °C. The crude reaction mixture was filtered through a plug of silica on celite, then concentrated. Purification via chromatography on basic alumina using 10% CH2Cl2/hexanes as eluant gave 1c as a dark purple solid (640 mg, 99 % yield). m.p. 190.0 - 192.0 °C (dec.); R<sub>f</sub> 0.30 (20% EtOAc/hexanes); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) 3.83 (s, 3 H), 6.60 (d, J = 4.5 Hz, 2 H), 6.78 (d, J = 4.2 Hz, 2 H), 6.94 (d, J = 9.0 Hz, 4 H), 7.27 (d, J = 8.1 Hz), 7.84 (d, J = 7.5 Hz, 2 H), 7.87 (d, J = 9.0 Hz, 4 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) 55.2, 96.3, 113.8, 120.7, 125.0, 130.0, 131.1, 131.2, 132.1, 134.0, 135.9, 137.4, 158.6, 160.8; IR (cm<sup>-1</sup>) 3152, 2835, 1565, 1471; HRMS (FAB, M.<sup>+</sup>) calc'd for C<sub>29</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>BF<sub>2</sub>INa 629.0690, found 629.0704.

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