SUPPLEMENTARY INFORMATION

for the article:

Facile synthesis of boronic acids on BODIPY core with promising sensibility towards polyols

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General

Solvents and reagents were used as received from commercial sources. p-Nitrophenyl-BODIPY 1a,1b were prepared following known procedures. The amine BODIPY derivatives 2, 3 were obtained according to the procedure described. The acid derivatives 4 and 5 are obtained, both for the hydrolysis of the corresponding ester 6 or 7, either by treatment with silica of the crude of the reaction and subsequent chromatographic separation. With the latter procedure it is always also isolated some amount of pinacol derivatives 6, 7. Merck Kieselgel 60F254 plates were used for TLC, and Merck Silica gel 60 (0.063–0.100 mm) for column chromatography. 1H, 13C and 11B-NMR spectra were obtained on a Varian 300 MHz and 500 MHz Instruments. UV/Vis absorption spectra were recorded on a Jasco 560 spectrophotometer. Steady-state luminescence spectra were recorded with a Horiba Jobin-Yvon Fluoromax P spectrofluorimeter equipped with a Hamamatsu R3896 photomultiplier and were corrected for photomultiplier response by using a program purchased with the fluorimeter. The MALDI-TOF mass spectra were collected by a Voyager DE (PerSeptive Biosystem) using a delay extraction procedure (25 kV applied after 2600 ns with a potential gradient of 454 V mm⁻¹ and a wire voltage of 25 V) with ion detection in linear mode. The instrument was equipped with a nitrogen laser (emission at 337 nm for 3 ns) and a flash AD converter (time base 2). In order to avoid fragmentation of the sample, the laser irradiance was maintained slightly above threshold (ca. 10⁶ W cm⁻²). Each spectrum was an average of 32 laser shots. The MALDI-TOF investigations were performed by loading on the plate 0.4 mmol matrix trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]-malonitrile (DCTB) and 0.01 mmol of sample, using CH₂Cl₂ as solvent. Both 5,10-di(p-dodecanoxyphenyl)-15,20-di(p-hydroxyphenyl) porphyrin (C₉₂H₁₂₆N₄O₄, 1350 Da), tetrakis(p-dodecanoxyphenyl)porphyrin (C₉₂H₁₂₆N₄O₄, 1014 Da), and a PEG sample of known structure were used as external standards for m/z calibration. The MALDI-TOF mass spectra were elaborated with Grams software (ver. 3.04), from Perseptive Biosystems.

Synthesis and analytical data of compounds

2,8-Diethyl-5,5-difluoro-1,3,7,9-tetramethyl-10-ethyl-aniline-dipyrrlo 2a and 2,8-Diethyl-5,5-difluoro-1,3,7,9-tetramethyl-10-aniline-depyrrlo 3a

1a (525 mg, 1.5 mmol) was solubilized in a solution of CH₃CN/ EtOH (50/50 ml), and the solution was allowed to stir under argon for 2h. Subsequently was added palladium on carbon (79 mg) and insufflated hydrogen at atmospheric pressure, the mixture was stirred at 70 °C for 7h. After cooling, the crude was filtered to remove the residual carbon. The products 2a, 3a obtained were separated by chromatography on silica gel (Hexane/AcOEt 80:20).

2a (Rf=0.6, 286 mg, yield 45%) ¹H-NMR (300MHz, CDCl₃): δ 0.98 (3H, J=15Hz, t), 1.28 (6H, s), 1.40 (6H, s), 2.29 (4H, J=24Hz, q), 2.51 (6H, s), 3.20 (2H, J=24Hz, q), 6.7 (2H, J=6Hz, d), 7.0 (2H, J=6Hz, d). MALDI-TOF (m/z): 424 [MH⁺]

3a (Rf=0.3, 249 mg, yield 42%) ¹H-NMR (300MHz, CDCl₃): δ 0.98 (6H, J=15Hz, t), 1.49 (6H, s), 2.31 (4H, J=24Hz, q), 2.54 (6H, s), 6.77 (2H, J=6Hz, d), 7.01 (2H, J=6Hz, d). MALDI-TOF (m/z): 396 [MH⁺]
5,5-difluoro-1,3,7,9-tetramethyl-10-ethylaniline-dipyrrolo 2b and 5,5-difluoro-1,3,7,9-tetramethyl-10-aniline-dipyrrolo 3b

1b (500 mg, 1.5 mmol) was solubilized in a solution of CH₃CN/EtOH (50/50 ml), and the solution was allowed to stir under argon for 2h. Subsequently was added palladium on carbon (79 mg) and insufflated hydrogen at atmospheric pressure, the mixture was stirred at 70 °C for 5h. After cooling, the crude was filtered to remove the residual carbon. The products 2b, 3b obtained were separated by chromatography on silica gel (Hexane/AcOEt 80:20).

2b (R_f = 0.5, 240 mg, yield 42%) ¹H-NMR (300MHz, CDCl₃): δ 1.30 (3H, J=15Hz, t), 1.50 (6H, s), 2.51 (6H, s), 3.20 (2H, J=21Hz, q), 6.7 (2H, J=9Hz, d), 7.0 (2H,J=9Hz, d). ¹³C-NMR (75MHz, CDCl₃): δ 14.33, 14.37, 14.45, 14.56, 14.61, 14.66, 14.72, 14.77, 38.34, 76.52, 77.03, 77.34, 112.66, 113.03, 120.70, 120.94, 123.09, 128.01, 128.88, 129.65, 132.13, 143.07, 143.23, 148.87, 154.73. ¹¹B-NMR (96MHz, CDCl₃): δ 0.79 (t, J=123Hz)

3b (R_f = 0.25, 170 mg, yield 41%) ¹H-NMR (300MHz, CDCl₃): δ 1.49 (6H, s), 2.54 (6H, s), 3.83 (2H, s), 5.97 (2H, s), 6.77 (2H, J=9Hz, d), 7.01 (2H, J=9Hz, d).

10-(((2-(ethylaniline)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2,8-Diethyl-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrolo 6a

2a (100 mg, 0.23 mmol), Cs₂CO₃ (82 mg, 0.42 mmol) and NaI (25 mg, 0.18 mmol) in acetonitrile (50 ml) were dissolved, was finally added 2-(2-(Bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80 mg, 0.27 mmol). The mixture was stirred at reflux for 6h. After cooling the solvent was evaporated and the solid obtained was resolubilized in dichloromethane (30 ml) and the solution obtained was washed with water (3x20 ml), dried over sodium sulfate and finally evaporated the solvent. The product was purified by chromatography on silica gel (hexane/acetate 80:20) R_f=0.7. Obtained 91 mg of pure product 6a (yield 71%).

6a ¹H-NMR (300MHz, CDCl₃): δ 0.98 (3H, J=15Hz, t), 1.25 (3H, J=15 Hz, t), 1.36 (12H, s), 1.42 (6H,s), 2.30 (4H, J=21 Hz, q), 2.51 (6H, s), 3.50 (2H, q), 4.84 (2H, s), 6.71 (2H, J=9 Hz, d), 6.97 (2H, J=9 Hz, d), 7.10-7.86 (3H, m), 7.88 (1H, J=9 Hz, d). ¹¹C-NMR (75MHz, CDCl₃): δ 11.95, 12.15, 12.24, 12.33, 12.50, 14.63, 14.73, 17.09, 24.89, 24.97, 45.18, 53.43, 76.59, 77.01, 77.43, 83.72, 111.98, 112.15, 122.28, 125.89,
125.95, 129.06, 131.05, 132.62, 136.39, 136.56, 138.59, 141.82, 145.05, 148.84, 152.78. MALDI-TOF (m/z): 640 [MH$^+$]

10-(((2-(aniline)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-2,8-Diethyl-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrolo 7a

3a (50 mg, 0.126 mmol) and 2-formylphenylboronic acid pinacol ester (29.24 mg, 0.126 mmol) were dissolved in anhydrous methanol (10 ml) and the mixture was stirred for 30 minutes in Ar atmosphere, then sodium cyano borohydride (15.83 mg, 0.252 mmol) was added and the mixture was stirred in Ar for 2 days. The solvent was removed under vacuum and brine (10 ml) was added, the mixture was subsequently extracted with dichloromethane (3 x 20 ml), the organic fraction collected were dried over sodium sulfate and the solvent evaporated. The obtained crude product was purified in column with eluent Hexane / EtOAc 80:20. Obtained 65.5 mg of pure product 7a (yield 85%).

7a $^1$H-NMR (300MHz, CDCl$_3$): δ 1.00 (6H, J=15Hz, t), 1.31 (12H, s), 1.43 (6H, s), 2.32 (4H, J=21Hz, q), 2.52 (6H, s), 4.99 (2H, s), 6.75 (2H, J=9Hz, d), 6.96 (2H, J=9Hz, d), 7.26-7.43 (3H, m), 7.88 (1H, J=9Hz, d)

10-(((2-(ethylaniline)methyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrolo 6b

2b (100 mg, 0.29 mmol), Cs$_2$CO$_3$ (94 mg, 0.48 mmol) and NaI (33 mg, 0.24 mmol) in acetonitrile (50 ml) were dissolved, was finally added 2-(2-(Bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80 mg, 0.27 mmol). The mixture was stirred at reflux for 5h. After cooling the solvent was evaporated and the solid obtained was resolubilized in dichloromethane (30 ml) and the solution obtained was washed with water (3x20 ml), dried over sodium sulfate and finally evaporated the solvent. The product was purified by chromatography on silica gel (hexane/acetate 80:20) Rf=0.7. Obtained 101 mg of pure product 6b (yield 75%).

6b $^1$H-NMR (300MHz, CDCl$_3$): δ 1.25 (3H, J=15Hz, t), 1.36 (12H, s), 1.51 (6H, s), 2.54 (6H, s), 3.50 (2H, J=21Hz, q), 4.83 (2H, s), 5.96 (2H, J=9Hz, d), 6.97 (2H, J=9Hz, d), 7.08-7.31 (3H, m), 7.86 (1H, J=9Hz, d); $^{13}$C-NMR (75MHz, CDCl$_3$): δ 12.08, 12.39, 14.36, 14.59, 14.74, 24.71, 25.05, 25.26, 45.18,
53.35, 76.61, 76.83, 77.45, 83.73, 111.95, 112.27, 120.64, 129.90, 121.40, 125.85, 126.01, 128.84, 132.22, 136.30, 136.71, 143.21, 143.47, 144.97, 149.02, 154.54.

General procedure for hydrolysis of pinacol boronic esters

Pinacol ester 6 or 7 was dissolved in methanol and silica was added, the mixture was stirred at room temperature for 24 hours. After filtration the solvent was evaporated and the crude reaction was purified in column chromatography on silica gel and as the eluent a mixture of hexane/acetate in gradient from 80:20 to 100% acetate.

10-(((2-(ethylaniline)methyl)phenylboronicAcid)-2,8-Diethyl-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrrolo 4a

![Image of 4a](image)

6a (200 mg, 0.358 mmol) in methanol (20 ml) and 5 g of silica. Rf=0.3 in hexane/acetate 60:40. The product obtained was crystallized in hexane. Was obtained about 120 mg of pure product 4a (yield 60%).

4a 1H-NMR (300MHz, CDCl3): δ 0.97 (6H, J=15Hz, t), 1.03 (3H, J=15Hz, t), 1.18 (6H, s), 2.28 (4H, J=21Hz, q), 2.51 (6H, s), 3.24 (2H, J=21Hz, q), 4.31 (2H, s), 7.04-7.30 (3H, m), 7.89 (1H, d); 13C-NMR (75MHz, CDCl3): 12.58, 14.76, 17.03, 48.20, 60.42, 76.57, 77.00, 77.42, 123.92, 130.15, 132.11, 132.75, 136.27, 138.24, 139.55, 140.83, 147.92, 150.53, 153.67; 11B-NMR (96MHz, CDCl3): δ 0.76 (BF2, J=123Hz, t), 29.3 (B, s)

10-(((2-(aniline)methyl)phenylboronicAcid)-2,8-Diethyl-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrrolo 5a

![Image of 5a](image)

7a (100 mg, 0.19 mmol) in methanol (10 ml) and 3 g of silica. Rf=0.25 in hexane/acetate 60:40. The product obtained was crystallized in hexane. Was obtained about 48 mg of pure product 5a (yield 47%).

Spectroscopic data are complex, due to the free rotation of the aromatic system bearing the boronic acid group. Cannot be assigned any data as reference.

In support of this hypothesis, it was added pinacol in the same NMR tube and we noted the unique formation of the ester derivative 7a.
10-((2-(ethylaniline)methyl)phenylboronic Acid)-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrolo 4b

6b (250 mg, 0.42 mmol) in methanol (20 ml) and 5 g of silica. Rf=0.25 in hexane/acetate 60:40. The product obtained was crystallized in hexane. Was obtained about 125 mg of pure product 4b (yield 59%).

4b 1H-NMR (300MHz, CDCl3): δ 1.02 (3H, J=15Hz, t), 1.26 (6H, s), 2.54 (6H, s), 3.22 (2H, J=21Hz, q), 4.28 (2H, s), 5.96 (2H, s), 7.08-7.31 (3H, m), 7.77 (1H, J=9Hz, d). MALDI-TOF (m/z): 474.5 [M-BOH] H⁺

10-((2-(aniline)methyl)phenylboronic Acid)-5,5-difluoro-1,3,7,9-tetramethyl-dipyrrolo 5b

7b (200 mg, 0.36 mmol) in methanol (20 ml) and 5 g of silica. Rf=0.25 in hexane/acetate 60:40. The product obtained was crystallized in hexane. Was obtained about 105 mg of pure product 5b (yield 62%).

5b 1H-NMR (500MHz, CDCl3): δ 1.40 (6H, s), 2.55 (6H, s), 4.47 (2H, s), 5.96 (2H, s), 6.86 (1H, J=5Hz, t) 6.96 (1H, J=10Hz, d), 7.03 (2H, J=10Hz, d), 7.12 (3H, m), 7.23 (1H, J=5Hz, t); 13C-NMR (125MHz, CDCl3): 14.55, 14.67, 24.87, 48.47, 116.60, 116.79, 120.35, 120.87, 121.10, 128.84, 128.98, 129.33, 129.36, 131.76, 140.03, 155.29, 156.06; 11B-NMR (96MHz, CDCl3): δ 0.75 (BF₂, J=100Hz, t); MALDI-TOF (m/z): 446.6 [M-BOH] H⁺
1H, 13C, 11B-NMR and MALDI-TOF spectra of compounds
Table 1. Absorption spectra and luminescence data

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Absorption $\lambda_{\text{max}}$ [nm]$^a$ (ε [m$^{-1}$cm$^{-1}$])</th>
<th>Luminescence $\lambda_{\text{max}}$ [nm] 298 K$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>520 (75000)</td>
<td>535</td>
</tr>
<tr>
<td>4b</td>
<td>500 (68000)</td>
<td>510</td>
</tr>
<tr>
<td>5a</td>
<td>520 (75000)</td>
<td>535</td>
</tr>
<tr>
<td>5b</td>
<td>500 (68000)</td>
<td>510</td>
</tr>
</tbody>
</table>

[a] in deaerated acetone.
Kinetics of formation of the ester from the acid pinacol boronic BODIPY

To determine the stoichiometry of the adduct BODIPY-fructose and its thermodynamic stability, need to consider a balance of association. Our initial hypothesis is that the adduct has a stoichiometry of 1:1, so is possible to write the simplified balance:

\[
\text{BODIPY} \text{(acetone)} + \text{Fructose} \text{(acetone)} \rightleftharpoons \text{BOD-FRUCTOSE} \text{(acetone)} \quad (\text{eq. 1})
\]

This balance is adjusted at 298 K by an equilibrium constant and a degree of dissociation. The values of these parameters have been determinate by fluorimetric measurements on the basis of the fact that the initial emission of the BODIPY is quenched by the formation of the ester. Quantitative measures thus allowing to determine the relative amounts of the different species in solution added fructose.

Figure 1. Stacked protonic NMR spectra of pinacol esterification of 4a in CDCl₃
Using five samples at fixed concentration of BODIPY, but at different concentrations of fructose was measured and the variation of emission intensity ($\lambda_{\text{exc}} = 400$ nm) with respect to $I_0$ (initial intensity of BODIPY in the absence of sugar), fig. 2

![Figure 2. Absorption and emission spectra of 4a in acetone, in absence (red line) and in presence of an excess of fructose (blue line) ($\lambda_{\text{exc}}= 400$ nm)](image)

The equilibrium constant for eq. 1 can be approximated to:

$$k_{eq} = \frac{\alpha}{(1-\alpha)(L_0 - C_0\alpha)}$$

where $L_0$ is the concentration of added fructose (different in each experiment), $C_0$ is the concentration of BODIPY 4a (constant for each experiment), $\alpha$ is the degree of dissociation calculated according to the following equation:

$$\alpha = \frac{\Delta I_{\text{MIX}}}{\Delta I_{\text{MAX}}}$$

Where $\Delta I_{\text{MIX}}$ is the variation of emission intensity at different additions of sugar ($L_0$), therefore considerable proportional to the concentration of adduct product, while $\Delta I_{\text{MAX}}$ is the maximum intensity variation obtained to massive addition of fructose and therefore can be considered, with good approximation, proportional to the total concentration of the BODIPY. This type of approximation is reasonable in that the spectroscopic properties of the adduct are not known.

Drawing a diagram with $\frac{\alpha}{(1-\alpha)}$ respect to $(L_0 - C_0\alpha)$ was obtained a straight line (fig. 3), whose slope is the $K_{eq}$ and that is equal to $7.4x10^4$. The linear trend obtained confirms that the stoichiometry (1:1) hypothesized equilibrium on reported is correct.
The positive MALDI-TOF spectrum (Fig. 4) of the product of the reaction between BODIPY and pinacol is essentially featured by the presence of a signal at m/z 640 due to a molecular system (detected as MH\(^+\)) constituted of a pinacol bound to BODIPY by means of cyclic boronic ester link.
Instead, the fig. 5 shows the mass spectrum of the reaction product between BODIPY and Fructose; it is essentially constituted of a peak at m/z 702 due a species (detected as MH$^+$) formed by the association of a fructose molecule and BODIPY with the loss of two water molecules and formation of cyclic boronic ester links.

Figure 5. positive MALDI-TOF mass spectrum of compound 4a+fructose