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Tunable BODIPY derivatives amenable to ‘click’ and peptide chemistry[☆]



Anna Mette Hansen^a, Alan L. Sewell^a, Rasmus H. Pedersen^b, De-Liang Long^a,
Nikolaj Gadegaard^b, Rodolfo Marquez^{a,*,†}

^aSchool of Chemistry, University of Glasgow, Glasgow G12 8QQ, United Kingdom

^bSchool of Engineering, University of Glasgow, Glasgow G12 8LT, United Kingdom

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ABSTRACT

Novel azido- and amino-functionalised fluorescent probes based on the BODIPY framework have been developed. The probes can be easily and cheaply synthesised, exhibit the highly desirable BODIPY fluorescent properties, and are amenable to ‘click’ and peptide chemistry methodologies. These probes provide a stable and readily available tool amenable for the visualisation of both solution and solid supported events.

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1. Introduction

Visualisation of intracellular processes is a key and integral part of biological chemistry and drug discovery. As such, a wide variety of fluorescent probes has been designed and synthesised incorporating a wide variety of fluorophores. 4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) has emerged as an excellent fluorescent dye due to its large molar absorption coefficient, tunable fluorescence and high quantum yield, which is responsible for their brightness (Fig. 1).^{1–3}

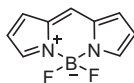


Fig. 1. BODIPY basic framework.

The BODIPYs also exhibit excellent photostability, and a small Stokes shift between their absorption and emission spectra. Furthermore, their absorption and emission spectra is located in the visible spectrum and is not affected by the choice of solvent used.

Thus, it is not surprising that a large number of BODIPY analogues have been generated and a set of them is commercially available.⁴

2. Results and discussion

As part of our own investigations into intracellular processes, we became interested in the development of 3-azido-BODIPY units as visualisation tools amenable for ‘click’ and peptide chemistry ligation. Although there have been reports of BODIPY derivatives bearing an azide substituent, the derivatives reported thus far lack the wavelength range of the original BODIPY dyes.⁵ A wide range of 8-azido and 8-amino-BODIPY derivatives on the other hand, have also been developed, however substitution at the C8 position causes significant wavelength shifts and can make these units difficult to visualise and distinguish from background emissions.⁶

Thus, it was decided to focus on the synthesis of novel 3-azido and 3-amino substituted BODIPY units able to match the wavelength range of commercially available BODIPY dyes, and as such facilitate their practical use in biological and material applications. A key part of our BODIPY synthesis was focused on the development of a simple, reliable and economic approach that could be reproduced without the need of elaborate set-ups or specialist training and would also yield significant amounts of compound quickly and efficiently.

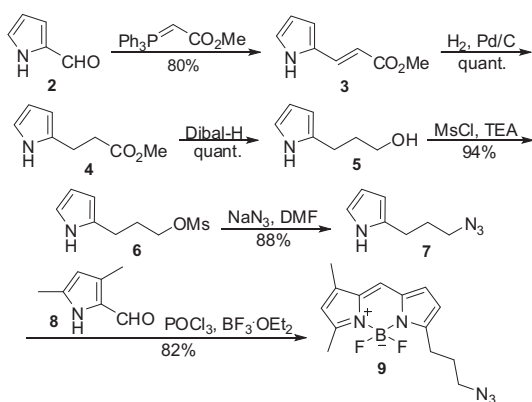
Our synthesis began with pyrrole carbaldehyde **2**, which was subjected to a Wittig olefination to afford conjugated ester **3** as a single double bond isomer.⁷ Sequential 1,4 and 1,2-reductions yielded primary alcohol **5** in excellent yield for both steps.⁸

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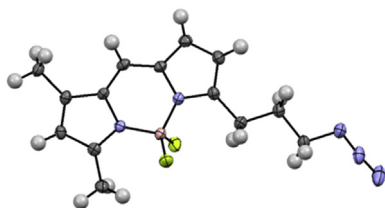
* Corresponding author. Tel.: +44 0141 330 5953; fax: +44 0141 330 488; e-mail address: rudi.marquez@glasgow.ac.uk (R. Marquez).

[†] Ian Sword Reader of Organic and Bioorganic Chemistry.

Activation of the alcohol unit as mesylate **6** followed by azide displacement then gave the desired azide building block **7** in good yield. Finally, phosphorous oxychloride promoted coupling of azido-pyrrole **7** with 3,5-dimethyl-1*H*-pyrrole-2-carboxaldehyde **8**⁹ followed by treatment with boron trifluoride diethyl etherate gave the desired azido-BODIPY analogue **9** in good yield (Scheme 1). The structure of azido-BODIPY **9** was corroborated by X-ray crystallography (Fig. 2).¹⁰

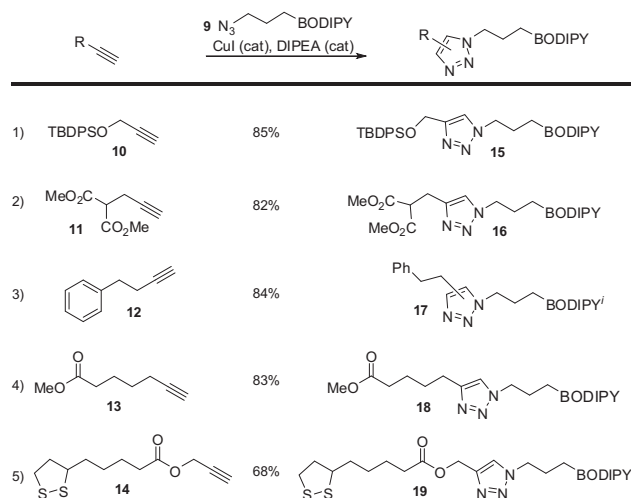


Scheme 1.

Fig. 2. Crystal structure of azido-BODIPY **9**.

Having ascertained the fluorescence spectrum of the azido-BODIPY dye **9**, its reaction with a set of alkynes was explored (Table 1).¹¹ We are pleased to report that in all cases, azido-BODIPY **9** underwent smooth Cu(I) catalysed [2,3]-dipolar cycloaddition with a variety of terminal alkynes without the loss of fluorescence. As expected, the regiochemical outcome of the addition was dictated by the steric nature of the alkyne substituent. The exception

Table 1
'Click' couplings of azido-BODIPY **9**

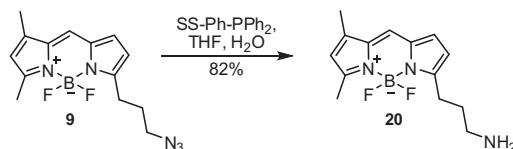


i) Obtained as 1:1 mixture of regioisomers

being the reaction with alkyne **12**, which resulted in a 1:1 ratio of regioisomeric products. The lack of selectivity is likely due to the π stacking interaction between the phenyl ring of alkyne **12** with the BODIPY core unit, which counteracts the steric repulsion.

Having demonstrated the ability of azido-BODIPY **9** to undergo 'click' cycloadditions without any detrimental effects, we decided to evaluate its synthetic flexibility and versatility. We were particularly keen to explore its suitability as a 3-amino-BODIPY precursor, which would allow for the quick fluorescent labelling of carboxylate derived units.

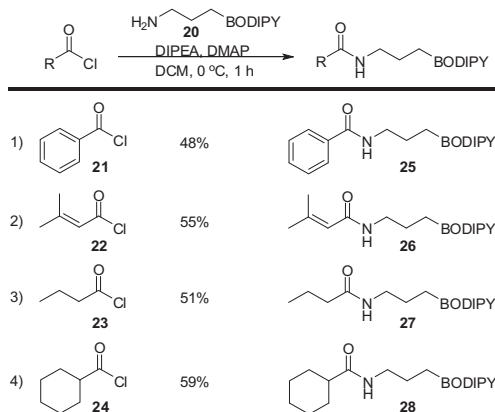
In practice, the selective reduction of azido-BODIPY **9** proved extremely difficult to achieve without loss of fluorescence, presumably due to reduction of the difluoroboronate motif. Gratifyingly however, after a significant amount of experimentation, the selective reduction of azido-BODIPY **9** was achieved through the use of Staudinger conditions¹² using solid supported triphenylphosphine to yield the desired 3-amino substituted BODIPY derivative **20** in very good yield, without the need for chromatographic purification (Scheme 2).



Scheme 2.

As expected, coupling of amino-BODIPY **20** with a variety of different acid chlorides proceeded to yield the desired BODIPY derived amides in reasonable yields. Fluorescence was retained throughout the coupling and purification procedures (Table 2).

Table 2
Peptide couplings of amino-BODIPY **20**



After having determined the suitability of azido-BODIPY **9** as a stable labelling reagent and labelling intermediate under both 'click' and peptide couplings conditions, respectively, we returned our attention to the design and development of an analogous azido-BODIPY unit with different absorption and emission spectral bands.

The synthesis of the new azido-BODIPY dye was readily achieved starting from styryl-pyrrole **29**¹³, which was subjected to Vilsmeier–Haack conditions to generate carbaldehyde **30**. Coupling of carbaldehyde **30** with azido-pyrrole **7** under our previously used conditions yielded the desired novel azido-BODIPY analogue **31** (Scheme 3). The structure of azido-BODIPY **31** was corroborated by X-ray crystallographic analysis (Fig. 3).¹⁴

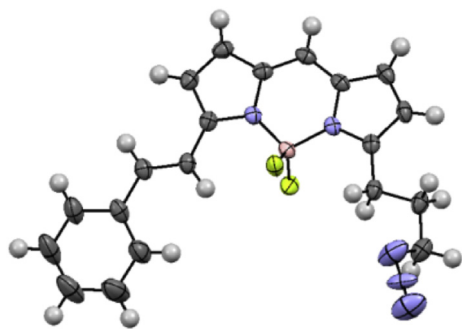
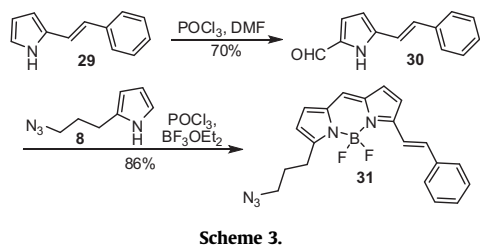


Fig. 3. Crystal structure of azido-BODIPY **31**.

As intended, both azido-BODIPY **9** and azido-BODIPY **31** display absorption and emission bands in close proximity to each other, and closely match those of commercially available BODIPY-FL[®] and BODIPY-564/570[®], respectively (Fig. 4).

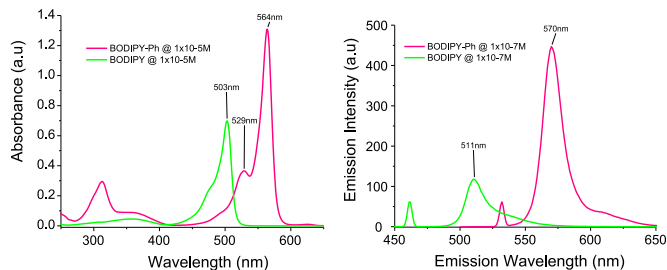


Fig. 4. Absorption and emission spectra of azido-BODIPY **9** (green) and azido-BODIPY **31** (pink). Slit width 3×3 nm.

The successful ‘click’ cycloaddition of azido-BODIPY **9** with propargyl liponic acid derivative **14** provided us with a potentially useful tool for the quick and easy visualization of solid surface patterning.¹⁵ The principle being based on the use of BODIPY dyes for micro- and nano-pattern visualisation on gold surfaces through microcontact printing.¹⁶

Thus, a polydimethylsiloxane (PDMS) master with a micron-scale honeycomb test pattern was inked with a solution of the BODIPY derived liponic acid derivative **19** in acetonitrile at a concentration of approximately 0.2 mg/mL. The substrate was prepared by e-beam evaporation of 30 nm of Au on a clean glass slide. Master and substrate were pressed together at gentle pressure in a home-built imprint stepper. The obtained pattern was imaged using fluorescent microscopy and AFM. As seen in Fig. 5, a clear honeycomb pattern was obtained on the gold surface.

In conclusion, we have developed a new set of azido- and amino-functionalised fluorescent probes based on the BODIPY framework. The probes can be cheaply, easily and quickly synthesised without the need for specialist training or equipment. The probes exhibit the highly desirable BODIPY fluorescent properties, and are amenable to ‘click’ and peptide chemistry methodologies

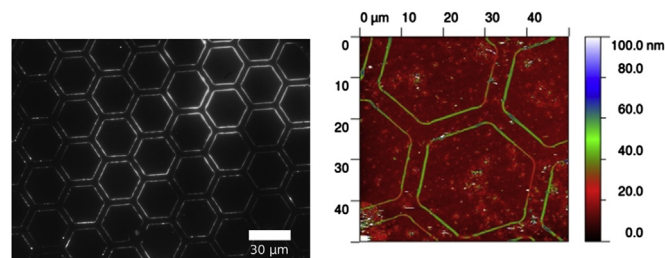


Fig. 5. Fluorescence (left) and atomic force (right) microscope images of patterned BODIPY material on a gold surface, obtained by microcontact printing.

and provide access to different parts of the visible spectrum. These probes provide a stable and readily available tool amenable for the visualisation of both solution and solid supported events and as such will be a useful tool in biological chemistry, drug discovery, materials science and nano-fabrication.

3. Experimental

3.1. General

The reactions were carried out in glassware dried in an oven (130 °C) under an argon atmosphere. Tetrahydrofuran, toluene and dichloromethane were purified through a Pure Solv 400-5MD solvent purification system (Innovative Technology, Inc). All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C.

Column chromatography was performed under pressure using silica gel (Fluoro Chem Silica LC 60A) as the stationary phase. Reactions were monitored by thin layer chromatography on aluminium sheets pre-coated with silica gel (Merck Silica Gel 60 F254). The plates were visualised by the quenching of UV fluorescence (λ_{\max} 254 nm) and/or by staining with a KMnO₄ solution or anisaldehyde dip.

Proton magnetic resonance spectra (¹H NMR) and carbon magnetic resonance spectra (¹³C NMR) were recorded at 400 MHz and 100 MHz or at 500 MHz and 125 MHz using either a Bruker DPX Avance400 instrument or a Bruker AvanceIII500 instrument, respectively. IR spectra were obtained employing a Golden Gate™ attachment that uses a type IIa diamond as a single reflection element so that the IR spectrum of the compound (solid or liquid) was detected directly (thin layer) without any sample preparation (Shimadzu FTIR-8400). Only significant absorptions are reported.

High resolution mass spectra were recorded by the analytical group of the School of Chemistry at Glasgow University & the University of Dundee using a JEOL JMS-700 mass spectrometer by electrospray and chemical ionisation operating at a resolution of 15,000 full widths at half height. UV/vis data was acquired on a Perkin Elmer Lambda 25. A Shimadzu RF-3501 spectrofluorophotometer was used to obtain the emission data.

3.1.1. (E)-Methyl 3-(1H-pyrrol-2-yl)acrylate, 3. 1H-Pyrrole-2-carboxaldehyde **2** (2.50 g, 26.3 mmol) and methyl (triphenylphosphoranylidene)acetate (17.6 g, 52.6 mmol) were heated in benzene (200 mL) until completion by TLC analysis (18 h). The reaction was cooled down and the solvent was removed in vacuo to give the crude product as yellow oil. Purification by flash column chromatography (silica gel, elution gradient 15–20% EtOAc/petroleum ether) afforded the desired conjugated ester **3** as a single trans isomer (3.15 g, 80%) and as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ : 8.78 (1H, br s), 7.58 (1H, d, J =15.9 Hz), 6.95–6.94 (1H, m), 6.58–6.57 (1H, m), 6.30–6.28 (1H, m), 6.03 (1H, d, J =15.9 Hz), 3.79 (3H, s). ¹³C NMR (CDCl₃, 100 MHz) δ : 168.2, 134.5, 128.4, 122.5, 114.5,

111.0, 110.8, 51.4. The NMR data obtained is in accordance with the literature.⁷

3.1.2. Methyl 3-(1H-pyrrol-2-yl)propanoate, 4. A solution of (E)-methyl 3-(1H-pyrrol-2-yl)acrylate **3** (3.15 g, 21.1 mmol) in MeOH (160 mL) was placed under an atmosphere of argon. Pd/C (246 mg, 10%) was added, followed by replacement of the argon with a hydrogen atmosphere. The reaction was then stirred at rt until completion as indicated by TLC analysis (16 h). The crude mixture was filtered over a bed of Celite, and the Celite plug was eluted a further aliquot of MeOH (50 mL). The combined MeOH washes were then concentrated in vacuo to afford ester **4** (3.13 g, 100%) as a pale yellow oil, which required no further purification. The NMR data obtained for ester **4** is in accordance with the literature. ¹H NMR (CDCl₃, 400 MHz) δ : 8.53 (1H, br s), 6.69–6.68 (1H, m), 6.13–6.10 (1H, m), 5.94–5.93 (1H, m), 3.71 (3H, s), 2.93 (2H, t, *J*=6.6 Hz), 2.66 (2H, t, *J*=6.6 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ : 174.5, 130.9, 116.8, 108.0, 105.5, 51.8, 34.4, 22.5.

3.1.3. 3-(1H-Pyrrol-2-yl)propan-1-ol, 5. A 0 °C solution of methyl 3-(1H-pyrrol-2-yl)propanoate **4** (2.64 g, 17.5 mmol) in Et₂O (130 mL) was treated by the slow addition of LiAlH₄ (996 mg, 26.3 mmol). The resulting suspension was allowed to warm up to rt and stirred until completion as indicated by TLC analysis (16 h). The reaction mixture was then quenched with the dropwise addition of 1 M aq NaOH until pH neutral. The Et₂O layer was decanted off, and the remaining aluminium salts were washed with Et₂O (3×50 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo to yield alcohol **5** (2.15 g, quant.) as a clear oil, which required no further purification. ¹H NMR (CDCl₃, 400 MHz) δ : 8.24 (1H, br s), 6.70–6.68 (1H, m), 6.15–6.13 (1H, m), 5.95–5.94 (1H, m), 3.73 (2H, t, *J*=5.9 Hz), 2.75 (2H, t, *J*=7.3 Hz), 2.72 (1H, br), 1.93–1.87 (2H, m). ¹³C NMR (CDCl₃, 100 MHz) δ : 131.8, 116.4, 108.3, 105.2, 62.3, 32.2, 24.2. The NMR data is in accordance with the literature.⁸

3.1.4. 2-(3-Azidopropyl)-1H-pyrrole, 7. A 0 °C solution of 3-(1H-pyrrol-2-yl)propan-1-ol **5** (1.00 g, 8.13 mmol) in CH₂Cl₂ (60 mL) was treated sequentially with Et₃N (2.26 mL, 16.26 mmol) and methanesulfonyl chloride (755 μ L, 9.76 mmol). The resulting reaction mixture was stirred at 0 °C for 1 h before being allowed to warm up to rt at which point, TLC analysis indicated reaction completion. The reaction was then transferred to a separating funnel and was washed with 1 M HCl (20 mL), followed by aq satd NaHCO₃ (20 mL) and brine (20 mL). The solution was dried over Na₂SO₄, filtered and concentrated in vacuo to afford mesylate **6** (1.52 g, 94%). The crude mesylate was then dissolved in DMF (60 mL), treated with sodium azide (1.48 g, 22.7 mmol) and the resulting homogeneous solution was heated to 70 °C until completion as indicated by TLC analysis (16 h). The reaction was cooled down to rt and diluted with EtOAc (60 mL) and H₂O (60 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2×60 mL). The combined organics were washed with brine (5×100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford azide **7** (947 mg, 88%) as a yellow oil, which required no further purification. ¹H NMR (CDCl₃, 400 MHz) δ : 7.98 (1H, br s), 6.70–6.69 (1H, m), 6.16–6.15 (1H, m), 5.96–5.95 (1H, m), 3.34 (2H, t, *J*=6.6 Hz), 2.73 (2H, t, *J*=7.4 Hz), 1.95–1.89 (2H, m). ¹³C NMR (CDCl₃, 100 MHz) δ : 130.7, 116.5, 108.5, 105.5, 50.7, 28.9, 24.7. IR ν_{\max} (film)/cm⁻¹ 3379, 2940, 2870, 2091. HRMS (EI) calcd for C₇H₁₁N₄ [M+H]⁺ 151.0984 *m/z*, found 151.0987 *m/z*.

3.1.5. 2-Formyl-3,5-dimethyl-1H-pyrrole, 8. POCl₃ (1.00 mL, 11 mmol) was added dropwise at 0 °C to DMF (20 mL) and the resulting mixture was stirred for 5 min. The solution was then stirred at rt for 30 min before being cooled back down to 0 °C. The solution was then treated with 3,5-dimethyl-1H-pyrrole (1.0 mL,

10 mmol). The resulting mixture was allowed to warm up to rt, and then heated to 40 °C until completion as indicated by TLC analysis (18 h). The reaction was then cooled down to rt and diluted with EtOAc (30 mL). The resulting solution was washed with H₂O (8×50 mL), brine (3×50 mL), dried (Na₂SO₄) and concentrated in vacuo to afford the crude as a dark brown solid. Column chromatography (silica gel, 50% Et₂O/petroleum ether) afforded (1.1 g, 82%) of the desired pyrrole carbaldehyde **8** as an off white solid. ¹H NMR (CDCl₃, 400 MHz) δ : 10.14 (1H, br s), 9.49 (1H, s), 5.89 (1H, s), 2.32 (3H, s), 2.30 (3H, s). ¹³C NMR (CDCl₃, 100 MHz) δ : 176.0, 138.5, 134.8, 128.8, 112.1, 13.2, 10.5.

3.1.6. 7-(3-Azidopropyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, 9. A 0 °C solution of 2-(3-azidopropyl)-1H-pyrrole **7** (400 mg, 2.66 mmol) in CH₂Cl₂ (20 mL) was treated with 3,5-dimethyl-1H-pyrrole-2-carboxaldehyde **8** (360 mg, 2.93 mmol) and the resulting solution was treated by the dropwise addition of POCl₃ (431 μ L, 2.93 mmol). The reaction mixture was stirred for 6 h at rt before being cooled back down to 0 °C. The mixture was then treated with BF₃·(OEt)₂ (1.31 mL, 10.6 mmol) and *N,N*-diisopropylethylamine (1.9 mL, 11.2 mmol) and the reaction was stirred at rt for 12 h. The mixture was then diluted with H₂O (15 mL) and CH₂Cl₂ (10 mL) before being filtered through a bed of Celite. The Celite was washed through with CH₂Cl₂ (2×15 mL) and the organic phases combined. The solution was then dried over Na₂SO₄ and concentrated in vacuo to afford a dark red/green crude solid residue. Purification of the crude solid by flash column chromatography (silica gel, elution gradient 2–7% EtOAc/petroleum ether) afforded 660 mg (82%) of the desired azide **9** as red oil, which solidified upon cooling. Mp 49–50 °C. ¹H NMR (CDCl₃, 500 MHz) δ : 7.09 (1H, s), 6.91 (1H, d, *J*=3.9 Hz), 6.28 (1H, d, *J*=3.9 Hz), 6.12 (1H, s), 3.40 (2H, t, *J*=7.0 Hz), 3.05 (2H, t, *J*=7.4 Hz), 2.57 (3H, s), 2.27 (3H, s), 2.07–2.01 (2H, m). ¹³C NMR (CDCl₃, 125 MHz) δ : 160.3, 157.6, 143.7, 135.0, 133.2, 128.1, 123.6, 120.3, 116.5, 50.8, 28.0, 25.6, 14.8, 11.1. IR ν_{\max} (film)/cm⁻¹ 2959, 2932, 2870, 2091. HRMS (ESI) calcd for C₁₄H₁₇BF₂N₅ [M+H]⁺ 304.1545 *m/z*, found 304.1528 *m/z*.

3.1.7. Methyl-6-heptynoate, 13.¹⁷ A solution of 6-heptynoic acid (500 μ L, 3.95 mmol) in acetone was treated with K₂CO₃ (273 mg, 1.98 mmol). The mixture was then stirred for 30 min and MeI (2.5 mL, 39 mmol) was then added. The reaction mixture was stirred for 18 h and then quenched with aq satd. NaHCO₃ (5 mL). The solution was washed with 10% aq Na₂S₂O₃ (20 mL), brine (20 mL), and dried over Na₂SO₄. The solvent was then removed under vacuum to give 406 mg (75%) of the desired methyl ester **13** as a colourless oil. ¹H NMR (CDCl₃, 500 MHz) δ : 3.69 (3H, s), 2.36 (2H, t, *J*=7.3 Hz), 2.23 (2H, td, *J*=7.0, 2.6 Hz), 1.95 (1H, t, *J*=2.7 Hz), 1.81–1.75 (2H, m), 1.62–1.56 (2H, m). ¹³C NMR (CDCl₃, 125 MHz) δ : 174.1, 83.8, 68.6, 51.4, 33.4, 27.9, 23.9, 18.0.

3.1.8. 2-Propynyl 5-(1,2-dithiolan-3-yl)pentanoate, 14. A solution of propargyl alcohol (130 μ L, 2.2 mmol) in CH₂Cl₂ (30 mL) was treated with thioctic acid (500 mg, 2.42 mmol) and the resulting mixture was stirred for 30 min at 0 °C. The solution was then treated with EDC (404 mg, 2.42 mmol) followed by DMAP (188 mg, 1.54 mmol). The reaction mixture was allowed to warm up to rt and was then stirred for 18 h. The reaction was then washed with water (30 mL), brine (30 mL), and the organic phase was dried over Na₂SO₄. The solution was then concentrated under reduced pressure to yield a crude oil, which was then purified by flash column chromatography (silica gel, 20% EtOAc/petroleum ether) to afford 505 mg (94%) of the desired ester as a yellow oil. The NMR data obtained is in accordance with the literature.¹⁴ ¹H NMR (CDCl₃, 500 MHz) δ : 4.61 (2H, d, *J*=2.4 Hz), 3.50 (1H, ddt, *J*=14.8, 8.3, 6.4 Hz), 3.14–3.09 (1H, m), 3.07–3.02 (1H, m),

2.43–2.36 (1H, m), 2.41 (1H, t, $J=2.4$ Hz), 2.31 (2H, t, $J=7.5$ Hz), 1.88–1.80 (1H, m), 1.69–1.57 (4H, m), 1.49–1.34 (2H, m). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 172.8, 77.7, 74.9, 56.3, 51.8, 40.2, 38.5, 34.6, 33.8, 28.7, 24.6. IR ν_{max} (film)/ cm^{-1} 3284, 2918, 1735, 1159. HRMS (CI/Isobutane) exact mass calculated for $\text{C}_{11}\text{H}_{17}\text{O}_2\text{S}_2$ [M] $^+$ 244.0592 m/z , found 244.0595 m/z .

3.1.9. 7-(3-(4-((*tert*-Butyldimethylsilyloxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **15**. A solution of *tert*-butyldimethyl(prop-2-ynyloxy)silane **10** (37 mg, 0.21 mmol) in THF (2 mL) was treated with azido-BODIPY **9** (50 mg, 0.16 mmol), CuI (5 mg, 0.03 mmol), DIPEA (100 μL , 0.59 mmol) in a sealed tube. The reaction mixture was then heated up to 70 $^\circ\text{C}$ for 18 h. Solvent evaporation followed by purification of the crude residue by flash column chromatography (silica gel, elution gradient 25–50% EtOAc/petroleum ether) afforded 66 mg (85%) of the desired triazole **15** as an orange solid. Mp 93–95 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz) δ : 7.50 (1H, s), 7.09 (1H, s), 6.89 (1H, d, $J=4.2$ Hz), 6.26 (1H, d, $J=4.2$ Hz), 6.12 (1H, s), 4.84–4.83 (2H, m), 4.41 (2H, t, $J=7.3$ Hz), 3.03 (2H, t, $J=7.6$ Hz), 2.57 (3H, s), (2H, quint, $J=7.4$ Hz), 2.26 (3H, s), 0.91 (9H, s), 0.09 (6H, s). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 160.4, 157.0, 148.6, 143.8, 135.2, 133.3, 128.0, 123.8, 121.6, 120.5, 116.8, 57.9, 49.7, 29.5, 25.8, 25.7, 23.7, 18.3, 14.8, 11.1, –5.3. IR ν_{max} (film)/ cm^{-1} 2951, 2928, 2858, 1600, 1259. HRMS (CI/Isobutane) exact mass calculated for $\text{C}_{23}\text{H}_{35}\text{BF}_2\text{N}_5\text{OSi}$ [$\text{M}+\text{H}$] $^+$ 474.2672 m/z , found 474.2677 m/z .

3.1.10. 5,5-Difluoro-7-(3-(4-(3-methoxy-2-(methoxycarbonyl)-3-oxopropyl)-1H-1,2,3-triazol-1-yl)propyl)-1,3-dimethyl-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **16**. A solution of dimethyl 2-(prop-2-ynyl)malonate **11** (32 μL , 0.21 mmol) in THF (2 mL) was treated with azido-BODIPY **9** (50 mg, 0.16 mmol), CuI (5 mg, 0.03 mmol), DIPEA (100 μL , 0.59 mmol) in a sealed tube. The reaction mixture was then heated up to 70 $^\circ\text{C}$ for 18 h. Solvent evaporation followed by purification of the crude residue by flash column chromatography (silica gel, elution gradient 50–80% Et₂O/petroleum ether) afforded 64 mg (82%) of the desired triazole **16** as an orange solid. Mp 117–119 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 500 MHz) δ : 7.29 (1H, s), 7.00 (1H, s), 6.80 (1H, d, $J=4.0$ Hz), 6.16 (1H, d, $J=4.0$ Hz), 6.04 (1H, s), 4.30 (2H, t, $J=7.6$ Hz), 3.81 (1H, t, $J=7.4$ Hz), 3.64 (6H, s), 3.33 (2H, d, $J=7.4$ Hz), 3.03 (2H, t, $J=7.3$ Hz), 2.59 (3H, s), 2.37 (2H, quintet, $J=7.4$ Hz), 2.28 (3H, s). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 169.1, 160.7, 156.8, 143.9 (2C), 135.2, 133.2, 128.2, 123.9, 122.0, 120.5, 116.7, 51.5, 49.7, 30.3, 29.4, 25.6, 25.0, 14.8, 11.2. IR ν_{max} (film)/ cm^{-1} 3053, 2958, 2847, 1747, 1730, 1138. HRMS (CI/Isobutane) exact mass calculated for $\text{C}_{22}\text{H}_{27}\text{BF}_2\text{N}_5\text{O}_4$ [$\text{M}+\text{H}$] $^+$ 474.2124 m/z , found 474.2128 m/z .

3.1.11. 5,5-Difluoro-1,3-dimethyl-7-(3-(4-phenethyl-1H-1,2,3-triazol-1-yl)propyl)-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **17a** and 5,5-difluoro-1,3-dimethyl-7-(3-(5-phenethyl-1H-1,2,3-triazol-1-yl)propyl)-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **17b**. A solution of 3-butylnylbenzene **12** (30 μL , 0.21 mmol) in THF (2 mL) was treated with azido-BODIPY **9** (50 mg, 0.16 mmol), CuI (5 mg, 0.03 mmol), DIPEA (100 μL , 0.59 mmol) in a sealed tube. The reaction mixture was then heated up to 70 $^\circ\text{C}$ for 18 h. Solvent evaporation followed by purification of the crude residue by flash column chromatography (silica gel, elution gradient 50–80% Et₂O/petroleum ether) afforded 60 mg (84%) of the triazole **17** as a 1:1 mixture of regioisomers.

Compound **17a**: ^1H NMR (CDCl_3 , 500 MHz) δ : 7.21–7.16 (2H, m), 7.11–7.08 (3H, m), 7.06 (1H, s), 6.99 (1H, s), 6.79 (1H, d, $J=4.0$ Hz), 6.15 (1H, d, $J=4.0$ Hz), 6.03 (1H, s), 4.28 (2H, t, $J=7.1$ Hz), 2.96–2.89 (6H, m), 2.48 (3H, s), (2H, quintet, $J=7.3$ Hz), 2.17 (3H, s). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 160.4, 157.0, 147.2, 143.9, 141.3, 135.2, 133.3, 128.4, 128.3, 128.1, 126.0, 123.7, 120.9, 120.4, 116.7, 49.5, 35.6, 29.5,

27.5, 25.7, 14.8, 11.1. IR ν_{max} (film)/ cm^{-1} 2960, 2924, 2848, 1599, 1527, 1481. Mp 85–88 $^\circ\text{C}$.

Compound **17b**: ^1H NMR (CDCl_3 , 500 MHz) δ : 7.20–7.16 (3H, m), 7.12–7.08 (3H, m), 7.00 (1H, s), 6.82 (1H, d, $J=4.3$ Hz), 6.24 (1H, d, $J=4.3$ Hz), 6.03 (1H, s), 4.32 (2H, t, $J=7.4$ Hz), 2.99–2.92 (4H, m), 2.90–2.86 (2H, m), 2.49 (3H, s), (2H, quintet, $J=7.4$ Hz), 2.18 (3H, s). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 160.5, 157.1, 150.9, 143.9, 141.1, 135.3, 133.3, 128.5, 128.3, 128.0, 126.0, 125.5, 123.7, 120.4, 116.7, 50.1, 35.2, 30.3, 28.2, 25.5, 14.9, 11.2. IR ν_{max} (film)/ cm^{-1} 3122, 3028, 2541, 2848, 1599, 1529, 1485, 775. Mp 120–124 $^\circ\text{C}$. HRMS (EI $^+$) exact mass calculated for $\text{C}_{24}\text{H}_{26}\text{BF}_2\text{N}_5$ [$\text{M}+\text{H}$] $^+$ 433.2249 m/z , found 433.2246 m/z .

3.1.12. 5,5-Difluoro-7-(3-(4-(7-methoxy-7-oxoheptyl)-1H-1,2,3-triazol-1-yl)propyl)-1,3-dimethyl-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **18**. A solution of methyl-6-heptynoate **13** (30 mg, 0.21 mmol) in THF (2 mL) was treated with azido-BODIPY **9** (50 mg, 0.16 mmol), CuI (5 mg, 0.03 mmol), DIPEA (100 μL , 0.59 mmol) in a sealed tube. The reaction mixture was then heated up to 70 $^\circ\text{C}$ for 18 h. Solvent evaporation followed by purification of the crude residue by flash column chromatography (silica gel, elution gradient 50–100% Et₂O/petroleum ether) afforded 61 mg (83%) of the desired triazole **18** as an orange oil. ^1H NMR (CDCl_3 , 400 MHz) δ : 7.36 (1H, s), 7.13 (1H, s), 6.92 (1H, d, $J=3.9$ Hz), 6.29 (1H, d, $J=3.9$ Hz), 6.16 (1H, s), 4.43 (2H, t, $J=6.9$ Hz), 3.70 (3H, s), 3.05 (2H, t, $J=7.5$ Hz), 2.77–2.73 (2H, m), 2.60 (3H, s), 2.43–2.35 (4H, m), 2.29 (3H, s), 1.76–1.71 (4H, m). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 174.1, 160.5, 157.1, 147.8, 144.1, 135.2, 133.4, 128.2, 123.8, 120.7, 120.4, 116.8, 51.2, 49.5, 33.7, 30.4, 29.4, 28.8, 25.7, 25.3, 14.8, 11.2. IR ν_{max} (film)/ cm^{-1} 2947, 2926, 2858, 1732, 1599, 1435, 729. HRMS (CI/Isobutane) exact mass calculated for $\text{C}_{22}\text{H}_{28}\text{BF}_2\text{N}_5\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 444.2382 m/z , found 444.2387 m/z .

3.1.13. 7-(3-(4-((5-(1,2-Dithiolan-3-yl)pentanoyloxy)methyl)-1H-1,2,3-triazol-1-yl)propyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **19**. A solution of 2-propynyl 5-(1,2-dithiolan-3-yl)pentanoate **14** (40 mg, 0.16 mmol) in THF (2 mL) was treated with azido-BODIPY **9** (41 mg, 0.14 mmol), CuI (5 mg, 0.03 mmol), DIPEA (100 μL , 0.59 mmol) in a sealed tube. The reaction mixture was then heated up to 70 $^\circ\text{C}$ for 18 h. Solvent evaporation followed by purification of the crude residue by flash column chromatography (silica gel, elution gradient 50–100% Et₂O/petroleum ether) afforded 50 mg (68%) of the desired triazole **19** as an orange oil. ^1H NMR (CDCl_3 , 500 MHz) δ : 7.61 (1H, s), 7.09 (1H, s), 6.88 (1H, d, $J=3.9$ Hz), 6.25 (1H, d, $J=3.9$ Hz), 6.13 (1H, s), 5.20 (2H, s), 4.43 (2H, t, $J=7.4$ Hz), 3.57–3.50 (1H, m), 3.19–3.06 (2H, m), 3.02 (2H, t, $J=7.6$ Hz), 2.57 (3H, s), 2.47–2.31 (5H, m), 2.26 (3H, s), 1.92–1.84 (1H, m), 1.70–1.60 (4H, m), 1.43–1.30 (2H, m). ^{13}C NMR (CDCl_3 , 125 MHz) δ : 173.2, 160.7, 156.6, 144.1, 142.9, 135.4, 133.3, 128.1, 123.9, 123.8, 120.6, 116.6, 57.6, 56.3, 49.8, 40.2, 38.4, 34.5, 33.9, 29.4, 28.6, 25.6, 24.5, 14.9, 11.2. IR ν_{max} (film)/ cm^{-1} 3005, 2924, 2858, 1732, 1593, 1479, 1431, 1244, 709. HRMS (ESI) exact mass calculated for $\text{C}_{25}\text{H}_{33}\text{BF}_2\text{N}_5\text{O}_2\text{S}_2$ [$\text{M}+\text{H}$] $^+$ 548.2137 m/z , 548.2137 found m/z .

3.1.14. 7-(3-Aminopropyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,2]diazaborinin-4-ium-5-uide, **20**. To a solution of azido-BODIPY **9** (25 mg, 83 μmol) in THF (1 mL) was added polymer bound triphenylphosphine (103 mg, 1.6 mmol g^{-1}) and H₂O (50 μL). The resultant suspension was heated at 50 $^\circ\text{C}$ for 4 h, following reaction progress by TLC. Upon completion, the suspension was allowed to cool down to rt before filtering through a bed of Celite. Solvent removal under reduced pressure afforded the desired amino-BODIPY **20** as red oil (70%). The material was used without any further purification.

3.1.15. General procedure for the coupling of amino-BODIPY **20** to acid chlorides. To a 0 $^\circ\text{C}$ solution of 3-amino-BODIPY **20** (1 equiv) in

CH₂Cl₂ was sequentially added the desired acid chloride (1.5 equiv), DIPEA (1.5 equiv) and a catalytic amount of DMAP. The reaction was then stirred at 0 °C until completion as indicated by TLC analysis (1 h). The crude mixture was then concentrated in vacuo and the crude residue was purified by flash column chromatography (silica gel, eluting with CH₂Cl₂) to afford the desired products as red oils.

3.1.16. 7-(3-Benzamidopropyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, **25**. 3-Amino-BODIPY **20** (18 mg, 65 μmol) was dissolved in CH₂Cl₂ (0.5 mL) and cooled down to 0 °C before the sequential addition of benzoyl chloride (12 μL, 97 μmol), DIPEA (17 μL, 97 μmol) and DMAP (cat). TLC analysis showed reaction completion after 1 h. Column chromatography (neat CH₂Cl₂) afforded the desired amide **25** as red oil (12 mg, 48%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.81–7.79 (2H, m), 7.48–7.44 (1H, m), 7.39–7.35 (2H, m), 7.05 (1H, s), 6.90 (1H, d, J=4.0 Hz), 6.88 (1H, br), 6.34 (1H, d, J=4.0 Hz), 6.14 (1H, s), 3.52–3.49 (2H, m), 3.10 (2H, t, J=7.2 Hz), 2.60 (3H, s), 2.27 (3H, s), 2.13–2.06 (2H, m). ¹³C NMR (CDCl₃, 100 MHz) δ: 167.36, 159.5, 159.4, 143.5, 134.8, 134.7, 133.2, 131.1, 128.9, 128.3, 127.0, 123.6, 120.2, 117.2, 39.0, 28.9, 25.8, 14.9, 11.3. IR ν_{max} (film)/cm⁻¹ 3416, 3306, 2957, 2920, 2851, 1597. HRMS (ESI) calcd for C₂₁H₂₂BF₂N₃NaO [M+Na]⁺ 404.1716 m/z, found 404.1715 m/z.

3.1.17. 5,5-Difluoro-1,3-dimethyl-7-(3-(3-methylbut-2-enamido)propyl)-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, **26**. 3-Amino-BODIPY **20** (14 mg, 51 μmol) was dissolved in CH₂Cl₂ (0.5 mL) and cooled down to 0 °C before being treated with 3,3-dimethyl acryloyl chloride (11 μL, 76 μmol), DIPEA (13 μL, 76 μmol) and DMAP (cat). TLC analysis showed reaction completion after 1 h. Column chromatography of the crude residue (neat CH₂Cl₂) afforded the desired amide **26** as a red oil (10 mg, 55%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.09 (1H, s), 6.92 (1H, d, J=4.0 Hz), 6.32 (1H, d, J=4.0 Hz), 6.12 (1H, s), 5.86 (1H, br), 5.53–5.52 (1H, m), 3.38–3.28 (2H, m), 3.02 (2H, t, J=7.2 Hz), 2.58 (3H, s), 2.26 (3H, s), 2.15 (2H, d, J=1.2 Hz), 2.01–1.95 (2H, m), 1.82 (2H, d, J=1.2 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ: 167.1, 159.5, 159.3, 150.1, 143.4, 134.8, 133.2, 128.7, 123.6, 120.1, 118.8, 117.1, 38.2, 28.8, 27.1, 25.8, 19.7, 14.9, 11.3. IR ν_{max} (film)/cm⁻¹ 3418, 3298, 2955, 2924, 2857, 1597. HRMS (ESI) calcd for C₁₉H₂₄BF₂N₃NaO [M+Na]⁺ 382.1853 m/z, found 382.1857 m/z.

3.1.18. 7-(3-Butyramidopropyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, **27**. 3-Amino-BODIPY **20** (11 mg, 39 μmol) was dissolved in CH₂Cl₂ (0.5 mL) and cooled down to 0 °C before being treated with butyryl chloride (6 μL, 59 μmol), DIPEA (10 μL, 59 μmol) and DMAP (cat). TLC analysis showed reaction completion after 1 h. Column chromatography of the crude residue (neat CH₂Cl₂) afforded the desired amide **27** as a red oil (7 mg, 51%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.09 (1H, s), 6.93 (1H, d, J=4.0), 6.32 (1H, d, J=4.0 Hz), 6.12 (1H, s), 6.00 (1H, br), 3.32–3.28 (2H, m), 3.02 (2H, t, J=7.2 Hz), 2.57 (3H, s), 2.26 (3H, s), 2.12 (2H, t, J=7.5 Hz), 2.00–1.93 (2H, m), 1.69–1.60 (2H, m), 0.94 (3H, t, J=7.4 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ: 173.1, 159.6, 159.2, 143.5, 134.9, 133.2, 128.7, 123.6, 120.2, 117.1, 38.8, 38.4, 28.7, 25.7, 19.1, 14.9, 13.8, 11.3. IR ν_{max} (film)/cm⁻¹ 3420, 3295, 2961, 2928, 2872, 1597. HRMS (ESI) calcd for C₁₈H₂₄BF₂N₃NaO [M+Na]⁺ 370.1873 m/z, found 370.1881 m/z.

3.1.19. 7-(3-(Cyclohexanecarboxamido)propyl)-5,5-difluoro-1,3-dimethyl-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, **28**. 3-Amino-BODIPY **20** (11 mg, 39 μmol) was dissolved in CH₂Cl₂ (0.5 mL) and cooled down to 0 °C before being treated with cyclohexanecarbonyl chloride (8 μL, 59 μmol), DIPEA (10 μL, 59 μmol) and DMAP (cat). TLC analysis showed reaction completion after 1 h. Column chromatography of the crude residue (neat CH₂Cl₂) afforded the desired amide **28** as red oil (9 mg, 59%). ¹H NMR (CDCl₃, 400 MHz) δ: 7.09 (1H, s), 6.93 (1H, d, J=4.0 Hz), 6.31

(1H, d, J=4.0 Hz), 6.01 (1H, s), 6.00 (1H, br), 3.31–3.28 (2H, m), 3.00 (2H, t, J=7.2 Hz), 2.57 (3H, s), 2.26 (3H, s), 2.08–2.04 (1H, m), 1.98–1.91 (2H, m), 1.89–1.84 (2H, m), 1.78–1.74 (2H, m), 1.67–1.64 (2H, m), 1.45–1.35 (2H, m), 1.29–1.20 (2H, m). ¹³C NMR (CDCl₃, 100 MHz) δ: 176.26, 159.5, 159.3, 143.5, 134.8, 133.2, 128.7, 123.6, 120.2, 117.1, 45.6, 38.4, 29.6, 28.8, 25.9 (2C), 25.7, 14.9, 11.3. IR ν_{max} (film)/cm⁻¹ 3423, 3291, 2926, 2853, 1599. HRMS (ESI) calcd for C₂₁H₂₈BF₂N₃NaO [M+Na]⁺ 410.2186 m/z, found 410.2184 m/z.

3.1.20. (E)-5-Styryl-1H-pyrrole-2-carboxaldehyde, **30**. POCl₃ (163 μL, 1.11 mmol) was added dropwise to DMF (5 mL) at 0 °C and the resulting mixture was stirred for 5 min. The solution was then warmed up to rt and stirred for an additional 30 min. The reaction was then cooled back down to 0 °C, and treated with (E)-2-styryl-1H-pyrrole **29**¹² (171 mg, 1.0 mmol). The resulting reaction mixture was left to warm up to rt and subsequently heated to 40 °C for 18 h. The reaction was then cooled back down to rt and diluted with EtOAc (30 mL). The solution was washed with H₂O (8×20 mL), brine (3×20 mL), dried (Na₂SO₄) and concentrated in vacuo to yield a crude dark brown solid. Purification of the crude residue by flash column chromatography (50% Et₂O/petroleum ether) afforded 48 mg (24%) of aldehyde **30** as a dark brown solid. ¹H NMR (CDCl₃, 400 MHz) δ: 10.15 (1H, br s), 9.51 (1H, s), 7.54–7.50 (2H, m), 7.42–7.37 (2H, m), 7.34–7.29 (1H, m), 7.16 (1H, d, J=16.6 Hz), 7.03 (1H, d, J=16.5 Hz), 7.01 (1H, dd, J=4.0, 2.3 Hz), 6.52 (1H, dd, J=4.0, 2.3 Hz). ¹³C NMR (CDCl₃, 100 MHz) δ: 178.5, 139.0, 136.3, 132.9, 130.9, 128.8, 128.3, 126.6, 122.9, 117.3, 110.7. IR ν_{max} (film)/cm⁻¹ 3209, 2958, 2922, 2852, 1631. HRMS (EI⁺) calcd for C₁₃H₁₁NO [M]⁺ 197.0841 m/z, found 197.0843 m/z.

3.1.21. 3(E)-7-(3-Azidopropyl)-5,5-difluoro-3-styryl-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, **31**. A 0 °C solution of 2-(3-azidopropyl)-1H-pyrrole **8** (48 mg, 0.24 mmol) and 5-styryl-1H-pyrrole-2-carboxaldehyde **30** (33 mg, 0.22 mmol) in CH₂Cl₂ (5 mL) was treated by the dropwise addition of POCl₃ (22 μL, 0.24 mmol). The mixture was then allowed to warm up to rt and was then stirred for 6 h before being cooled back down again to 0 °C. Once at 0 °C, the reaction mixture was treated with BF₃·(OEt)₂ (109 μL, 0.89 mmol) and N,N-diisopropylethylamine (162 μL, 0.93 mmol). The reaction was then allowed to warm up to rt and was stirred for a further 12 h. The reaction was then diluted with H₂O (10 mL) and CH₂Cl₂ (5 mL) before being filtered through a bed of Celite. The Celite was washed with CH₂Cl₂ (2×10 mL), and the organic phases were combined, dried over Na₂SO₄ and concentrated under reduced pressure to yield a dark pink/purple solid. Purification of the crude residue by flash column chromatography (silica gel, elution gradient 15–20% Et₂O/petroleum ether) afforded 79 mg (86%) of the desired azide (79 mg, 86%) as a purple oil, which solidified upon standing. Mp 137–138 °C. ¹H NMR (CDCl₃, 500 MHz) δ: 7.63 (1H, d, J=16.4 Hz), 7.64–7.62 (2H, m), 7.43–7.33 (4H, m), 7.08 (1H, s), 7.04 (1H, d, J=4.3 Hz), 6.98 (1H, d, J=4.3 Hz), 6.92 (1H, d, J=4.4 Hz), 6.37 (1H, d, J=4.0 Hz), 3.44 (2H, t, J=6.7 Hz), 3.14 (2H, t, J=7.9 Hz), 2.11–2.05 (2H, m). ¹³C NMR (CDCl₃, 125 MHz) δ: 160.0, 156.2, 137.7, 136.3, 136.2, 134.9, 130.2, 129.3 (2C), 128.8, 127.6, 125.6, 119.0, 117.9, 116.7, 50.9, 28.0, 26.0. IR ν_{max} (film)/cm⁻¹ 2956, 2924, 2858, 2096. HRMS (ESI) calcd for C₂₀H₁₉BF₂N₅ [M+H]⁺ 378.1702 m/z, found 378.1690 m/z.

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