Chapter 2

Green-light-sensitive BODIPY photoprotecting groups for amines

Introduction

The bright prospects of the application of light in chemistry and biology have stimulated the research on photochemical control of function in recent years. Light can be used as a regulatory element in biological systems because of its low toxicity (especially in the so-called therapeutic window $\lambda = 650-900\ nm$), orthogonality with most bioactive compounds, high spatio-temporal precision of delivery, control over quality and quantity, tissue penetration and lack of contamination of samples.

At the molecular level, photocontrol over bioprocesses can be achieved by incorporation of photosensitive moieties in the structure of bioactive compounds. Two fundamental approaches are currently being explored. In the first one, molecular photoswitches are used to reversibly turn on and off the activity of a drug. In the second one, photoprotecting groups (PPGs) are being used to suppress the activity of the drug until it is activated with light. With this approach, more pronounced changes in activity prior to and after irradiation are often obtained. Commonly applied PPGs include coumarin, ortho-nitrobenzyl, salicylic alcohol and nitroindolinyl derivatives; the synthesis and mechanism of action of these groups is well described.

Functional groups protected by PPGs are usually carboxylic acids, alcohols and amines. These groups are abundant in drugs and biomolecules and usually play an important role in their activity. Amines, in particular, function as neurotransmitters, antibiotics and anticancer drugs. Photoprotection of dopamine, histidine, GABA and Vemurafenib has been reported. Photoprotecting groups can also be used for controlling complex biological processes, like protein dimerization or gene activation and gene silencing.

Despite many successful applications, new PPGs that address the drawbacks of existing agents are needed. Foremost among these drawbacks are slow deprotection reactions and deprotections that require UV light, which is toxic to tissues and is often scattered before reaching the drug in the body.
Because of the many potential applications, we were interested in addressing these challenges by designing a novel PPG with better kinetic and absorption properties for the use in biological systems.

In general, when designing PPGs for biological applications, one has to ensure a few of their key properties:\cite{6c,24} efficiency of uncaging, narrow absorption maximum and low absorbance outside this range, high molar absorptivity at a chosen irradiation wavelength, chemical stability and solubility in aqueous media and lack of toxicity of the PPGs as well as the products resulting of their deprotection. Another important factor is the wavelength of light needed for the deprotection, which should be as long as possible (up to red and near-IR) for better light penetration of tissue and lower toxicity.

Recently, the group of Klan and Wirz presented data suggesting that BODIPY (boron-dipyrromethene) has a similar frontier orbital structures to that of coumarines or xanthenes,\cite{25} making it a possible PPG candidate. BODIPY derivatives are widely used as probes,\cite{26} laser dyes,\cite{27} photosensitizers,\cite{28} sensors,\cite{29} dyads,\cite{30} catalysts,\cite{31} emission contrasts\cite{32} and cell visualization agents.\cite{33} This wide variety of applications are enabled by their advantageous properties, such as stability in various media, sharp absorbance peaks, low toxicity, high quantum yields and vivid color shifts obtained when changing various stimuli.

Throughout literature, there are three cases where meso-BODIPY derivatives were used as PPGs. Winter and coworkers\cite{34} studied deprotection of carboxylic acids from BODIPY with different substituents on the BODIPY core (Figure 9 a). Their modifications of the electronic properties of the BODIPY moiety resulted in a different $\lambda_{\text{max}}$ and a variation of the efficiency of its deprotection in DCM. The authors observed that the BODIPY derivative with chlorine as substituents on the ring ($X = \text{Cl}$) was the fastest to react, releasing acetic acid within an hour, which, however, remains not efficient enough for the compound to be used in most biological applications.

A faster and more efficient BODIPY-based PPG has been proposed by the group of Weinstain.\cite{17} Their model compound, in which its amine is connected to the BODIPY protecting group through a carbamate linker (Figure 9 b), could be uncaged fast (under an hour) and proved to be stable in aqueous media. The $\lambda_{\text{max}}$ of this
compound was slightly red-shifted when comparing to a non-substituted BODIPY core (540 nm).

\[ \lambda_{\text{max}} = 520 - 560 \text{ nm} \]

- Deprotection time in hours
- Deprotected carboxylic acids

\[ \lambda_{\text{max}} = 540 \text{ nm} \]

- Deprotection time in minutes
- Deprotected primary amines

\[ \lambda_{\text{max}} \text{ up to } 560 \text{ nm} \]

- Deprotection time in minutes
- Deprotected primary and secondary amines
- Preparation from easily accessible substrates

**Figure 9.** Comparison of existing BODIPY photoprotecting groups and those described in this work

Weinstain et al. also used their PPG to release dopamine and histidine. These uncaged amines were active, as was shown on rat cortical/hippocampal neurons for dopamine and HeLa cells for histidine. Their experiments also proved that this approach could be compatible with biological systems by showing the difference in activity of protected and deprotected amines in vitro. Although the PPG was efficient and worked fast, it was synthesized form a pre-made, difficult to prepare and expensive BODIPY dye. During the course of this project, the groups of Winter and Weinstain also reported the use of dimethyl-boron based BODIPYs for the fast release of methanol, chlorine and a variety of (thio)acids.\textsuperscript{[35]}
A different approach was proposed by the group of Urano,[36] who used a BODIPY protecting group for phenols by attaching the phenol oxygen to the boron atom of the BODIPY core. Deprotection with blue-green light of $\lambda_{\text{max}} = 500$ nm proceeded relatively fast (20 – 30 min). In this system, protection of amines was also shown, but it required the use of an additional phenolic linker. The two aforementioned initial reports inspired our design: To enhance practicality of PPG’s we have chosen the BODIPY core because of its stability in various media and long wavelength of light needed for the deprotection compared to the other commonly used PPGs. To ensure no overlap with commonly used bioactive compounds and the penetration of the tissue, our aim was to shift the deprotection wavelength even further while achieving fast deprotection. To achieve this, we decided to modify the BODIPY core with halogen atoms, instead of alkyl groups, with the ease of synthesis in mind. However, as opposed to the literature approach that uses halogenated BODIPYs,[37] we also installed the carbamate functionality to facilitate the deprotection reaction. Furthermore 4-Fluorobenzylamine and 4-Fluoro-N-methylbenzylamine were chosen as model amines for protection because of the ease of observing the photodeprotection by $^{19}$F NMR (Figure 9 c).
Results and discussion

Model protected amines 7 – 14 were prepared using the synthetic route shown below (Scheme 19).

Scheme 19. Synthesis of activated carbonates 4 - 6 and protection of 4-fluorobenzylamine and 4-fluoro-N-methylbenzylamine

The synthesis started with the preparation of BODIPY ester 1 in 47% yield, using an adapted procedure, based on experimental results described in literature.[37-38] Subsequent hydrolysis of the ester gave desired alcohol 2 in 75% yield. Next, because of the difficulties we encountered when we attempted the formation of carbonate 3, we decided to extensively screen the reaction conditions. An extract of the explored conditions is summarized below (Table 2).
Table 2. Reaction conditions for the formation of carbonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Base [equiv.]</th>
<th>Chloroformate [equiv.]</th>
<th>Additive</th>
<th>Time [h]</th>
<th>Yield [%]</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIPEA</td>
<td>1</td>
<td>1</td>
<td>DMAP cat.</td>
<td>24h</td>
<td>0%</td>
<td>mixed in an open vial, NaH in mineral oil</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>1</td>
<td>1.2</td>
<td>-</td>
<td>5 min</td>
<td>0%</td>
<td>-78°C</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>24h</td>
<td>0%</td>
<td>-78°C</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>24h</td>
<td>0%</td>
<td>-78°C</td>
</tr>
<tr>
<td>5</td>
<td>t-BuLi</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>24h</td>
<td>0%</td>
<td>-78°C</td>
</tr>
<tr>
<td>6</td>
<td>NaH</td>
<td>1</td>
<td>1</td>
<td>DMAP</td>
<td>3h</td>
<td>37%</td>
<td>added 2 in last step, -78°C</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>DMAP 4 equiv.</td>
<td>3h</td>
<td>62%</td>
<td>Suspension of chloroformate/pyridine added</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>DMAP 4 equiv.</td>
<td>3h</td>
<td>79%</td>
<td>to compound 2, 0°C</td>
</tr>
<tr>
<td>9</td>
<td>DIPEA</td>
<td>5</td>
<td>4</td>
<td>pyridine</td>
<td>3h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We found out that using a stronger base to activate compound 2, it led mostly to its decomposition, not yielding the desired product at all. Using DMAP as an additive also did not help in producing the carbonate. Adding 4 equivalents of the chloroformate led finally to some formation of the product, especially after cooling down the reaction mixture to 0°C. However, the best results were obtained with pyridine and DIPEA. In our hands, this reaction proved to be scalable up to 0.5 g. It is worth mentioning that performing the reaction in a different solvent (such as THF) or adding the suspension of chloroformate with pyridine to the reaction mixture can lead to the formation of a side product. Under these conditions, the described reaction will yield a BODIPY derivative bearing a chloride atom instead of
the hydroxy group of the substrate. Optimizing the process could provide a viable alternative for the preparation of these kind of compounds.

In the next step, we attempted halogenation of carbonate 3 (Table 3).

Table 3. Conditions of halogenation reactions

<table>
<thead>
<tr>
<th>No.</th>
<th>Time</th>
<th>Temp. [°C]</th>
<th>Yield [%]</th>
<th>Reagent [equiv.]</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 min</td>
<td>23</td>
<td>96</td>
<td>NBS [5]</td>
<td>Br</td>
</tr>
<tr>
<td>2</td>
<td>3 d</td>
<td>23</td>
<td>85</td>
<td>NCS [5 x 2]</td>
<td>Cl</td>
</tr>
<tr>
<td>3</td>
<td>overnight</td>
<td>23</td>
<td>80</td>
<td>NIS [10]</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>overnight</td>
<td>0</td>
<td>55</td>
<td>ICl [3]</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>5 min</td>
<td>0</td>
<td>95</td>
<td>ICl [3], ZnO [3.6]</td>
<td>I</td>
</tr>
</tbody>
</table>

All reactions performed in THF

Chlorination was performed using NCS (2 portions of 5 equiv. each), employing a modified the procedure from Cosa et al.\textsuperscript{[37]} Compound 4 was obtained in a very good yield (90%). Analogously, bromination using NBS preceded faster (30 min) and did not require a second addition of the reagent, providing 93% yield for compound 5. This approach was, however, much less successful for the iodination. Considerable amount of mono-halogenated product was being formed, even when 10 equiv. of fresh NIS was being used. In this case, we chose to use iodine monochloride (ICl) as the iodinating agent. Addition of an ICl solution to a suspension of ZnO and compound 3 in THF at 0°C gave the iodo-disubstituted carbonate 6 in 87% yield.

With the activated carbonates 3 - 6 in hand, the protection of the model primary and secondary amines, 4-fluorobenzylamine and 4-fluoro-N-methylbenzylamine, was performed, by simply stirring the solution of the amine, carbonate and pyridine in THF at rt.

Unsubstituted carbamates 7 and 11 (X = H) were obtained in 92 and 90% yield, respectively. Halogenated carbamates 8 - 10 were obtained in moderate yields (61-65%), starting from Cl, Br and I substituted carbonates. We hypothesize that the drop in yield when comparing the formation of halogenated and unsubstituted carbamates (7, 11 vs. 8 - 10 and 12 - 14) is a result of a change of electron density in the BODIPY conjugated system, where the benzylic position becomes more
electrophilic. An attack of the amine is also feasible at this position, with concurrent liberation of CO$_2$ from the carbonate, leading to formation of amines instead of carbamates (Scheme 1, 15). The ratio of the formation of amines to carbamates was approximately 1:2 for carbamates prepared from primary amines and about 1:1 for carbamates prepared from secondary amines as estimated from the crude NMR spectra (Figure 10). The effect was found to be more pronounced for 4-fluoro-$N$-methylbenzylamine.

To solve this problem, our synthesis route was modified by halogenating carbamates 7 and 11 instead of carbonate 3 (Scheme 20).

![Figure 10. $^{19}$F NMR spectra for crude mixtures from the preparation of: a) compound 9; b) compound 13](image)

Scheme 20. Late stage halogenation of carbamates

8, 12, $X = $Cl; NCS
9, 13, $X = $Br; NBS,
10, 14, $X = $I; ICl, ZnO

7, $R = $H
11, $R = $CH$_3$
The reactions were performed in a similar manner to the ones described before for the halogenation of carbonate. The desired compounds were obtained in 73-80% yield for the derivatives of compound 7 and 69-73% for the derivatives of compound 11, respectively. This synthetic route provides higher overall yields and is a valuable alternative provided that the late-stage halogenation reaction does not affect the moiety being protected.

With the protected amines in hand, the efficiency of the uncaging was studied following the process with UV-VIS spectroscopy, $^{19}$F NMR and UPLC, which were also used to measure the stability of the compounds in aqueous media.

![Figure 11. UV-Vis spectra of compounds 9 (a) and 13 (b) (20 µM in 20% DMSO / 5 mM phosphate buffer pH = 7.5) under irradiation with $\lambda$=530 nm LED light. Spectra measured every 30 s](image)

For UV-vis measurements, compounds 7 – 14 in DMSO / phosphate buffer pH=7.5 were irradiated with LED light source ($\lambda = 530$ nm, 810 mW, 0.2 cm distance) for 10 min and UV-Vis spectra were recorded every 30 sec.
A rapid decrease of absorbance of the bands attributed to the BODIPY core was observed, in accordance with the anticipated uncaging (Figure 11). Using a monoexponential fitting, we calculated the half-lives of caged molecules under irradiation (Table 4).

Table 4. Photochemical properties and half – lives of compounds 7 – 14 upon irradiation with \( \lambda = 530 \) nm

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>R</th>
<th>Half – life [min]</th>
<th>( \lambda_{\text{max}1} )</th>
<th>( \lambda_{\text{max}2} )</th>
<th>( \varepsilon_{\lambda_{\text{max}1}}/10^3 ) 1/(cm * mol)</th>
<th>( \varepsilon_{\lambda_{\text{max}2}}/10^3 ) 1/(cm * mol)</th>
<th>( \varepsilon_{530\text{nm}}/10^3 ) 1/(cm * mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>H</td>
<td>H</td>
<td>0.73</td>
<td>518</td>
<td>-</td>
<td>42</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>H</td>
<td>0.94</td>
<td>516</td>
<td>544</td>
<td>9.4</td>
<td>9.2</td>
<td>9.1</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>H</td>
<td>1.62</td>
<td>505</td>
<td>550</td>
<td>19</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>10</td>
<td>I</td>
<td>H</td>
<td>1.99</td>
<td>511</td>
<td>550</td>
<td>14</td>
<td>0.6</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>CH₃</td>
<td>2.12</td>
<td>518</td>
<td>-</td>
<td>46</td>
<td>-</td>
<td>29</td>
</tr>
<tr>
<td>12</td>
<td>Cl</td>
<td>CH₃</td>
<td>2.06</td>
<td>519</td>
<td>550</td>
<td>22</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>Br</td>
<td>CH₃</td>
<td>0.96</td>
<td>521</td>
<td>553</td>
<td>30</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>14</td>
<td>I</td>
<td>CH₃</td>
<td>1.87</td>
<td>531</td>
<td>565</td>
<td>27</td>
<td>25</td>
<td>27</td>
</tr>
</tbody>
</table>

According to the obtained data, all carbamates react fast (similar half-lives, less than 5 min) under irradiation. For compounds 9 and 13, we measured the quantum yields for the deprotection reaction under irradiation with green light using potassium ferrioxalate as the standard. The obtained values were 4.2 x 10⁻⁵ for compound 9 and 3.8 x 10⁻⁵ for compound 13. Substitution of the pyrrole ring with halogens slightly shifts the main UV-VIS peak maximum attributed to the BODIPY core and gives rise to another, red-shifted band. The effect is more pronounced for carbamates obtained from secondary amines.

To establish if the formed compound is indeed the uncaged amine we used UPLC measurements. Samples of compounds 7 – 14 were prepared in DMSO / phosphate buffer and UPLC traces of the fresh samples and after 1 h of irradiation with \( \lambda = 530 \) nm light were measured. In parallel, we prepared a second set of samples for every carbamate. These samples were used to check the stability of compounds 7 – 14 in aqueous media and instead of being irradiated; they were stored at room temperature in the dark. UPLC traces of these samples were measured alongside the irradiated set: once for fresh samples, then after 3 h and 24 h (Figure 12, Figure 13).
Figure 12. UPLC trace for compound 9, 0.125 mM in 25% DMSO / 5 mM phosphate buffer, pH=7.5. λ_{obs}=520 nm. a-d: stability study; a) freshly prepared sample, b) sample after 3h at rt, c) sample after one day at rt, d) MS trace with selected mass of the uncaged amine in the sample after one day at rt, presenting no spontaneous hydrolysis to the product. e-g: photodeprotection study; e) freshly prepared sample, f) sample after irradiation with λ_{irr}=530 nm for 1 h, g) MS trace with selected mass of the uncaged amine in the sample after irradiation, presenting the formation of the product.
Figure 13. UPLC trace for compound 13, 0.125 mM in 25% DMSO / 5 mM phosphate buffer, pH=7.5. $\lambda_{ob}$=520 nm. a-d: stability study; a) freshly prepared sample, b) sample after 3h at rt, c) sample after one day at rt, d) MS trace with selected mass of the uncaged amine in the sample after one day at rt, presenting no spontaneous hydrolysis to the product. e-g: photodeprotection study; e) freshly prepared sample, f) sample after irradiation with $\lambda_{irr}$=530 nm for 1 h, g) MS trace on selected mass of the uncaged amine in the sample after irradiation, presenting the formation of the product.

To estimate the relative amount of carbamates in the samples, the absorbance of their BODIPY signals at $\lambda = 520$ nm was compared in chromatograms presented in Figures 5 and 6 (Figure 14).
Most of the studied compounds could be uncaged upon green light irradiation ($\lambda = 530$ nm) for one hour. The UPLC retention times of products formed in these samples were consistent with those measured for appropriate amine standards. In general, 4-fluoro-$N$-methylbenzylamine was released more efficiently (compounds 11–14) than 4-fluorobenzylamine (compounds 7–10). For compounds 7 and 14, partial precipitation from the solution was observed, proving its inferior water solubility properties compared to the other carbamates. Other protected amines proved to be soluble and stable (<10% degradation) under aqueous conditions even after 24 h of incubation at room temperature.
Conclusion

Green-light-sensitive (\(\lambda = 530\) nm) BODIPY photoprotecting groups were designed and used to protect primary and secondary amines. The deprotection reaction occurred fast in aqueous media and yielded the amines in unmodified forms. Protected compounds based on a halogenated BODIPY core proved to be more soluble in aqueous media. Brominated carbamates 9 and 13 had the best characteristics for PPGs under the conditions studied: the deprotection was fast, \(\lambda_{\text{max}}\) shifted to 560 nm and the compounds were stable in aqueous solutions. Finally, iodinated carbamates 10 and 14 showed nearly no fluorescence and fast cleavage, but their solubility in aqueous media was limited. Carbonates obtained in the synthesis can be readily reacted with a variety of amines, making them highly versatile building blocks. Short times for deprotection, wavelength used and stability of the obtained compounds make the PPGs an attractive alternative to commonly used ortho-nitrobenzyl compounds and coumarines. Although the new protecting groups can be used for in vitro and cell studies by avoiding the use of toxic UV light, their use in vivo is still limited due to poor body penetration of green light. The next step for the development of BODIPY photoprotecting groups would be shifting their \(\lambda_{\text{max}}\) to the therapeutic window region (650 – 900 nm) and enhance their solubility in aqueous media. The novel PPGs presented here and the readily photodeprotection of amines with visible light makes these systems also highly attractive for various other future applications.
Experimental Procedures

General Information

Starting materials, reagents and solvents were purchased from Sigma–Aldrich, Acros and Combi-Blocks and were used without any additional purification. Solvents for the reactions were purified by passage through solvent purification columns (MBraun SPS-800). 4-nitrophenol chloroformate was obtained from Combi-Blocks. Unless stated otherwise, all reactions were carried using standard Schlenk techniques and were run under nitrogen atmosphere in the dark. The reaction progress was monitored by TLC. Thin Layer Chromatography analyses were performed on commercial Kieselgel 60, F254 silica gel plates with fluorescence-indicator UV254 (Merck, TLC silica gel 60 F254). For detection of components, UV light at λ = 254 nm or λ = 365 nm was used. Column chromatography was performed on commercial Kieselgel 60, 0.04-0.063 mm, Macherey-Nagel.

UPLC traces were measured on Thermo Fisher Scientific LC/MS: UPLC model Vanquish, MS model LTQ with an iontrap and HESI (Heated ESI) ionisation source with positive and negative mode. UV-Vis absorption spectra were recorded on an Agilent 8453 UV/vis absorption Spectrophotometer. Irradiation at 532 nm was performed using Sahlmann Photochemical Solutions LEDs, type LXMLPM01, opt. power 810 mV. UV/vis spectra were baseline corrected. Nuclear Magnetic Resonance spectra were measured with an Agilent Technologies 400-MR (400/54 Premium Shielded) spectrometer (400 MHz) at room temperature (25°C). Chemical shifts for the specific NMR spectra were reported relative to the residual solvent peak in ppm; CDCl₃: δ_H = 7.26; CDCl₃: δ_C = 77.16; d₆-DMSO: δ_H = 2.50; d₆-DMSO: δ_C = 39.52. The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). All ¹³C-NMR spectra are ¹H-broadband decoupled. High-resolution mass spectrometric measurements were performed using a Thermo scientific LTQ OrbitrapXL (ion trap) spectrometer with ESI ionization. The molecule-ion M+, [M + H]+ and [M–X]+ respectively are given in m/z-units. Melting points were recorded using a Stuart analogue capillary melting point SMP11 apparatus.
Compound Characterisation

(5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl acetate (1) (according to combined literature procedures\(^{38,40}\))

2-Chloro-2-oxoethyl acetate (0.60 mL, 5.6 mmol, 1.2 equiv.) was added to a solution of 2,4-dimethylpyrrole (1.0 mL, 9.3 mmol, 2.0 equiv.) in dry DCM (40 mL) under nitrogen atmosphere. The reaction mixture was stirred in the dark at room temperature for 24 h, followed by the addition of TEA (3.2 mL, 28 mmol, 6.0 equiv.). The resulting mixture was allowed to stir for 15 minutes. Then, the flask was again put under nitrogen atmosphere and boron trifluoride diethyl etherate (5.2 mL, 42 mmol, 9.0 equiv.) was added. After one hour, another portion of TEA (3.2 mL, 28 mmol, 6.0 equiv.) and boron trifluoride diethyl etherate (5.2 mL, 42 mmol, 9.0 equiv.) were added. Then, silica was added to the flask and the solvents were evaporated. Compound 1 was purified by column chromatography using pentane/Et\(_2\)O (2:1; v/v) as the eluent. The product was obtained as red-gold solid (700 mg, 47% yield).

Rf. = 0.7 (DCM), M.p. = 184-187°C, \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 2.13 (s, 3H, CO\(CH_3\)), 2.36 (s, 6H), 2.53 (s, 6H, 2 x Ar\(CH_3\)), 5.30 (s, 2H, Ar\(CH_2CO\)), 6.08 (s, 2H, 2 x ArH), \(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) \(\delta\) -146.43 (dd, \(J = 65.1, 32.5\) Hz). HRMS (ESI+) calc. for [M+H]+ (C\(_{16}\)H\(_{20}\)BF\(_2\)N\(_2\)O\(_2\)): 321.1580, found: 321.1585. \(^1\)H spectrum in agreement with published data.\(^{39}\)

(5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methanol (2) (according to a literature procedure\(^{38,40}\))

A mixture of aqueous NaOH solution (6.3 mL, 0.10 M, 0.40 equiv.) and methanol (30 mL) was stirred for 10 minutes and then added to a solution of compound 1 (0.50 g, 1.6 mmol) in DCM (15 mL). The reaction mixture was stirred for 4 h in the dark at room temperature. After this time, the solvents were partially evaporated and the residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with aq. 1 M HCl (2 x 20 mL) and brine (1 x 20 mL), and dried with MgSO\(_4\). Compound 2 was purified by column chromatography (pentane/Et\(_2\)O,
gradient: 2:1 → 0:1; v/v). The product was obtained as red solid (350 mg, 81% yield).

Rf. = 0.3 (DCM), M.p. = 247-249°C, $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 2.51 (s, 6H, 2 x ArCH$_3$), 2.52 (s, 6H, 2 x ArCH$_3$), 4.91 (s, 2H, ArCH$_2$CO), 6.08 (s, 2H, 2 x ArH), $^{19}$F NMR (376 MHz, Chloroform-d) $\delta$ -146.52 (dd, $J = 65.3, 32.4$ Hz). HRMS (ESI+) calc. for [M+H]$^+$ (C$_{14}$H$_{18}$BF$_2$N$_2$O): 279.1475, found: 279.1488. $^1$H spectrum in agreement with published data.$^{[39]}$

(5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ^4,5λ^4-dipyrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl (4-nitrophenyl) carbonate (3)

To a solution of 4-nitrophenyl chloroformate (870 mg, 4.3 mmol, 3.4 equiv.) in dry DCM (50 mL), pyridine (0.35 mL, 4.3 mmol, 3.4 equiv.) was added under nitrogen atmosphere. The formed suspension was then added dropwise to a solution of compound 2 (350 mg, 1.3 mmol), in dry DCM (100 mL) and DIPEA (0.63 mL, 4.3 mmol, 4.3 equiv.) at 0°C, in the dark. The reaction mixture was allowed to warm and stirred for 4 h. After this time the solution was filtered through silica using DCM. The solvents were evaporated and the product was purified by column chromatography using pentane/Et$_2$O/DCM as the eluent (2 stages with a gradient: pentane/Et$_2$O 5/1 → 2:1, then DCM 100%). Compound 3 was obtained as pink solid (440 mg, 79% yield).

Rf. = 0.8 (DCM), M.p. = 203-205°C, $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 2.46 (s, 6H, 2 x ArCH$_3$), 2.55 (s, 6H, 2 x ArCH$_3$), 5.57 (s, 2H, ArCH$_2$OCO), 6.12 (s, 2H, 2xBArH), 7.40 (d, $^3$J = 9.1 Hz, 2H, 2 x OCCH), 8.29 (d, $^3$J = 9.2 Hz, 2H, 2 x NO$_2$CH), $^{19}$F NMR (376 MHz, Chloroform-d) $\delta$ -146.16 (dd, $J = 64.9, 32.3$ Hz), $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 14.8, 15.8, 61.7, 121.6, 122.7, 125.4, 130.9, 132.6, 141.4, 145.6, 152.2, 155.2, 157.3. HRMS (ESI+) calc. for [M+H]$^+$ (C$_{21}$H$_{21}$BF$_2$N$_3$O$_3$): 444.1537, found: 444.1533.
(5,5-difluoro-2,8-dichloro-1,3,7,9-tetramethyl-5H-4λ4,5λ4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl(4-nitrophenyl) carbonate (4)

To a solution of compound 3 (50 mg, 0.11 mmol) in dry THF (0.5 mL), a solution of NCS (75 mg, 0.56 mmol, 5.0 equiv.) in dry THF (0.5 mL) was added under nitrogen atmosphere. The reaction mixture was stirred until full consumption of the starting material was observed (TLC). After this time (up to 3 days), the solvent was evaporated and the crude mixture was purified by flash chromatography using DCM as the eluent. The product was obtained as dark purple solid (52 mg, 90% yield).

Rf. = 0.9 (DCM), M.p. = 208-211°C, 1H NMR (400 MHz, Chloroform-d) δ 2.49 (s, 6H, 2 x ArCH3), 2.61 (s, 6H, 2 x ArCH3), 5.59 (s, 2H, ArCH2OCO), 7.40 (d, J = 9.2 Hz, 2H, 2 x OCCH), 8.30 (d, J = 9.2 Hz, 2H, 2 x NO2CH), 19F NMR (376 MHz, Chloroform-d) δ -145.91 (dd, J = 62.9, 31.4 Hz). 13C NMR (101 MHz, Chloroform-d) δ 12.7, 13.2, 61.43, 121.6, 124.1, 125.4, 130.9, 131.7, 136.1, 145.7, 152.1, 154.4., 155.1. HRMS (ESI+) calc. for [M+H]+ (C21H19BCl2F2N3O5): 512.0757, found: 512.0756.

(5,5-difluoro-2,8-dibromo-1,3,7,9-tetramethyl-5H-4λ4,5λ4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl (4-nitrophenyl) carbonate (5)

To a solution of compound 3 (50 mg, 0.11 mmol) in dry THF (0.5 mL) a solution of NBS (100 mg, 0.56 mmol, 5 equiv.) in dry THF (0.5 mL) was added under nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at room temperature. After that time, the solvent was evaporated and the crude mixture was purified by flash chromatography using DCM as the eluent. The product was obtained as a violet-green solid (63 mg, 93% yield).

Rf. = 0.9 (DCM), M.p. = 214-217°C, 1H NMR (400 MHz, Chloroform-d) δ 2.49 (s, 6H, 2 x ArCH3), 2.61 (s, 6H, 2 x ArCH3), 5.59 (s, 2H, ArCH2OCO), 7.40 (d, J = 9.0 Hz, 2H, 2 x OCCH), 8.30 (d, J = 9.0 Hz, 2H, 2 x NO2CH), 19F NMR (376 MHz, Chloroform-d) δ -146.27 (dd, J = 62.7, 31.4 Hz). 13C NMR (101
MHz, Chloroform-\(d\)) \(\delta\) 14.0, 15.0, 61.6, 113.4, 121.6, 125.4, 131.3, 131.6, 138.7, 145.7, 152.1, 155.1, 155.8. HRMS (ESI+) calc. for [M+H]\(^+\) (\(C_{21}H_{15}BBr_2F_2N_3O_5\)): 601.9727, found: 601.9729.

\((5,5\text{-difluoro-2,8-diido-1,3,7,9-tetramethyl-5H-4}\lambda^4,5\lambda^4\text{-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)}\)methyl (4-nitrophenyl) carbonate (6)

To a suspension of compound 3 (44 mg, 99 \(\mu\)mol) and ZnO (29 mg, 0.36 mmol, 3.6 equiv.) in dry THF (7 mL), a solution of ICl (50 mg, 0.31 mmol, 3.1 equiv.) in dry THF (2 mL) was added under nitrogen atmosphere, at 0\(^\circ\)C. The reaction mixture was stirred for 15 minutes. Subsequently, the solvent was evaporated and the crude mixture was purified by flash chromatography using DCM as the eluent. The product was obtained as violet-gold solid (60 mg, 87 % yield).

Rf. = 0.9 (DCM), M.p. = 194-197\(^\circ\)C, \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 2.52 (s, 6H, 2 x ArCH\(_3\)), 2.65 (s, 6H, 2 x ArCH\(_3\)), 5.60 (s, 2H, ArCH\(_2\)OCO), 7.40 (d, \(J\) = 9.1 Hz, 2H, 2 x OCCH), 8.30 (d, \(J\) = 9.1 Hz, 2H, 2 x NO\(_2\)CH)., \(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) \(\delta\) -145.59 (dd, \(J\) = 63.3, 31.6 Hz). \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 16.4, 18.4, 61.9, 121.6, 125.4, 130.3, 131.7, 132.5, 143.4, 145.7, 152.0, 155.1, 158.6. HRMS (ESI+) calc. for [M+H]\(^+\) (\(C_{21}H_{19}BI_2F_2N_3O_5\)): 695.9469, found: 695.9470.

\((5,5\text{-difluoro-1,3,7,9-tetramethyl-5H-4}\lambda^4,5\lambda^4\text{-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)}\)methyl (4-fluorophenyl)carbamate (7)

To a solution of compound 3 (100 mg, 0.23 mmol) in dry THF (5 mL), a solution of pyridine in THF (1.0 M, 75 \(\mu\)L, 75 \(\mu\)mol, 0.24 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluorobenzylamine in THF (1.0 M, 0.34 mL, 0.34 mmol, 0.9 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Subsequently, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 20 mL), 0.1 M aq. NaOH (4 x
20 mL) and brine (2 x 20 mL), it was dried with MgSO₄ and the solvent was evaporated. The crude mixture was then purified by flash chromatography using DCM as the eluent. The product was obtained as orange-gold solid (89 mg, 92% yield).

Rf. = 0.5 (DCM), M.p. = 182-184°C, 1H NMR (400 MHz, Chloroform-d) δ 2.39 (s, 6H, 2 x ArCH₃), 2.52 (s, 6H, 2 x ArCH₃), 4.35 (d, J = 5.9 Hz, 2H,CCH₂NH), 5.11 (s, 1H, CONH), 5.33 (s, 2H, ArCH₂OCO), 6.07 (s, 2H, 2 x ArH), 7.02 (t, J = 8.6 Hz, 2H, CH₂CCH), 7.23 (t, J = 5.5 Hz, 2H, FCCH), 19F NMR (376 MHz, Chloroform-d) δ -146.43 (m, J = 65.1, 32.6 Hz), -114.72 (m), 13C NMR (101 MHz, Chloroform-d) δ 14.6, 15.6, 44.5, 58.1, 115.6 (d, J = 21.4 Hz), 122.2, 129.1 (d, J = 8.2 Hz), 132.6, 133.5, 133.8, 141.6, 155.7, 156.5, 162.2 (d, J = 254.9 Hz). HRMS (ESI+) calc. for [M+H]⁺ (C₂₂H₂₄BF₃N₃O₂): 430.1908, found: 430.1906.

(2,8-dichloro-5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ⁴,5λ⁴-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl (4-fluorobenzyl)carbamate (8)

**Method a:** To a solution of compound 4 (10 mg, 20 µmol) in dry THF (0.5 mL), a solution of pyridine in THF (1.0 M, 4.7 µL, 4.7 µmol, 0.24 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluorobenzylamine in THF (1.0 M, 30 µL, 30 µmol, 1.5 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Next, DCM (10 mL) and brine (10 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 10 mL), 0.1 M aq. NaOH (4 x 10 mL) and brine (2 x 10 mL), it was dried with MgSO₄ and the solvent was evaporated. The crude mixture was then purified by flash chromatography using DCM as the eluent. The product was obtained as purple solid (6.0 mg, 62%).

**Method b:** To a solution of compound 7 (10 mg, 23 µmol) in dry THF (0.5 mL), a solution of NCS (16 mg, 116 µmol, 5 equiv.) in dry THF (0.5 mL) was added under nitrogen atmosphere. The reaction was allowed to stir at RT overnight. After this time, another portion of NCS was added (16 mg, 0.12 mmol, 5 equiv.). After full conversion of the starting material (TLC), the crude mixture was purified by flash
chromatography using DCM as the eluent. The product was obtained as purple solid (8.5 mg, 73% yield).

Rf. = 0.6 (DCM), M.p. = 191-193°C, \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 2.40 (s, 6H, 2 x ArCH\(_3\)), 2.56 (s, 6H, 2 x ArCH\(_3\)), 4.36 (d, J = 5.9 Hz, 2H, CCH\(_2\)NH), 5.10 (s, 1H, CONH), 5.34 (s, 2H, ArCH\(_2\)OCO), 7.03 (t, J = 8.5 Hz, 2H, CH\(_2\)CCH), 7.14-7.28 (m, 2H, FCCH), \(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) \(\delta\) -146.42 (dd, J = 63.2, 31.6 Hz), -114.49 (td, J = 8.6, 4.4 Hz), \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 12.6, 13.0, 44.6, 58.0, 115.7 (d, J = 8.2 Hz), 123.5, 129.2 (d, J = 21.6 Hz), 130.9, 133.6, 134.3, 136.3, 153.6, 155.4, 162.3 (d, J = 246.1 Hz). HRMS (ESI+) calc. for [M+NH\(_4\)]\(^+\) (C\(_{22}\)H\(_{25}\)BCl\(_2\)F\(_3\)N\(_4\)O\(_2\)) : 515.1394, found: 515.1391.

\(\text{[2,8-dibromo-5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ^4,5λ^4-dipyrrolo[1,2-c:2',1'-}\]
\(\text{f}[1,3,2]\)diazaborinin-10-yl)methyl (4-fluorobenzyl)carbamate (9)

**Method a:** To a solution of compound 5 (50 mg, 83.2 µmol) in dry THF (10 mL), a solution of pyridine in THF (0.50 M, 0.17 mL, 83.2 µmol, 1 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluorobenzylamine in THF (0.50 M, 0.16 mL, 74.9 µmol, 0.9 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Next, DCM (10 mL) and brine (10 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 10 mL), 0.1 M aq. NaOH (4 x 10 mL) and brine (2 x 10 mL), it was dried with MgSO\(_4\) and the solvent was evaporated. The crude mixture was then purified by flash chromatography using DCM as the eluent. The product was obtained as purple solid (16 mg, 36% yield).

**Method b:** To a solution of compound 7 (10 mg, 23 µmol) in dry THF (0.5 mL) a solution of NBS (12 mg, 70 µmol, 3 equiv.) in dry THF (0.5 mL) was added under nitrogen atmosphere. The reaction was then stirred at room temperature for 0.5 h. After this time the crude mixture was purified by flash chromatography using DCM as the eluent. The product was obtained as purple solid (11 mg, 80%).
Rf. = 0.6 (DCM), M.p. = 216-219°C, $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 2.42 (s, 6H, 2 x ArCH$_3$), 2.58 (s, 6H, 2 x ArCH$_3$), 4.36 (d, $J$ = 5.8 Hz, 2H, CCH$_2$NH), 5.10 (s, 1H, CONH), 5.35 (s, 2H, ArCH$_2$OCO), 7.03 (t, $J$ = 8.5 Hz, 2H, CH$_2$CCH), 7.19-7.29 (m, 2H, FCCH). $^{19}$F NMR (376 MHz, Chloroform-d) $\delta$ -146.12 (m, $J$ = 63.0, 31.8 Hz), -114.50 (m). $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 13.9, 14.8, 44.6, 58.2, 112.9, 115.7 (d, $J$ = 21.7 Hz), 129.2 (d, $J$ = 8.3 Hz), 131.7, 133.5, 133.9, 138.9, 155.1, 155.4, 162.3 (d, $J$ = 245.8 Hz). HRMS (ESI+) calc. for [M+NH$_4$]$^+$ (C$_{22}$H$_{25}$BBr$_2$F$_3$N$_4$O$_2$): 605.0364, found: 605.0361.

(2,8-diiodo-5,5-difluoro-1,3,7,9-tetramethyl-5H-4$\lambda^4$,5$\lambda^4$-dipyrrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl (4-fluorobenzyl)carbamate (10)

**Method a:** To a solution of compound 6 (50 mg, 71.9 µmol) in dry THF (10 mL), a solution of pyridine in THF (0.50 M, 0.14 mL, 72 µmol, 1.0 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluorobenzylamine in THF (0.50 M, 0.13 mL, 65 µmol, 0.90 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Next, DCM (10 mL) and brine (10 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 10 mL), 0.1 M aq. NaOH (4 x 10 mL) and brine (2 x 10 mL), it was dried with MgSO$_4$ and the solvent was evaporated. The crude mixture was then purified by flash chromatography using DCM as the eluent. The product was obtained as purple solid (30 mg, 61% yield).

**Method b:** To a suspension of compound 7 (10 mg, 23 µmol) and ZnO (6.8 mg, 84 µmol, 3.6 equiv.) in dry THF (0.5 mL) a solution of ICl (11 mg, 70 µmol, 3.0 equiv.) in dry THF (0.5 mL) was added at 0°C in nitrogen atmosphere. The reaction mixture was allowed to stir for 10 minutes after which the solvent was evaporated and the crude mixture filtrated through silica using DCM. The product was obtained as dark violet solid (12 mg, 76%).

Rf. = 0.6 (DCM), M.p. = 203-204°C, $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 2.44 (s, 6H, 2 x ArCH$_3$), 2.62 (s, 6H, 2 x ArCH$_3$), 4.36 (d, $J$ = 5.5 Hz, 2H, CCH$_2$NH), 5.12 (s, 1H, CONH), 5.35 (s, 2H, ArCH$_2$OCO), 7.03 (t, $J$ = 8.0 Hz, 2H, CH$_2$CCH), 7.20-7.29 (m, 2H,
To a solution of compound 3 (100 mg, 230 µmol) in dry THF (5 mL), a solution of pyridine in THF (1.0 M, 0.054 mL, 54 µmol, 0.24 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluoro-N-methylbenzylamine in THF (1.0 M, 0.34 mL, 340 µmol, 0.90 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Next, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 20 mL), 0.1 M aq. NaOH (4 x 20 mL) and brine (2 x 20 mL), it was dried with MgSO₄ and the solvent was evaporated. The crude mixture was then purified by flash chromatography using DCM as the eluent. The product was obtained as orange solid (90 mg, 90% yield).

_{Rf} = 0.5 (DCM), M.p. = 123-125°C, \_1^H NMR (mixture of rotamers, 400 MHz, Chloroform-d) δ 2.31 (s, 3H, ArCH₃), 2.40 (s, 3H, ArCH₃), 2.53 (s, 6H, 2 x ArCH₃), 2.78 (s, 1.5H, 0.5 x NCH₃), 2.97 (s, 1.5H, 0.5 x NCH₃), 4.34 (s, 1H, CH₂NCH₃), 4.46 (s, 1H, CH₂NCH₃), 5.32 (s, 1H, ArCH₂OCO), 5.35 (s, 1H, ArCH₂OCO), 6.05 (s, 1H, ArH), 6.08 (s, 1H, ArH), 6.87-6.96 (m, 1H, FCCH), 6.97 – 7.11 (m, 2H, CH₂CCH), 7.18 – 7.24 (m, 1H, FCCH). \_1^F NMR (376 MHz, Chloroform-d) δ -146.34 (ddd, J = 65.2, 32.1, 9.2 Hz), -114.94 (dt, J = 47.0, 7.9 Hz). \_1^C NMR (mixture of rotamers, 101 MHz, Chloroform-d) δ 16.7, 18.2, 44.6, 58.5, 115.7 (d, J = 21.4 Hz), 129.2 (d, J = 8.3 Hz), 129.5, 132.5, 133.0, 133.6, 143.5, 155.4, 157.9, 162.3 (d, J = 246.1 Hz). HRMS (ESI+) calc. for \[M+NH₄]⁺ (C₂₂H₂₅BF₃N₄O₂): 444.2065, found: 444.2062.
(2,8- dichloro-5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ\textsubscript{4},5λ\textsubscript{4}-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)methyl (4-fluorobenzyl)(methyl)carbamate (12)

Method a: To a solution of compound 4 (10 mg, 20 µmol) in dry THF (0.5 mL), a solution of pyridine in THF (1.0 M, 4.7 µL, 4.7 µmol, 0.24 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluoro-N-methylbenzylamine in THF (1.0 M, 30 µL, 30 µmol, 1.5 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Next, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. The organic layer was washed with 1 M aq. HCl (3 x 20 mL), 0.1 M aq. NaOH (4 x 20 mL) and brine (2 x 20 mL). Then it was dried with MgSO\textsubscript{4} and the solvent was evaporated. The crude mixture was then purified by flash chromatography using pentane/diethyl ether (3:1; v/v) as the eluent. The product was obtained as purple solid (3.5 mg, 35% yield).

Method b: To a solution of compound 11 (10 mg, 23 µmol) in dry THF (0.5 mL) a solution of NCS (15 mg, 0.11 mmol, 5 equiv.) was added under nitrogen atmosphere. The reaction was allowed to stir at RT overnight. After this time, another portion of NCS was added (15 mg, 0.11 mmol, 5 equiv.). Then the reaction was monitored with TLC every hour. After completion, the crude mixture was purified by flash chromatography using DCM as the eluent. The product was obtained as purple solid (8 mg, 69% yield).

Rf. = 0.7 (DCM), M.p. = 157-159°C, \textsuperscript{1}H NMR (mixture of rotamers, 400 MHz, Chloroform-d) δ 2.30 (s, 3H, ArCH\textsubscript{3}), 2.41 (s, 3H, ArCH\textsubscript{3}), 2.57 (s, 6H, 2 x ArCH\textsubscript{3}), 2.78 (s, 1.5H, 0.5 x NCH\textsubscript{3}), 3.00 (s, 1.5H, 0.5 x NCH\textsubscript{3}), 4.34 (s, 1H, CCH\textsubscript{2}NCH\textsubscript{3}), 4.47 (s, 1H, CCH\textsubscript{2}NCH\textsubscript{3}), 5.33 (s, 1H, ArCH\textsubscript{2}OCO), 5.35 (s, 1H, ArCH\textsubscript{2}OCO), 6.88-6.96 (m, 1H, J = 8.3 Hz, FCCH), 6.97 – 7.06 (m, 2H, CH\textsubscript{2}CCH), 7.16 – 7.25 (m, 1H, FCCH), \textsuperscript{19}F NMR (376 MHz, Chloroform-d) δ -146.37 (ddd, J = 63.0, 31.2, 18.8 Hz), -114.67, \textsuperscript{13}C NMR (mixture of rotamers, 101 MHz, Chloroform-d) δ 12.6, 12.7, 33.7, 35.4, 52.04, 52.2, 58.5, 58.6, 115.44 (d, J = 12.6 Hz), 115.65 (d, J = 12.4 Hz), 123.5, 128.65 (d, J = 7.4 Hz), 129.47 (d, J = 7.5 Hz), 130.9, 131.1, 132.5, 132.6, 134.5, 134.6, 136.3, 153.6,
Method a: To a solution of compound 5 (50 mg, 83.2 µmol) in dry THF (10 mL), a solution of pyridine in THF (0.50 M, 0.17 mL, 54 µmol, 0.24 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluoro-N-methylbenzylamine in THF (0.50 M, 0.16 mL, 74.9 µmol, 0.90 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. After that time, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 20 mL), 0.1 M aq. NaOH (4 x 20 mL) and brine (2 x 20 mL), it was dried with MgSO₄ and the solvent was evaporated. The crude mixture was then purified by flash chromatography using pentane/diethyl ether (3:1; v/v) as the eluent. The product was obtained as dark violet solid (16 mg, 32%).

Method b: To a solution of compound 11 (10 mg, 23 µmol) in dry THF (0.5 mL) a solution of NBS (12 mg, 70 µmol, 3 equiv.) in dry THF (0.5 mL) was added under nitrogen atmosphere. The reaction mixture was then stirred at room temperature for 0.5 h. After this time the crude mixture was purified by flash chromatography using DCM as the eluent. The product was obtained as purple solid (11 mg, 81% yield).

Rf. = 0.7 (DCM), M.p. = 168-170°C, ¹H NMR (mixture of rotamers, 400 MHz, Chloroform-d) δ 2.30 (s, 3H, ArCH₃), 2.42 (s, 3H, ArCH₃), 2.59 (s, 6H, 2 x ArCH₃), 2.78 (s, 1.5H, NCH₃), 3.00 (s, 1.5H, NCH₃), 4.33 (s, 1H, CCH₂NCH₃), 4.47 (s, 1H, CCH₂NCH₃), 5.33 (s, 1H, ArCH₂OCO), 5.35 (s, 1H, ArCH₂OCO), 6.92 (m, 1H, FCCHCH), 6.96 – 7.08 (m, 2H, CH₂CCH), 7.18 – 7.24 (m, 1H, FCCH), ¹⁹F NMR (376 MHz, Chloroform-d) δ -146.05 (ddd, J = 63.4, 31.2, 20.9 Hz), -114.67, -114.57. ¹³C NMR (mixture of rotamers, 101 MHz, Chloroform-d) δ 13.9, 14.7, 33.7, 35.4, 52.1, 52.2,
Method a: To a solution of compound 6 (50 mg, 72.0 µmol) in dry THF (10 mL), a solution of pyridine in THF (0.50 M, 0.14 mL, 64.8 µmol, 0.24 equiv.) was added under nitrogen atmosphere. After stirring for 15 minutes at room temperature, a solution of 4-fluoro-N-methylbenzylamine in THF (0.50 M, 0.13 mL, 72.0 µmol, 0.90 equiv.) was added. The reaction mixture was then stirred for additional 3 hours. Next, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After washing the organic layer with 1 M aq. HCl (3 x 20 mL), 0.1 M aq. NaOH (4 x 20 mL) and brine (2 x 20 mL), it was dried with MgSO₄ and the solvent was evaporated. The crude mixture was then purified by flash chromatography using pentane/diethyl ether (3:1; v/v) as the eluent. The product was obtained as dark violet solid (16 mg, 34% yield).

Method b: To a suspension of compound 11 (10 mg, 23 µmol) and ZnO (6.6 mg, 81 µmol, 3.6 equiv.) in dry THF (0.5 mL) a solution of ICl (11 mg, 68 µmol, 3.0 equiv.) in dry THF (0.5 mL) was added at 0°C under nitrogen atmosphere. The reaction mixture was allowed to stir for 10 minutes after which the solvent was evaporated and the crude mixture filtrated through silica using DCM. The product was obtained as dark violet solid (12 mg, 73% yield).

Rf. = 0.7 (DCM), M.p. = 193-194°C, ¹H NMR (mixture of rotamers, 400 MHz, Chloroform-d) δ 2.33 (s, 3H, ArCH₃), 2.45 (s, 3H, ArCH₃), 2.63 (s, 6H, 2 x ArCH₃), 2.79 (s, 1.5H, 0.5 x NCH₃), 3.00 (s, 1.5H, 0.5 x NCH₃), 4.33 (s, 1H, CCH₂NCH₃), 4.47 (s, 1H, CCH₂NCH₃), 5.34 (s, 1H, ArCH₂OCO), 5.36 (s, 1H, ArCH₂OCO), 6.93 (t, J = 8.3 Hz, 1H, FCCHCH), 6.98 – 7.10 (m, 2H, CH₂CCH), 7.21 (t, J = 5.3 Hz, 1H, FCCH), ¹⁹F NMR (376
MHz, Chloroform-d) δ -145.69 (ddd, J = 63.0, 30.7, 22.6 Hz), -114.67, -114.42. $^{13}$C NMR (mixture of rotamers, 101 MHz, Chloroform-d) δ 16.3, 18.0, 33.7, 35.4, 52.1, 52.2, 58.9, 59.0, 115.5 (d, J = 8.3 Hz), 115.7 (d, J = 8.4 Hz), 128.7 (d, J = 7.9 Hz), 129.5 (d, J = 8.2 Hz), 132.5, 132.6, 132.7, 133.2, 133.3, 143.6, 155.2, 155.8, 157.8, 162.0 (d, J = 267.5 Hz), 162.2 (d, J = 265.3 Hz). HRMS (ESI+) calc. for [M+NH$_4$]$^+$ (C$_{23}$H$_{27}$BF$_3$I$_2$N$_4$O$_2$): 713.0269, found: 713.0266.

1-(2,8-dibromo-5,5-difluoro-1,3,7,9-tetramethyl-5H-4λ$^4$,5λ$^4$-dipyrrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)-N-(4-fluorobenzyl)-N-methylmethanamine (15)

$^1$H NMR (400 MHz, Chloroform-d) δ 2.19 (s, 3H). 2.46 (s, 6H), 2.60 (s, 3H), 2.66 (s, 3H), 3.55 (s, 2H), 3.88 (s, 2H), 6.95 (t, J = 8.8 Hz, 2H), 7.35 (dd, J = 8.5, 5.7 Hz, 2H).

MS (ESI+) calc. for [M+H]$^+$ (C$_{22}$H$_{27}$BBr$_2$F$_3$N$_4$): 558.03, found: 558.06.
References


