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Green-Light-Sensitive BODIPY Photoprotecting Groups for Amines

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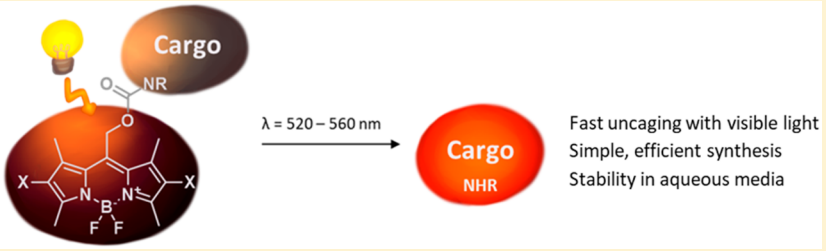
Supporting Information



ABSTRACT: We describe a series of easily accessible, visible-light-sensitive (λ > 500 nm) BODIPY (boron-dipyrromethene)-based photoprotecting groups (PPGs) for primary and secondary amines, based on a carbamate linker. The caged compounds are stable under aqueous conditions for 24 h and can be efficiently uncaged in vitro with visible light (λ = 530 nm). These properties allow efficient photodeprotection of amines, rendering these novel PPGs potentially suitable for various applications, including the delivery of caged drugs and their remote activation.

INTRODUCTION

The bright prospects for the application of light in chemistry and biology stimulates increasing attention for photochemical control of function in recent years.[1] Light can be used as a regulatory element for biological systems because of its low toxicity (in the so-called therapeutic window λ = 650−900 nm[2]), orthogonality with most bioactive compounds, high spatiotemporal precision of delivery, control over quality and quantity, tissue penetration, and lack of contamination of samples.[3]

At the molecular level, photocontrol over bioprocesses can be achieved by the incorporation of photosensitive moieties in the structure of bioactive compounds. Two fundamental approaches are being explored. In the first one,[4] molecular photoswitches are used to reversibly turn on and off the activity of the drug.[5] In the second one, photoprotecting groups (PPGs) are being used to suppress the activity of the drug until it is activated with light.[1a,6] In this approach, frequently, more pronounced changes in activity prior to and after irradiation are obtained.[7] Commonly applied PPGs include coumarin,[8] *ortho*-nitrobenzyl,[9] salicylic alcohol,[10] and nitroindolinyl derivatives;[11] the synthesis and mechanism of action of these groups are well-described.[12]

Functional groups protected by PPGs are usually carboxylic acids,[13] alcohols,[14] and amines.[15] These groups are abundant in drugs and biomolecules and are usually playing an important role in their activity.[16] Amines, in particular, function as neurotransmitters, antibiotics, and anticancer drugs. Photoprotection of dopamine,[17] histidine,[17] GABA[18,19] and Vemurafenib[20] has been reported. Photoprotecting groups can also be used for controlling complex biological processes, like protein dimerization[21] or gene activation[22] and gene silencing.[23]

Despite many successful applications, new PPGs are needed that address drawbacks of existing agents, including slow deprotection reactions and deprotections that require UV light,[24] 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 PPG with beneficial 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:[6a,25] efficiency of uncaging, narrow absorption maximum and low absorbance outside of this range, high molar absorptivity at irradiation wavelength, chemical stability and solubility in aqueous media, and lack of toxicity of the PPGs as well as the products of 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 tissues and a lower toxicity.

Recently, the group of Klan and Wirz presented data suggesting that BODIPY (boron-dipyrromethene) has a similar frontier orbital structure to that of coumarines or xanthenes,[26]

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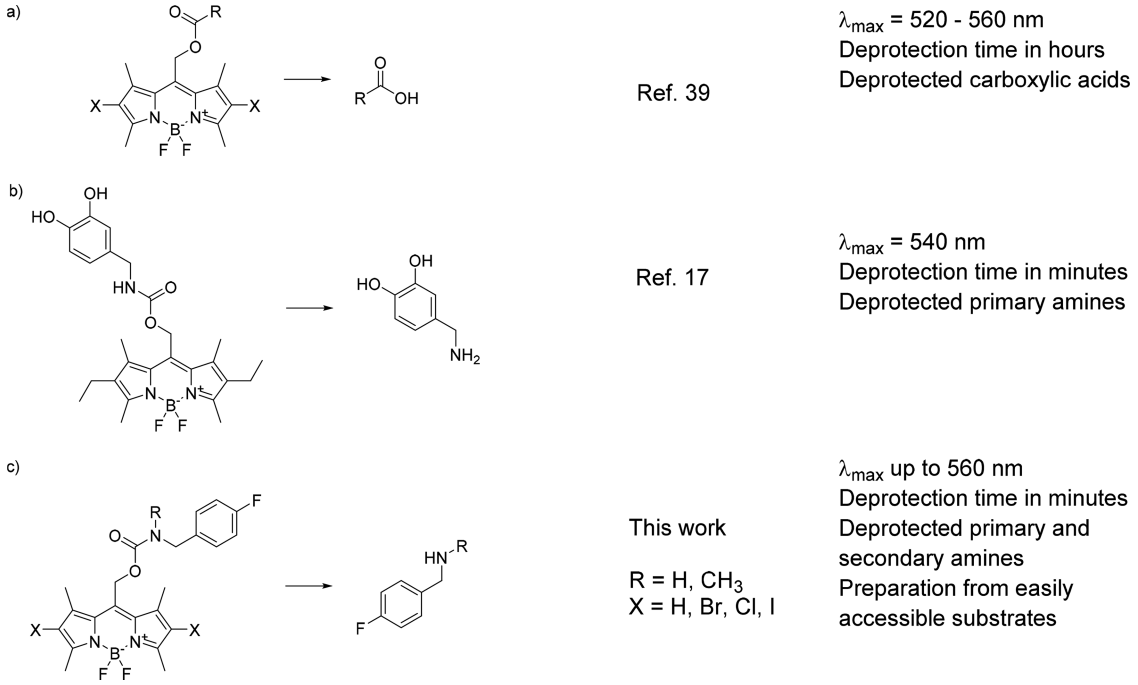
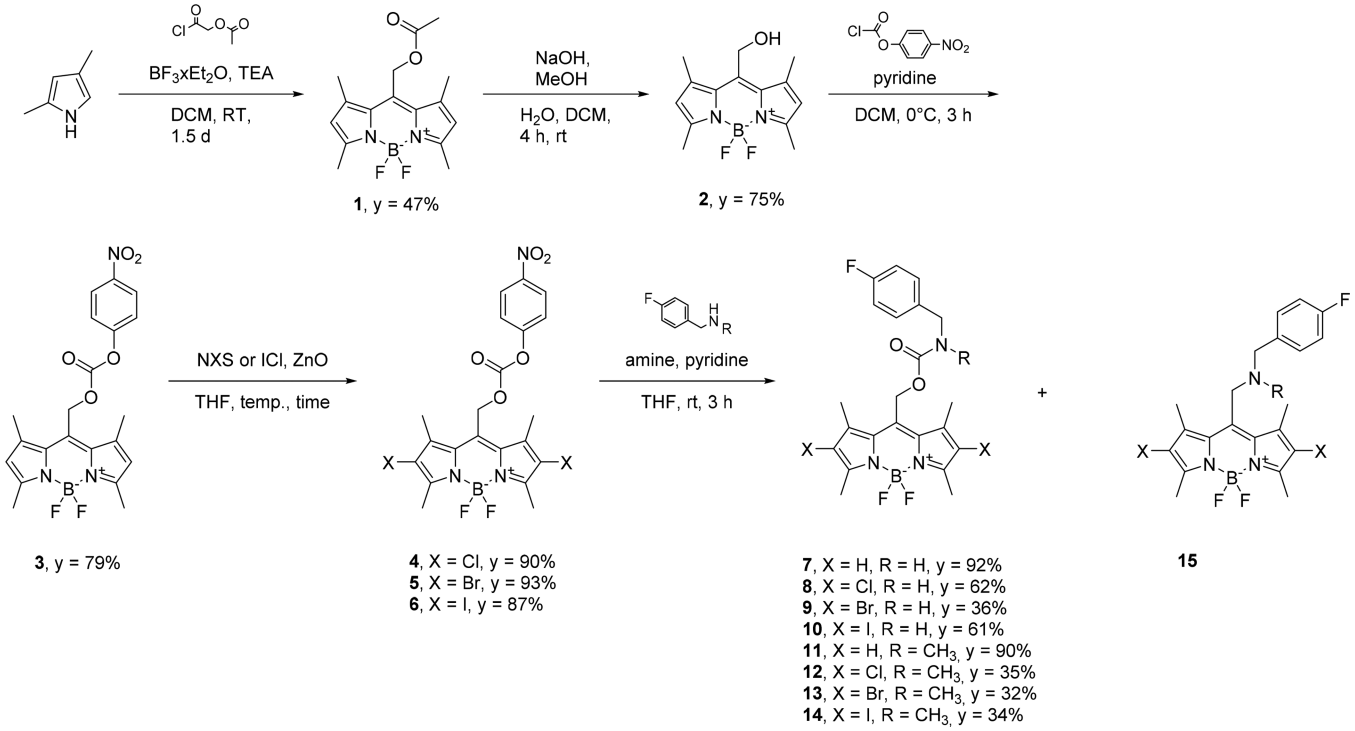


Figure 1. Comparison of reported BODIPY photoprotecting groups and those described in this work.

Scheme 1. Synthesis of Activated Carbonates 4−6 and Protection of 4-Fluorobenzylamine and 4-Fluoro-*N*-methylbenzylamine



rendering it a possible PPG. BODIPY derivatives are widely used as probes,[27] laser dyes,[28] photosensitizers,[29] sensors,[30] dyads,[31] catalysts,[32] emission contrasts,[33] and cell visualization agents.[34,35] This wide variety of applications is enabled by the 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.

In the literature, there are three cases where *meso*-BODIPY derivatives were used as PPGs. Winter and co-workers[36] studied the deprotection of carboxylic acids from BODIPY with different substituents (Figure 1a). The modifications of the electronic properties of the BODIPY moiety resulted in different λ_{max} and efficiency of deprotection in DCM. The authors observed that the BODIPY derivative with chlorine as substituents on the ring (X = Cl) was the fastest to react, releasing acetic acid within an hour, which is, however, 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.[17] The compound, in

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which the amine is connected to the BODIPY protecting group through a carbamate linker (Figure 1b), could be uncaged fast and was proved to be stable in aqueous media. The λ_{max} of these compounds was slightly red-shifted compared to a nonsubstituted BODIPY core (540 nm). The authors also used their PPG to release dopamine and histidine. The uncaged amines were active, as was shown on rat cortical/hippocampal neurons for dopamine and HeLa cells for histidine. The experiments proved that the approach was 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 from a premade, difficult to prepare, and expensive BODIPY dye. During the preparation of this article, the groups of Winter and Weinstain reported the use of dimethyl-boron based BODIPYs for the fast release of methanol, chlorine, and a variety of (thio)acids.[37] A different approach was proposed by the group of Urano,[38] 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 λ_{max} = 500 nm proceeded relatively fast (20−30 min). In this system, the protection of amines was also shown, but it required the use of an additional phenolic linker. The two initial reports inspired our design: To enhance the practicality of PPGs, 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 the commonly used bioactive compounds and the penetration of the tissue, our aim was to shift the deprotection wavelength even further while achieving a 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,[39] 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 in ^{19}F NMR (Figure 1c).

RESULTS AND DISCUSSION

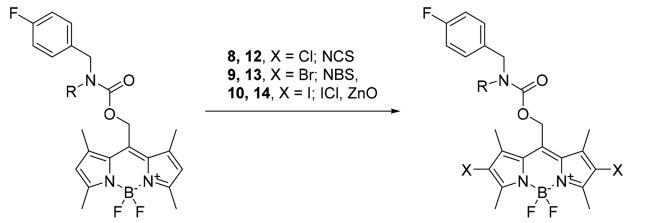
Model protected amines **7**−**14** were prepared using the synthetic route shown below (Scheme 1).

The synthesis started with the preparation of BODIPY ester **1** in 47% yield, using an adapted procedure, based on experimental results described in the literature.[39,40] Subsequent hydrolysis of the ester and reaction with 4-nitrophenyl chloroformate yielded carbonate **3** in 59% overall yield. In our hands, this reaction proved to be scalable up to 0.5 g. In the next step, we attempted halogenation of carbonate **3**. Chlorination was performed using NCS (2 portions of 5 equiv), modifying the procedure from Cosa et al.[37] With a reaction time of up to 3 d, the compound was obtained in a very good yield of 90%. Analogous bromination using NBS proceeded faster (30 min) and did not require a second addition of the reagent, providing 93% of compound **5**. This approach was, however, much less successful for iodination. Considerable amounts of monohalogenated product were being formed, even when 10 equiv of fresh NIS was being used. (For details, see the Supporting Information.) In this case, we chose to use ICl as the iodinating agent. The addition of an ICl solution to a suspension of ZnO and compound **3** in THF at 0 °C gave the disubstituted carbonate in 87% yield. With the activated carbonates **3**−**6** in hand, the protection of 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% yields, respectively. Halogenated carbamates **8**−**10** were obtained in moderate yields (61−65%), starting with Cl, Br, and I substituted carbonates. We hypothesize that the drop in yield comparing the formation of halogenated and unsubstituted carbamates (**7** and **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 the formation of amines instead of carbamates (Scheme 1). (For the NMR of one of the side products, **15**, see section 6 in the Supporting Information.) 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. (See the sections 5 and 6 in the Supporting Information.) 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 2). The reactions were performed in a similar manner

Scheme 2. Late-Stage Halogenation of Carbamates



to the ones described before for the halogenation of carbonate. The desired compounds were obtained in 73−80% yields 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 was also used to measure the stability of the compounds in aqueous media. For UV−vis measurements, compounds **7**−**14** in DMSO/phosphate buffer pH = 7.5 were irradiated with an LED light source (λ = 530 nm, 810 mW, 0.2 cm distance) for 10 min and UV−vis spectra were recorded every 30 s.

A rapid decrease of the absorbance of the bands attributed to the BODIPY core was observed, in accordance with the anticipated uncaging (Figure 2). Using the monoexponential fitting (Supporting Information), we calculated the half-lives of the caged molecules under irradiation (Table 1).

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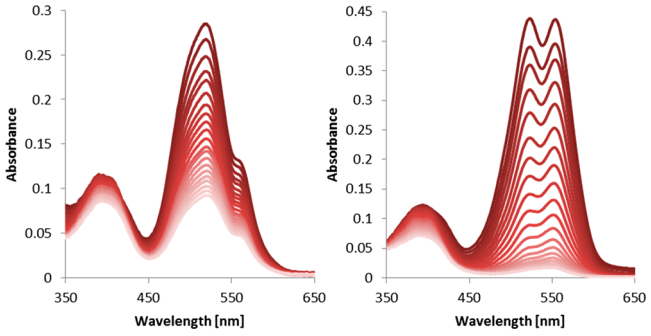

Figure 2. UV−Vis spectra of compounds **10** and **14** (20 μM in 20% DMSO/5 mM phosphate buffer pH = 7.5) under irradiation with λ = 530 nm LED light. Spectra were measured every 30 s.

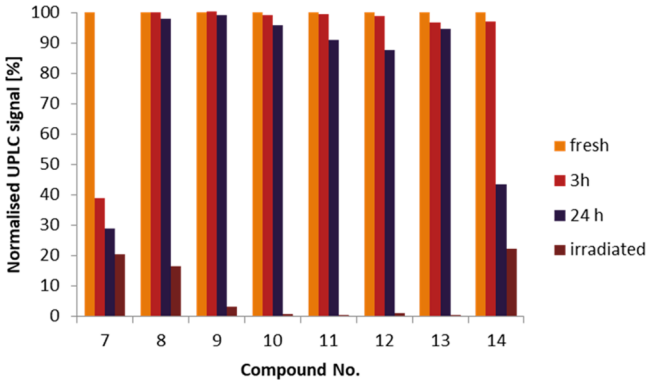

Figure 3. Stability and photocleavage of BODIPY carbamates. Comparison of normalized absorbance signals for compounds **7**−**14**, 0.125 mM in 25% DMSO/5 mM phosphate buffer, pH = 7.5, at λ = 520 nm. (For non-normalized values, see the Supporting Information.)

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. The obtained values were 4.2×10^{-5} for compound **9** and 3.8×10^{-5} for compound **13**. (See the details in the Supporting Information.) 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 check if the deprotection reaction proceeds in a clean fashion, we followed the process by ^{19}F NMR. (See the Supporting Information for details.) The spectra proved that one fluorinated compound is being released. To establish that this compound is indeed the uncaged amine, we used UPLC measurements. Samples of compounds **7**−**14** were prepared in DMSO/phosphate buffer (details in the Supporting Information), and UPLC traces of the fresh samples and after 1 h of irradiation with λ = 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 and 24 h. To estimate the relative amount of carbamates in the samples, the absorbance of their BODIPY signals at λ = 520 nm was measured (Figure 3). (For the UPLC traces, see the Supporting Information.)

Most of the studied compounds could be uncaged upon green-light irradiation (λ = 530 nm) for 1 h. The UPLC retention times of the products formed in these samples were consistent with those measured for appropriate amine standards (Supporting Information). 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 (λ = 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; λ_{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 λ_{max} to the therapeutic window region (650−900 nm) and enhance their solubility in aqueous media. The novel PPGs presented here for

Table 1. Photochemical Properties and Half-Lives of Compounds 7−14 upon Irradiation with λ = 530 nm

compound no.	X	R	half-life [min]	λ_{max1}	λ_{max2}	$\varepsilon_{\lambda max1}/10^3$ [cm^{-1} mol^{-1}]	$\varepsilon_{\lambda max2}/10^3$ [cm^{-1} mol^{-1}]	$\varepsilon_{530nm}/10^3$ [cm^{-1} mol^{-1}]
7	H	H	0.73	518		42		16
8	Cl	H	0.94	516	544	9.4	9.2	9.1
9	Br	H	1.62	505	550	19	11	16
10	I	H	1.99	511	558	14	0.6	12
11	H	CH_3	2.12	518		46		29
12	Cl	CH_3	2.06	519	550	22	21	21
13	Br	CH_3	0.96	521	553	30	28	29
14	I	CH_3	1.87	531	565	27	25	27

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the facile 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 ran under a 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 the fluorescence indicator UV254 (Merck, TLC silica gel 60 F254). For the 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 a Thermo Fisher Scientific LC/MS: UPLC model Vanquish, MS model LTQ with an iontrap and HESI (heated ESI) ionization source with positive and negative modes. 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. The obtained 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). All spectra were measured at room temperature (25 °C). Chemical shifts for the specific NMR spectra were reported relative to the residual solvent peak in ppm: $CDCl_3$, δ_H = 7.26; $CDCl_3$, δ_C = 77.16; DMSO-d_6, δ_H = 2.50; DMSO-d_6, δ_C = 39.52. The multiplicities of the signals are denoted by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). All ^{13}C NMR spectra are ^1H-broad band decoupled. High-resolution mass spectrometric measurements were performed using a Thermo scientific LTQ OrbitrapXL (ion trap) spectrometer with ESI ionization. The molecule ions M^+, $[M + H]^+$, and $[M - X]^+$ are given in m/z. Melting points were recorded using a Stuart analogue capillary melting point SMP11 apparatus.

*(5,5-Difluoro-1,3,7,9-tetramethyl-5H-4λ⁴,5λ⁴-dipyrrolo[1,2-c:2′,1′-f][1,3,2]diazabo-rinin-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 a nitrogen atmosphere. The reaction mixture was stirred in the dark at room temperature for 24 h. After this time, the flask was opened and TEA (3.2 mL, 28 mmol, 6.0 equiv) was added. The resulting mixture was allowed to stir for 15 min. Then, the flask was again put under a nitrogen atmosphere, and boron trifluoride diethyl etherate (5.2 mL, 42 mmol, 9.0 equiv) was added. After 1 h, 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) was added. Then, silica was added to the flask, and the solvents were evaporated. Compound **1** was purified by column chromatography using pentane/Et_2O (2:1; v/v) as the eluent. The product was obtained as red-gold crystals (700 mg, 47% yield): R_f = 0.7 (DCM); mp = 184–187 °C; ^1H NMR (400 MHz, chloroform-*d*) δ 2.13 (s, 3H, CO**CH**$_3$), 2.36 (s, 6H, 2 × Ar**CH**$_3$), 2.53 (s, 6H, 2 × Ar**CH**$_3$), 5.30 (s, 2H, Ar**CH**$_2$CO), 6.08 (s, 2H, 2 × Ar**H**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.43 (dd, J = 65.1, 32.5 Hz); HRMS (ESI+) calcd for $[M + H]^+$ ($C_{16}H_{20}BF_2N_2O_2$) 321.1580, found 321.1585. ^1H spectrum is in agreement with published data.[38]

*(5,5-Difluoro-1,3,7,9-tetramethyl-5H-4λ⁴,5λ⁴-dipyrrolo[1,2-c:2′,1′-f][1,3,2]diazaborinin-10-yl)methanol (**2**) (According to a Literature Procedure[38,41]).* A mixture of aqueous NaOH solution (6.3 mL, 0.10 M, 0.40 equiv) and methanol (30 mL) was stirred for 10 min 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 × 30 mL). The combined organic layers were washed with 1 M HCl (2 × 20 mL) and brine (1 × 20 mL) and dried with $MgSO_4$. Compound **2** was purified by column chromatography (pentane/Et_2O, gradient 2:1 → 0:1; v/v). The product was obtained as a red precipitate (350 mg, 81% yield): R_f = 0.3 (DCM); mp = 247–249 °C; ^1H NMR (400 MHz, chloroform-*d*) δ 2.51 (s, 6H, 2 × Ar**CH**$_3$), 2.52 (s, 6H, 2 × Ar**CH**$_3$), 4.91 (s, 2H, Ar**CH**$_2$CO), 6.08 (s, 2H, 2 × Ar**H**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.52 (dd, J = 65.3, 32.4 Hz); HRMS (ESI+) calcd for $[M + H]^+$ ($C_{14}H_{18}BF_2N_2O$) 279.1475, found 279.1488. ^1H spectrum is in agreement with published data.[41]

*(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-Nitrophenyl)carbonate (**3**).* To a solution of 4-nitrophenyl chloroformate (870 mg, 4.3 mmol, 3.4 equiv) in dry DCM (50 mL) was added pyridine (0.35 mL, 4.3 mmol, 3.4 equiv) under a 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 up and was 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_2O/DCM as the eluent (2 stages with a gradient of pentane/Et_2O 5:1 → 2:1, then DCM 100%). Compound **3** was obtained as a pink precipitate (440 mg, 79% yield): R_f = 0.8 (DCM); mp = 203–205 °C; ^1H NMR (400 MHz, chloroform-*d*) δ 2.46 (s, 6H, 2 × Ar**CH**$_3$), 2.55 (s, 6H, 2 × Ar**CH**$_3$), 5.57 (s, 2H, Ar**CH**$_2$OCO), 6.12 (s, 2H, 2 × BAr**H**), 7.40 (d, ^3J = 9.1 Hz, 2H, 2 × OC**CH**), 8.29 (d, ^3J = 9.2 Hz, 2H, 2 × NO$_2$**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.16 (dd, J = 64.9, 32.3 Hz); ^{13}C NMR (101 MHz, chloroform-*d*) δ 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+) calcd for $[M + H]^+$ ($C_{21}H_{21}BF_2N_3O_5$) 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) was added a solution of NCS (75 mg, 0.56 mmol, 5.0 equiv) in dry THF (0.5 mL) under a nitrogen atmosphere. The reaction 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 a dark purple precipitate (52 mg, 90% yield): R_f = 0.9 (DCM); mp = 208–211 °C; ^1H NMR (400 MHz, chloroform-*d*) δ 2.49 (s, 6H, 2 × Ar**CH**$_3$), 2.61 (s, 6H, 2 × Ar**CH**$_3$), 5.59 (s, 2H, Ar**CH**$_2$OCO), 7.40 (d, J = 9.2 Hz, 2H, 2 × OC**CH**), 8.30 (d, J = 9.2 Hz, 2H, 2 × NO$_2$**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −145.91 (dd, J = 62.9, 31.4 Hz); ^{13}C 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+) calcd for $[M + H]^+$ ($C_{21}H_{19}BCl_2F_2N_3O_5$) 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) was added a solution of NBS (100 mg, 0.56 mmol, 5 equiv) in dry THF (0.5 mL) under a nitrogen atmosphere. The reaction was stirred for 30 min 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 precipitate (63 mg, 93% yield): R_f = 0.9 (DCM); mp = 214–217 °C; ^1H NMR (400 MHz, chloroform-*d*) δ 2.49 (s, 6H, 2 × Ar**CH**$_3$), 2.61 (s, 6H, 2 × Ar**CH**$_3$), 5.59 (s, 2H, Ar**CH**$_2$OCO), 7.40 (d, J = 9.0 Hz, 2H, 2 × OC**CH**), 8.30 (d, J = 9.0 Hz, 2H, 2 × NO$_2$**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.27 (dd, J = 62.7, 31.4 Hz); ^{13}C NMR (101 MHz, chloroform-*d*) δ 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+) calcd for $[M + H]^+$ ($C_{21}H_{19}BBr_2F_2N_3O_5$) 601.9727, found 601.9729.

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*(5,5-Difluoro-2,8-diiodo-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 (**6**).* To a suspension of compound **3** (44 mg, 99 μmol) and ZnO (29 mg, 0.36 mmol, 3.6 equiv) in dry THF (7 mL) was added a solution of ICl (50 mg, 0.31 mmol, 3.1 equiv) in dry THF (2 mL) under a nitrogen atmosphere, at 0 °C. The reaction was stirred for 15 min. After this 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-gold precipitate (60 mg, 87% yield): R_f = 0.9 (DCM); mp = 194−197 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.52 (s, 6H, 2 × Ar**CH**$_3$), 2.65 (s, 6H, 2 × Ar**CH**$_3$), 5.60 (s, 2H, Ar**CH**$_2$OCO), 7.40 (d, *J* = 9.1 Hz, 2H, 2 × OC**CH**), 8.30 (d, *J* = 9.1 Hz, 2H, 2 × NO$_2$**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −145.59 (dd, *J* = 63.3, 31.6 Hz); ^{13}C NMR (101 MHz, chloroform-*d*) δ 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+) calcd for [M + H]$^+$ ($C_{21}H_{19}BI_2F_2N_3O_5$) 695.9469, found 695.9470.

*(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-Fluorophenyl)carbamate (**7**).* To a solution of compound **3** (100 mg, 0.23 mmol) in dry THF (5 mL) was added a solution of pyridine in THF (1.0 M, 75 μL, 75 μmol, 0.24 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 20 mL), 0.1 M NaOH (4 × 20 mL), and brine (2 × 20 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 an orange-gold precipitate (89 mg, 92% yield): R_f = 0.5 (DCM); mp = 182−184 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.39 (s, 6H, 2 × Ar**CH**$_3$), 2.52 (s, 6H, 2 × Ar**CH**$_3$), 4.35 (d, *J* = 5.9 Hz, 2H, C**CH**$_2$NH), 5.11 (s, 1H, CO**NH**), 5.33 (s, 2H, Ar**CH**$_2$OCO), 6.07 (s, 2H, 2 × Ar**H**), 7.02 (t, *J* = 8.6 Hz, 2H, CH$_2$C**CH**), 7.23 (t, *J* = 5.5 Hz, 2H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.43 (m, *J* = 65.1, 32.6 Hz), −114.72 (m); ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.6, 15.6, 44.5, 58.1, 115.5, 115.7, 129.1, 129.1, 132.6, 133.5, 133.8, 141.6, 155.7, 156.5, 161.0, 163.4; HRMS (ESI+) calcd for [M + H]$^+$ ($C_{22}H_{24}BF_3N_3O_2$) 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) was added a solution of pyridine in THF (1.0 M, 4.7 μL, 4.7 μmol, 0.24 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min at room temperature, a solution of 4-fluorobenzylamine in THF (1.0 M, 30 μL, 30 μmol, 1.5 equiv) was added. The reaction was then stirred for an additional 3 h. After that time, DCM (10 mL) and brine (10 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 10 mL), 0.1 M NaOH (4 × 10 mL), and brine (2 × 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 a purple precipitate (6.0 mg, 62%).

Method B. To a solution of compound **7** (10 mg, 23 μmol) in dry THF (0.5 mL) was added a solution of NCS (16 mg, 116 μmol, 5 equiv) in dry THF (0.5 mL) under a 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 a purple precipitate (8.5 mg, 73% yield).

Compound data: R_f = 0.6 (DCM); mp = 191−193 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.40 (s, 6H, 2 × Ar**CH**$_3$), 2.56 (s, 6H, 2 × Ar**CH**$_3$), 4.36 (d, *J* = 5.9 Hz, 2H, C**CH**$_2$NH), 5.10 (s, 1H, CO**NH**), 5.34 (s, 2H, Ar**CH**$_2$OCO), 7.03 (t, *J* = 8.5 Hz, 2H, CH$_2$C**CH**), 7.23 (d, *J* = 5.5 Hz, 2H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −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*) δ 12.6, 13.0, 44.6, 58.0, 115.6, 115.8, 129.1, 129.2, 130.9, 133.6, 134.3, 136.3, 153.6, 155.4, 161.1, 163.5; HRMS (ESI+) calcd for [M + NH$_4$]$^+$ ($C_{22}H_{25}BCl_2F_3N_4O_2$) 515.1394, found 515.1391.

*(2,8-Dibromo-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 (**9**). Method A.* To a solution of compound **5** (50 mg, 83.2 μmol) in dry THF (10 mL) was added a solution of pyridine in THF (0.50 M, 0.17 mL, 83.2 μmol, 1 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (10 mL) and brine (10 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 10 mL), 0.1 M NaOH (4 × 10 mL), and brine (2 × 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 a purple precipitate (16 mg, 36% yield).

Method B. To a solution of compound **7** (10 mg, 23 μmol) in dry THF (0.5 mL) was added a solution of NBS (12 mg, 70 μmol, 3 equiv) in dry THF (0.5 mL) under a 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 a purple precipitate (11 mg, 80%).

Compound data: R_f = 0.6 (DCM); mp = 216−219 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.42 (s, 6H, 2 × Ar**CH**$_3$), 2.58 (s, 6H, 2 × Ar**CH**$_3$), 4.36 (d, *J* = 5.8 Hz, 2H, C**CH**$_2$NH), 5.10 (s, 1H, CO**NH**), 5.35 (s, 2H, Ar**CH**$_2$OCO), 7.03 (t, *J* = 8.5 Hz, 2H, CH$_2$C**CH**), 7.24 (d, *J* = 8.0 Hz, 2H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.12 (m, *J* = 63.0, 31.8 Hz), −114.50 (m); ^{13}C NMR (101 MHz, chloroform-*d*) δ 13.9, 14.8, 44.6, 58.2, 112.9, 115.6, 115.8, 129.2, 131.7, 133.5, 133.9, 138.9, 155.1, 155.4, 161.1, 163.5; HRMS (ESI+) calcd for [M + NH$_4$]$^+$ ($C_{22}H_{25}BBr_2F_3N_4O_2$) 605.0364, found 605.0361.

*(2,8-Diiodo-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 (**10**). Method A.* To a solution of compound **6** (50 mg, 71.9 μmol) in dry THF (10 mL) was added a solution of pyridine in THF (0.50 M, 0.14 mL, 72 μmol, 1.0 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (10 mL) and brine (10 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 10 mL), 0.1 M NaOH (4 × 10 mL), and brine (2 × 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 a purple precipitate (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) was added a solution of ICl (11 mg, 70 μmol, 3.0 equiv) in dry THF (0.5 mL) at 0 °C in a nitrogen atmosphere. The reaction was allowed to stir for 10 min, after which the solvent was evaporated and the crude mixture filtrated through silica using DCM. The product was obtained as a dark violet precipitate (12 mg, 76%).

Compound data: R_f = 0.6 (DCM); mp = 203−204 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.44 (s, 6H, 2 × Ar**CH**$_3$), 2.62 (s, 6H, 2 × Ar**CH**$_3$), 4.36 (d, *J* = 5.5 Hz, 2H, C**CH**$_2$NH), 5.12 (s, 1H, CO**NH**), 5.35 (s, 2H, Ar**CH**$_2$OCO), 7.03 (t, *J* = 8.0 Hz, 2H, CH$_2$C**CH**), 7.24 (t, *J* = 6.0 Hz, 2H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −145.90 (m), −145.26 (m), −114.50; ^{13}C NMR (101 MHz, chloroform-*d*) δ 16.3, 18.2, 44.6, 58.5, 115.6, 115.8, 129.2, 129.5, 132.5, 133.0, 133.6, 143.5, 155.4, 157.9, 160.1, 161.1; HRMS (ESI+) calcd for [M + NH$_4$]$^+$ ($C_{22}H_{25}BI_2F_3N_4O_2$) 699.0112, found 699.0167.

*(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)(methyl)-carbamate (**11**).* To a solution of compound **3** (100 mg, 230 μmol) in dry THF (5 mL) was added a solution of pyridine in THF

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(1.0 M, 0.054 mL, 54 μmol, 0.24 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 20 mL), 0.1 M NaOH (4 × 20 mL), and brine (2 × 20 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 an orange precipitate (90 mg, 90% yield): R_f = 0.5 (DCM); mp = 123−125 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.31 (s, 3H, Ar**CH$_3$**), 2.40 (s, 3H, Ar**CH$_3$**), 2.53 (s, 6H, 2 × Ar**CH$_3$**), 2.78 (s, 1.5H, 0.5 × NC**H$_3$**), 2.97 (s, 1.5H, 0.5 × NC**H$_3$**), 4.34 (s, 1H, C**CH$_2$**NCH$_3$), 4.46 (s, 1H, C**CH$_2$**NCH$_3$), 5.32 (s, 1H, Ar**CH$_2$**OCO), 5.35 (s, 1H, Ar**CH$_2$**OCO), 6.05 (s, 1H, Ar**H**), 6.08 (s, 1H, Ar**H**), 6.92 (t, *J* = 8.2 Hz, 1H, FC**CH**), 6.97−7.11 (m, 2H, CH$_2$C**CH**), 7.18−7.24 (m, 1H, FC**CH**); ^{19}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); ^{13}C NMR (101 MHz, chloroform-*d*) δ 14.7, 15.5, 33.7, 35.0, 51.9, 52.1, 115.3, 115.4, 115.5, 115.6, 122.2, 128.9, 129.5, 132.7, 132.7, 133.7, 133.9, 141.6, 155.5, 156.1, 156.5, 160.9, 161.0, 163.4, 163.5; HRMS (ESI+) calcd for $[M + H]^+$ ($C_{23}H_{26}BF_3N_3O_2$) 444.2065, found 444.2062.

*(2,8-Dichloro-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 (4-Fluorobenzyl)(methyl)carbamate (**12**). Method A.* To a solution of compound **4** (10 mg, 20 μmol) in dry THF (0.5 mL) was added a solution of pyridine in THF (1.0 M, 4.7 μL, 4.7 μmol, 0.24 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. The organic layer was washed with 1 M HCl (3 × 20 mL), 0.1 M NaOH (4 × 20 mL), and brine (2 × 20 mL). Then it was dried with $MgSO_4$, 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 a purple precipitate (3.5 mg, 35% yield).

Method B. To a solution of compound **11** (10 mg, 23 μmol) in dry THF (0.5 mL) was added a solution of NCS (15 mg, 0.11 mmol, 5 equiv) under a 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 a purple precipitate (8 mg, 69% yield).

Compound data: R_f = 0.7 (DCM); mp = 157−159 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.30 (s, 3H, Ar**CH$_3$**), 2.41 (s, 3H, Ar**CH$_3$**), 2.57 (s, 6H, 2 × Ar**CH$_3$**), 2.78 (s, 1.5H, 0.5 × NC**H$_3$**), 3.00 (s, 1.5H, 0.5 × NC**H$_3$**), 4.34 (s, 1H, C**CH$_2$**NCH$_3$), 4.47 (s, 1H, C**CH$_2$**NCH$_3$), 5.33 (s, 1H, Ar**CH$_2$**OCO), 5.35 (s, 1H, Ar**CH$_2$**OCO), 6.92 (t, *J* = 8.3 Hz, 1H, FC**CH**), 6.97−7.06 (m, 2H, CH$_2$C**CH**), 7.16−7.25 (m, 1H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.37 (ddd, *J* = 63.0, 31.2, 18.8 Hz), −114.67; ^{13}C NMR (101 MHz, chloroform-*d*) δ 12.6, 12.7, 33.7, 35.4, 52.04, 52.2, 58.5, 58.6, 115.4, 115.5, 115.6, 115.7, 123.5, 128.6, 128.7, 129.4, 129.5, 130.9, 131.1, 132.5, 132.6, 134.5, 134.6, 136.3, 153.6, 155.2, 155.3, 155.7, 155.8; HRMS (ESI+) calcd for $[M + NH_4]^+$ ($C_{23}H_{27}BCl_2F_3N_4O_2$) 529.1556, found 529.1548.

*(2,8-Dibromo-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 (4-Fluorobenzyl)(methyl)carbamate (**13**). Method A.* To a solution of compound **5** (50 mg, 83.2 μmol) in dry THF (10 mL) was added a solution of pyridine in THF (0.50 M, 0.17 mL, 54 μmol, 0.24 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 20 mL), 0.1 M NaOH (4 × 20 mL), and brine (2 × 20 mL), it was dried with $MgSO_4$ 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 a dark violet precipitate (16 mg, 32%).

Method B. To a solution of compound **11** (10 mg, 23 μmol) in dry THF (0.5 mL) was added a solution of NBS (12 mg, 70 μmol, 3 equiv) in dry THF (0.5 mL) under a 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 a purple precipitate (11 mg, 81%).

Compound data: R_f = 0.7 (DCM); mp = 168−170 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.30 (s, 3H, Ar**CH$_3$**), 2.42 (s, 3H, Ar**CH$_3$**), 2.59 (s, 6H, 2 × Ar**CH$_3$**), 2.78 (s, 1.5H, NC**H$_3$**), 3.00 (s, 1.5H, NC**H$_3$**), 4.33 (s, 1H, C**CH$_2$**NCH$_3$), 4.47 (s, 1H, C**CH$_2$**NCH$_3$), 5.33 (s, 1H, Ar**CH$_2$**OCO), 5.35 (s, 1H, Ar**CH$_2$**OCO), 6.92 (t, *J* = 8.2 Hz, 1H, FC**CH**), 6.96−7.08 (m, 2H, CH$_2$C**CH**), 7.18−7.24 (m, 1H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −146.05 (ddd, *J* = 63.4, 31.2, 20.9 Hz), −114.67, −114.57; ^{13}C NMR (101 MHz, chloroform-*d*) δ 13.9, 14.7, 33.7, 35.4, 52.1, 52.2, 58.6, 58.7, 112.8, 112.9, 115.4, 115.5, 115.6, 115.7, 128.6, 128.7, 129.4, 129.5, 131.6, 131.8, 132.6, 132.6, 134.1, 134.2, 138. 9, 154.9, 155.2, 155.7, 160.9, 161.1, 163.4, 163.5; HRMS (ESI+) calcd for $[M + NH_4]^+$ ($C_{23}H_{27}BBr_2F_3N_4O_2$) 619.0520, found 619.0518.

*(2,8-Diiodo-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 (4-Fluorobenzyl)(methyl)carbamate (**14**). Method A.* To a solution of compound **6** (50 mg, 72.0 μmol) in dry THF (10 mL) was added a solution of pyridine in THF (0.50 M, 0.14 mL, 64.8 μmol, 0.24 equiv) under a nitrogen atmosphere. After the mixture was stirred for 15 min 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 was then stirred for an additional 3 h. After that time, DCM (20 mL) and brine (20 mL) were added and the formed phases were separated. After the organic layer was washed with 1 M HCl (3 × 20 mL), 0.1 M NaOH (4 × 20 mL), and brine (2 × 20 mL), it was dried with $MgSO_4$ 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 a dark violet precipitate (16 mg, 34%).

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) was added a solution of ICl (11 mg, 68 μmol, 3.0 equiv) in dry THF (0.5 mL) at 0 °C in a nitrogen atmosphere. The reaction was allowed to stir for 10 min, after which the solvent was evaporated and the crude mixture filtrated through silica using DCM. The product was obtained as a dark violet precipitate (12 mg, 73%).

Compound data: R_f = 0.7 (DCM); mp = 193−194 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 2.33 (s, 3H, Ar**CH$_3$**), 2.45 (s, 3H, Ar**CH$_3$**), 2.63 (s, 6H, 2 × Ar**CH$_3$**), 2.79 (s, 1.5H, 0.5 × NC**H$_3$**), 3.00 (s, 1.5H, 0.5 × NC**H$_3$**), 4.33 (s, 1H, C**CH$_2$**NCH$_3$), 4.47 (s, 1H, C**CH$_2$**NCH$_3$), 5.34 (s, 1H, Ar**CH$_2$**OCO), 5.36 (s, 1H, Ar**CH$_2$**OCO), 6.93 (t, *J* = 8.3 Hz, 1H, FC**CH**), 6.98−7.10 (m, 2H, CH$_2$C**CH**), 7.21 (t, *J* = 5.3 Hz, 1H, FC**CH**); ^{19}F NMR (376 MHz, chloroform-*d*) δ −145.69 (ddd, *J* = 63.0, 30.7, 22.6 Hz), −114.67, −114.42; ^{13}C NMR (101 MHz, chloroform-*d*) δ 16.3, 18.0, 33.7, 35.4, 52.1, 52.2, 58.9, 59.0, 87.1, 115.4, 115.5, 115.7, 115.7, 128.7, 128.8, 129.4, 129.5, 132.5, 132.6, 132.7, 133.2, 133.3, 143.6, 155.2, 155.8, 157.8; HRMS (ESI+) calcd for $[M + NH_4]^+$ ($C_{23}H_{27}BF_3I_2N_4O_2$) 713.0269, found 713.0266.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02729.

Synthesis optimization tables, spectral data for all compounds, UPLC traces for compounds (**7**−**14**), before and after deprotection UV−vis spectra for

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compounds (**7**−**14**), quantum yields, characterization of the side product **15**, and the LED light source specification (PDF)

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Notes

The authors declare no competing financial interest.

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