Green-Light-Sensitive BODIPY Photoprotecting Groups for Amines
Kaja Sitkowska,†,§ Ben. L. Feringa,†,⊥ and Wiktor SzymanSKI*,†,‡
†Centre for Systems Chemistry, Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
§University of Warsaw, Faculty of Chemistry, Pasteura 1, 02-093 Warsaw, Poland
‡Department of Radiology, University of Groningen, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands

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 stimulate 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), 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.6a,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 GABA18,19 and Vemurafenib20 has been reported. Photoprotecting groups can also be used for controlling complex biological processes, like protein dimerization21 or gene activation22 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
rendering it a possible PPG. BODIPY derivatives are widely used as probes, laser dyes, photosensitizers, sensors, dyads, catalysts, emission contrasts, and cell visualization agents. 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 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 \( \lambda_{\text{max}} \) 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. The compound, in

![Scheme 1. Synthesis of Activated Carbonates 4–6 and Protection of 4-Fluorobenzylamine and 4-Fluoro-N-methylbenzylamine](image)

![Figure 1. Comparison of reported BODIPY photoprotecting groups and those described in this work.](image)
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 $\lambda_{\text{max}}$ of these compounds was slightly red-shifted compared to a nonsubstituted BODIPY core ($\lambda_{\text{max}} = 540$ nm). The authors also used their PPG to release dopamine and histidine. The uncaged amines were active, as 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 unprotected amines in vitro. Although the PPG was efficient and worked fast, it was synthesized from a premed, difficult to prepare, and expensive BODIPY dye. To improve 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 observing the photo-deprotection.

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](image)

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 ($\lambda = 530$ 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 obtained, 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).
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 $4.2 \times 10^{-5}$ for compound 9 and $3.8 \times 10^{-5}$ 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 $\lambda = 530$ 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 used to check the stability of compounds 7–14 upon irradiation with green light. The next step for the development of BODIPY photoprotecting groups would be shifting their 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 for

### Table 1. Photochemical Properties and Half-Lives of Compounds 7–14 upon Irradiation with $\lambda = 530$ nm

| compound no. | X   | R     | half-life [min] | $\lambda_{\text{max}}$ | $\lambda_{\text{max}}$ | $\epsilon_{103}/10^3$ [cm$^{-1}$ mol$^{-1}$] | $\epsilon_{203}/10^3$ [cm$^{-1}$ mol$^{-1}$] | $\epsilon_{333}/10^3$ [cm$^{-1}$ mol$^{-1}$] |
|-------------|-----|-------|-----------------|------------------------|------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 7           | H   | H     | 0.73            | 518                    | 518                    | 42                                            | 9.4                                           | 9.2                                           |
| 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                    | 518                    | 46                                            | 22                                            | 21                                            |
| 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                                            |
the facile photodeprotection of amines with visible light makes this system 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 purif{ed by passage through solvent purification columns (MBrAin 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 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 \( \lambda = 254 \) nm or \( \lambda = 365 \) 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 indicator UV254 (Merck, TLC silica gel 60 F254). For the detection of components, UV light at \( \lambda = 254 \) nm or \( \lambda = 365 \) nm was used.

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To a suspension of compound 3 (44 mg, 99 μmol) and ZnO (29 mg, 0.36 mmol, 3.6 equiv) in dry THF (5 mL) was added a solution of ICI (50 mg, 0.31 mmol, 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): Rf = 0.9 (DCM); mp = 194–197 °C; 1H NMR (400 MHz, chloroform-d) δ = 2.52 (s, 6H, 2 × ArCH3), 2.65 (s, 6H, 2 × ArCH2), 5.60 (s, 2H, ArCH2OCO), 7.40 (d, J = 9.1 Hz, 2H, 2 × OCCH3), 8.30–8.1 (m, J = 9.1 Hz, 2H, 2 × NO2CH3); 13C NMR (101 MHz, chloroform-d) δ = 145.59 (dd, J = 63.3, 31.6 Hz). 1C NMR (101 MHz, chloroform-d) δ = 164.1, 18.4, 61.9, 121.6, 152.4, 130.3, 131.7, 132.5, 143.4, 145.7, 152.0, 155.1, 158.6; HRMS (ESI+) calcld for [M + H]+ ([C6H17BBrF3N6O4]) 695.9469, found 695.9470.

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, 34 μL, 34 μmol, 0.99 equiv) was added. The reaction was then stirred for an additional 3 h. After that time, DCM (5 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 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 a deep purple precipitate (16%, 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 deep purple precipitate (11%, 50% yield).

Compound data: Rf = 0.6 (DCM); mp = 171–180 °C; 1H NMR (400 MHz, chloroform-d) δ = 2.42 (s, 6H, 2 × ArCH3), 2.58 (s, 6H, 2 × ArCH2), 4.36 (d, J = 5.8 Hz, 2H, CCH3NH), 5.10 (s, 1H, CONH), 5.35 (s, 2H, ArCH2OCO), 7.03 (t, J = 8.5 Hz, 2H, CH2CH3), 7.24 (t, J = 8.5 Hz, 2H, FCCH3); 13C NMR (101 MHz, chloroform-d) δ = 139.4, 139.8, 144.6, 58.2, 112.9, 115.6, 129.2, 131.7, 133.5, 133.9, 148.3, 151.1, 155.4, 161.1, 163.5; HRMS (ESI+) calcld for [M + NH4]+ ([C22H25BBr2F3N4O2]) 605.0364, found 605.0361.

To a solution of compound 6 (50 mg, 71.9 μmol) in dry DCM (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 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 a deep violet 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 DCM (0.5 mL) was added a solution of ICI (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 filtered through silica using DCM. The product was obtained as a dark violet precipitate (12 mg, 76% yield).

Compound data: Rf = 0.6 (DCM); mp = 203–204 °C; 1H NMR (400 MHz, chloroform-d) δ = 2.44 (s, 6H, 2 × ArCH3), 2.62 (s, 6H, 2 × ArCH3), 4.36 (d, J = 5.5 Hz, 2H, CCH3NH), 5.12 (s, 1H, CONH), 5.35 (s, 2H, ArCH2OCO), 7.03 (t, J = 8.0 Hz, 2H, CH2CH3), 7.24 (t, J = 6.0 Hz, 2H, FCCH3); 13C NMR (376 MHz, chloroform-d) δ = 145.59 (s), 145.26 (m), −114.50 (s); 1C NMR (101 MHz, chloroform-d) δ = 163.2, 182.4, 44.6, 58.5, 115.6, 115.8, 129.2, 132.5, 133.0, 133.6, 143.5, 155.4, 157.9, 160.1, 161.1; HRMS (ESI+) calcld for [M + NH4]+ ([C6H17BBrF3N6O4]) 699.0112, found 699.0167.

To a solution of compound 3 (100 mg, 230 μmol) in dry DCM (5 mL) was added a solution of pyridine in THF
(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 still 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 (3 × 20 mL), and brine (2 × 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 an orange precipitate (90 mg, 90% yield): R₆ = 0.5 (DCM); mp = 123–125 °C; ¹H NMR (400 MHz, chloroform-d) δ 2.31 (s, 3H, ArCH₂), 2.40 (s, 3H, ArCH₂), 2.53 (s, 6H, 2 × ArCH₂), 2.78 (s, 1.5H, 0.5 × NC₅H₅), 2.97 (s, 1.5H, 0.5 × NC₅H₅), 4.34 (s, 1H, CCH₂NC₅H₅), 4.46 (s, 1H, CCH₂NC₅H₅), 5.32 (s, 1H, ArCH₂OCO), 5.35 (s, 1H, ArCH₂OCO), 6.05 (s, 1H, ArH), 6.08 (s, 1H, ArH), 6.92 (t, J = 8.2 Hz, 1H, FCCH), 7.07–7.11 (m, 2H, CH₂CCH), 7.18–7.24 (m, 1H, FCCH); ¹³F NMR (376 MHz, chloroform-d) δ = −146.34 (dd, J = 65.2, 32.1, 9.2 Hz), −114.94 (dt, J = 47.0, 7.9 Hz); ¹³C 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, 133.7, 133.9, 141.6, 155.5, 156.1, 156.9, 161.0, 163.4, 163.5; HRMS (ESI+) calcd for [M + NH₄⁺]⁺ (C₂₃H₂₇BCl₂F₃N₄O₂) 529.1556, found 529.1558.

Method B. To a solution of compound 11 (10 mg, 23 μmol) in dry THF (0.5 mL) was added a solution of pentane/diethyl ether (3:1; v/v) as the eluent. The product was obtained as a purple precipitate (11 mg, 81%).

Compound data: R₆ = 0.7 (DCM); mp = 168–170 °C; ¹H NMR (400 MHz, chloroform-d) δ 2.30 (s, 3H, ArCH₂), 2.42 (s, 3H, ArCH₂), 2.59 (s, 6H, 2 × ArCH₂), 2.78 (s, 1.5H, NCH₃), 3.00 (s, 1.5H, NCH₃), 4.33 (s, 1H, ArCH₂OCO), 4.47 (s, 1H, ArCH₂OCO), 5.33 (s, 1H, ArCH₂OCO), 5.35 (s, 1H, ArCH₂OCO), 6.93 (s, 1H, ArH), 6.92 (s, 1H, ArH), 6.92 (t, J = 8.2 Hz, 1H, FCCH), 7.08–7.12 (m, 2H, CH₂CCH), 7.19–7.24 (m, 1H, FCCH); ¹³F NMR (376 MHz, chloroform-d) δ = −146.05 (dd, J = 63.4, 31.2, 20.9 Hz), −114.67, −114.57; ¹³C 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, 145.9, 155.2, 155.7, 160.9, 161.1, 161.3, 161.6; HRMS (ESI+) calcd for [M + NH₄⁺]⁺ (C₂₃H₂₈BF₂C₂N₄O₂) 535.1387, found 535.1389.

Method C. To a solution of compound 11 (20 mg, 40 μmol) in dry THF (10 mL) was added pyridine in THF (1.0 M, 4.7 mL) and DCC (50 mg, 0.24 equiv) was added. The reaction was then stirred for an additional 3 h at room temperature. 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 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 a dark violet precipitate (16 mg, 34%).

Method D. To a suspension of compound 11 (10 mg, 23 μmol) and ZnO (6.6 mg, 81 μmol, 3 equiv) 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%).

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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