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Perspective

meso-Methyl BODIPY Photocages: Mechanisms, Photochemical Properties, and Applications

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ABSTRACT: *meso*-methyl BODIPY photocages have recently emerged as an exciting new class of photoremovable protecting groups (PPGs) that release leaving groups upon absorption of visible to near-infrared light. In this Perspective, we summarize the development of these PPGs and highlight their critical photochemical properties and applications. We discuss the absorption properties of the BODIPY PPGs, structure−photoreactivity studies, insights into the photoreaction mechanism, the scope of functional groups that can be caged, the chemical synthesis of these structures, and how substituents can alter the water solubility of the PPG and direct the PPG into specific subcellular compartments. Applications that exploit the unique optical and photochemical properties of BODIPY PPGs are also discussed, from wavelength-selective photoactivation to biological studies to photoresponsive organic materials and photomedicine.

1. INTRODUCTION

Photoremovable protecting groups (PPGs), or photocages, are light-sensitive chromophores that release a leaving group upon absorption of light. In biological experiments, photocages engender spatial and temporal control over activating (photoreleasing) substrates such as proteins, nucleotides, ions, neurotransmitters, pharmaceuticals, fluorescent dyes, and other biologically active molecules.[1,2] Photocages also have critical applications in organic synthesis,[3] super-resolution imaging,[4] light-responsive materials,[5] photoacids,[6] and photolithographic synthesis of microarrays (e.g., gene chips).[7]

The most popular PPGs used in biological settings are the *o*-nitrobenzyl-based systems and their derivatives.[8] Still, other PPGs such as phenacyl,[9] coumarinyl,[10] benzoinyl,[11] and *o*-hydroxynaphthyl[12] are in routine use. The appeal of PPGs within a biochemical context is that light is, in principle, a nonperturbing external signal that can be focused and pulsed, engendering spatiotemporal control at high resolution. Light offers additional control attributes, such as over the intensity, giving dosing control if the photorelease is coupled with an optical response, as well as over the wavelength, which can be tuned to provide independent optical control over mixtures of photocaged compounds.

In practice, however, most PPGs are activated using UV light, which can be absorbed by native biological chromophores (e.g., DNA bases) leading to background cellular phototoxicity.[13] UV light is also readily scattered and thus has limited penetration into biological tissues.[14,15] In contrast, photocages that absorb light in the visible region of the spectrum can be externally controlled with nonperturbing wavelengths, while those PPGs absorbing light in the biological window (∼600−1000 nm) offer the potential to be photoactivated in deep tissues,[14,16] enabling new avenues for photocaging within animals or as platforms for human phototherapeutics.[17−19]

Among the recently emerging visible light activatable PPGs, *meso*-methyl boron dipyrromethene (BODIPY) PPGs offer an especially exciting new photocaging platform primarily because of their tunable absorption properties over the visible to near-IR portions of the optical spectrum, allowing single-photon photouncaging experiments to be conducted with effectively any wavelength of light in the visible to near-IR, experiments that would have been impossible even a decade ago. Other favorable properties of *meso*-methyl BODIPY are that the parent structure itself is biologically benign, does not undergo thermal release in the dark, and has a potent chromophore that strongly absorbs light (ε = 40 000−150 000 M^{-1} cm^{-1} are typical). Furthermore, BODIPY PPGs can cross cell membranes without a carrier, can be directed to different subcellular compartments by targeting substituents, and can photorelease a wide variety of functional groups with high chemical and quantum yields. Other BODIPY-based photocaging platforms, such as those substituted at boron[20] or using BODIPY oximes,[21] have been reported but they are not discussed here.

We highlight key aspects of *meso*-methyl BODIPY photocages including the mechanism of uncaging, tuning the light absorbing properties of the chromophore across the visible and near-IR portions of the light spectrum, and strategies to increase the photosensitivity of the chromophore to light, and we review the biological, materials, and

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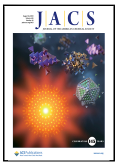

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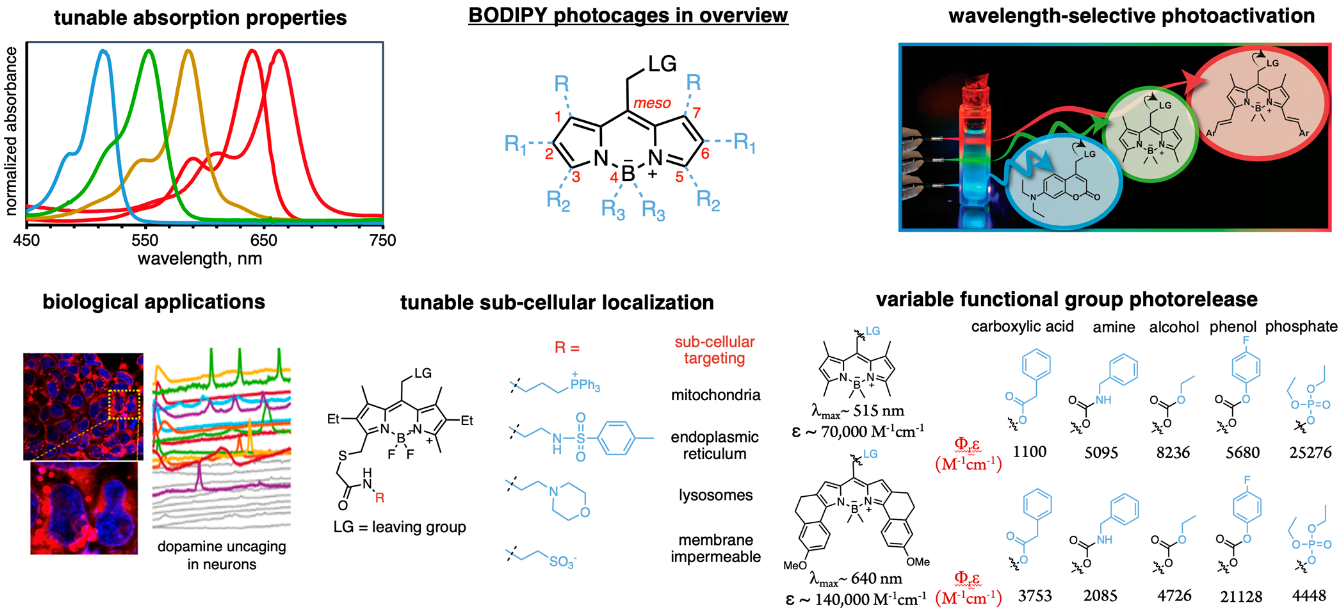


Figure 1. Overview of key properties of BODIPY photocages discussed in this review.

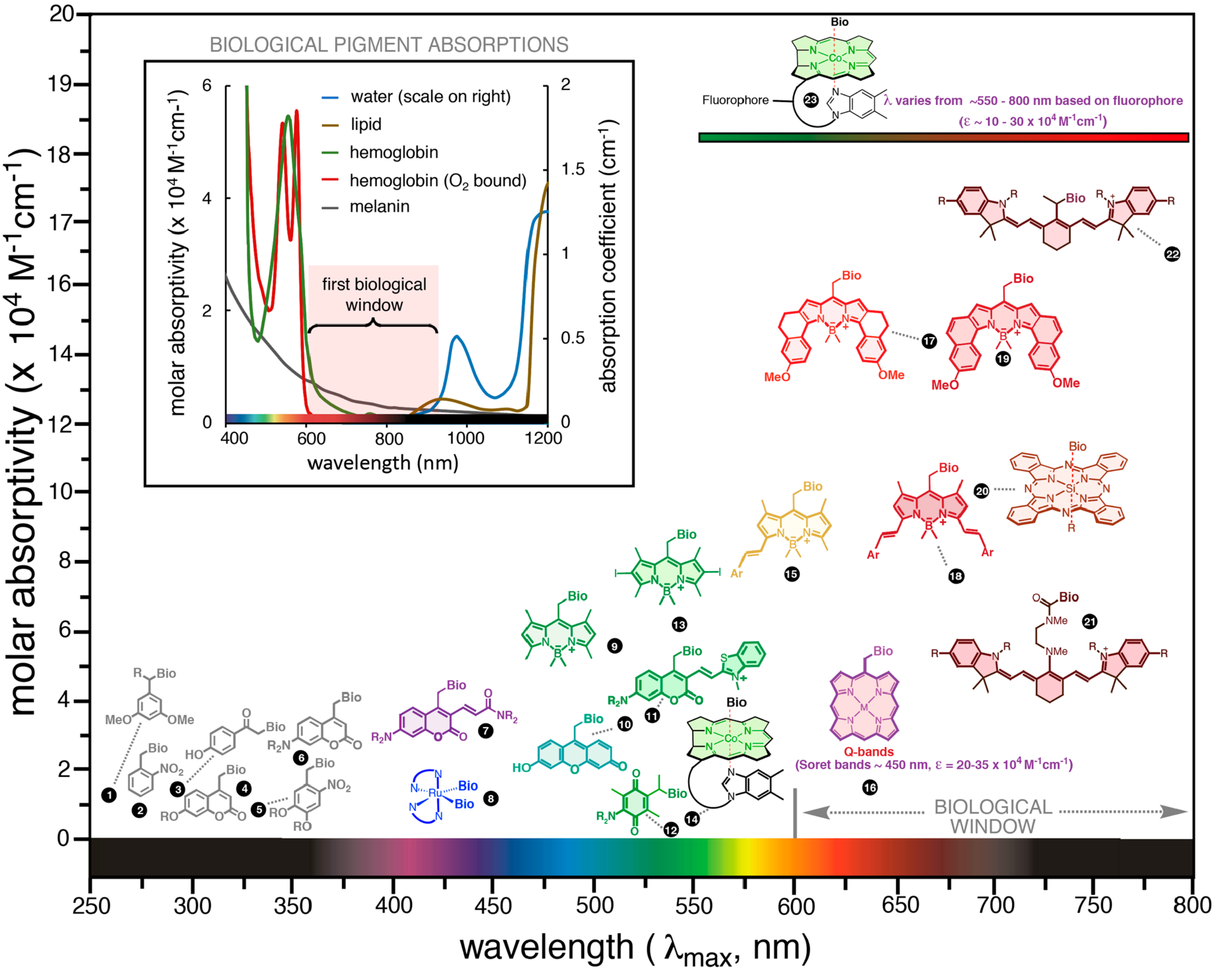


Figure 2. Absorption properties of select photocages (note: λ_{max} and ε sometimes vary by solvent or substitutions). Inset: Absorption properties of common biological pigments showing the location of the first mammalian biological window (hemoglobin and melanin use scale on left).

phototherapeutic applications of BODIPY PPGs that have been explored to date (Figure 1).

2. ABSORPTION PROPERTIES OF BODIPY PHOTOCAGES

One of the major appeals of repurposing BODIPY dyes as PPGs is the possibility to achieve red-shifted light absorption properties compared to most conventional PPGs, avoiding the requirement for photoexcitation with UV light. For other PPGs that natively absorb UV light, tremendous efforts over many decades have been undertaken to prepare derivatives with substituents that bathochromically shift the chromophore absorbances (Figure 2).[2,22] Among these, extended coumarins are notable,[23] such as DEAC$_{450}$[24] (**7** in Figure 2), which undergo photorelease by irradiation with ∼350−550 nm light. The xanthene photocages (**10** in Figure 2) were among the first organic photocages developed to absorb above 500 nm, but have not seen significant use, perhaps because they have not been obtained yet as pure substances.[25] Photocleavage of metal−ligand bonds have also been exploited, typically using ruthenium[17,26] or cobalt[27,28] as the metal center (e.g., **8** or **14** in Figure 2), providing the ability for photoactivation using visible light.

BODIPY PPGs are especially attractive for their ability to be activated by tunable wavelengths in the visible (Figure 3) or by long-wavelength light in the biological window (∼600−1000 nm). Indeed, decades of research to understand how the parent BODIPY structure can be modified to tune the absorbance for use as imaging/laser dyes has been exploited to prepare BODIPY PPGs that absorb across the visible (500−700 nm) by extending the conjugation.[33,34]

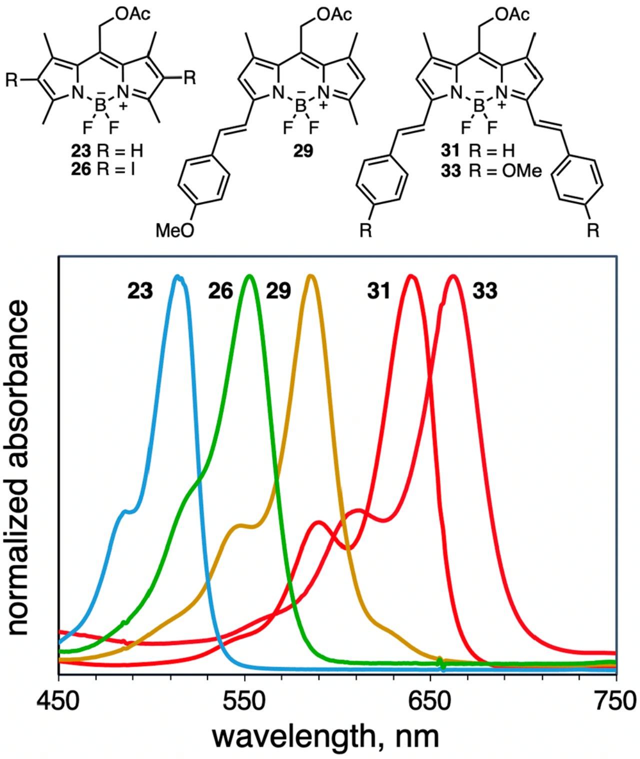


Figure 3. Normalized absorptions of representative BODIPY PPGs with varying conjugation.

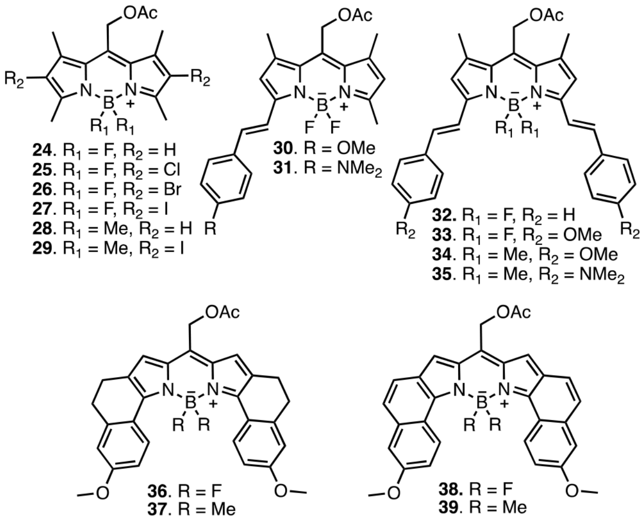
Specifically, the parent BODIPY PPG **24** absorbs at 517 nm. Dihalalogenation at the 2,6-positions red-shifts the absorbance up to 553 nm for iodination. Monostyryl derivatives **30** and **31** absorb yellow to red light (586 and 633 nm for the methoxyphenyl and dimethylaminophenyl derivatives, respectively). Distyryl derivatives **32−35** are further red-shifted, up to 689 nm for **35**. In general, B-methylation, a common strategy to improve the photorelease quantum yield, blue-shifts the absorbance by 5−30 nm compared to B-fluorinated derivatives. The ring-fused conformationally restrained BODIPY PPGs **36−39** absorb far-red to near-IR light, with **38** absorbing the longest wavelength light at 708 nm. Extinction coefficients are generally 45 000−140 000 M^{-1} cm^{-1}, with longer-wavelength absorbing derivatives generally featuring higher extinction coefficients, although as is generally true of BODIPY dyes, the extinction coefficients are strongly solvent dependent (typically larger in DCM than water, for example).

PPGs that operate by single photon absorption at such long wavelengths are scarce.[2,35] Others include dye-sensitized cobalamine PPGs (**23** in Figure 2),[28] which are believed to operate via a dye-sensitized photoinduced electron transfer from the dye to cobalt (λ_{irr} = 550 to 800 nm, depending on the fluorophore), resulting in homolytic scission of the Co−C bond. H atom abstraction by the released leaving group radical then provides the free ligand. Such structures are exquisitely photosensitive, among the most photosensitive structures known, with impressive quantum yields of ∼0.1−0.4 for dye-sensitized photolysis depending on the derivative.[28] Because cobalamin itself is not cell-permeable, and the linked biomolecule or drug typically remains active in the "caged" form, these PPGs typically require a carrier (e.g., red blood cell[36]) for biological photoactivation.[36,37] In related work, it was shown that irradiating the Q-bands of silicon phthalocyanines can homolytically release ligands at far-red wavelengths (**20** in Figure 2, λ_{irr} ∼ 675 nm).[38] Another class of PPGs are cyanine-based PPGs that exploit singlet-oxygen mediated cascades,[39] which operate by oxidative cleavage of the PPG by $^1O_2$, resulting in thermal reaction cascades that lead to substrate release(**21**, **22** in Figure 2). These cyanine-derived PPGs feature an exceptionally powerful light-absorbing chromophore, and one cyanine dye (indocyanine green) has been clinically approved for fluorescence-guided surgeries, suggesting the possibility for clinical application. More recently, it was shown that irradiating porphyrin PPGs (**16** in Figure 2) can photorelease substrates using red wavelengths (up to 640 nm).[40] During revisions of this Perspective, a report on a highly promising class of visible light absorbing xanthenium PPG platform was also published.[41] Nevertheless, for a simple organic photocage that retains the "plug-and-play" simplicity of the nitrobenzyl photocages, that requires no carrier to cross the cell membrane, that works both in the presence and absence of oxygen, but that strongly absorbs single photons of 600−700 nm light, BODIPY photocages such as **17−19** (Figure 2) represent an exceptionally attractive PPG platform.

3. MECHANISM

The precise mechanism of photorelease from *meso*-methyl BODIPY photocages remains unknown, although several observations suggest a simple photo-S$_N$1 type mechanism. Evidence for a photo-S$_N$1 mechanism includes that an isolated byproduct of the BODIPY photocage is the solvolysis product[42] (e.g., the methyl ether in MeOH solvent and the alcohol in water) and that there is insufficient light energy to match the bond dissociation energy of a C−O bond, making an initial homolytic step to generate a radical pair energetically unlikely. For example, some BODIPY PPGs absorb at >700 nm (Table 1),[30,32] which provides ~40 kcal/mol of photon energy, smaller than the energy required to homolytically cleave typical C−O bonds (e.g., 92 kcal/mol bond dissociation energy for CH_3−OC(O)H[43]). Additionally, the quality of the leaving group perturbs the photoreaction quantum yield (Φ_r), with better leaving groups (e.g., Cl) generally featuring higher quantum yields[44] than derivatives with poor leaving groups (e.g., OR),[45] which is consistent with a photo-S_N1 pathway. Given that the cation derived from the BODIPY is highly unstable, it is perhaps surprising that such a heterolysis mechanism should be operant at all. However, substrate preferences for photoreactions differ from ground-state reactions, and there is some evidence that cations that are unstable in the ground state may have lowered excited state barriers for formation and a favorable productive conical intersection along the excited state heterolysis coordinate (Figure 4).[46] An underappreciated practical benefit of such an unstable cation is that the BODIPY C-LG bond is thermally stable in the dark, which is a necessary requirement for any useful PPG.

Table 1. Absorption Properties of Representative BODIPY PPGs



PPG	λ_{abs}, nm	λ_{em}, nm	Φ_r^{aer}	ε ($\times10^4$) M^{-1} cm^{-1}	$\Phi_r\varepsilon$ M^{-1} cm^{-1}	ref
24	517	529	0.0014	7.1	99	29
25	544	562	0.0029	4.8	139	29
26	545	565	0.0070	5.6	392	29
27	553	575	0.0099	4.9	485	29
28	512	550	0.055	6.9	3795	29
29	538	572	0.156	6.1	9516	29
30	586	607	0.000098	6.1	6	30
31	633	650	0.000069	6.0	4	30
32	640	656	0.000045	6.5	3	30
33	661	684	0.000041	6.5	3	30
34	647	660	0.00084	4.9	41	30
35	689	728	0.0011	7.8	86	30
36	672	695	0.0014	13.3	186	32
37	641	663	0.027	13.9	3753	32
38	708	735	0.0005	10.8	53	32
39	681	708	0.0375	12.4	4650	32

Initial mechanistic studies[44,47] indicate that photorelease can occur on either the singlet or triplet excited state surface. For example, photorelease can be initiated by triplet sensitization, demonstrating that the triplet state is a photoreactive state. Using $Ru(bpy)_3]Cl_2$ as a triplet sensitizer, an efficient photorelease from the BODIPY derivative **41** is observed (Table 2). Furthermore, appending heavy atoms (e.g., I or Br) to the BODIPY core (**42**, **43**) increases the photoreaction quantum yield by accelerating intersystem crossing.

Involvement of the excited singlet state in the release process has thus far been inferred. The photoreaction quantum yield for **41** is 0.20 under inert atmosphere, while the photoreaction quantum yield in the presence of oxygen (Φ_r^{aer}) is 0.09.[44] Assuming that oxygen fully quenches the triplet state, the upper limit of the quantum yield of release from the singlet state (Φ_r^S) is then 0.11. Indeed, for a range of BODIPY photocaging structures, quantum yields in air were found to be roughly half the quantum yield determined under inert gas. This observation suggests that both singlet and triplet excited states are photoreactive states.

A postulated mechanism is depicted in Figure 4, with photorelease from either the singlet state or the triplet state (**II** and **V**) to generate a singlet cation or a triplet cation intermediate (**III** and **VI**). A puzzling observation is that the BODIPY cation is computed by density functional theory (DFT) to have a triplet ground state,[30,42] yet an isolated product is the solvolysis product (**IV**).[47] The reactivity patterns of triplet carbocations is unclear, but generally triplet species react via H atom abstractions rather than nucleophilic additions.[48,49] Furthermore, photoheterolysis from the excited triplet state of the BODIPY would provide the triplet cation irrespective of the ground state to preserve spin. However, the singlet and triplet states of the cation are computed to be close in energy and may be in equilibrium, with solvent addition occurring with the singlet cation.[47] On the other hand, the carbocation has not been directly detected, so whether the singlet carbocation is truly a discrete intermediate or a transition structure for solvent addition remains unconfirmed. At this point, more work to elucidate the precise mechanism of these photoreactions is clearly needed.

4. STRUCTURE−PHOTOREACTIVITY STUDIES OF BODIPY PHOTOCAGES

A major consideration for any photocage is its sensitivity to light. Here, two parameters are important: (1) the photoreaction quantum yield (Φ_r), and (2) the extinction coefficient at the excitation wavelength (ε_{irr}). The product of these two parameters, called the quantum efficiency or cross-section ($\Phi_r\varepsilon_{irr}$), provides a quantitative measure of the photosensitivity of any reactive chromophore to light of a specific wavelength. The quantum efficiency is the best way to compare the photosensitivity of PPGs. PPGs with higher quantum efficiencies will generally have faster photoconversion times to achieve complete decaging, although other factors also impact bulk photoconversion time, such as the properties of the light source (wavelength, intensity), the photoreaction conditions (air or inert gas, the concentration of the PPG, presence of absence of quenchers) and if there is competitive light absorption by the PPG byproduct (which can act as an optical filter).

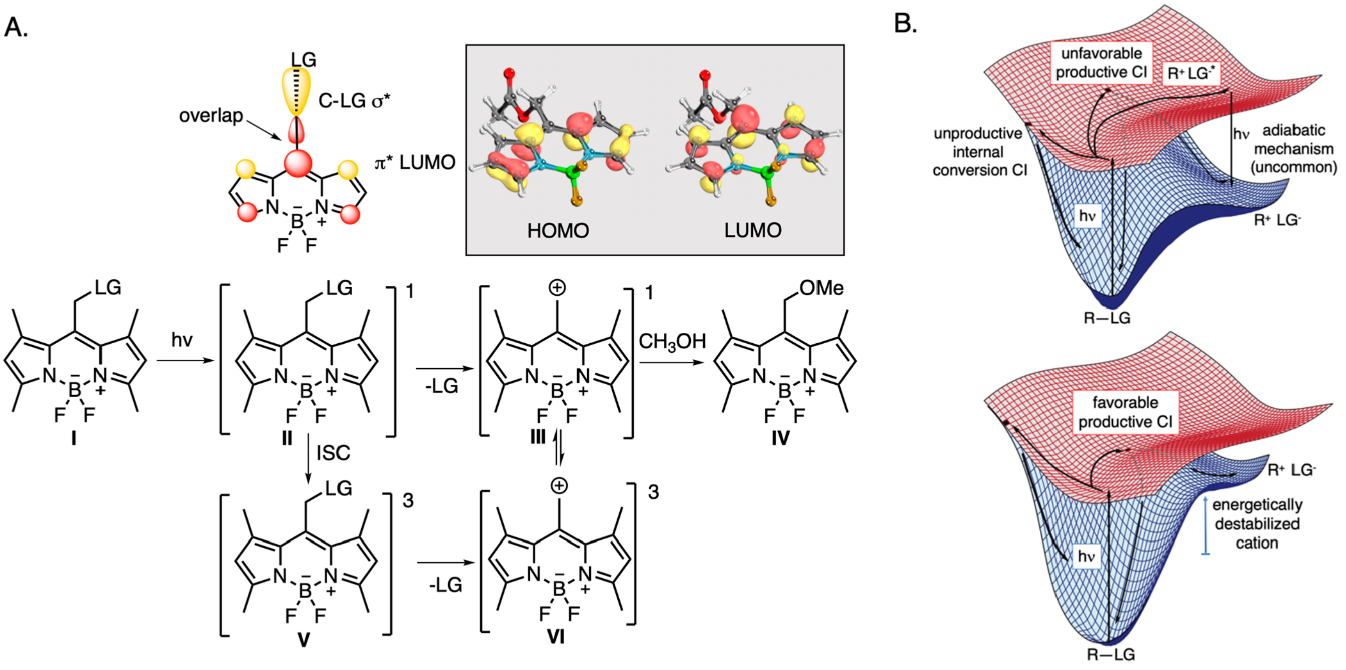


Figure 4. A. Top: HOMO and LUMO, with overlap of the LUMO with the C-LG σ^*. Bottom: Postulated mechanism of BODIPY photorelease. B. Singlet coordinate diagrams depicting how a destabilized cation could lead to a productive conical intersection (CI) along the excited-state heterolysis coordinate.

Table 2. Effect of Substitution of Heavy Atoms on the 2,6-Positions of BODIPY on Quantum Yields of Fluorescence (Φ_f), Intersystem Crossing (Φ_{ISC}), Photodegredation under Air (Φ_r^{aer}), and Photodegradation under Degassed Conditions (Φ_r^{inert}).[44]

	Φ_f	Φ_{ISC}	Φ_r^{aer}	Φ_r^{inert}
40 (X = H)	0.195	<0.05	0.016	0.024
41 (X = Cl)	0.167	0.121	0.095	0.203
42 (X = Br)	0.105	n.d.[a]	0.271	0.506
43 (X = I)	0.012	n.d.	0.445	0.805

[a] n.d. = not determined.

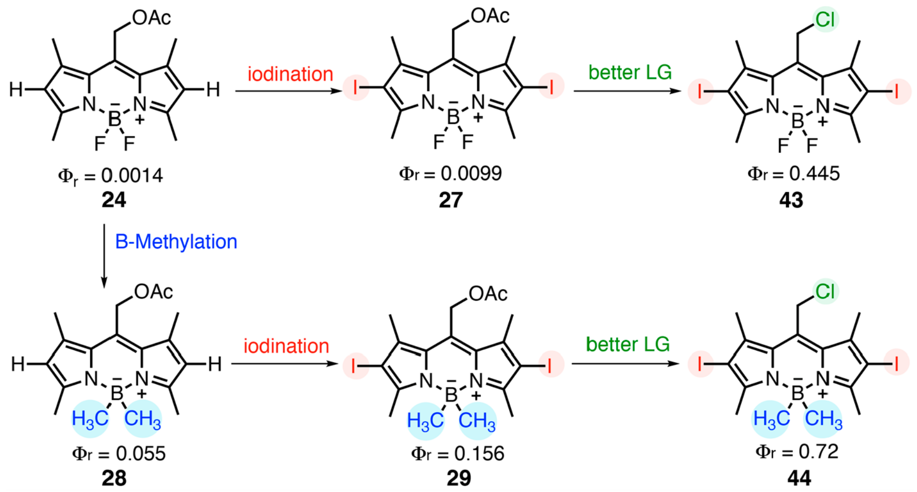
Starting with the absorption properties, BODIPY chromophores feature large extinction coefficients at the λ_{max} ($\varepsilon \sim$ 40 000−150 000 M^{-1} cm^{-1}, see section 2).[33] These values compare favorably with the conventional UV-absorbing PPGs such as *o*-nitrobenzyls ($\varepsilon < 20\,000$ M^{-1} cm^{-1}) and even the PPGs based on the coumarin dyes ($\varepsilon < 40\,000$ M^{-1} cm^{-1}).

On the other hand, the quantum yields measured for the first-generation of *meso*-methyl BODIPY PPGs are low (e.g., $\Phi_r < 0.01$),[47,50] although even in these cases the quantum efficiencies are still sufficiently large for biological studies ($\Phi_r\varepsilon_{irr}$ = 50−500 M^{-1} cm^{-1} for releasing AcOH) due to the high ε values. Nevertheless, efforts have been undertaken to modify the BODIPY structure to improve the quantum yields from the initially reported structures. For comparison purposes, all the quantum yields listed here were determined under air, noting that, in the cases that have been tested, the quantum yields are typically higher by a factor of ∼2 under inert atmosphere (oxygen can quench productive triplet excited states that would otherwise result in leaving group release). Additionally, some quantum yields represent photodegradation quantum yields (Φ_{deg} as measured by disappearance of starting material) while some represent photoreaction quantum yields (Φ_r, as measured by the appearance of the free photoreleased leaving group) leading to some variance in reported values. In principle, the two values should be the same but may differ if there are competitive photoreactions. Fortunately, side photoreactions for BODIPY PPGs are generally rare, with a few exceptions.[30,51]

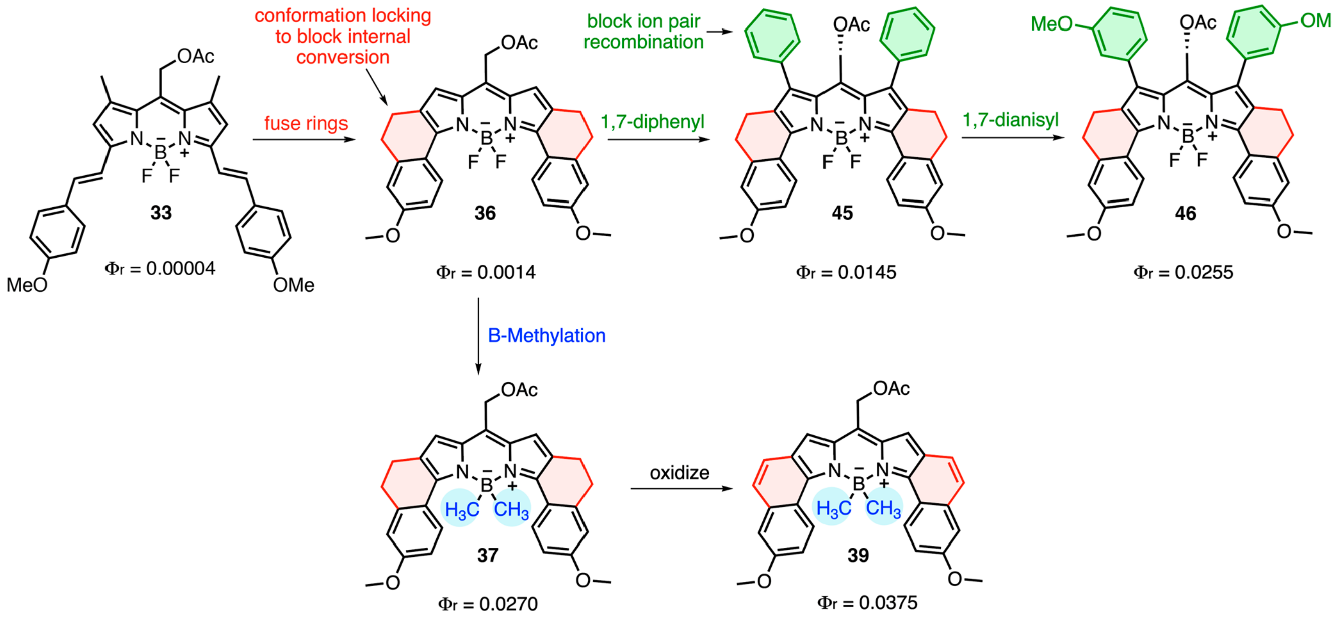
An early discovery was that iodination improves the quantum yield by nearly 1 order of magnitude by accelerating intersystem crossing via the heavy atom effect (see Table 2).[47] Triplet excited states are generally orders of magnitude longer-lived than singlet excited states,[48] so if the photocleavage rate constant is identical in both excited spin states, the quantum yield will be higher for BODIPY PPGs that preferentially populate the triplet excited state. Additionally, ion pair recombination on the triplet state is spin forbidden. It may well be the case that cleavage from the excited singlet state is faster than from the excited triplet state, but the overall quantum yield for PPGs that undergo an efficient ISC is higher due to a longer triplet lifetime and diminished ion pair recombination. Additionally, it has been found that BODIPY PPG derivatives bearing better leaving groups generally (although not always) have higher Φ_r,[44,51] which is expected from the postulated photo-S_N1 mechanism (see section 3). For example, photoreleasing alcohols using the better carbonate leaving group (which thermally loses CO_2 to make the alcohol) rather than the direct ether linkage is much more photochemically efficient.

A dramatic effect comes from switching the conventional BF_2 unit of the BODIPY to a BMe_2 unit. The “magic methyl” effect[52] is well-appreciated in drug discovery where adding a methyl group to a ligand can lead to unexpected increases in ligand binding affinity, but it is surprising that the photorelease

Scheme 1. Structure−Reactivity Relationships for Parent "Green-Absorbing" BODIPY Photocage



Scheme 2. Structure−Reactivity Relationships for "Red-Absorbing" BODIPY Photocage



quantum yields jump by more than 50-fold for the parent green-absorbing BODIPY photocage upon boron-methylation (Scheme 1).

This effect is also apparent for the red-absorbing derivatives, although it is less pronounced for the 1,7-diaryl derivatives (Scheme 2).[32] Likely, such a dramatic effect comes from the convergence of multiple factors. First, B-methylation appears to accelerate intersystem crossing, as observed by the ability of B-methylated BODIPY alcohol (**49** in Scheme 4) to generate $^1O_2$ upon irradiation. Accelerating ISC is a known strategy for achieving higher Φ_r values (as seen with the iodinated derivatives, for example).[44] Second, donating substituents attached to the BODIPY appear to lower the barrier for photorelease. Conversely, withdrawing groups raise the barrier. For example, substitution of the 2,6-positions of the BODIPY with electron-withdrawing sulfonate groups shuts down the photoreactivity of the BODIPY PPG.[53] Probably some combination of these three factors leads to the dramatic effect of B-methylation on the Φ_r values. This boron-substitution effect appears to be correlated with the σ-donating capacity of the substituent, as aryl rings and methoxy groups show diminished enhancements, while cyano groups slow the photorelease compared to the parent BF_2 derivative.[3]

The longer-wavelength absorbing photocages are inherently less photochemically efficient than the shorter-wavelength absorbing derivatives due to lower-energy excited states having shorter lifetimes from the energy gap law.[54] The first-prepared red/near-IR absorbing photocages,[30] achieved by appending styryl groups to the BODIPY (compound **28**), were the first examples of direct single-photon PPGs operating with red/near-IR wavelengths, but these structures featured very low quantum yields (e.g., $\Phi_r \leq 10^{-3}$, Scheme 2). A significant strategy undertaken to increase the quantum yields for these long wavelength-absorbing derivatives involves blocking unproductive light-wasting channels (see Figure 5) by hindering access to unproductive conical intersections (CIs). Passage through an unproductive CI returns the molecule to the ground state. For example, to minimize internal conversion, either from vibrational decay, through twisted internal charge transfer states (TICT), or by cis−trans

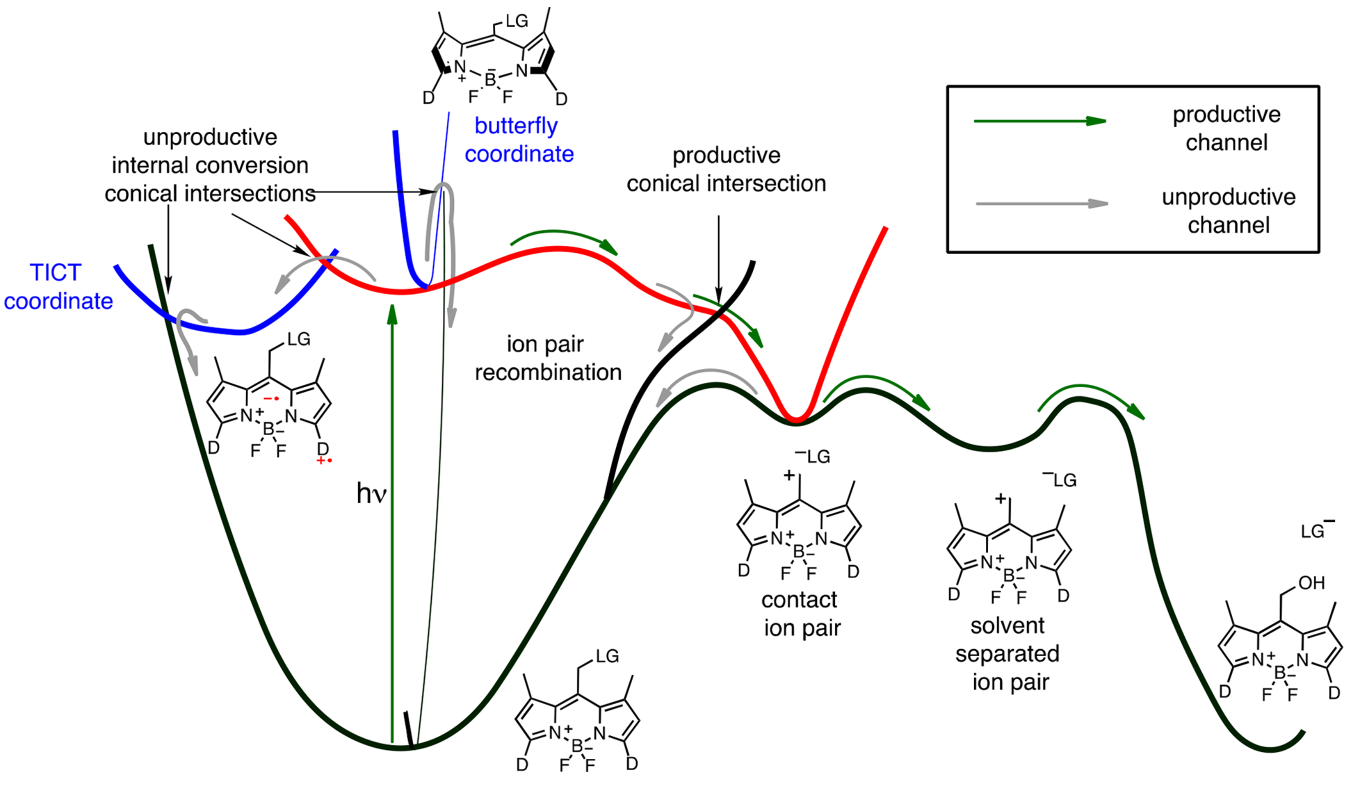
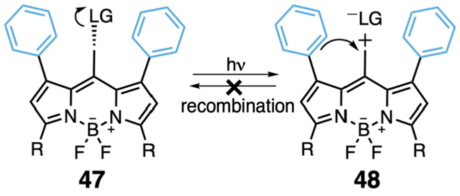


Figure 5. Approximate schematic of plausible singlet decay channels for distyryl BODIPY photocages.

photoisomerization of the styryl groups, more rigid ring-fused derivatives were prepared that were hypothesized to hinder access to these CIs.[32] In general, these derivatives feature much higher quantum yields than the styryl derivatives. The greater efficiency is currently thought to arise by blocking access to these competitive decay channels and lengthening the excited state lifetime.

Another strategy pursued to increase the quantum yield involves attempting to block ion pair recombination by adding adjacent internal nucleophiles (aryl groups) that can trap the nascent carbocation, blocking ion pair recombination and allowing cage escape (**47**, Scheme 3).[32] This strategy was also effective at increasing the quantum yield; however, in a case where the photoproducts were examined, the trapping product was the minor product while the major product remained the typical solvent trapping adduct, suggesting that other factors may also be at play in these derivatives that increase the quantum yield. Possibly, the steric bulk of the aryl rings also helps to increase the rate of photorelease or block ion pair recombination. Alternatively, the aryl rings may participate directly in the photoreaction mechanism. It is also possible that the Wheland intermediate (arenium ion) is trapped at the *meso*-methyl position by solvent, leading to the typical solvent adduct product rather than an intramolecularly trapped adduct. While these derivatives with adjacent aryl groups feature higher quantum yields, more detailed mechanistic work is needed to identify the cause of the photosensitivity improvement.

Scheme 3. Incorporation of Adjacent Internal Nucleophiles for Blocking Ion Pair Recombination

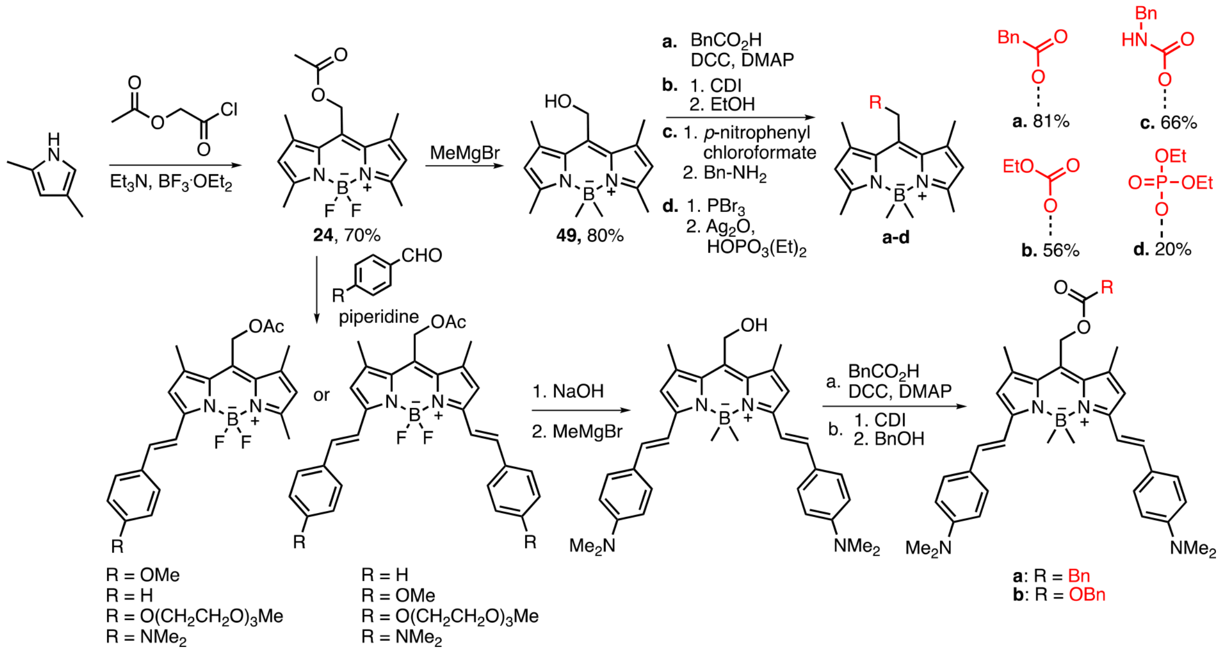


Scheme 2 shows the evolution of these improvements for derivatives absorbing >600 nm (e.g., red light). The starting bis(styryl) derivative **33** features a very low quantum yield ($\Phi_r \sim 10^{-5}$), while conformational locking (**36**) provides 2 orders of magnitude of improvement ($\Phi_r \sim 10^{-3}$). Further improvements can be made by adding adjacent 1,7-diaryl rings (**45**, **46**) with the more electron-rich ring (**46**) featuring the larger quantum yield of the two ($\Phi_r = 0.0255$). Alternatively, **36** can be boron-methylated to make **37**, which provides greater than 1 order of magnitude improvement ($\Phi_r = 0.0270$) and oxidation to make an even more rigid ring system **39** increases the Φ_r to the largest value for any red-light absorbing ($\Phi_r = 0.0375$).

5. SCOPE OF FUNCTIONAL GROUP CAGING

Caging of many of the key functional groups has been demonstrated for *meso*-methyl BODIPY photocages (see Figure 6).[44,51] These include carboxylic acids,[42,44] amines,[55−57] alcohols,[3,45,51] phenols,[45] thiols,[58] and phosphates.[59] Simple leaving groups generally have near-quantitative chemical yields of decaging, and quantum yields that depend loosely on leaving group quality, with better leaving groups typically having higher quantum yields. For this reason, caging alcohols via the carbonate is to be preferred over the direct caging via the ether. There is some evidence that larger leaving groups feature lower quantum yields than with simple leaving groups for the same photocage, possibly by the larger leaving group introducing competitive decay channels such as quenching mechanisms or by accelerating internal conversion by adding new vibrational modes.[60] Photorelease of amines has been accomplished using

Scheme 4. Synthetic Scheme for BODIPY Photocages



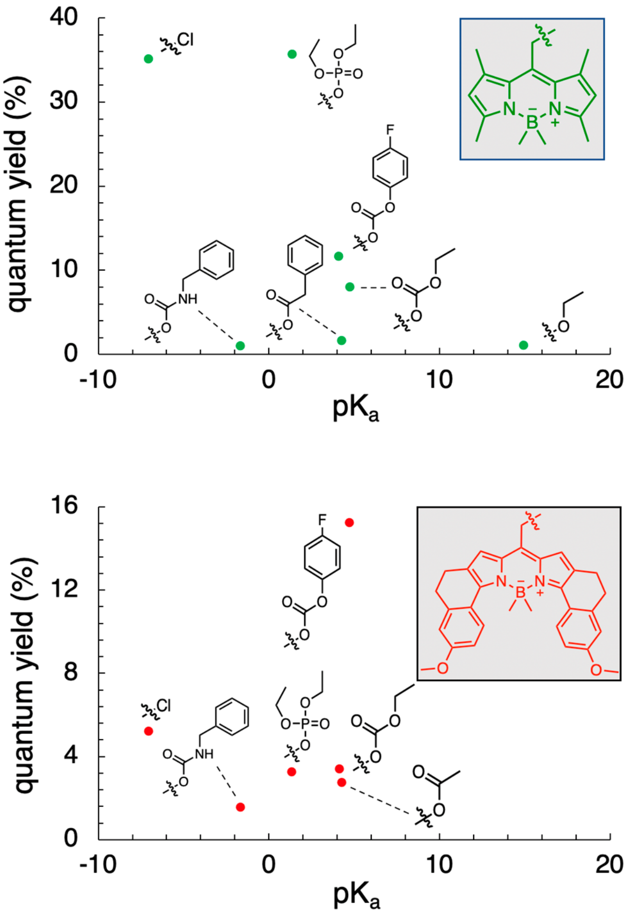


Figure 6. Photorelease quantum yields for different functional groups using a green-light- and red-light-absorbing BODIPY photocage.

a carbamate linker;[50,55,56,61] in contrast, direct photorelease of an amine has not been demonstrated. With benzyl amine caged as the carbamate, concomitantly generated singlet oxygen from the photocages reacts with the released amine, leading to lower chemical yields and apparent quantum yields.[51] However, irradiations conducted under inert atmosphere restores high quantum and chemical yields. It is presently unclear if this photo-oxidation of amines represents a general challenge for caging amines with BODIPY PPGs or if benzylamine is a special case that happens to be especially susceptible to oxidation by $^1O_2$.

6. WAVELENGTH-SELECTIVE CONTROL OVER MIXTURES

The ability to separate the absorptions of BODIPY photocages across the visible light spectrum has enabled wavelength-selective control over mixtures of photocaged species. It is possible to accomplish wavelength-selective photocleavage of UV-absorbing PPGs,[62,63] but the task is made difficult because it is hard to sufficiently separate the absorptions to enable selective photoexcitation. As proof of concept, a mixed solution of three photocages, a red-absorbing photocage, a green-absorbing photocage, and a UV-absorbing coumarin photocage, could be sequentially reacted by single-color LED irradiations using red light, green light, and then far-UV light (Figure 7).[63] Pairs of photocages could also be reacted, with complete selectivity for reacting the longer-wavelength absorbing species and some selectivity for reacting the lower-wavelength absorbing species.[63] Figure 8 shows that a green-absorbing BODIPY PPG and a UV-absorbing coumarin photocage could be selectively excited using either green or UV LED irradiation as well as pairs of green- and red-absorbing BODIPY PPGs.

Synthesis of BODIPY Photocages. The synthesis of BODIPY photocages typically begins by reacting pyrroles with a leaving-group-substituted acid chloride (e.g., acetoxyacetyl chloride or chloroacetyl chloride)[33] (Scheme 4). Extended conjugation can be achieved by Knoevenagel reactions between the BODIPY methyl groups with aldehydes to make styryl-substituted BODIPY PPGs or by using tetralones to make conformationally constrained BODIPY PPGs with improved photosensitivities (Scheme 5). Different leaving

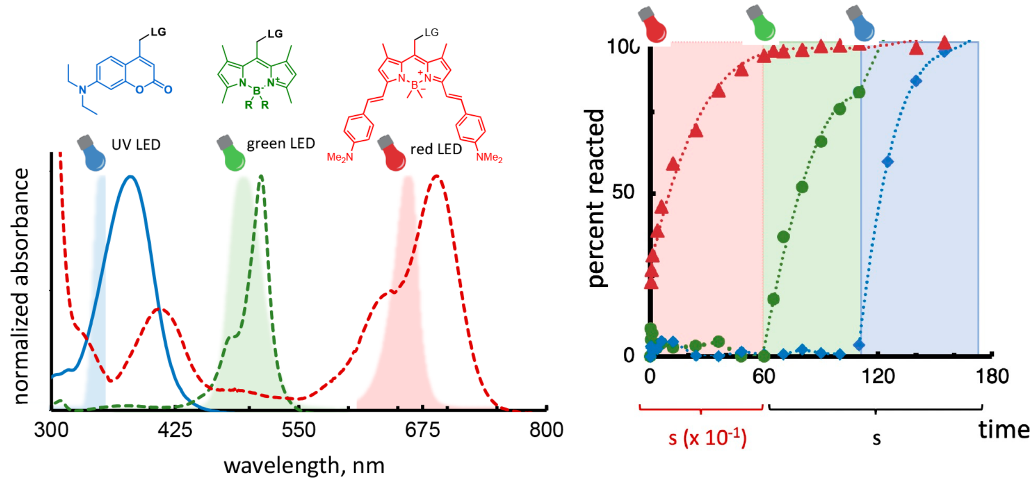


Figure 7. Left: Separated absorptions of a DEAC coumarin photocage and a green- and red-absorbing BODIPY photocage. Right: Sequential photolysis by irradiation with a red, green, and then UV LEDs.

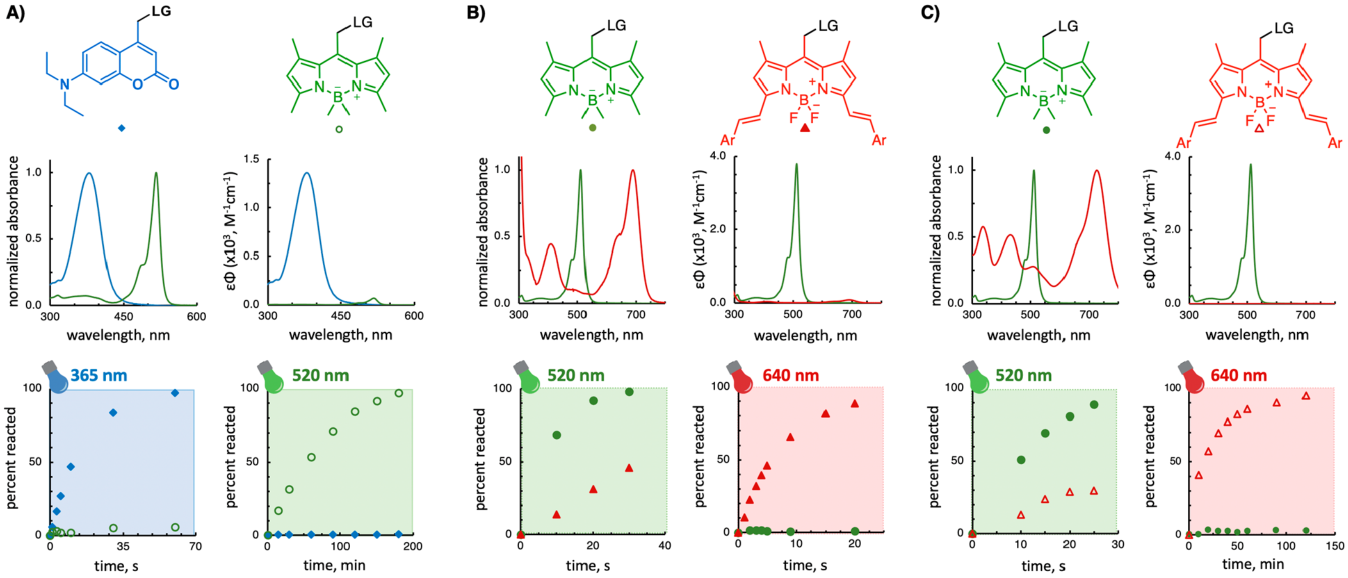


Figure 8. Pairs of photocages testing wavelength-selective reactivity using UV (360 nm, represented with blue), green (520 nm), and red (635 nm) LEDs. Complete selectivity for the longer-wavelength absorbing PPG is observed and some selectivity for the lower-wavelength PPG.

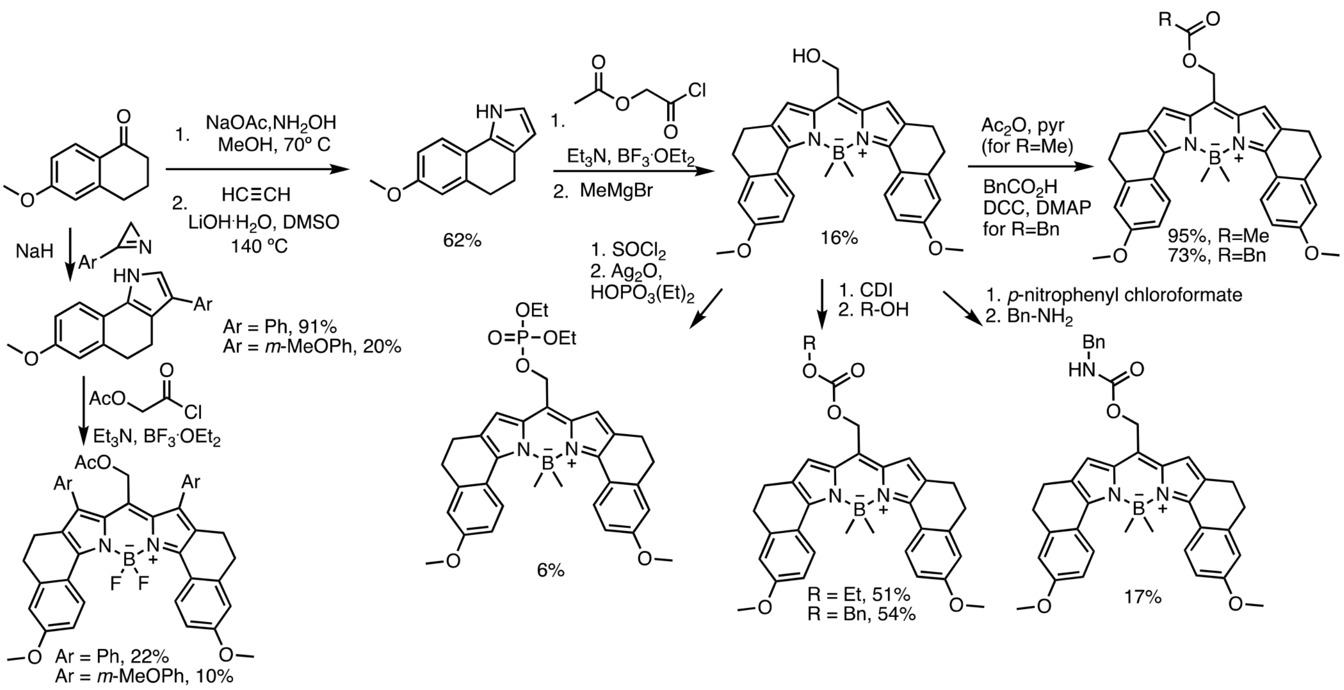
groups can be substituted using standard coupling reactions starting with the *meso*-methyl BODIPY alcohols (e.g., DCC couplings to make esters, CDI couplings to make carbonates, *p*-nitrophenyl carbonates to make carbamates).

Although the BODIPY chromophore can be sensitive to some harsh chemical conditions, *meso*-methyl BODIPYs were found to be sturdy enough to tolerate many common transformations. For example, strong bases and acids such as KOH, LiOH, K_2CO_3, and HCl were used to hydrolyze BODIPY acetyl and benzoyl esters to *meso*-methyl BODIPY alcohol.[32,45,57] Likewise, Grignard reagents were used to hydrolyze an acetyl group and swap BF_2 for BR_2 concomitantly.[30] Knoevenagel condensations were performed with piperidine.[30] PBr_3 was applied to transform an alcohol into bromide and silver oxide with a phosphate to attach phosphates at the *meso*-methyl position.[51] Oxidants such as DDQ are also tolerated.[32] NaH was used to deprotonate the OH group to generate a better nucleophile of the BODIPY *meso*-methyl alcohol that could then be further reacted.[45,61] Nevertheless, some unique synthetic challenges also exist. For example, nucleophilic attacks on an activated carbonate at the *meso*-methyl position in order to introduce an LG often result in complete displacement of the carbonate by the nucleophile.[55] In addition, the need to derivatize the BODIPY chromophore without affecting the photorelease process calls for the development and implementation of new synthetic strategies. An example for this is the functionalization of the ubiquitous 3,5-methyls to introduce various functional groups.[61]

7. APPLICATIONS OF *MESO*-METHYL BODIPY PPGS IN BIOLOGICAL SETTINGS

One of the main contemporary applications of PPGs is in biological studies.[17,64,65] As a result, photorelease from *meso*-methyl BODIPY derivatives was examined and demonstrated in various biological settings, mostly in cultured cells; they are summarized in Table 3. Photorelease of 4-nitro- or 2,4-dinitrobenzoic acid from **54a** or from the *π*-extended derivatives **55b** and **56a** to unquench the fluorescence emission of the *meso*-methyl BODIPY chromophore was

Scheme 5. Synthetic Scheme for Conformationally-Constrained Far-Red Absorbing BODIPY Photocages



utilized to demonstrate the PPGs functionality in cell cultures.[30,32,47]

The photorelease of signaling molecules has also been explored to provide spatiotemporal control over their activation. For example, dopamine was photoreleased with green light (λ_{irr} = 540 nm) from **54c** and **54e** in cultured neurons to evoke intracellular calcium oscillations[53,57] and with red light (λ_{irr} = 652 nm) from **55a** to manipulate the contractions of spontaneously beating human embryonic stem cells (hESC) derived cardiomyocytes.[56] Nevertheless, faster photolysis conditions should be sought in order to be relevant for the fast processes in which dopamine is involved.[66] Histamine was released from **54d**, leading to calcium oscillations inside the cells that were monitored by a fluorescent probe (fura-2).[53] Spatial control over the photoactivation in select cells was demonstrated. Signaling lipids such as sphingosine and oleate were also photoreleased with green and red light (λ = 542 nm from **54e** and λ_{irr} = 633 nm from **55c**, respectively) in cultured cells. In these cases, the high hydrophobicity of the combined PPG and LG required the use of sulfonated *meso*-methyl BODIPY derivatives in order to achieve sufficient water solubility for application in cellular environment.

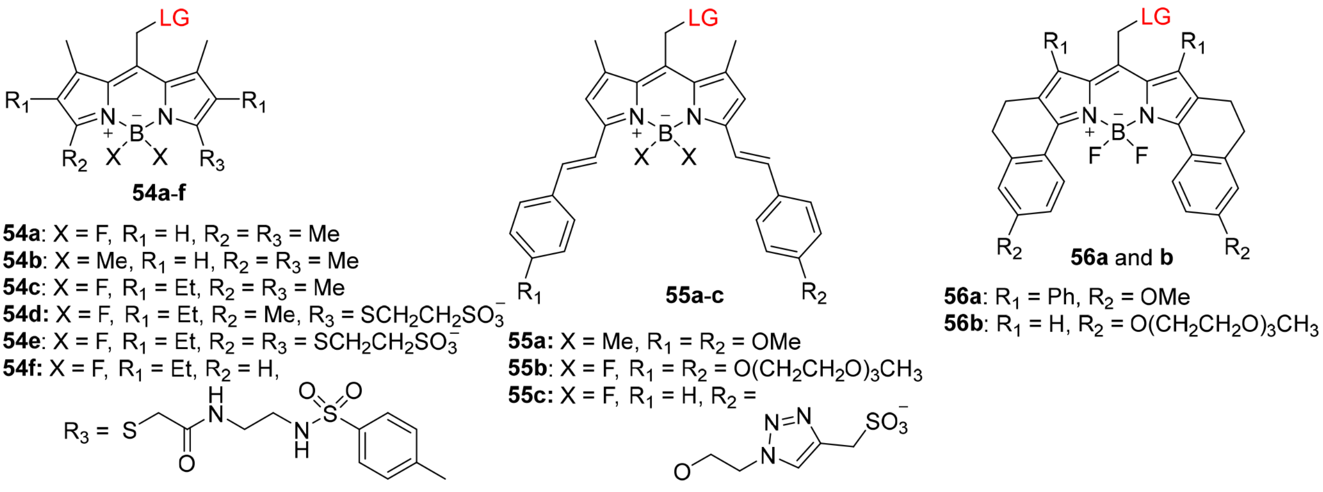
Photorelease of therapeutic agents is another area in which the use of PPGs is gaining traction, especially when it comes to activation using visible or near-infrared (NIR) light.[17,65] The cysteine protease cathepsin B (CTSB) inhibitor CA-074 was released from **54b** using blue light (λ_{irr} = 465 nm), leading to rapid necrotic response in MDA-MB-231 triple negative breast cancer cells with high phototherapeutic indexes (>30) and selectivity vs noncancerous cells.[60] Chlorambucil, a chemotherapeutic agent in clinical use, was released in HeLa cells upon irradiation of **54c** with green light (λ_{irr} = 550 nm), resulting in significant cytotoxicity compared to a nonirradiated control.[67] In both examples, singlet oxygen production was found to contribute to the overall cytotoxicity. Ciprofloxacin, a fluoroquinolone antibiotic, was released from **54a** using green light (λ_{irr} = 520 nm) and from **56b** using red light (λ_{irr} = 625 nm).[68] Both compounds showed light-dependent toxicity against a fluoroquinolone-susceptible *E. coli* strain in culture.

Given the challenges of direct administration of gasotransmitters such as nitric oxide (NO), hydrogen sulfide (H_2S), and hydrogen monoxide (CO), the use of light for their controlled release has received significant attention.[64] In the context of *meso*-methyl BODIPY PPGs, the light-mediated generation of NO was achieved by photorelease of *N*-nitroso-*N*-phenylhydroxylamine (cupferron), which subsequently decomposes to generate NO, from **54a** using green light (λ_{irr} = 535 nm).[69,70] The compound was applied to provide temporal control over the NO-stimulated vasodilation of rat aorta.[69] Photorelease of carbonyl sulfide (COS) was used for indirect generation of H_2S. In turn, COS is enzymatically converted into H_2S via carbonic anhydrase, a ubiquitous enzyme found in many mammalian tissues. The photogeneration of H_2S from **55b** by red light (λ_{irr} = 700 nm) was confirmed in cultured cells using a fluorogenic H_2S probe (SF7-AM).[71] Functionalized derivatives of *meso*-methyl BODIPY enabled their targeting to specific cellular organelles such as the endoplasmic reticulum (ER), mitochondria, or lysosomes.[61] For example, **54f** was applied to inhibit protein synthesis specifically in the ER via localized photorelease (λ_{irr} = 545 nm) of puromycin.

Nevertheless, the BODIPY chromophore is inherently highly hydrophobic, a property that can severely limit the potential concentration and thus utility in water-based solutions. Several strategies have been reported for increasing the water solubility of the BODIPY chromophore, including modifications at the boron center, the 2,6-, 3,5-, or 8-*meso* position(s) using quaternary ammonium salts,[73,74] sulfonates,[73,75] phosphonates,[76] carbohydrates,[77] amides,[78] zwitterions moieties,[79] or oligo(ethylene glycol) moieties,[73,80] or alternatively, formation of water-soluble nanoparticles via polymer encapsulation or host−guest interactions.[81]

Table 3. Biological Applications of *meso*-Methyl BODIPY PPGs

***Meso*-methyl BODIPY PPG derivatives**

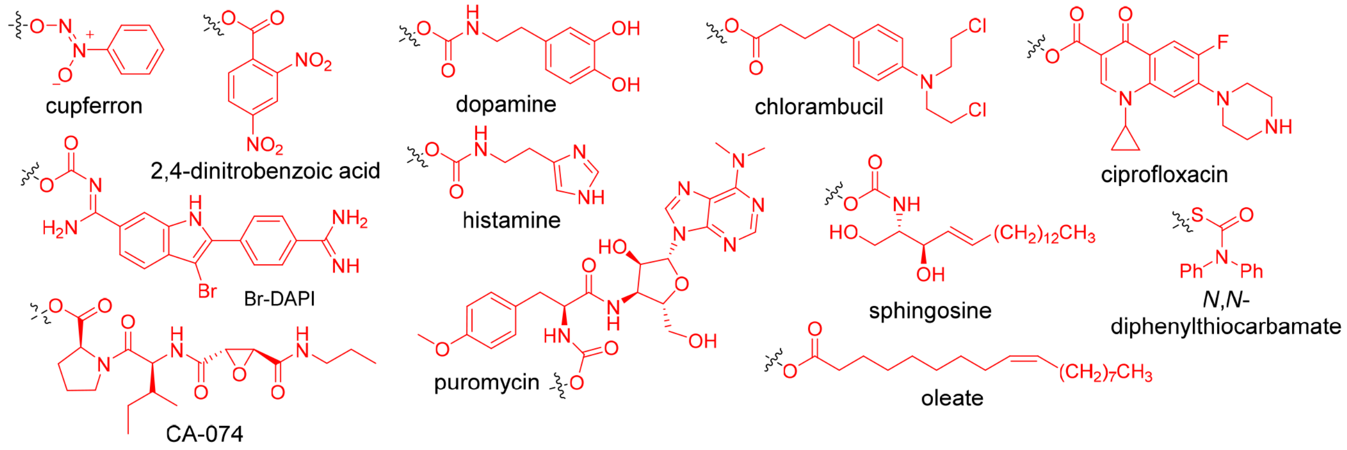


54a: X = F, R_1 = H, R_2 = R_3 = Me
54b: X = Me, R_1 = H, R_2 = R_3 = Me
54c: X = F, R_1 = Et, R_2 = R_3 = Me
54d: X = F, R_1 = Et, R_2 = Me, R_3 = $SCH_2CH_2SO_3^-$
54e: X = F, R_1 = Et, R_2 = R_3 = $SCH_2CH_2SO_3^-$
54f: X = F, R_1 = Et, R_2 = H,

55a: X = Me, R_1 = R_2 = OMe
55b: X = F, R_1 = R_2 = $O(CH_2CH_2O)_3CH_3$
55c: X = F, R_1 = H, R_2 =

56a: R_1 = Ph, R_2 = OMe
56b: R_1 = H, R_2 = $O(CH_2CH_2O)_3CH_3$

Leaving groups released

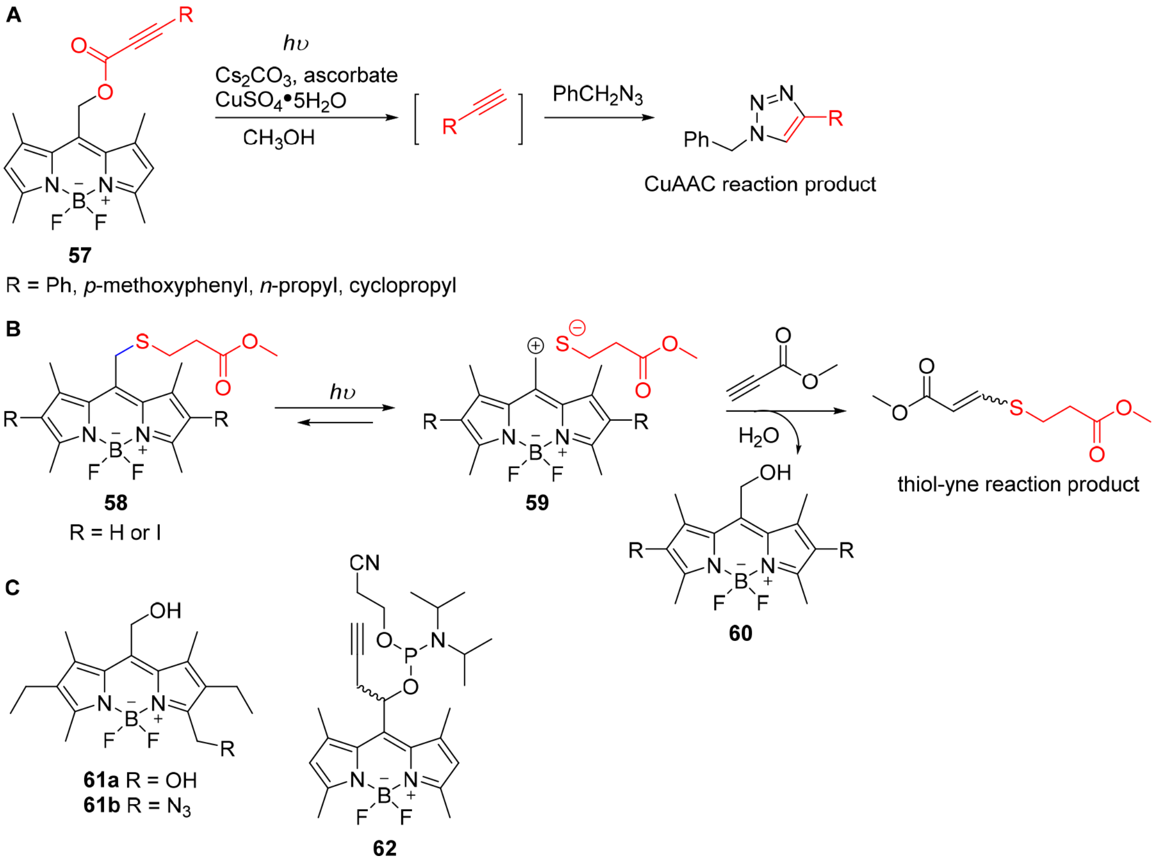


PPG	LG	photolysis parameters	setup	ref
54a	cupferron (NO)	LED lamp, 535/20 nm, 6.5 mW cm^{-2}, 1−3 min	vasodilatation of rat aorta	69,70
	ciprofloxacin	100 W LED lamp, 520 nm, 1 h	*E. coli* (ATCC 25922)	68
	2,4-dinitrobenzoic acid	mercury lamp, 500 nm	S2 cells	47
54b	CA-074[a]	LED lamp, 465/5 nm, 15 min	MDA-MB-231 breast cancer cells	60
	Br-DAPI[b]	mercury lamp, 480 nm, 20 min	MCF7 tumor spheroids	72
54c	dopamine	confocal lamp, 542/33 nm, 15 s	KCl-primed rat cortical and hippocampal neurons	57
	histamine	confocal lamp, 542/33 nm, 15 s	HeLa cells	57
	chlorambucil	50 W LED lamp, 550/10 nm, 15−60 min	HeLa cells	67
54d	histamine	confocal lamp, 542/33 nm, 10 s	HeLa cells	53
54e	sphingosine	confocal lamp, 542/33 nm, 10 s	HeLa cells	53
	dopamine	confocal lamp, 542/33 nm, 10 s	KCl-primed rat cortical and hippocampal neurons	53
54f	puromycin	LED lamp, 545/30 nm, 42 mW cm^{-2}, 5 min	HeLa cells	61
55a	dopamine	652 nm, 4 min	hESC-derived cardiomyocytes	56
55b	*N*,*N*-diphenylthiocarbamate (H_2S)	700/30 nm, 30−120 min	HepG2 cells	71
	4-nitrobenzoic acid	mercury lamp, 635/15 nm, 4−12 min	HeLa, GM07373, and S2 cells	30
55c	oleate	confocal laser, 633 nm, 75 s	GPR40-expressing HeLa cells	31
56a	4-nitrobenzoic acid	mercury lamp, 635/15 nm, 3 min	HeLa cells	32
56b	ciprofloxacin	50 W LED lamp, 625 nm, 1 h	*E. coli* (ATCC 25922)	68

[a] A cysteine protease cathepsin B (CTSB) inhibitor. [b] A DNA-binding PDT agent.

In the context of BODIPY as a PPG, only a limited number of these approaches have been explored so far. Mono- or disulfonation at the 2,6-positions was shown to impart water solubility on a simple BODIPY PPG derivative but resulted in complete loss of photorelease activity, presumably due to the electron-withdrawing effect of the sulfonates at these positions (see section 4).[53] In comparison, introduction of one or two sulfonate groups through a linker on the 3,5-methyls (**54d**,**e**)

Scheme 6. Structures of *meso*-Methyl BODIPY Derivatives Releasing Various Reactive Intermediates Such as (A) alkyne (57) or (B) thiols (58). (C) Structures of *meso*-Methyl BODIPY Derivatives Incorporated into Polymers (61) or Oligonucleotides (62)

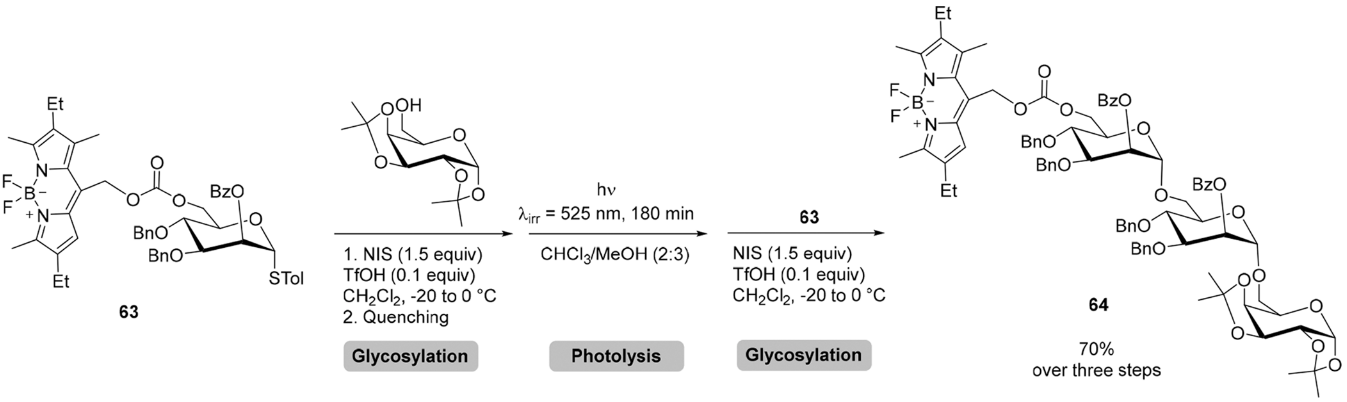


did not affect photorelease properties. Derivatives of compound **54d** bearing different leaving groups showed high water solubility and were able to penetrate into and accumulate inside cultured mammalian cells. Derivatives of compound **54e** were fully water-soluble (tested at 20 μM) but were completely cell-impermeable.[53]

Sulfonates were also effective for improving the water solubility of larger, more hydrophobic red-shifted BODIPY derivatives; compound **55c**, with one appended sulfonate, showed higher water solubility compared to **54a**, which lack any sulfonates, while compound **54b** was completely water-soluble at concentrations up to 1 mM.[31] However, when the acetate LG in **54a−c** was replaced with oleic acid, the disulfonated derivative was found to be amphiphilic, with low water solubility (~10 μM) and a high tendency to aggregate.[31] In comparison, the monosulfonated derivative was soluble in pure water at concentrations of up to 0.5 M. Thus, the chemical and physical properties of the leaving group contribute to the water solubility of the overall molecule and therefore should be additionally considered ad hoc. Short oligo(ethylene glycol) moieties appended to the boron center were found to improve the water solubility of a simple *meso*-methyl BODIPY derivative compared to its fluorinated version (**54a**,**b**).[71] In accordance, their installation on the chromophores of π-extended derivatives (**54a−c**) was also found to be effective in improving their water solubility.[30,68,71] The neutral charge of the oligo(ethylene glycol) moiety has the advantage of not affecting the cellular permeability of the compound. Clearly, the challenge of rendering *meso*-methyl BODIPY PPGs water-soluble is critical for their successful use in biological environments, yet so far it has only been narrowly addressed. Thus, more research should be directed toward providing solutions to the critical challenge of providing water solubility without compromising cellular permeability and photorelease efficiency.

Characteristically, the capacity of unmodified BODIPY derivatives to generate singlet oxygen is quite low but can be increased through the introduction of heavy atoms (e.g., Br, I) into the chromophore, typically at the 2,6-positions.[82] In accord, unmodified *meso*-methyl BODIPY derivatives were found to generate singlet oxygen at low yields in response to light irradiation but at higher yields when heavy atoms were introduced.[70] Interestingly, alkylation of the boron, originally introduced to increase photorelease quantum yield,[83] was also found to significantly increase singlet oxygen generation.[60] For example, B-methylated alcohol **40** (Scheme 4) was found to be 1.5-times more effective as a photosensitizer than the commonly used singlet oxygen sensitizer methylene blue.[60] In addition, it should be noted that the use of a poor LG (e.g., OH, aniline) seems to increase the photoactivity through the triplet state, resulting in increased generation of singlet oxygen.[84] Although singlet oxygen generation is not desired in many research applications, this phenomenon could be utilized to combine drug release with photodynamic therapy.[60,70,72,85] Thus, exploring additional strategies to increase singlet oxygen generation from *meso*-methyl BODIPY PPGs while retaining efficient photorelease could be of significant value.

Scheme 7. Structure of a Glycan Building Block (63) Protected by a *meso*-Methyl BODIPY Derivative Utilized in an Oligosaccharide Synthesis



The choice of light source and irradiation conditions directly influences the efficiency, selectivity, and spatiotemporal resolution of the photodeprotection process, and they are especially important when utilized in a biological environment, such as cultured cells. The wavelength emitted by the light source should match the absorption characteristics of the photoprotecting group as closely as possible to ensure effective and selective activation. This is especially important when orthogonal photolysis of multiple PPGs is attempted.[86] In that sense, visible light-activatable PPGs, such as *meso*-methyl BODIPY derivatives, are easy to match with many types of readily available diffused or focused illumination light sources (see Table 2). The choice between diffused and focused illumination is mainly dependent on the application, where focused illumination enables higher spatial resolution while diffused illumination typically provides higher throughput of leaving group release over comparatively larger surface areas. *meso*-Methyl BODIPY derivatives have been shown to be compatible with both illumination types (see Table 2). The light intensity (a function of power and irradiation time) should be sufficient to activate the photolysis process and provide an appropriate amount of the leaving group within a time frame compatible with the application. For example, the photorelease of cytotoxic compounds such as CA-074 within 15 min (see Table 2) is adequate for inducing cell death. On the other hand, although *meso*-methyl BODIPY derivatives were used to release neurotransmitters (see Table 2), flash photolysis in a milliseconds time scale, which is typically required in order to study immediate downstream effects of neurotransmitters, has not been demonstrated yet. It should be noted that the phototoxicity associated with visible light is often underestimated,[87] yet can compromise experimental setups by directly or indirectly affecting biological samples, including cultured cells.[88] Therefore, the intensity of the irradiated light should be minimized to prevent undesired photoinduced effects and, in any case, appropriate control experiments using only light should always be included. Despite their potentially favorable characteristics, the application of *meso*-methyl BODIPY derivatives has not yet been demonstrated *in vivo*. Nevertheless, a closely related BODIPY analogue was shown to release CO in living mice in response to irradiation with a broad-band halogen lamp,[89] suggesting that *meso*-methyl BODIPY derivative could be similarly photolyzed in vivo. Alternative light delivery technologies, such as biodegradable fiber optics[90] or implantable wireless devices,[91] may serve as substitutes to traditional external light sources for whole organism applications.

8. SYNTHETIC AND OTHER APPLICATIONS OF BODIPY PPGS

Spatiotemporally controlled photorelease of reactive species followed by tandem subsequent chemical reaction can significantly expand the applications of photochemistry in organic synthesis and materials engineering.[18,92] The photorelease of alkynoic acids from **57**, followed by efficient decarboxylation to give terminal alkynes, was applied to achieve light-mediated control over a CuI-catalyzed alkyne−azide cycloaddition (CuAAC) reaction (Scheme 6A).[93] The photorelease of thiols from derivatives of **58** was applied to control a thiol−yne click reaction (Scheme 6B).[58] The utility of this photochemical ligation was demonstrated by the fabrication of hydrogels with specific architectures for photoimmobilization of biomacromolecules and live cell encapsulation.[94] In a different approach, a *meso*-methyl BODIPY diol AA-type bifunctional monomer and a clickable, azide-functionalized AB-type heterobifunctional monomer were prepared (**61a** and **61b**, respectively, Scheme 6C). The BODIPY-based monomers were incorporated into water-soluble macromolecular systems, namely polyurethane hydrogels and a brush-like poly(organo)phosphazene, which were demonstrated to undergo selective cleavage in response to green light (λ_{irr} = 550 nm).[95] Photo-cross-linking/curing of hydrogels was achieved by BODIPY-caged amines that can cross-link with dialdehydes upon photorelease, which allows spatiotemporal control over gel stiffness.[96] An alkyne-functionalized *meso*-methyl BODIPY phosphoramidite derivative (**62**, Scheme 6D) was developed as a 5′-cap and incorporated in oligonucleotides via solid-phase synthesis. A CuAAC reaction provided cyclic oligonucleotides that could be relinearized by irradiation with green light (λ_{irr} = 530 or 565 nm).[59] A comparable 5′-cap based on a coumarin derivative was demonstrated to cleave at a faster rate.

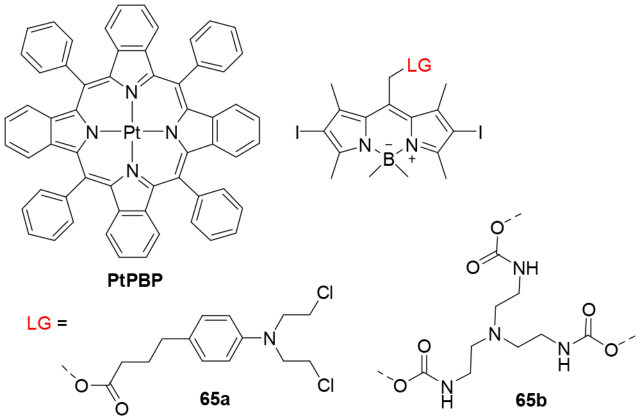
In another example, a set of *meso*-methyl BODIPY-protected glycan building blocks were synthesized and evaluated for their compatibility with glycan synthesis (Scheme 7).[3] The boron-fluorinated *meso*-methyl BODIPY derivative **63** was found to be stable under glycan synthesis conditions and was quantitatively photodeprotected with a green LED lamp (λ_{irr} = 525 nm) during the construction of an oligosaccharide. Finally, during revisions, a remarkable report of using BODIPY

PPGs to activate biomolecules (including peptides and proteins) under high vacuum conditions was reported.[97]

9. PHOTOSENSITIZED RELEASE FROM *MESO*-METHYL BODIPY PPGS

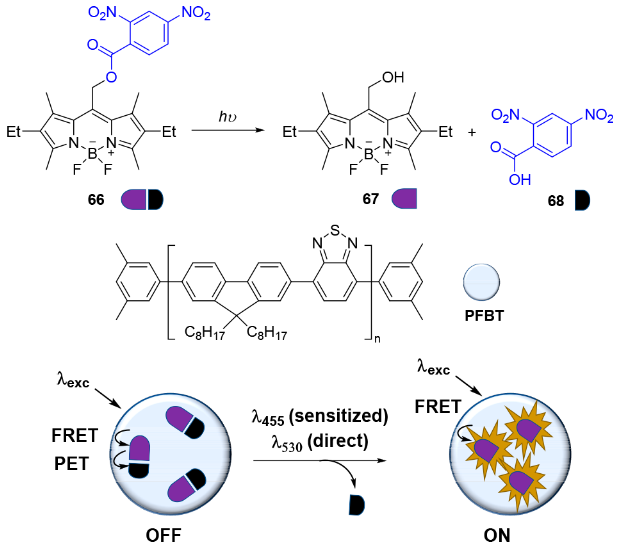
Photon upconversion provides an opportunity to carry out photochemical reactions at higher energies than those typically allowed by the absorption window.[98] For example, chlorambucil was released from *meso*-methyl BODIPY **65a** (Scheme 8) via photoexcitation (λ_{irr} = 625 nm) of the platinum(II) tetraphenyltetrabenzoporphyrin (PtTPBP) photosensitizer in organic solvents.[99] However, both molecules are hydrophobic and their energy transfer process was found to be sensitive to oxygen. To overcome these drawbacks, they were loaded in biocompatible, biodegradable polymeric micelles that were stable in aqueous solutions and protected the photolysis reaction from oxygen quenching.[100] In a closely related approach, the hydrophobic tri-*meso*-methyl BODIPY-protected compound **65b** was utilized as a trigonal building block[101] to assemble nanoparticles enclosing PtTPBP and paclitaxel.[102] Upon excitation of PtTPBP with red light (λ_{irr} = 635 nm), an upconversion-like photolysis process led to nanoparticle disassembly and drug release, resulting in antitumor activity both in vitro and in vivo.

Scheme 8. Structures of *meso*-Methyl BODIPY Derivatives Photolyzed via a One-Photon Upconversion Process



Fluorescence resonance energy transfer (FRET)-based sensitization is another way to manipulate photochemical processes.[103] *meso*-Methyl BODIPY **66**-doped conjugated polymer nanoparticles (CPNs) based on poly[(9,9-dioctylfluorenyl-2,7-diyl)-*co*-1,4-benzo-{2,1′,3}-thiadiazole] excited via the CPN-mediated FRET pathway (λ_{irr} = 455 nm) led to significant enhancement (>60 fold) in photorelease efficiency compared to that measured under direct excitation conditions (λ_{irr} = 530 nm)[104] (Scheme 9).

Scheme 9. Components of *meso*-Methyl BODIPY-Doped CPNs and Photolysis via Either Direct or Sensitized Irradiation



10. CONCLUSIONS

The future of BODIPYs as reactive chromophores for photocaging is bright. Although less than a decade old, they have been developed sufficiently to offer tunable absorption properties, high extinction coefficients, and good quantum yields. Furthermore, they offer the ability to synthetically attach leaving groups via a variety of functional group handles and use substituents on the BODIPY itself to tune its cellular permeability or direct the photocage to different subcellular compartments. Unlike the related photoswitches, photocaging experiments are irreversible, so applications where such an irreversible photoreaction is desired should be targeted. Looking to the future, although considerable progress has been made to improve upon the low quantum yields of the first-generation structures, next-generation derivatives with improved photosensitivities and further red-shifted absorbance profiles will almost certainly be synthesized. Additionally, pairs of photo-orthogonal photocages that can be addressed individually in cells with different wavelengths of light may soon become possible. Moreover, taking advantage of BODIPY derivatives with near-IR absorbing properties, the exciting prospect of using these chromophores as platforms for photocaging experiments in animals and as phototherapeutics will require them to be tested first in animal models rather than just in cultured cells. Here, a variety of possibilities may be explored, such as photocaging therapeutics directly as light-activated prodrugs or using them as gates for opening channels in different chemical delivery systems (e.g., mesoporous silica, liposomes). Finally, their use as synthetic protecting groups for glycan synthesis, as well as their use in light-responsive materials, such as in light-cleavable hydrogels, demonstrates that their use is not limited to biological experiments.

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Notes

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