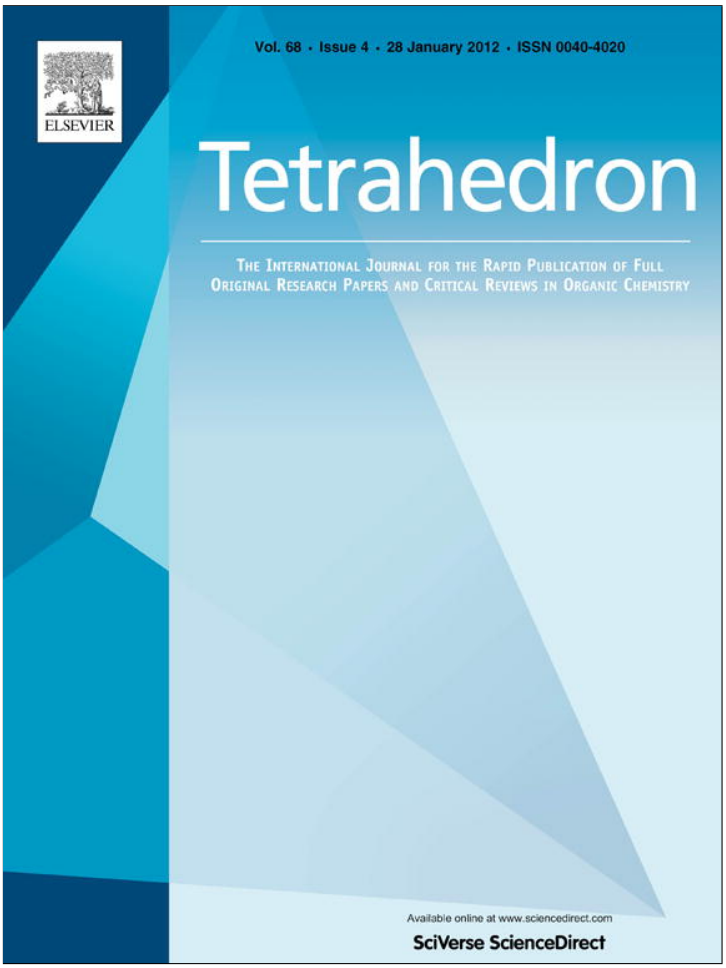

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# Synthesis and functionalization of new polyhalogenated BODIPY dyes. Study of their photophysical properties and singlet oxygen generation

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ABSTRACT

A theoretical and experimental study on the iodination of BODIPY dyes with different degrees of substitution has been developed. Polyhalogenated BODIPYs synthesized in this work are the first examples of this type of dyes with more than two halogen atoms in the BODIPY core and they can be selectively functionalized. Surprisingly, the position in which halogen is attached has a marked effect in the photophysical properties and modulates the fluorescence capacity of the resulting BODIPY. These iodinated BODIPYs are efficient singlet oxygen generators.



## 1. Introduction

Along the last years the number of contributions in the literature about 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes has increased exponentially, due to their advantageous photophysical properties, such as a high fluorescence quantum yield, low triplet–triplet absorption, and high photostability.[1] In addition, these dyes present a high number of applications.[2] The contributions directed at modifying the structure using new synthetic procedures have grown clearly in a similar way. In general, most synthetic routes are focused on the introduction of suitable substituents at an appropriate position of the indacene core, in most cases to extend the conjugation and to optimize their spectroscopic properties. Typical approaches to this problem include: Knoevenagel-type condensation of methyl-substituted BODIPYs,[1,3] nucleophilic substitution,[1,4] Liebeskind–Srögl reaction[5] or palladium coupling reactions (Sonogashira, Suzuki…).[1,3i,4f,6] Halogenated BODIPYs are the most useful building blocks for these synthetic strategies.[1,4,6]

In addition, halogenated BODIPY dyes can find applications as probes for photodynamic therapy (PDT), a noninvasive methodology for the treatment of malignant tumours and age related macular degeneration. The treatment requires a combined application of a photosensitizer and light of a wavelength matched to the $\lambda_{max}$ of the photosensitizer in order to generate cytotoxic reactive oxygen species (e.g., $^1O_2$) that eradicate tumours via cellular damage, via vasculature damage and, possibly, by response of the immune system.[7] The generation of reactive oxygen species requires the population of the triplet state of the dye. BODIPYs do not undergo efficient intersystem crossing to the triplet excited state. However, the presence of heavy atoms increases the quantum yield of intersystem crossing. Thus, it has been shown that iodine or bromine incorporation into the BODIPY nucleus enhanced intersystem crossing and a few promising sensitizers for use in PDT have been reported in the last few years as an alternative to the porphyrin-based photosensitizers.[8]

There are three different ways to achieve halogenated BODIPYs: halogenation of the pyrrole ring,[6a,9] halogenation of the dipyrromethane precursors[4a,10] or electrophilic substitution reactions on the BODIPY dye previously synthesized.[1,6c–e,g,8b–g,11] The latter reactions have been studied,[1] showing that positions 2 and 6 of the BODIPY core are the most susceptible to electrophilic attack. However, there is not a definitive study on the regioselectivity in

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these reactions for unsubstituted BODIPYs. In most cases studied some of the other positions are blocked by substituents, although the bromination with NBS of a 1,3,5,7-unsubstituted BODIPY has been described recently,[12] providing mono- and dibrominated BODIPYs at the 2- and 6-positions with high regioselectivity. In this study none of the regioisomeric products, such as α-bromo-BODIPYs, were detected in the reaction mixture, even when an excess of the brominating agent was used.[12]

Based on this background, in this work we report a novel theoretical, experimental, and photophysical study on the iodination of a series of BODIPYs **1**–**3** with different degrees of substitution (Fig. 1). In addition, we have carried out a preliminary study of the selective functionalization and singlet oxygen generation of some of these halogenated BODIPYs.

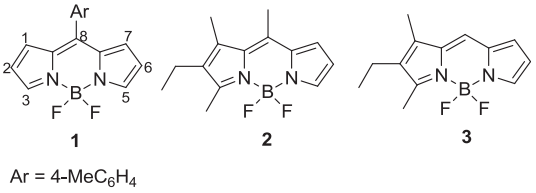



**Fig. 1.** Chemical structures of the BODIPY dyes **1**–**3**.

## 2. Results and discussion

### 2.1. Theoretical study

The mesomeric structures of the BODIPY core indicate that the 2- and 6-positions have the lower positive charge, so they should be most susceptible to electrophilic attack.[1] In this work, a computational study on compounds **1**–**3** gives the Mulliken charge distribution and the electrostatic potential map shown in Fig. 2. The electronic charge distribution of these BODIPY dyes is characteristic of a cyanine-like delocalized π-system[13] (Fig. 2, and Figs. 1S–3S in ESI).

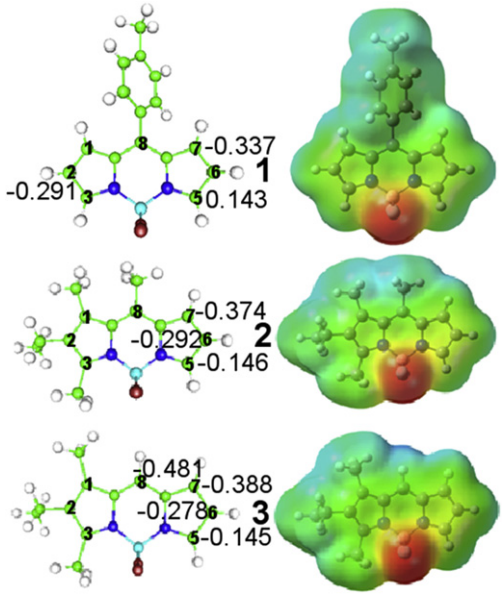



**Fig. 2.** Electrostatic potential map (blue-positive and red-negative) and Mulliken charge of BODIPYs **1**–**3**.

According to the values shown in Fig. 2, for dye **1**, positions 1- and 7 are the most favourable for an electrophilic attack. However, in order to predict the iodination site steric interactions should also be taken into account. Thus, there is a considerable sterical hindrance at 1- and 7-positions, due to the bulky phenyl group at *meso*-position, and also to the large size of the iodine atom, avoiding the incorporation of iodine at those sites.

Therefore, the combination of electronic and steric factors predicts that positions 2 and 6 are the most favourable for electrophilic substitution in compound **1**. The presence of the halogen atom modifies the charge distribution as shown in the ESI (Fig. 1S, ESI). Successive iodinations should occur on the most negative charged carbons, but taking into account that the adjacent positions of the phenyl group in compound **1** are inaccessible to iodine due to steric factors.

The sterical hindrance at positions 1 and 7 in compound **1** is not present in alkyl-substituted BODIPY **2** and **3**. As a consequence, the iodination should be controlled by electronic factors, meaning that the reaction should take place at the positions with the highest negative charge. At a first sight, all the free positions are susceptible to be iodinated. However, the electrostatic potential map shows a high positive density around the *meso* carbon (Fig. 2), hampering the approach of the electrophilic iodine atom. Indeed, such effect should be clearer at 8-position since typically the dipole moment of BODIPYs is oriented along the transversal axis, with the negative charge density located in the fluorine atoms and the positive density centred at the *meso*-position. Thus, in BODIPY **3** the *meso*-position cannot be iodinated, although is free and the carbon is characterized by a negative charge (Fig. 3S, ESI). Therefore, it should be expected that 5- and 6-positions will be first iodinated in BODIPY **2** and **3**, since the halogen can easily come around, although they have lower negative charge than 7- and 8-position.

### 2.2. Synthesis

To test these hypotheses, we have synthesized BODIPY dyes **1**,[14] **2**[15] and **3**,[16] using the methods previously described, and we have investigated the iodination reactions of these compounds with ICl or $I_2/HIO_3$ by using different concentrations of the iodination reagents and at different reaction times. The products obtained in the halogenation reactions of these BODIPY dyes are shown in Fig. 3 and Table 1.

The experimental results show that is possible to obtain selectively mono-, di-, tri- and tetraiodinated products of BODIPYs **1**, **2** and **3**. These are the first examples of this type of dyes with more than two halogen atoms in the BODIPY core. Thus, iodination of these dyes with ICl in almost equimolecular ratio (Table 1, entries 1, 10 and 14), gives the monoiodo-BODIPYs **4a**, **5a** and **6a**, respectively, in high yield. When two and a half equivalents are used (Table 1, entries 2, 11 and 15), diiodo-BODIPYs **4b**, **5b**, **5c**, **6b** and **6c**, are obtained. These compounds can be separated easily by column chromatography. Compound **5b** is obtained with much lower yield than **6b** probably due to steric hindrance by the methyl group in the *meso*-position.

Although it is possible to obtain the triiodo derivative **4c** (Table 1, entry 3), the yield is low because it is always accompanied of diiodo **4b** and tetraiodo **4d** derivatives, furthermore, in this case it is hard to separate the isomers chromatographically. A mixture of polyhalogenated derivatives with iodide and chlorine (**4d**, **4e**, **4f** and **4g**) in different positions of the BODIPY **1** are obtained with higher ratios of reagents (Table 1, entries 4 and 5). Similarly, BODIPY dyes **2** and **3** give rise to trihalogenated derivatives **5d**, **5e**, **6d** and **6e**, respectively (Table 1, entries 12 and 16). The formation of chlorinated products is in agreement with bibliographic data[17] showing that the reaction of iodine chloride with aromatic compounds can lead to chlorinated and/or iodine derivatives depending on the reaction conditions.

To prevent the formation of chlorinated derivatives, we carried out the iodination reactions using $I_2/HIO_3$ as a halogenating agent

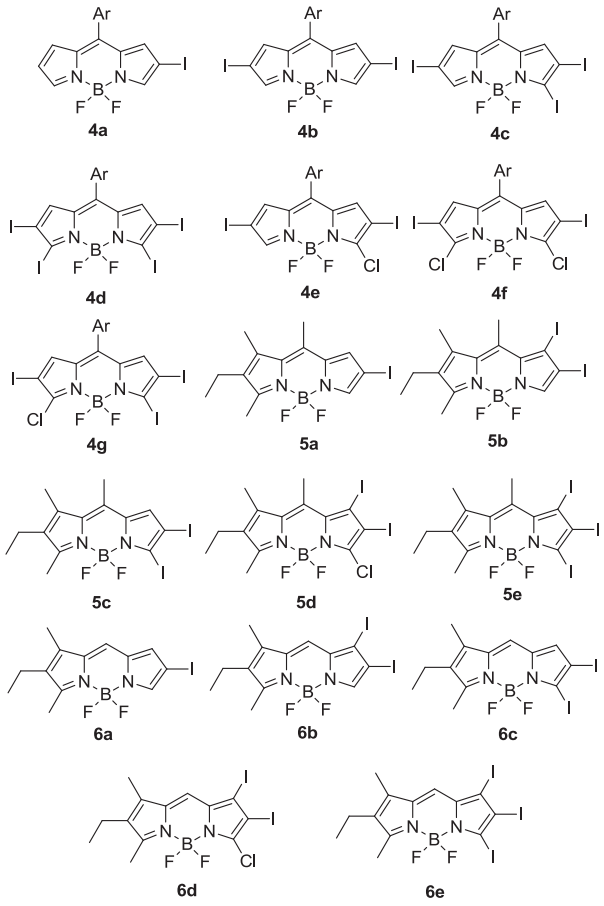



**Fig. 3.** Structures of the halogenated BODIPY dyes.

(Table 1, entries 6–9, 13 and 17). In these conditions, tetraiodo **4d** and triiodo derivatives **5e** and **6e** are obtained with good yields.

The data obtained indicate that, in principle, any free BODIPY position can undergo the electrophilic attack, which increase the synthetic utility of this reaction. Thus, whereas the 1- and 7-positions of BODIPY **1** do not undergo electrophilic substitution, due to the steric hindrance of the phenyl group, and then the halogenation occurs at the 2- and 6-positions, followed by the 3- and 5-positions. In the case of the BODIPY **2**, the electrophilic attack takes place in all positions, while in the BODIPY **3** the iodination reaction does not occur in the *meso*-position. The lack of iodination at this position is probably due to the high positive charge density at the *meso*-position, which prevents electrophilic substitution (Fig. 2).

**Table 1**
Reaction conditions and yields of isolated products of BODIPYs **1**–**3**

| Entry | Agent[a] | Ratio | *t* (min) | Products (yield, %)[d] |
|---|---|---|---|---|
| BODIPY **1** | | | | |
| 1 | A | 1:1[b] | 30 | **4a** (75) |
| 2 | A | 1:2.5[b] | 60 | **4a** (14), **4b** (72) |
| 3 | A | 1:3.5[b] | 120 | **4b** (22), **4c** (45), **4d** (8) |
| 4 | A | 1:4.5[b] | 180 | **4d** (10), **4e** (5), **4f** (21), **4g** (40) |
| 5 | A | 1:8[b] | 360 | **4d** (25), **4f** (24), **4g** (20) |
| 6 | B | 1:1:0.8[c] | 30 | **4a** (70) |
| 7 | B | 1:2.5:2[c] | 60 | **4a** (15), **4b** (69) |
| 8 | B | 1:3.5:3[c] | 60 | **4b** (15), **4c** (30), **4d** (30) |
| 9 | B | 1:4.5:4[c] | 180 | **4d** (64) |
| BODIPY **2** | | | | |
| 10 | A | 1:1.3[b] | 30 | **5a** (95) |
| 11 | A | 1:2.5[b] | 60 | **5a** (8), **5b** (10), **5c** (67) |
| 12 | A | 1:6[b] | 180 | **5c** (6), **5d** (35), **5e** (20) |
| 13 | B | 1:4.5:4[c] | 180 | **5c** (5), **5e** (48) |
| BODIPY **3** | | | | |
| 14 | A | 1:0.8[b] | 30 | **6a** (81) |
| 15 | A | 1:2.5[b] | 90 | **6a** (13), **6b** (34), **6c** (35) |
| 16 | A | 1:8[b] | 300 | **6d** (30), **6e** (35) |
| 17 | B | 1:5:4.5[c] | 300 | **6e** (54) |

[a] Halogenating reagent: A=ICl, B=$I_2$/$HIO_3$.
[b] Molar ratio BODIPY/ICl.
[c] Molar ratio BODIPY/$I_2$/$HIO_3$.
[d] Yield of isolated product.

## 2.3. Selective functionalization

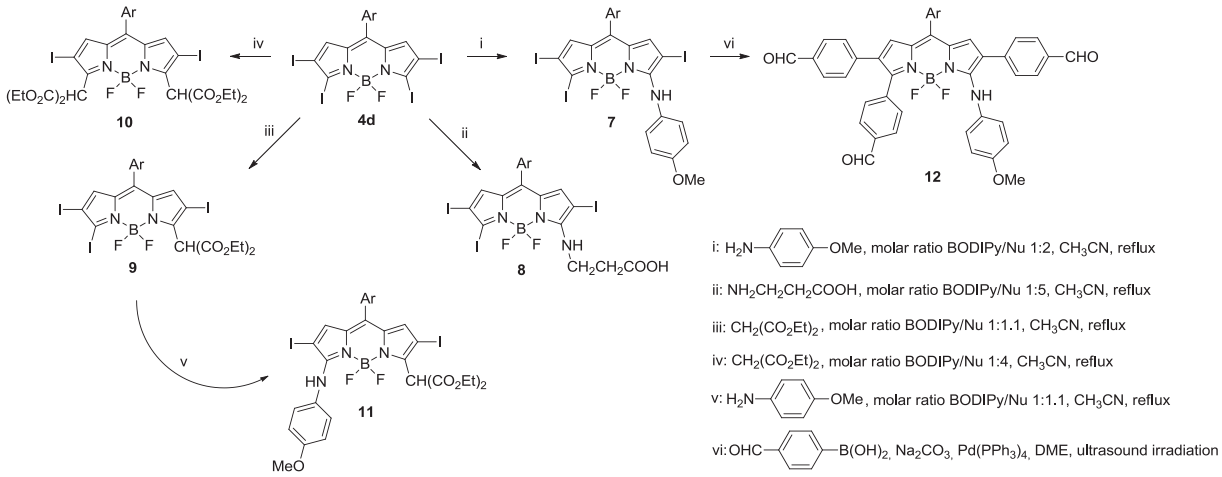
The easily obtained polyhalogenated derivatives are valuable synthetic precursors for selective functionalization allowing the development of a variety of symmetric and asymmetric BODIPY compounds that are difficult to obtain by alternative procedures.[1,4,6] It is known that 3,5-dichloroBODIPY derivatives can undergo substitution of the chlorine atoms by a wide range of oxygen, carbon, nitrogen, and sulfur nucleophiles. Furthermore, the reaction conditions can be adjusted to obtain either mono- or disubstituted products.[1,4]

In this work, we have carried out nucleophilic substitution reactions of 2,3,5,6-tetraiodo BODIPY **4d** with 4-metoxyaniline, β-alanine and sodium diethyl malonate. In the first two cases only monosubstituted derivatives **7** and **8** were obtained, respectively, even when the reaction is carried out with an excess of the reagent and under reflux (Scheme 1).

These results contrast with those previously reported for the 3,5-dicloroderivatives[4] and a possible explanation could be that the presence of iodine atoms next to electron-donor groups increase the charge density of the system preventing the second nucleophilic substitution reaction to occur. To test this hypothesis, we treated compound **4d** with sodium diethyl malonate. Under these conditions, the mono and disubstituted BODIPY derivatives **9** and **10** were obtained. Furthermore, compound **9** afford the asymmetric derivative **11** by reaction with 4-methoxyaniline. In these cases, the absence of electron-donating groups allows the second $S_NAr$. The iodinated derivatives can be used in Pd-coupling reactions. Thus, a triplet Suzuki coupling reaction of **7** yielded the highly functionalized dye **12** (Scheme 1).

## 2.4. Photophysical properties

The photophysical properties of BODIPY **1** (Table 2, and Table 1S in ESI) are conditioned by the presence of the phenyl group at *meso*-position. It has been previously reported that the free rotation of such ring greatly increases the internal conversion processes and it can interact with the BODIPY core distorting the indacene planarity.[18] The absence of substituents at 1- and 7-positions enables the rotation of the phenyl ring (twisted 50° from the BODIPY plane).[19] Hence, compound **1** is characterized by a very low fluorescence quantum yield ($\phi$<0.04) and lifetime ($\tau$<700 ps). Successive iodination gives rise to a progressive bathochromic shift of the spectral bands (Table 2 and Fig. 4). In fact, the tetraiodinated derivative **4d** emits in the red region of the visible spectra (around 590 nm). The halogenation of the BODIPY core should induce a decrease in the fluorescence capacity due to the heavy atom effect, which increases the intersystem crossing probability (Fig. 4). This influence is observed for the monoiodo and the diiodo derivatives **4a** and **4b**, respectively. Surprisingly, further addition of iodine atoms to the BODIPY core leads to an increase in the intensities of the absorption and also in the fluorescence emission. For instance, the tetraiodinated derivative **4d** shows a very high molar absorption (around $11\times10^4\,M^{-1}\,cm^{-1}$, twice the non-iodinated BODIPY **1**) and even higher than other non-halogenated BODIPYs ($9\times10^4\,M^{-1}\,cm^{-1}$).[18b] Besides, the fluorescence quantum yield for compound **4d** is 0.1, much higher than 0.034, which is the value reported for the non-iodinated BODIPY **1**.[14]




**Scheme 1.** Synthetic scheme for the preparation of BODIPY dyes **7**–**12**.

**Table 2**
Photophysical properties of BODIPY **1**, **2** and **3** and their iodinated derivatives in *c*-hexane. (The full data list for BODIPYs **1**, **2** and **3** series are included in Tables 1S, 3S and 4S in the ESI)

| | $\lambda_{ab}$ (nm) | $\varepsilon_{max}$ ($10^4$ $M^{-1}$ $cm^{-1}$) | $\lambda_{fl}$ (nm) | $\phi$ | $\tau$ (ps) |
|---|---|---|---|---|---|
| BODIPY **1** | | | | | |
| **1** | 500.5 | 6.9 | 516.0 | 0.036 | 323 |
| **4a** | 523.5 | 2.2 | 540.0 | 0.034 | 184 |
| **4b** | 548.5 | 4.3 | 567.5 | 0.012 | 117 |
| **4c** | 563.5 | 4.8 | 577.5 | 0.060 | 327 |
| **4d** | 581.0 | 11.6 | 593.0 | 0.099 | 678 |
| BODIPY **2** | | | | | |
| **2** | 504.0 | 3.3 | 515.0 | 0.96 | 5460 |
| **5a** | 517.5 | 4.6 | 532.0 | 0.13 | 560 |
| **5b** | 515.5 | 2.9 | 538.5 | 0.05 | 259 |
| **5c** | 532.0 | 9.8 | 546.0 | 0.20 | 1021 |
| **5e** | 531.5 | 1.7 | 554.5 | 0.10 | 331 |
| BODIPY **3** | | | | | |
| **3** | 512.5 | 2.9 | 517.5 | 0.70 | 5240 |
| **6a** | 528.0 | 6.3 | 538.5 | 0.11 | 489 |
| **6b** | 527.5 | 5.6 | 537.0 | 0.05 | 212 |
| **6c** | 542.0 | 7.6 | 550.5 | 0.26 | 1041 |
| **6e** | 543.5 | 6.9 | 551.5 | 0.07 | 358 |

Absorption ($\lambda_{ab}$) and fluorescence ($\lambda_{fl}$) wavelength of the maximum; molar absorption ($\varepsilon_{max}$) at the maximum wavelength; fluorescence quantum yield ($\phi$) and lifetime ($\tau$). Present lifetimes are the main component of the decay curve, which is analyzed as biexponential but with a negligible long lifetime.

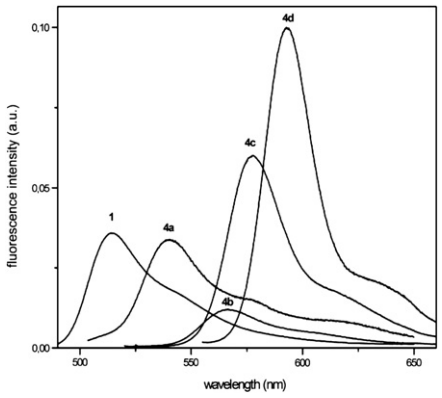



**Fig. 4.** Fluorescence spectra of BODIPY **1** and its iodinated derivatives **4a**–**d** in *c*-hexane, scaled by their fluorescence quantum yield.

Theoretical simulations of the absorption transition confirm the progressive bathochromic shift with the iodination degree and the enhancement of the absorption probability of **4d** with regard to the rest of derivatives (Table 2S, ESI). Compound **4d** shows a uniform charge distribution in the pyrrole moiety, whereas in the rest of the series it is more irregular (Fig. 1S, ESI). That means that the negative charge on nitrogen, and on positions 1-, 2- and 3, and their corresponding symmetrical ones, is nearly the same (around −0.255). Accordingly, the delocalization is improved, in concordance with the push–pull effect (substitution at the beginning and ending of the delocalized system).[14] Therefore, substitution at 3- and 5-positions counteracts in part the non-radiative processes (heavy atom effect and phenyl free rotation) improving the fluorescence efficiency of the dye. It seems that the iodine presence at those positions extents the chromophoric electronic density far away from the phenyl ring (Fig. 1S, ESI) diminishing the deleterious effect in fluorescence owing to its free motion.

On the other hand, the absence of the bulky phenyl group in BODIPY **2** and **3** leads to highly fluorescence molecules, as is characteristic of this dye family (Table 2, and Tables 3S–4S, ESI). The absorption probability is not very high due to the asymmetric substitution pattern, which leads to charge separation between the pyrroles (Fig. 2). The incorporation of an iodine atom at 6-position (**5a** and **6a**) implies a drastic decrease of the intensity of the fluorescence emission, which is attributed to the enhancement in the probability of intersystem crossing, as mentioned above (Table 2). However, further halogenation leads to entirely different results depending of the position in which the iodine is attached. The incorporation of a second iodine atom at position 7 (**5b** and **6b**) has a minimum effect on the wavelength of the absorption band position but induces a reduction of the intensity of the fluorescence emission, in agreement with the heavy atom effect. In contrast, the incorporation of a second iodine atom at position 5 (**5c** and **6c**) gives rise to a bathochromic spectral shift and increases the absorption probability and fluorescence efficiency (Table 2) in concordance with the push–pull effect. Again, the electronic distribution of **5c** and **6c** in the pyrrole rings is uniform (Figs. 2S–3S, ESI), in good agreement with the influence observed for the iodo-derivatives from BODIPY **1**. Therefore, the results obtained in the present study confirm that substitution at the ends of the delocalized $\pi$-system is advantageous for the fluorescence ability of the dye. In the triiodinated derivatives (**5e** and **6e**), the incorporation of iodine at 7- and 5-positions has the opposite influence in the photophysics of the dye. As a result, the effect of both iodine atoms is counteracted. That means, whereas substitution at 7-position should increase the intersystem crossing, without altering the band position,

substitution at 5-position should favour the fluorescence ability and give rise to a bathochromic shift. Consequently, their spectral bands are placed close to those of the diiodinated derivative (**5c** and **6c**) and their fluorescence capacity is similar to that of the monoiodinated ones (**5a** and **6a**) (Table 2). Indeed, the electronic distribution in the triiodinated derivatives is less uniform and the system is less aromatic (Figs. 2S–3S, ESI). Quantum mechanical simulation of the absorption transition nicely reproduces the shift of the band depending on the iodine position in the chromophore and describes qualitatively well the evolution of the absorption probability (Table 2S, ESI).

Finally, we should note the close correlation between the fluorescence quantum yield and the lifetime with both changing the number of halogens appended to BODIPY and the environmental properties. Such evolutions are controlled mainly by the non-radiative processes, thus the lower the fluorescence efficiency the faster the decay from the excited state.

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### 2.5. Singlet oxygen generation

Typically BODIPYs are characterized by very low triplet state population. However, iodinated derivatives **4**, **5** and **6** show low fluorescence yields mainly due to the triplet state population via the intersystem crossing process promoted by the so-called internal heavy atom effect.[2a,9a] Therefore they could be good singlet oxygen ($^1O_2$) generators after energy transfer from excited triplet state to ground state oxygen.

The transient absorption spectra of **4b** and **4d** dyes obtained by laser flash photolysis in MeCN solution were recorded in the range between 250 and 850 nm. The spectra of each dye present negative bands caused by depletion of the ground state, which are practically the same that the corresponding one for ground state absorption, revealing the lack of photoproduct generation under the selected laser experimental conditions. As a typical example, the case of **4b** is shown in Fig. 5.

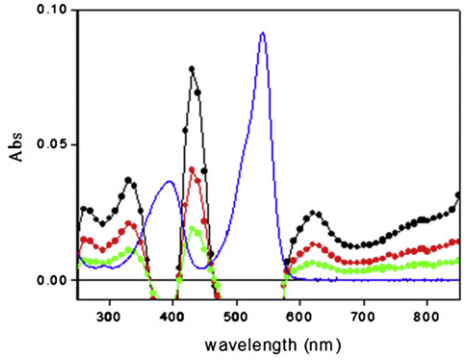


**Fig. 5.** Transient absorption spectra of **4b** in MeCN recorded at different times after the laser pulse: (○, 1 μs), (○, 4 μs), (○, 8 μs) and ground state absorption spectrum (▬).

The monoexponential decay of the spectrum for **4b** and **4d** is in agreement with the recovery in the bleaching regions. It worth noting that similar transient spectra were reported for the triplet state of others dipyrromethene dyes.[20] All these observations strongly suggest that the observed absorptions correspond to a unique transient species, which is assigned to the electronically excited triplet state of the dyes investigated.

We examined the ability of compounds **4b**–**d** with two or more atoms of iodine to generate $^1O_2$. This was done in $CH_3CN$ using 532 nm-excitation. The reference was Rose Bengal (RB) with a quantum yield $\Phi_{\Delta RB}$ for $^1O_2$ production of 0.71 determined in this work using perinaphthenone (PN) with $\Phi_{\Delta RB}=1$ as a reference compound (Fig. 4S, ESI). The results obtained are $\Phi_{\Delta \mathbf{4b}}=0.83+7\%$, $\Phi_{\Delta \mathbf{4c}}=0.86+9\%$ and $\Phi_{\Delta \mathbf{4d}}=0.87+6\%$, all these values are in the range of those exhibited by compounds recognized as efficient $^1O_2$ photosensitizer (Fig. 5S, ESI).

The results obtained show that the introduction of iodine atoms in 3 and/or 5 positions does not produce a significant increase in the efficiency of $^1O_2$ generation and they are in good agreement with those arising from the photophysical properties, showing that substitution at 3 or 5-position favours the fluorescence ability. It is clear that additional studies are needed to clarify the influence of the iodine atoms positions over the efficiency of singlet oxygen generation of these compounds. Nevertheless, the obvious consequence of the investigation described above is that these polyiodinated BODIPYs are efficient photosensitizers for the generation of $^1O_2$ and additionally they can be suitably functionalized at of 3- and 5-positions for their possible use as PDT agents.

## 3. Conclusion

We have demonstrated that it is possible to control the degree of iodination in the BODIPY core, which allows the synthesis of mono-, di- and polyiodinated derivatives. These are the first examples of this type of dyes with more than two halogen atoms in the BODIPY core. Moreover, considering the easy synthetic route of these polyhalogenated derivatives, the reaction could be extended to other dyes of this family, with different degrees of substitution. Another interesting observation in this study is that polyhalogenated compounds can be valuable synthetic precursors for the selective incorporation of the desired functional groups in a specific position of the BODIPY. Quantum mechanical calculations can predict the position in which iodine atoms will be incorporated and explain why some positions are inaccessible to the iodine atom. Moreover, the position in which halogen is attached modulates the photophysical properties of the resulting BODIPY. In general, substitution at 3- or 5-positions improves the absorption and fluorescence transition probability efficiency while in the rest of positions leads to an important reduction of the fluorescence ability owing to the heavy atom effect, which activates the intersystem crossing processes. Triplet state population via intersystem crossing leads to a high efficiency of **4b**–**d** as $^1O_2$ generators. Further work is in progress to complete the study over the triplet state (singlet oxygen generation and phosphorescence spectra) and finally to explore the applicability of these novel BODIPYs appropriately functionalized in PDT.

## 4. Experimental section

### 4.1. General

Starting materials and reagents used in the preparation of BODIPYs are commercially available unless synthesis is described. The solvents were dried and distilled, before use. Spectral data of the known compounds were in accordance with the literature data. Flash column chromatography was performed using silica gel Merck 60 (230–400 mesh). $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker Avance-DPX-300 spectrometer (300 MHz for $^1H$ and 75 MHz for $^{13}C$) and a Bruker Avance III spectrometer (700 MHz for $^1H$ and 176 MHz for $^{13}C$). The spectra were recorded in $CDCl_3$ or $CD_3OD$. $^1H$ NMR chemical shifts are reported in parts per million relative to tetramethylsilane ($\delta=0.00$ ppm), using the residual solvent signal as the internal reference. $^{13}C$ NMR chemical shifts are reported in ppm with $CDCl_3$ ($\delta=77.67$ ppm) as the internal standard. Chemical shift multiplicities are reported as s=singlet,

d=doublet, t=triplet, q=quartet and m=multiplet. IR spectra (in $cm^{-1}$) were recorded in a Bruker Tensor-27-FTIR spectrophotometer. Melting points were determined in open capillaries and are uncorrected. Mass spectra were registered by electron impact (EI) at 70 eV, by electrospray ionization (ESI) and by atmospheric pressure chemical injection (APCI) in a VGI2-250 spectrometer. High resolution mass spectra were determined by electrospray ionization in the positive mode ($ESI^+$) in an Accurate-Mass Q-TOF LC/MS 6520 (Agilent Technologies).

### 4.2. General procedure for the synthesis of halogenated BODIPYs

*4.2.1. Method A: iodination reaction with ICl.* To a solution of BODIPY in a $CH_2Cl_2$/MeOH mixture (1:1) was added dropwise a solution of ICl in MeOH. The BODIPY/ICl ratio is indicated in each case. This mixture was refluxed for 30–360 min. After cooling, the solvent was evaporated under vacuum. The crude product was dissolved in $CH_2Cl_2$, washed with $H_2O$, dried over $MgSO_4$, filtered and concentrated to dryness. The halogenated BODIPYs were purified by flash chromatography on silica gel (eluent hexane/EtOAc).

*4.2.2. Method B: iodination reaction with $I_2$/$HIO_3$.* Iodic acid dissolved in a minimum amount of water was added dropwise to a solution of BODIPY and iodine in EtOH. The BODIPY/$I_2$/$HIO_3$ ratio is indicated in each case. This mixture was refluxed for 30–300 min. After cooling, the solvent was evaporated under vacuum. The crude product was dissolved in $CH_2Cl_2$, washed with $H_2O$, dried over $MgSO_4$, filtered and concentrated to dryness. The halogenated BODIPYs were purified by flash chromatography on silica gel (eluent hexane/EtAcO).

### 4.3. Iodination reactions of BODIPYs 1–3

*4.3.1. BODIPY **1** with ICl (1:1).* According to the method A, BODIPY **1** (70 mg, 0.25 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (41 mg, 0.25 mmol) in MeOH (5 mL) for 30 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, 4,4-difluoro-2-iodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**4a**) (76 mg, 75%) as an orange solid and starting BODIPY **1** (10 mg, 14%).

*4.3.1.1. Compound **4a**.* Mp 166.2–166.8 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.92 (1H, s, H-5), 7.76 (1H, s, H-3), 7.39 (2H, d, $J$=7.7 Hz, H-2′), 7.28 (2H, d, $J$=7.7 Hz, H-3′), 6.97 (1H, s, H-1), 6.96 (1H, d, $J$=4.2 Hz, H-7), 6.53 (1H, d, $J$=4.2 Hz, H-6), 2.41 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 147.0 (C), 146.4 (CH), 145.6 (CH), 141.9 (C), 136.1 (CH), 135.8 (C), 135.1 (C), 133.1 (CH), 130.6 (CH), 129.4 (CH), 119.6 (CH), 70.8 (C–I), 21.5 ($CH_3$); IR (neat): 1539, 1258, 1111 $cm^{-1}$; MS ($APCI^-$) $m/z$ (%): 408 ($M^-$, 100); HRMS-$ESI^+$: calcd for ($C_{16}H_{12}BF_2IN_2$+$H^+$) 409.0182 found 409.0178.

*4.3.2. BODIPY **1** with ICl (1:2.5).* According to the method A, BODIPY **1** (70 mg, 0.25 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (102 mg, 0.63 mmol) in MeOH (5 mL) for 60 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, 4,4-difluoro-2,6-diiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**4b**) (96 mg, 72%) as a green solid and **4a** (14 mg, 14%).

*4.3.2.1. Compound **4b**.* Mp 210.0–210.7 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.80 (2H, s, H-3 and H-5), 7.37 (2H, d, $J$=7.7 Hz, H-2′), 7.29 (2H, d, $J$=7.7 Hz, H-3′), 7.05 (2H, s, H-1 and H-7), 2.41 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 147.1 (CH), 145.1 (C), 141.4 (C), 136.6 (CH), 134.9 (C), 129.5 (CH), 129.2 (C), 128.5 (CH), 71.1 (C–I), 20.5 ($CH_3$); IR (neat): 1539, 1254, 1114 $cm^{-1}$; MS (EI) $m/z$ (%): 534 ($M^+$, 100), 407 (7), 280 (22), 265 (18), 203 (10), 139 (10); HRMS-$ESI^+$: calcd for ($C_{16}H_{11}BF_2I_2N_2$+$H^+$) 534.9153 found 534.9146.

*4.3.3. BODIPY **1** with ICl (1:3.5).* According to the method A, BODIPY **1** (70 mg, 0.25 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (142 mg, 0.87 mmol) in MeOH (5 mL) for 120 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, **4b** (29 mg, 22%), 4,4-difluoro-2,3,6-triiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**4c**) (74 mg, 45%) as a green solid and 4,4-difluoro-2,3,5,6-tetraiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**4d**) (16 mg, 8%) as a green solid.

*4.3.3.1. Compound **4c**.* Mp 253.2–253.7 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.80 (1H, s, H-5), 7.34 (2H, d, $J$=8.1 Hz, H-2′), 7.27 (2H, d, $J$=8.1 Hz, H-3′), 7.00 (1H, s, H-1), 6.96 (1H, s, H-7), 2.40 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 148.6 (CH), 143.4 (C), 142.3 (C), 139.3 (C), 137.8 (CH), 137.4 (CH), 135.9 (C), 130.5 (CH), 129.7 (C), 129.6 (CH), 115.1 (C–I), 90.2 (C–I), 72.8 (C–I), 21.6 ($CH_3$); IR (neat): 1536, 1237, 1089 $cm^{-1}$; MS ($APCI^-$) $m/z$ (%): 660 ($M^-$, 100), 602 (40), 585 (25), 533 (42); HRMS-$ESI^+$: calcd for ($C_{16}H_{10}BF_2I_3N_2$+$H^+$) 660.8119 found 660.8109.

*4.3.3.2. Compound **4d**.* Mp 283.2–284.0 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.31 (2H, d, $J$=7.7 Hz, H-2′), 7.27 (2H, d, $J$=7.7 Hz, H-3′), 6.91 (2H, s, H-1 and H-7), 2.40 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 142.2 (C), 140.5 (C), 139.3 (C), 137.5 (CH), 130.4 (CH), 129.6 (CH), 129.1 (C), 115.9 (C–I), 90.9 (C–I), 21.6 ($CH_3$); IR (neat): 1536, 1320, 1215, 1086 $cm^{-1}$; MS ($APCI^-$) $m/z$ (%): 786 ($M^-$, 100), 677 (50); HRMS-$ESI^+$: calcd for ($C_{16}H_9BF_2I_4N_2$+$H^+$) 786.7086 found 786.7080.

*4.3.4. BODIPY **1** with ICl (1:4.5).* According to the method A, BODIPY **1** (70 mg, 0.25 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (183 mg, 1.12 mmol) in MeOH (5 mL) for 180 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, 3-chloro-4,4-difluoro-2,6-diiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**4e**) (7 mg, 5%) as a green solid, 3,5-dichloro-4,4-difluoro-2,6-diiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indacene (**4f**) (32 mg, 21%) as a green solid, 3-chloro-4,4-difluoro-2,5,6-triiodo-8-(4-tolyl)-4-bora-3a,4a-diaza -*s*-indacene (**4g**) (69 mg, 40%) as a green solid and **4d** (20 mg, 10%).

*4.3.4.1. Compound **4e**.* Mp 259.8–260.3 °C; $^1$H NMR (700 MHz): $\delta$ 7.79 (1H, s, H-5), 7.34 (2H, d, $J$=7.7 Hz, H-2′), 7.29 (2H, d, $J$=7.7 Hz, H-3′), 7.05 (1H, s, H-1), 7.01 (1H, s, H-7), 2.41 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz): $\delta$ 148.1 (C–Cl and CH), 144.5 (C), 142.4 (C), 138.4 (CH), 137.2 (CH), 135.7 (C), 135.0 (C), 130.6 (CH), 129.6 (CH), 129.4 (C), 76.3 (C–I), 72.4 (C–I), 21.6 ($CH_3$); IR (neat): 1373, 1239, 1046 $cm^{-1}$; MS ($APCI^-$) $m/z$ (%): 568 ($M^-$, 100), 549 (30), 473 (40), 441 (35); HRMS-$ESI^+$: calcd for ($C_{16}H_{10}BClF_2I_2N_2$+$H^+$) 568.8763 found 568.8759.

*4.3.4.2. Compound **4f**.* Mp 253.6–254.1 °C; $^1$H NMR (700 MHz): $\delta$ 7.31 (2H, d, $J$=7.7 Hz, H-2′), 7.28 (2H, d, $J$=7.7 Hz, H-3′), 7.00 (2H, s, H-1 and H-7), 2.41 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz): $\delta$ 148.2 (C–Cl), 142.9 (C), 142.3 (C), 137.9 (CH), 134.8 (C), 130.5 (CH), 129.6 (CH), 129.0 (C), 76.6 (C–I), 21.5 ($CH_3$); IR (neat): 1542, 1363, 1233, 1100 $cm^{-1}$; MS ($APCI^-$) $m/z$ (%): 602 ($M^-$, 100), 583 (22), 507 (28), 475 (28); HRMS-$ESI^+$: calcd for ($C_{16}H_9BCl_2F_2I_2N_2$+$H^+$) 602.9373 found 602.9369.

*4.3.4.3. Compound **4g**.* Mp 260.0–260.5 °C; $^1$H NMR (700 MHz): $\delta$ 7.31 (2H, d, $J$=7.7 Hz, H-2′), 7.28 (2H, d, $J$=7.7 Hz, H-3′), 7.00 (1H, s, H-7), 6.92 (1H, s, H-1), 2.41 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz): $\delta$ 148.6 (C–Cl), 142.3 (C), 141.7 (C), 139.1 (C), 138.1 (CH), 137.4 (CH), 135.0 (C), 130.5 (CH), 129.6 (CH), 129.1 (C), 115.3 (C–I), 90.6 (C–I), 77.2 (C–I), 21.6 ($CH_3$); IR (neat): 1542, 1224, 1094 $cm^{-1}$; MS ($APCI^-$)

*m*/*z* (%): 694 ($M^-$, 75), 585 (100), 439 (50); HRMS-ESI$^+$: calcd for ($C_{16}H_9BClF_2I_3N_2+H^+$) 694.7730 found 694.7721.

*4.3.5. BODIPY **1** with ICl (1:8).* According to the method A, BODIPY **1** (60 mg, 0.21 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (272 mg, 1.68 mmol) in MeOH (5 mL) for 360 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, **4f** (30 mg, 24%), **4g** (29 mg, 20%) and **4d** (39 mg, 25%).

*4.3.6. BODIPY **1** with $I_2$/$HIO_3$ (1:1:0.8).* According to the method B, BODIPY **1** (83 mg, 0.29 mmol), $I_2$ (74 mg, 0.29 mmol) in EtOH (20 mL) and $HIO_3$ (41 mg, 0.23 mmol) for 30 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded **4a** (83 mg, 70%) and starting BODIPY **1** (16 mg, 19%).

*4.3.7. BODIPY **1** with $I_2$/$HIO_3$ (1:2.5:2).* According to the method B, BODIPY **1** (83 mg, 0.29 mmol), $I_2$ (185 mg, 0.73 mmol) in EtOH (20 mL) and $HIO_3$ (102 mg, 0.58 mmol) for 60 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded **4b** (107 mg, 69%) and **4a** (18 mg, 15%).

*4.3.8. BODIPY **1** with $I_2$/$HIO_3$ (1:3.5:3).* According to the method B, BODIPY **1** (73 mg, 0.26 mmol), $I_2$ (231 mg, 0.91 mmol) in EtOH (20 mL) and $HIO_3$ (137 mg, 0.78 mmol) for 60 min were reacted. Flash chromatography using hexane/EtAcO (95:5) afforded, by order of elution, **4b** (21 mg, 15%), **4c** (51 mg, 30%) and **4d** (61 mg, 30%).

*4.3.9. BODIPY **1** with $I_2$/$HIO_3$ (1:4.5:4).* According to the method B, BODIPY **1** (70 mg, 0.25 mmol), $I_2$ (286 mg, 1.12 mmol) in EtOH (20 mL) and $HIO_3$ (176 mg, 1 mmol) for 180 min were reacted. Flash chromatography using hexane/EtAcO (95:5) afforded **4d** (126 mg, 64%).

*4.3.10. BODIPY **2** with ICl (1:1:3).* According to the method A, BODIPY **2** (60 mg, 0.23 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (49 mg, 0.30 mmol) in MeOH (5 mL) for 30 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded 2-ethyl-4,4-difluoro-6-iodo-1,3,8-trimethyl-4-bora-3a,4a-diaza-*s*-indacene (**5a**) (85 mg, 95%) as an orange solid. Mp 160.2–160.7 °C; $^1$H NMR (300 MHz): $\delta$ 7.39 (1H, s, H-5), 6.95 (1H, s, H-7), 2.49 (3H, s, $CH_3$–C8), 2.40 (3H, s, $CH_3$–C3), 2.34 (2H, q, $J$=7.6 Hz, $CH_2CH_3$), 2.25 (3H, s, $CH_3$–C1), 0.98 (3H, t, $J$=7.6 Hz, $CH_3CH_2$); $^{13}$C NMR (75 MHz): $\delta$ 162.8 (C), 142.0 (C), 139.7 (CH), 138.9 (C), 136.2 (C), 135.3 (C), 134.7 (C), 127.6 (CH), 67.0 (C–I), 17.1 ($CH_2$), 16.4 ($CH_3$), 14.4 ($CH_3$), 14.2 ($CH_3$), 13.3 ($CH_3$); IR (neat): 1561, 1177 cm$^{-1}$; MS (ESI$^-$): 387 [M–H]$^-$; HRMS-ESI$^+$: calcd for ($C_{14}H_{16}BF_2IN_2+H^+$) 389.0499 found 389.0491.

*4.3.11. BODIPY **2** with ICl (1:2.5).* According to the method A, BODIPY **2** (63 mg, 0.24 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (97 mg, 0.6 mmol) in MeOH (5 mL) for 60 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, 2-ethyl-4,4-difluoro-6,7-diiodo-1,3,8-trimethyl-4-bora-3a,4a-diaza-*s*-indacene (**5b**) (8 mg, 10%) as an orange solid, 2-ethyl-4,4-difluoro-5,6-diiodo-1,3,8-trimethyl-4-bora-3a,4a-diaza-*s*-indacene (**5c**) (83 mg, 67%) as a red solid and **5a** (8 mg, 8%).

*4.3.11.1. Compound **5b**.* Mp 201.5–202.0 °C; $^1$H NMR (700 MHz): $\delta$ 7.49 (1H, s, H-5), 2.87 (3H, s, $CH_3$–C3), 2.45 (3H, s, $CH_3$–C8), 2.36 (2H, q, $J$=7.7 Hz, $CH_2$), 2.30 (3H, s, $CH_3$–C1), 1.00 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 163.1 (C), 142.8 (C), 140.3 (C), 139.0 (CH), 137.1 (C), 135.6 (C), 132.6 (C), 89.8 (C–I), 85.5 (C–I), 18.7 ($CH_3$), 17.2 ($CH_2$), 15.3 ($CH_3$), 14.3 ($CH_3$), 13.5 ($CH_3$); IR (neat): 1567, 1370, 1221, 1072 cm$^{-1}$; MS (APCI$^-$) *m*/*z* (%): 514 ($M^-$, 50), 513 (100); HRMS-ESI$^+$: calcd for ($C_{14}H_{15}BF_2I_2N_2+H^+$) 514.9466 found 514.9458.

*4.3.11.2. Compound **5c**.* Mp 223.6–224.1 °C; $^1$H NMR (700 MHz): $\delta$ 6.96 (1H, s, H-7), 2.52 (3H, s, $CH_3$–C3), 2.37 (3H, s, $CH_3$–C8), 2.35 (2H, q, $J$=7.7 Hz, $CH_2$), 2.25 (3H, s, $CH_3$–C1), 1.00 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 163.8 (C), 141.9 (C), 138.8 (C), 136.9 (C), 136.6 (C), 134.8 (C), 128.3 (CH), 100.2 (C–I), 84.3 (C–I), 17.2 ($CH_2$), 15.8 ($CH_3$), 14.4 ($CH_3$), 14.2 ($CH_3$), 13.4 ($CH_3$); IR (neat): 1582, 1318, 1200, 1236 cm$^{-1}$; MS (EI) *m*/*z* (%): 514 ($M^+$, 98), 499 (100); HRMS-ESI$^+$: calcd for ($C_{14}H_{15}BF_2I_2N_2+H^+$) 514.9466 found 514.9451.

*4.3.12. BODIPY **2** with ICl (1:6).* According to the method A, BODIPY **2** (75 mg, 0.29 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (282 mg, 1.74 mmol) in MeOH (5 mL) for 180 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, **5c** (9 mg, 6%), 3-chloro-6-ethyl-1,2-diiodo-5,7,8-trimethyl-4-bora-3a,4a-diaza-*s*-indacene (**5d**) (55 mg, 35%) as an orange solid and 2-ethyl-5,6,7-triiodo-1,3,8-trimethyl-4-bora-3a,4a-diaza-*s*-indacene (**5e**) (37 mg, 20%) as a red solid.

*4.3.12.1. Compound **5d**.* Mp 275.1–275.6 °C; $^1$H NMR (700 MHz): $\delta$ 2.84 (3H, s, $CH_3$–C5), 2.47 (3H, s, $CH_3$–C8), 2.36 (2H, q, $J$=7.7 Hz, $CH_2$), 2.29 (3H, s, $CH_3$–C7), 1.00 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 163.5 (C), 142.5 (C), 138.9 (C), 137.6 (C), 137.5 (C–Cl), 135.4 (C), 132.6 (C), 90.0 (C–I), 89.5 (C–I), 19.1 ($CH_3$), 17.3 ($CH_2$), 15.3 ($CH_3$), 14.3 ($CH_3$), 13.5 ($CH_3$); IR (neat): 1566, 1369, 1186, 1088 cm$^{-1}$; MS (APCI$^-$) *m*/*z* (%): 548 ($M^-$, 98), 456 (30), 421 (100); HRMS-ESI$^+$: calcd for ($C_{14}H_{14}BClF_2I_2N_2+H^+$) 548.9076 found 548.9066.

*4.3.12.2. Compound **5e**.* Mp 235.6–236.1 °C; $^1$H NMR (700 MHz): $\delta$ 2.78 (3H, s, $CH_3$–C3), 2.46 (3H, s, $CH_3$–C8), 2.34 (2H, q, $J$=7.7 Hz, $CH_2$), 2.27 (3H, s, $CH_3$), 0.98 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 163.1 (C), 142.2 (C), 140.3 (C), 138.8 (C), 138.1 (C), 137.1 (C), 100.4 (C–I), 97.8 (C–I), 93.7 (C–I), 19.1 ($CH_3$), 17.2 ($CH_2$), 15.3 ($CH_3$), 14.3 ($CH_3$), 13.8 ($CH_3$); IR (neat): 1610, 1332, 1250, 1120, 1098 cm$^{-1}$; MS (APCI$^+$): 663 ([M+Na]$^+$, 100), 607 (30); HRMS-ESI$^+$: calcd for ($C_{14}H_{14}BF_2I_3N_2+H^+$) 640.8432 found 640.8420.

*4.3.13. BODIPY **2** with $I_2$/$HIO_3$ (1:4.5:4).* According to the method B, BODIPY **2** (85 mg, 0.32 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (366 mg, 1.44 mmol) in MeOH (5 mL) for 120 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, **5c** (8 mg, 5%) and **5e** (98 mg, 48%).

*4.3.14. BODIPY **3** with ICl (1:0.8).* According to the method A, BODIPY **3** (70 mg, 0.28 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (36 mg, 0.22 mmol) in MeOH (5 mL) for 30 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded 2-ethyl-4,4-difluoro-6-iodo-1,3-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (**6a**) (85 mg, 81%) as an orange solid and starting BODIPY **1** (10 mg, 14%).

*4.3.14.1. Compound **6a**.* Mp 174.4–174.8 °C; $^1$H NMR (700 MHz): $\delta$ 7.41 (1H, s, H-5), 6.96 (1H, s, H-8), 6.80 (1H, s, H-7), 2.49 (3H, s, $CH_3$–C3), 2.33 (2H, q, $J$=7.7 Hz, $CH_2$), 2.10 (3H, s, $CH_3$–C1), 1.00 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 165.9 (C), 142.2 (C), 140.8 (CH), 136.9 (C), 136.0 (C), 133.2 (C), 129.8 (CH), 122.0 (CH), 67.1 (C–I), 17.3 ($CH_2$), 14.1 ($CH_3$), 13.6 ($CH_3$), 9.6 ($CH_3$); IR (neat): 1601, 1368, 1346, 1140, 1090 cm$^{-1}$; MS (APCI$^-$) *m*/*z* (%): 374 ($M^-$, 70), 359 (100), 339 (20); HRMS-ESI$^+$: calcd for ($C_{13}H_{14}BF_2IN_2+H^+$) 375.0343 found 375.0335.

*4.3.15. BODIPY **3** with ICl (1:2.5).* According to the method A, BODIPY **3** (70 mg, 0.28 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (114 mg, 0.7 mmol) in MeOH (5 mL) for 90 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, 2-ethyl-4,4-difluoro-6,7-diiodo-1,3-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (**6b**) (48 mg, 34%) as an orange solid,

2-ethyl-4,4-difluoro-5,6-diiodo-1,3-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (**6c**) (49 mg, 35%) as a red solid and **6a** (14 mg, 13%).

*4.3.15.1. Compound* ***6b***. Mp 226.7–227.3 °C; $^1$H NMR (300 MHz): $\delta$ 7.45 (1H, s, H-5), 6.95 (1H, s, H-8), 2.48 (3H, s, $CH_3$–C3), 2.35 (2H, q, $J$=7.5 Hz, $CH_2$), 2.15 (3H, s, $CH_3$–C1), 1.02 (3H, t, $J$=7.5 Hz, $CH_3CH_2$); $^{13}$C NMR (75 MHz): $\delta$ 167.0 (C), 142.7 (C), 140.5 (CH), 138.0 (C), 136.6 (C), 134.9 (C), 122.6 (CH), 94.0 (C–I), 80.8 (C–I), 17.4 ($CH_2$), 14.0 ($CH_3$), 13.8 ($CH_3$), 9.7 ($CH_3$); IR (neat): 1613, 1241, 1183, 1120, 1073, 982 cm$^{-1}$; MS (APCI$^+$) $m/z$ (%): 500 ($M^+$, 50), 481 (100), 374 (98); HRMS-ESI$^+$: calcd for ($C_{13}H_{13}BF_2I_2N_2$+$H^+$) 500.9304 found 500.9311.

*4.3.15.2. Compound* ***6c***. Mp 222.4–222.8 °C; $^1$H NMR (700 MHz): $\delta$ 6.81 (1H, s, H-8), 6.78 (1H, s, H-7), 2.51 (3H, s, $CH_3$–C3), 2.34 (2H, q, $J$=7.7 Hz, $CH_2$), 2.09 (3H, s, $CH_3$–C1), 1.01 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 166.8 (C), 142.0 (C), 137.0 (C), 136.5 (C), 130.6 (CH), 120.0 (CH), 102.0 (C–I), 84.8 (C–I), 17.4 ($CH_2$), 14.1 ($CH_3$), 13.7 ($CH_3$), 9.6 ($CH_3$); IR (neat): 1615, 1322, 1265, 1138, 1109 cm$^{-1}$; MS (APCI$^+$) $m/z$ (%): 500 ($M^+$, 15), 481 (80), 374 (100), 361 (45); HRMS-ESI$^+$: calcd for ($C_{13}H_{13}BF_2I_2N_2^+$) 499.9226 found 499.9233.

*4.3.16. BODIPY* ***3*** *with ICl (1:8).* According to the method A, BODIPY **3** (70 mg, 0.28 mmol) in $CH_2Cl_2$/MeOH (10 mL/10 mL) and ICl (364 mg, 2.24 mmol) in MeOH (5 mL) for 300 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded, by order of elution, 3-chloro-6-ethyl-4,4-difluoro-1,2-diiodo-5,7-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (**6d**) (45 mg, 30%) as an orange solid and 2-ethyl-4,4-difluoro-5,6,7-triiodo-1,3-dimethyl-4-bora-3a,4a-diaza-*s*-indacene (**6e**) (61 mg, 35%) as a red solid.

*4.3.16.1. Compound* ***6d***. Mp 256.1–256.6 °C; $^1$H NMR (700 MHz): $\delta$ 6.86 (1H, s, H-8), 2.48 (3H, s, $CH_3$–C5), 2.33 (2H, q, $J$=7.7 Hz, $CH_2$), 2.13 (3H, s, $CH_3$–C7), 1.01 (3H, t, $J$=7.7 Hz, $CH_3$–$CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 167.2 (C), 142.4 (C), 138.8 (C–Cl), 137.7 (C), 136.9 (C), 134.6 (C), 121.6 (CH), 94.3 (C–I), 84.2 (C–I), 17.4 ($CH_2$), 14.0 ($CH_3$), 13.8 ($CH_3$), 9.7 ($CH_3$); IR (neat): 1617, 1373, 1238, 1139, 1020, 972 cm$^{-1}$; MS (APCI$^+$) $m/z$ (%): 534 ($M^+$, 15), 515 (100), 408 (40), 359 (75), 223 (65); HRMS-ESI$^+$: calcd for ($C_{13}H_{12}BClF_2I_2N_2$+$H^+$) 534.8920 found 534.8911.

*4.3.16.2. Compound* ***6e***. Mp 262.3–262.8 °C; $^1$H NMR (700 MHz): $\delta$ 6.82 (1H, s, H-8), 2.51 (3H, s, $CH_3$–C3), 2.36 (2H, q, $J$=7.7 Hz, $CH_2$), 2.15 (3H, s, $CH_3$–C1), 1.03 (3H, t, $J$=7.7 Hz, $CH_3CH_2$); $^{13}$C NMR (176 MHz): $\delta$ 167.7 (C), 142.4 (C), 138.7 (C), 138.0 (C), 137.1 (C), 121.1 (CH), 100.5 (C–I), 97.9 (C–I), 93.6 (C–I), 17.4 ($CH_2$), 14.0 ($CH_3$), 13.8 ($CH_3$), 9.7 ($CH_3$); IR (neat): 1616, 1235, 1133, 1089 cm$^{-1}$; MS (APCI$^+$) $m/z$ (%): 626 ($M^-$, 100); HRMS-ESI$^+$: calcd for ($C_{13}H_{12}BF_2I_3N_2$+$H^+$) 626.8276 found 626.8269.

*4.3.17. BODIPY* ***3*** *with $I_2$/$HIO_3$ (1:5:4.5).* According to the method B, BODIPY **3** (110 mg, 0.44 mmol) in $I_2$ (559 mg, 2.20 mmol) in EtOH (20 mL) and $HIO_3$ (348 mg, 1.98 mmol) for 300 min were reacted. Flash chromatography using hexane/EtAcO (98:2) afforded **6e** (149 mg, 54%).

### 4.4. Selective functionalization. General procedure

A solution of halogenated BODIPY and nucleophilic reagent in $CH_3CN$ (20 mL) was refluxed for 1–8 h under argon atmosphere. After that time, the solvent was removed under reduced pressure and the resulting mixture was dissolved in EtAcO and washed with $H_2O$. The extract was dried over $MgSO_4$, filtered and concentrated to dryness. The product was purified by flash chromatography on silica gel (eluent hexane/EtOAc).

### 4.5. Synthesis of 4,4-difluoro-2,3,6-triiodo-5-(4-methoxyphenylamino)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indecene (7)

BODIPY **4d** (40 mg, 0.05 mmol) and 4-methoxyaniline (13 mg, 0.1 mmol) in $CH_3CN$ (20 mL) were refluxed for 8 h. Flash chromatography using hexane/EtAcO (95:5) afforded BODIPY **7** (31 mg, 77%) as a purple solid. Mp 213.4–213.9 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 8.03 (1H, s, NH), 7.25 (2H, d, $J$=8.4 Hz, H-2′), 7.21 (2H, d, $J$=8.4 Hz, H-3′), 7.12 (2H, d, $J$=8.4 Hz, H-3″), 7.11 (1H, s, H-7), 6.86 (2H, d, $J$=8.4 Hz, H-2″), 6.52 (1H, s, H-1), 3.77 (3H, s, $OCH_3$), 2.36 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 159.6 (C), 157.0 (C), 144.9 (CH), 140.2 (C), 137.7 (C), 134.3 (C), 131.1 (C), 130.1 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 127.9 (C), 114.5 (CH), 96.0 (C–I), 83.9 (C–I), 66.8 (C–I), 55.6 ($OCH_3$), 21.4 ($CH_3$); IR (neat): 3363, 1583, 1249, 1091 cm$^{-1}$; MS (APCI$^-$) $m/z$ (%): 659 ($M^-$–122, 10), 558 (100), 508 (20), 340 (35); HRMS-ESI$^+$: calcd for ($C_{23}H_{17}BF_2I_3N_3O$+$H^+$) 781.8647 found 781.8638.

### 4.6. Synthesis of 3-(2-carboxyethylamino)-4,4-difluoro-2,5,6-triiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indecene (8)

BODIPY **4d** (60 mg, 0.08 mmol) and 3-aminopropanoic acid (40 mg, 0.46 mmol) in $CH_3CN$ (20 mL) were refluxed for 4 h. Flash chromatography using hexane/EtAcO (98:2) afforded BODIPY **8** (44 mg, 77%) as an orange solid. Mp >300 °C; $^1$H NMR (700 MHz, $CD_3OD$): $\delta$ 7.22 (4H, s, H-2′ and H-3′), 7.04 (1H, s, H-1), 6.20 (1H, s, H-7), 4.08 (2H, t, $J$=6.3 Hz, $NHCH_2$), 2.50 (2H, t, $J$=6.3 Hz, $CH_2COOH$), 2.33 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CD_3OD$): $\delta$ 177.6 (COOH), 159.3 (C), 141.8 (CH), 139.4 (C), 136.7 (C), 135.9 (C), 130.7 (C), 129.9 (CH), 128.8 (CH), 126.3 (C), 124.4 (CH), 91.2 (C–I), 81.6 (C–I), 72.8 (C–I), 41.6 ($NHCH_2$), 35.5 ($CH_2COOH$), 20.0 ($CH_3$); IR (neat): 3350, 1740, 1570, 1254, 1091 cm$^{-1}$; HRMS-ESI$^-$: calcd for ($C_{19}H_{15}BF_2I_3N_3O_2$–$H^+$) 745.8290 found 745.8300.

### 4.7. Synthesis of 3-diethoxycarbonylmethyl-4,4-difluoro-2,5,6-triiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indecene (9)

BODIPY **4d** (130 mg, 0.16 mmol), diethyl malonate (0.03 mL, 0.18 mmol) and NaH (6 mg, 0.25 mmol) in $CH_3CN$ (20 mL) were refluxed for 1 h. Flash chromatography using hexane/EtAcO (9:1) afforded BODIPY **9** (96 mg, 71%) as a pink solid. Mp 178.3–178.8 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.34 (2H, d, $J$=8.4 Hz, H-2′), 7.27 (2H, d, $J$=8.4 Hz, H-3′), 7.06 (1H, s, H-1), 6.91 (1H, s, H-7), 5.53 (1H, s, $CH(CO_2Et)_2$), 4.24 (4H, q, $J$=7.0 Hz, $OCH_2CH_3$), 2.40 (3H, s, $CH_3$), 1.25 (6H, t, $J$=7.0 Hz, $OCH_2CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 165.0 (COO), 152.2 (C), 143.0 (C), 142.2 (C), 139.8 (CH), 139.1 (C), 137.3 (CH), 135.4 (C), 130.5 (C), 129.6 (CH and C), 114.3 (C–I), 90.1 (C–I), 77.0 (C–I), 62.7 ($OCH_2CH_3$), 52.1 ($CH(CO_2Et)_2$), 21.6 ($CH_3$), 14.1 ($OCH_2CH_3$); IR (neat): 1761, 1740, 1570, 1251, 1089 cm$^{-1}$; HRMS-ESI$^+$: calcd for ($C_{23}H_{20}BF_2I_3N_2O_4$+$Na^+$) 840.8514 found 840.8499.

### 4.8. Synthesis of 3,5-bis(diethoxycarbonylmethyl)-4,4-difluoro-2,6-diiodo-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indecene (10)

BODIPY **4d** (50 mg, 0.06 mmol), diethyl malonate (0.04 mL, 0.26 mmol) and NaH (3 mg, 0.13 mmol) in $CH_3CN$ (20 mL) were refluxed for 1 h. Flash chromatography using hexane/EtAcO (98:2) afforded BODIPY **10** (40 mg, 73%) as a purple solid. Mp 212.3–212.8 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.36 (2H, d, $J$=8.1 Hz, H-2′), 7.28 (2H, d, $J$=8.1 Hz, H-3′), 7.05 (2H, s, H-1 and H-7), 5.48 (2H, s, $CH(CO_2Et)_2$), 4.23 (8H, q, $J$=7.2 Hz, $OCH_2CH_3$), 2.41 (3H, s, $CH_3$), 1.24 (12H, t, $J$=7.2 Hz, $OCH_2CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 165.1 (COO), 151.2 (C), 145.3 (C), 142.2 (C), 139.5 (CH), 135.1 (C), 130.6 (CH), 129.9 (C), 129.5 (CH), 76.2 (C–I), 62.6 ($OCH_2CH_3$), 52.1

(*CH*($CO_2Et$)$_2$), 21.5 ($CH_3$), 14.0 ($OCH_2CH_3$); IR (neat): 1760, 1743, 1580, 1255, 1090 $cm^{-1}$; HRMS-ESI$^-$: calcd for ($C_{30}H_{31}BF_2I_2N_3O-H^+$) 849.0163 found 849.0185.

### 4.9. Synthesis of 3-diethoxycarbonylmethyl-4,4-difluoro-2,6-diiodo-5-(4-methoxyphenylamino)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indecene (11)

BODIPY **9** (30 mg, 0.04 mmol) and 4-methoxyaniline (7 mg, 0.05 mmol) in $CH_3CN$ (20 mL) were refluxed for 2 h. Flash chromatography using hexane/EtAcO (8:2) afforded BODIPY **11** (20 mg, 70%) as a red solid. Mp 162.1–162.6 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 7.89 (1H, s, NH), 7.28 (2H, d, $J$=8.4 Hz, H-2′), 7.21 (2H, d, $J$=8.4 Hz, H-3′), 7.12 (1H, s, H-7), 7.11 (2H, d, $J$=8.4 Hz, H-3″), 6.86 (2H, d, $J$=8.4 Hz, H-2″), 6.62 (1H, s, H-1), 5.37 (1H, s, *CH*($CO_2Et$)$_2$), 4.24 (8H, q, $J$=7.0 Hz, $OCH_2CH_3$), 3.77 (3H, s, $OCH_3$), 2.37 (3H, s, $CH_3$), 1.25 (12H, t, $J$=7.0 Hz, $OCH_2CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 166.4 (COO), 159.5 (C), 156.7 (C), 144.8 (CH), 140.1 (C), 139.2 (C), 133.9 (C), 133.4 (C), 133.0 (C), 130.5 (C), 130.2 (CH and CH), 129.2 (CH), 129.1 (CH), 128.0 (C), 114.5 (CH), 70.3 (C–I), 65.9 (C–I), 62.2 ($OCH_2CH_3$), 55.6 ($OCH_3$), 52.0 (*CH*($CO_2Et$)$_2$), 21.4 ($CH_3$), 14.1 ($OCH_2CH_3$); IR (neat): 3363, 1765, 1740,1583, 1249, 1091 $cm^{-1}$; HRMS-ESI$^+$: calcd for ($C_{30}H_{28}BF_2I_2N_3O+Na^+$) 836.0077 found 836.0081.

### 4.10. Synthesis of 4,4-difluoro-2,3,6-(4-formylphenyl)-5-(4-methoxyphenylamino)-8-(4-tolyl)-4-bora-3a,4a-diaza-*s*-indecene (12)

BODIPY **7** (30 mg, 0.04 mmol) was dissolved in DME (20 mL). 4-Formylphenyl boronic acid (36 mg, 0.24 mmol) and $Na_2CO_3$ (13 mg, 0.12 mmol) were added in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium (3 mg, 0.0006 mmol). The reaction mixture was stirred under ultrasound irradiation for 5 h at 75 °C with a power of 720 W. After addition of $H_2O$ (50 mL), the organic layer was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated to dryness. Flash chromatography using hexane/EtOAc (95:5) afforded BODIPY **12** (57 mg, 46% yield) as a purple solid. Mp 190.6–191.1 °C; $^1$H NMR (700 MHz, $CDCl_3$): $\delta$ 10.0 (1H, s, CHO), 9.83 (1H, s, CHO), 9.78 (1H, s, CHO), 7.99 (1H, br s, NH), 7.86 (2H, d, $J$=8.3 Hz, 2CH), 7.69 (2H, d, $J$=8.1 Hz, 2CH), 7.60 (2H, d, $J$=8.3 Hz, 2CH), 7.44 (2H, d, $J$=7.9 Hz, 2CH), 7.43 (2H, d, $J$=8.3 Hz, 2CH), 7.28 (2H, d, $J$=7.9 Hz, 2CH), 7.14 (2H, d, $J$=8.3 Hz, 2CH), 7.03 (2H, d, $J$=8.1 Hz, 2CH), 6.99 (1H, s, CH), 6.76 (1H, s, CH), 6.69 (2H, d, $J$=8.8 Hz, 2CH), 6.39 (2H, d, $J$=8.8 Hz, 2CH), 3.53 (3H, s, $OCH_3$), 2.41 (3H, s, $CH_3$); $^{13}$C NMR (176 MHz, $CDCl_3$): $\delta$ 190.9 (CHO), 190.8 (CHO), 190.7 (CHO), 157.0 (C), 155.3 (C), 142.9–124.4 (C and CH), 120.5 (CH), 113.1 (CH), 54.4 ($OCH_3$), 20.4 ($CH_3$); IR (neat): 3370, 2854, 2732, 1698, 1597, 1449, 1205, 1099 $cm^{-1}$; MS (APCI$^-$) $m/z$ (%): 715 ($M^-$, 100), 666 (60), 576 (10); HRMS-ESI$^+$: calcd for ($C_{44}H_{32}BF_2N_3O_4+H^+$) 716.2534 found 716.2530.

### 4.11. Photophysical properties

*4.11.1. Photophysics.* Diluted BODIPY solutions were prepared by adding the corresponding solvent after evaporation of an adequate amount of a concentrated solution in acetone. Absorption and fluorescence spectra were recorded on a Varian model Cary 4E spectrophotometer and an SPEX Fluorolog 3-22 spectrofluorimeter, respectively. The fluorescence spectra were corrected from the wavelength dependence of the detector sensibility. Fluorescence quantum yield was determined using an adequate commercial BODIPY (PM567 and PM597)[18b] as reference. Radiative decay curves were registered with the time correlated single-photon counting technique (Edinburgh Instruments, model FL920, with picosecond resolution). Excitation was performed with a 470 nm diode laser and a 575 nm LED, both purchased by Picoquant. The emission was monitorized at the maximum emission wavelength. The fluorescence lifetime was obtained from the slope after deconvolution of the instrument response signal. The goodness of the deconvolution was controlled by the chi-squared statistical parameter and from the analysis of the residuals. Radiative and non-radiative rate constants were calculated as follows; $k_{fl}=\phi/\tau$ and $k_{nr}=(1-\phi)/\tau$.

*4.11.2. Computational details.* Ground state geometries and charge distributions were calculated at the Density Functional Theory using the hybrid method B3LYP, together with the lanl2dz basis set, especially parameterized to describe heavy atoms (i.e., iodine). Absorption transition was simulated by the Time Dependent method from the ground state.

### 4.12. Singlet oxygen generation

Individual argon-saturated solutions of **4b** and **4d** $Abs_{532}$ ca. 0.1 were irradiated with a flash photolysis apparatus. A nanosecond Nd/YAG laser system (Spectron) at 532 nm was used for excitation, employing a 150-W Xenon lamp as a source for the analyzing light. The detection system comprised a PTI monochromator and a red-extended photomultiplier (Hamamatsu R666). The signal, acquired and averaged by a digital oscilloscope (Hewlett–Packard 54504A), was transferred via an HPIB parallel interface to a PC where it was analyzed and stored.

The efficiency of $O_2(^1\Delta_g)$ production by **4b**, **4c** and **4d** in $CH_3CN$ was determined by the comparative method already described.[21,22] The initial intensities of the emission decay curves at 1270 nm ($I_0$) were determined for air-equilibrated solutions ($Abs_{532}$ ca. 0.2) as a function of laser fluence ($L_E$). The output at 532 nm of the already mentioned Spectron Nd/Yag laser was employed as the excitation source. $L_E$ was varied using neutral density filters. $\Phi_\Delta$ values for **4b** and **4d** were obtained by comparison of the slopes of the linear plots $I_0$ versus $L_E$ with that of a reference compound, all with absorbance matched solutions at 532 nm. The reference was Rose Bengal (RB) with a $\Phi_{\Delta RB}$=0.71 for $O_2(^1\Delta_g)$ generation determined in this work. For the determination of $\Phi_{\Delta RB}$ the already described technique was employed with emission at 355 nm. Perinaphthenone (PN), with $\Phi_{\Delta PN}$=1 in MeCN, was utilized as reference (Fig. 4S, ESI).[23]

The detection of $O_2(^1\Delta_g)$ phosphorescence was determined using a previously described system.[24] Briefly, a Nd/YAG laser (Spectron) was used for the excitation (532 nm) of the sensitizer RB ($Abs_{532}$=0.4), and the emitted radiation $O_2(^1\Delta_g)$ phosphorescence at 1270 nm was detected at right angles using an amplified Judson J16/8Sp germanium detector, after passing through two Wratten filters. The output of the detector was coupled to a digital oscilloscope and to a personal computer for the signal processing. Usually, six shots were needed for averaging, so as to achieve a good signal to noise ratio, from which the $I_0$ value was obtained.

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### Supplementary data

These data include copies of $^1$H and $^{13}$C NMR spectra for all compounds, tables and figures of photophysical properties and singlet oxygen generation. Supplementary data associated

with this article can be found in the online version, at doi:10.1016/j.tet.2011.11.070. These data include MOL files and InChiKeys of the most important compounds described in this article.

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