Carborane-BODIPY Dyads: New Photoluminescent Materials through an Efficient Heck Coupling

FULL PAPER

Carborane-BODIPY Dyads: New Photoluminescent Materials Through an Efficient Heck Coupling

Chiara Bellomo,[a] Mahdi Chaari,[b][d] Justo Cabrera-González,[b] Marco Blangetti,[a] Chiara Lombardi,[a] Annamaria Deagostino,[a] Clara Viñas,[a] Nerea Gaztelumendi,[c] Carme Nogués,[c] Rosario Nuñez,*[b] and Cristina Prandi*[a]

Abstract: a small library of carborane-BODIPY/aza-BODIPY dyads have been efficiently synthesized by means of a novel convergent synthetic approach where the key step is a Pd-catalyzed Heck coupling reaction. The structural characterization and photoluminescence properties of the newly synthesized dyads have been evaluated. The presence of the carborane does not alter significantly the photophysical patterns of the BODIPY or aza-BODIPY in the final fluorophores, but it produces a decrease of the emission fluorescent quantum yields that is in the range from 1.4% for aza-BODIPY to 48% for BODIPY-dyads. The carborane-BODIPY dyads are successfully internalized by the cells, especially compounds **2**, **4** and **13**, demonstrating their cytoplasmic localization. The fluorescent and biocompatibility properties make these compounds good candidates for *in vitro* cell tracking.

Introduction

Carborane clusters are fascinating chemical species part of the boron cluster chemistry, which has been the subject of intense and attractive research over the last 60 years.[1] Carboranes are very robust compounds characterized by a three-dimensional (3D) structure,[2] high stability (chemical, thermal and photochemical),[3] electron-withdrawing properties[4] low nucleophilicity, high hydrophobicity, and low toxicity in biological systems.[3b, c, 5] Many new synthetic procedures have been developed to functionalize these cluster and the physico-chemical properties of carborane-derivatives have been analyzed, showing that they can act differently even when compared to electronically similar organic species, such as phenyl rings.[6] Their physico-chemical properties, together with their versatility toward functionalization,[7] makes them suitable building blocks easily linkable to other molecules.[8] Thanks to their unique characteristics, carboranes have been exploited in varied fields, such as medicine,[5c, 9] where they are used in boron neutron capture therapy (BNCT) and drug delivery,[5c, 10] catalysis,[11] non-linear optical materials,[12] liquid crystals,[13] among other.

Dicarba-*closo*-dodecarboranes differ on the position of the two carbon atoms in the cluster, making the electronic properties of the *ortho-, meta-,* and *para*-isomer different, especially between the *ortho*- and the other two isomers.[14] Moreover, the electron withdrawing ability through the $C_{cluster}$ (C_c) atoms,[7f] and the distortion of the cage are crucial features, because they permit to choose between the three different isomers in order to tune the properties of the substituents attached to the cluster.

Since our seminal work in 2007, where the first example of a fluorescent molecules containing carboranyl moieties was reported,[15] our group[3a, b, 5b, 16] and others [16e, 17] have developed new fluorescent materials incorporating carboranes. As a result, the interest in studying the photoluminescent (PL) properties of these compounds in view of new applications has noticeably increased; they can find applications as luminescent materials, organic field-effect transistors (OFETs), phosphorescent organic light emitting diodes (PHOLEDs), or in biomedicine.[18] Moreover, the carboranyl cage can directly influence the PL properties of the final material and gives an additional thermal stability, which is crucial in tuning the final properties of a certain material.[3, 5b]

Owing to their unique spectroscopic properties and their easiness of functionalization, BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dyes[19] have emerged as an interesting new class of fluorophores for boron clusters functionalization, especially for solid state luminescent devices and BNCT applications.[20] This class of fluorophores, together with their aza-analogues, are well known especially for their biological applications,[21] because of their excellent features such as good photochemical stability, high quantum yield, and narrow absorption/emissions bands.[22]

Only in the last few years, some families of carboranyl-BODIPY dyads with unique PL properties have been synthesized, exploiting the reactivity of appropriately functionalized BODIPYs toward Sonogashira cross-coupling,[23] alkyne insertion into decaborane[24] and Pd-catalyzed Suzuki cross coupling reactions.[20b] However, to the best of our knowledge, a Heck coupling approach between carboranes and halogenated BODIPY dyes has not been reported yet.

The Heck reaction on BODIPY dyes is nowadays an established synthetic procedure for the post-functionalization of the dipyrromethene core.[25] As part of our studies aimed at tagging

[a] C. Bellomo, Dr. M. Blangetti, Dr. C. Lombardi, Dr. A. Deagostino, Prof. C. Prandi
Department of Chemistry
University of Turin
Via P. Giuria 7, 10125 Torino (ITALY)
E-mail: cristina.prandi@unito.it
[b] M. Chaari, Dr. J. Cabrera-González, Prof. C Viñas, Dr. R. Núñez
Instituto de Ciencia de Materiales de Barcelona (ICMAB-CSIC)
Campus de la UAB, E-08193- Bellatera, Barcelona (SPAIN)
E-mail: rosario@icmab.es
[c] Dr. N. Gaztelumendi, Dr. C. Nogués
Departament de Biologia Cellular, Fisiologia i Immunologia.
Universitat Autònoma de Barcelona, E-08193-Bellaterra, Barcelona (SPAIN)
[d] M. Chaari
Laboratoire des Sciences des Matériaux et de l'Environnement, Faculté des Sciences de Sfax, Université de Sfax, B.P. 1171, 3000 Sfax (TUNISIE).

biological relevant compounds using fluorescent probes for live-cell imaging applications,[26] we exploited the excellent photo-features of BODIPYs as optical probes and we recently reported the optimization of a Heck coupling reaction on an asymmetric aza-BODIPY core.[27] Likewise, styrene-containing carborane derivatives have demonstrated to be excellent starting molecules to achieve different fluorescent materials via Heck coupling reaction.[3a, 16a-d] Therefore we envisaged that the latter might represent a very suitable coupling partner for Heck reaction with halogenated BODIPY fluorophores and their aza-analogues. Additionally, the π-conjugated styrene moiety spacer might confer unique photoluminescent properties to the final dyes making them very attractive in this research field.

On the basis of these considerations, and motivated by our ongoing interest in extending the feasibility of functionalization of the carborane core with fluorescent scaffolds, we herein report the synthesis of a small library of carborane-BODIPY/aza-BODIPY dyads by means of an efficient convergent synthetic approach where the key step is a Pd-catalyzed Heck coupling reaction (Figure 1).

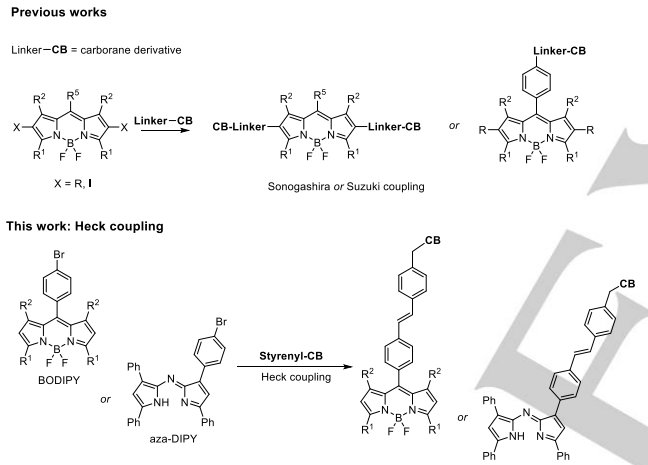


Figure 1. Aim of the work.

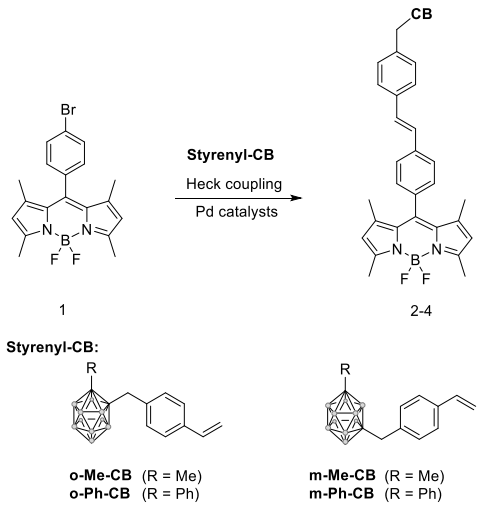
In fact, the rationale of this work focuses on the following key points: 1) extending the scope of different Pd-catalyzed cross coupling reactions to widen the array of photoluminescent carborane derivatives obtainable according to friendly synthetic pathways and 2) studying the properties of the new molecules whose applications in many research fields, from pharmaceutics to fluorescent materials, is a cutting edge-topic.

To this purpose, the Heck coupling between a set of styrenyl-carboranes (*ortho*- and *meta*-) and either BODIPY or aza-DIPY dyes has been successfully accomplished. The spectroscopic and photophysical properties of these new compounds, together with their visualization by confocal microscopy in HeLa cancer cells, are also discussed.

Results and Discussion

Synthesis and characterization of the compounds.

Since its discovery in the '70s, Heck coupling has become a straightforward method for functionalizing olefins with aryl substituents, and it finds wide applications in the field of natural product synthesis, bioorganic chemistry and material science.[28] Transition metal-catalyzed cross coupling reactions represent a straightforward strategy for the post functionalization of the BODIPY core, since boron-chelated dipyrromethene starting materials are less sensitive to Pd-catalyzed reaction conditions compared to their aza-analogues. This would allow to obtain an array of symmetrical and asymmetrical BODIPY compounds with tunable physical and spectroscopic properties.[25] However, as mentioned before, a Heck coupling between a styrenyl-containing carborane (**Styrenyl-CB**) and a dipyrromethene-based dye has never been reported yet. To this purpose, we identified the two Heck coupling partners to start our investigation and optimize our target reaction, as: a) a properly functionalized carborane bearing a styrene moiety (***o*-Me-CB**, ***o*-Ph-CB**, ***m*-Me-Cb** and ***m*-Ph-Cb**) and b) the high fluorescent BODIPY dye **1** (Scheme 1) that exhibits a maximum λ_{abs} = 502 nm. The 1,3,5,7-tetramethylBODIPY derivative **1** has been synthesized by acid catalyzed condensation of 2,4-dimethylpyrrole with *p*-bromobenzaldehyde,[29] while the styrenyl-containing carborane derivatives have been successfully synthesized by lithiation of the parent *closo*-carborane cluster followed by the addition of 4-vinylbenzyl chloride, as described in the literature.[16d, g]

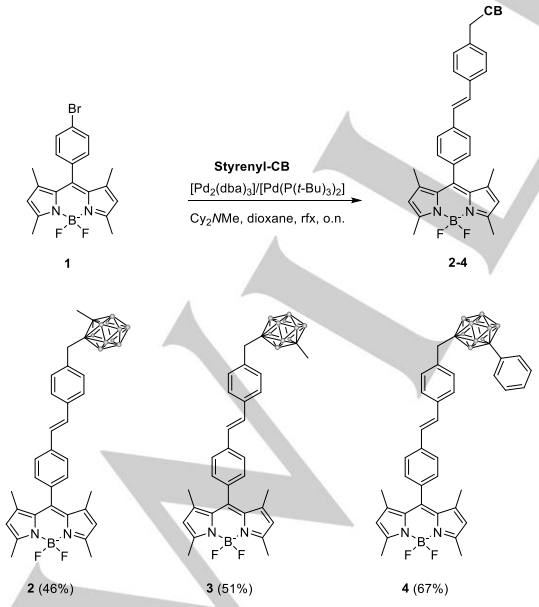


Scheme 1. Selected coupling partners for the Heck reaction optimization.

Based on our recent results concerning the functionalization of asymmetric aza-BODIPY derivatives by Heck reaction,[27] we tested our previously reported coupling procedure on carborane-containing olefins using a simple commercially available coupling partner. The ***o*-Me-CB** and bromobenzene were thus reacted using the $Pd(OAc)_2$/(*o*-Tol)$_3$P (10% and 20% respectively)

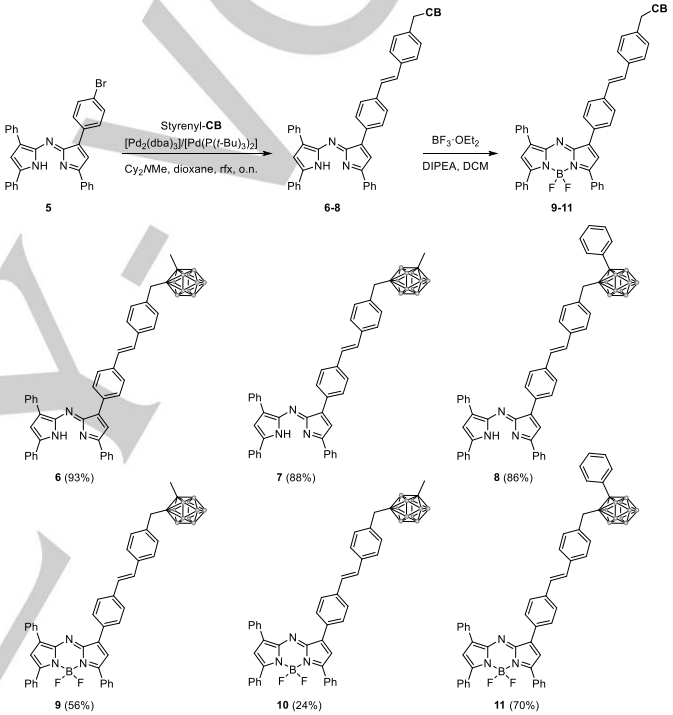
catalytic system, in the presence of TBAB (tetrabutyl ammonium bromide) as an additive, Bu_3N as base and dimethylformamide (DMF) as solvent at 100 °C. Under these conditions, no reaction was observed and the starting materials were recovered unchanged. Puzzled by this unexpected negative result, we speculated that the peculiar reactivity of the carborane cage might hamper the coupling reaction, since the challenging step of the Heck catalytic cycle is the coordination and transmetalation of the alkene. The connection of the styrenyl moiety to a strong electron withdrawing carboranyl cage might deactivate the olefin sterically and electronically, therefore we directed our efforts on finding a different procedure that could be more suitable for the **styrenyl-CB** Heck coupling reaction. Littke and Fu described in 2001 the $Pd_2(dba)_3$/$Pd(P(t\text{-}Bu)_3)_2$ catalytic system in the presence of dicyclohexylmethylamine (Cy_2NMe) as an effective tool for the Heck reactions on aryl chlorides and aryl bromides, both in extreme and mild conditions.[30] The unusual effectiveness of the base, which was proven to provide a more active catalyst compared to other bases (such as Cs_2CO_3), made this versatile procedure also efficient to introduce a variety of functional groups either on brominated and iodinated silicate cages (possessing similar characteristics with the carborane cluster) and on the carboranyl substrates of our interest.[3a, 16b-d, 31]

On these grounds, these conditions for the Heck coupling were applied to our substrates. Brominated BODIPY **1** was then reacted with ***o*-Me-CB** in the presence of $Pd_2(dba)_3$/$Pd(P(t\text{-}Bu)_3)_2$ (1.2% and 1.6% respectively) as catalyst, using Cy_2NMe as base in 1,4-dioxane at 100 °C. To our delight, the reaction proceeded smoothly in 12 h with full conversion of the starting materials to give **2** (Scheme 2) with 46% of final yield. The procedure has been successfully applied to ***m*-Me-CB** and ***m*-Ph-CB** affording the corresponding coupling products **3** and **4** in moderate yields (Scheme 2 and Table 1, entries 1-3). More details of the synthetic procedures are in the ESI.



Scheme 2. Heck coupling for the synthesis of carborane-BODIPY dyads **2**-**4.**

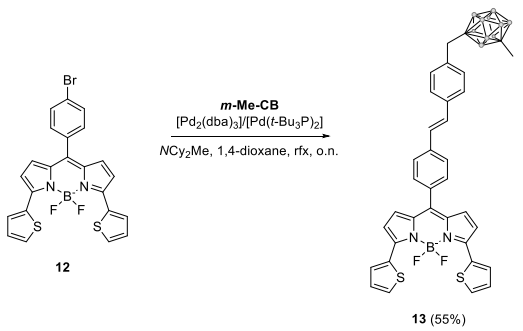
Nowadays, there is a great interest in the development of bright and stable fluorophores emitting in the red spectral region (wavelength >650 nm), owing to the advantages of this kind of radiation for sensing and bioimaging purposes.[32] Several synthetic strategies have been developed with the aim to modify the BODIPY and shift the spectral bands;[33] one example is the replacement of the *meso*-carbon atom by nitrogen to achieve aza-BODIPYs,[22a] or the extension of the conjugation via aromatic frameworks at 3,5-positions, such as thienyls, resulted in further bathochromic shift in S0→S1 transition. This is probably due to further enhancement of conjugation in BODIPY unit because of the presence of aryl substituents at 3,5-positions.



Scheme 3. Synthesis of aza-BODIPY-carborane derivatives **6**-**8** by Heck coupling reaction and subsequent complexed final products **9-11**.

As a further application of this methodology, we envisaged to extend the synthetic approach switching from the green emitting BODIPY dyes **2**-**4** to red/NIR emitting aza-BODIPY fluorophores, which exhibit a longer wavelength fluorescence emission more suitable for deep tissues penetration and bioimaging purposes.[34] Since aza-BODIPYs have a remarkable tendency to dechelation under the cross coupling conditions,[27, 35] we chose their parent asymmetrically brominated 3,3',5,5'-tetraarylazadipyrromethene dye aza-DIPY **5** (the precursor of aza-BODIPY derived of the BF_2 ligand) as the substrate for the Heck functionalization. This coupling partner was prepared starting from the corresponding chalcones derivatives according to the reported procedure by O'Shea and co-workers.[36] The Heck coupling has been subsequently attempted in the presence of $Pd_2(dba)_3$/$Pd(P(t\text{-}Bu)_3)_2$ catalytic system on **5** with different styrenyl-containing carboranes (***o*-Me-CB**, ***m*-Me-CB** and ***o*-Ph-CB**), giving the

corresponding coupling products **6**-**8** with high yields (Scheme 3 and Table 1, entries 4-6). Products **6**-**8** have been then subjected to the final complexation step, and BF_2 was introduced using boron trifluoride diethyletherate and DIPEA affording the final compounds **9-11** in high yields (Scheme 3).



Scheme 4. Synthesis of the BODIPY-carborane derivative **13** by Heck coupling reaction.

Furthermore, in order to compare the spectroscopic properties of fluorescent carboranes dyads which absorb and emit in the therapeutic window range, we envisaged the possibility of functionalize the carborane scaffold with a highly conjugated strongly fluorescent BODIPY dye emitting in the red visible light region. To this purpose, the brominated 3,5-dithienylBODIPY **12** (λ_{abs} = 622 nm) has been synthesized starting from the parent 3,5-dichloroderivative by Suzuki-Miyaura cross coupling as previously described.[37][38] A satisfactory result was then achieved using brominated BODIPY **12** and ***m*-Me-CB** as coupling partners, which were subjected to Heck coupling conditions, giving compound **13** in 55% yield (Scheme 4 and Table 1, entry 7).

Table 1. Summarized results of Heck reaction between brominated **1**, **5**, **12** and styrenyl-containing carborane derivatives (**styrenyl**-**CB**).

Entry[a]	(BO)DIPY-Br	Styrenyl-CB	Compound	Yield (%)[b]
1	**1**	***o*-Me-CB**	**2**	46
2	**1**	***m*-Me-CB**	**3**	51
3	**1**	***m*-Ph-CB**	**4**	67
4	**5**	***o*-Me-CB**	**6**	93
5	**5**	***m*-Me-CB**	**7**	88
6	**5**	***o*-Ph-CB**	**8**	86
7	**12**	***m*-Me-CB**	**13**	55

[a] Reaction conditions: **Styrenyl**-**CB** (1.0 eq.), (BO)DIPY-Br (1.1 eq.), $Pd_2(dba)_3$ (0.012 eq.), $Pd(P(t\text{-}Bu)_3)_2$ (0.016 eq.), Cy_2NMe (1.34 eq.), dioxane (3 mL), 100 °C, 12 h. [b] Isolated yields.

Final compounds **2-4**, **9**-**11** and **13** were fully characterized by ^1H, $^{13}C\{^1H\}$, $^{11}B\{^1H\}$ and ^{11}B NMR spectroscopy, together with ESI-HRMS and FTIR analyses. The ^1H NMR spectral data confirmed the complete (*E*)-stereoselectivity of the Heck coupling reaction[27] for all the compounds, as established by coupling constants analyses of the characteristic olefinic proton signals. The ^1H NMR spectra of compounds **2**-**4**, **9**-**11** and **13** feature the characteristic benzylic proton signals of the spacer in the 3.00-3.50 ppm range, while the ^1H NMR spectra of BODIPY derivatives **2**-**4** show the peculiar pyrrolic CH signals of the dipyrromethene core at δ 6.00 ppm. Additionally, protons from the *Ph*-carborane derivatives are identified in the aromatic region, whereas the *o*-Me derivatives **2** and **9** show the resonance corresponding to the C_c-CH_3 near 2.20 ppm, which is shifted upfield to 1.65 ppm for the *m*-Me derivatives (**3**, **10** and **13**). The $^{11}B\{^1H\}$ NMR spectra of all the compounds exhibit a triplet attributed to -BF_2 unit, centered at 0.61 ppm for the aza-BODIPYs and at 0.45 ppm for BODIPY derivatives. In addition to the -BF_2 resonance, those compounds bearing *o*-carborane clusters show the typical 1:1:8 or 2:8 distribution, whereas for *m*-isomers the pattern was 1:1:6:2 or 2:6:2, all of them in the region from -3.63 to -13.70 ppm.[16c] The $^{13}C\{^1H\}$ NMR spectra of all the compounds show a resonance in the range 41.0-43.0 ppm attributed to the benzylic carbon, and also for the Me-carborane derivatives the C_c-CH_3 can be identified from 23.0 ppm to 25.0 ppm.

Photophysical properties

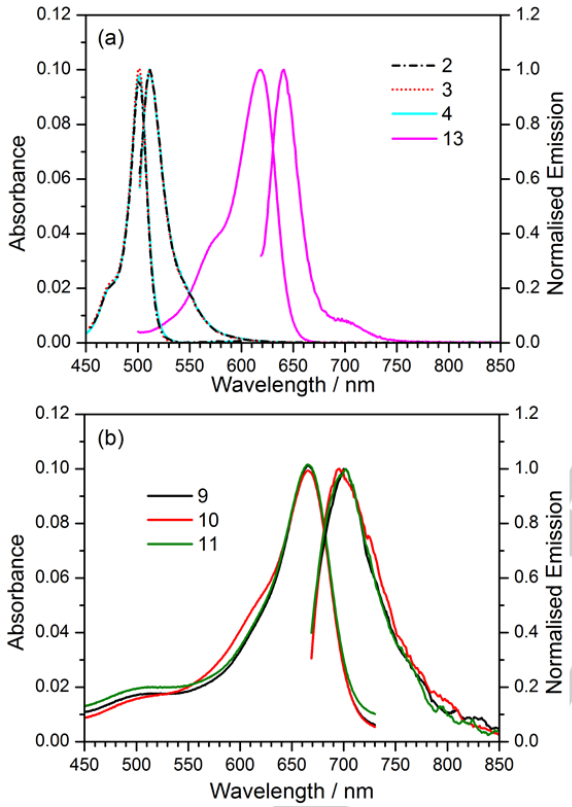
The photophysical behavior of the final compounds was investigated, and the most significant spectroscopic properties are collected in Table 2. Figure 2 shows UV/Vis and fluorescence spectra of the dyads in THF solution. As expected, the absorption and emission spectra of 1,3,5,7-tetramethyl-BODIPY derivatives **2**-**4** are dominated by the BODIPY moiety, showing the typical narrow bands with maxima at λ_{abs}=501 nm and λ_{em}=511 nm, respectively (Table 2, entries 2-4). A very small redshift (6 nm) is observed in the emission when these carborane-BODIPY derivatives are compared with their parent *meso*-phenyl-1,3,5,7-tetramethylBODIPY (**Ph-TMBDP**, entry 1). Therefore, despite the Heck coupling leads to extend the conjugation, the emission maxima and Stokes shifts are not significantly influenced in this case because of the orthogonal orientation of the *meso* substituent.[39]

Among the red-emitting dyes series, compounds **9-11** show the characteristic absorption and emission maxima of the aza-BODIPY core centered at λ_{abs} = 665 nm and λ_{em} = 700 nm, respectively (Table 2, entries 6-8), exhibiting a noticeable bathochromic shift when compared to their parent tetraphenyl-aza-BODIPY (**aza-BDP**, entry 5),[40] thanks to the higher degree of π-conjugation induced by the stilbenic moiety. Compound **13** shows absorption and emission maxima centered at λ_{abs} = 618 nm and λ_{em} = 641 nm, respectively (entry 10), showing no bathochromic shift compared to *meso*-phenyl-3,5-dithienylBODIPY (**Ph-THBDP**, entry 9), which is attributed to the presence of the stilbenic moiety on the *meso* position, as previously described for the green emitting probes **2-4**.

All the compounds show molar extinction coefficients in the range from 67000 to 83000 $M^{-1}cm^{-1}$, comparable to the typical values of BODIPY and aza-BODIPY dyes,[22b] although in all cases below the values of their respective parents **Ph-TMeBDP**, **aza-BDP** and **Ph-THBDP**.

Remarkably, substitution of BODIPYs with **styrenyl-CB** produces an increase of their Stokes shifts with respect to the non-substituted parents. Compounds **2**-**4** show Stokes shifts of 10-11 nm in front of 4 nm for **Ph-TMBDP**, which indicate larger dipole moments for our compounds in the excited state with respect to the ground state. Compounds **9-11** have Stokes shifts of 40-42 nm (entries 6-8), around 10 nm larger than **aza-BDP** (32 nm), while compound **13** shows the same Stokes shift as **Ph-THBDP.**

Figure 2. Absorption and normalised emission spectra in THF of (a) BODIPY-carborane (λ_{exc} = 501nm) and (b) aza-BODIPY-carborane derivatives (λ_{exc} = 665 nm).



It is worth noting that our systems show very different fluorescent quantum yields (Φ_F) depending on the type of BODIPY core; BODIPY derivatives **2-4** exhibit the highest values with Φ_F around 40-42%, though weaker than **Ph-TMBDP** (56%), whereas aza-BODIPY derivatives **9-11** show low Φ_F (1.4-1.5%), that is also slightly lower, but similar, than the **aza-BDP** (1.9%). It is known from the literature that not all the 3,5-dithienyl BODIPYs are strongly fluorescent;[41] most of them functionalized at their *meso*-positions were reported to have low fluorescence efficiencies, nevertheless *the meso*-phenyl-3,5-dithienylBODIPY (**Ph-THBDP**) represents an exception with a 84% of quantum yield. Noticeably, it seems that the substitution at the *meso*-position with the stilbene moiety ended with **CB** induces a strong knocking down of the Φ_F, which was largely diminished to 48%, as measured in THF. Therefore, we can conclude that for all the synthesized dyads the presence of the **styrenyl-CB** moiety seems to produce a decrease of the fluorescence efficiency when compared to the non-substituted BODIPYs. Besides, no significant differences were observed in the photophysical data for the different substituted-carborane isomers; the only difference is that ***o*-Me-CB** and ***o*-Ph-CB** derivatives show lower molar extinction coefficients when compared to their *meta*-**CB** analogous.

We have also calculated the brightness of these dyes, which is the product of the molar extinction coefficient at the excitation wavelength and the fluorescence quantum yield [$\varepsilon(\lambda)\cdot\Phi_F$]. The higher value of brightness was found for BODIPY derivative **4** (36105 M^{-1} cm^{-1}), followed by **3** and **13** that surprisingly exhibit the same values (32562 M^{-1} cm^{-1}), and **2** (31512 M^{-1} cm^{-1}). As expected, aza-BODIPY derivatives display much lower brightness, for **9** it was about 1800 M^{-1} cm^{-1}, whereas for **10** and **11** it was about 1148 M^{-1} cm^{-1}.

Table 2. Selected photophysical data for compounds the final compounds.[a] The photophysical properties of *meso*-phenyl-1,3,5,7-tetramethylBODIPY **Ph-TMBDP** (entry 1),[42] tetraphenyl-aza-BODIPY **aza-BDP** (entry 5),[40] and *meso*-phenyl-3,5-dithienylBODIPY **Ph-THBDP** (entry 9)[41] were added for comparison.

entry	Compound	λ_{abs} / λ_{em} (nm)	ε (M^{-1} cm^{-1})	Φ_F[b] (%)	Stokes shift (nm)
1	**Ph-TMBDP**	501/505	91200	56.0	4
2	**2**	501/512	78000	40.4	11
3	**3**	501/511	81000	40.2	10
4	**4**	501/511	83000	43.5	10
5	**aza-BDP**	650/682	84600	1.9	32
6	**9**	665/705	72000	1.5	40
7	**10**	665/706	82000	1.4	41
8	**11**	665/707	82000	1.4	42
9	**Ph-THBDP**	622/645	72000	84[c]	23
10	**13**	618/641	67000	48.6	23

[a] Measured in THF at room temperature [b] Fluorescence quantum yields were determined using a solution of Rhodamine 6G in ethanol as standard (Φ_F =0.94).[43] [c] Data for **Ph-THBDP** are reported in the literature in $CHCl_3$ (see ref.[41])

Bioimaging by confocal microscopy

Fluorescence imaging techniques have been used to visualize bio-components and bio-processes by transforming the chemical and biological information into detectable signals. In the context of bioimaging, fluorescent BODIPY dyes with absorption and emission located in the far-red and near-infrared (NIR) (650–900

nm), although not visible to the human eye, have arised as promising fluorescent probes and labelling for bio-imagingin living systems, since fluorescence in the long-wavelength region generates minimum phototoxicity to biological components, minimal auto-fluorescence by bio-molecules and deep tissue penetration.[44] To analyze the potential use of of compounds **2**-**4**, **9**-**11** and **13** as fluorescence probes for biological systems, cell internalization was assessed by confocal microscopy using Hela cells, a human cancer cell line. Remarkably, all the compounds, except **9**, can penetrate into cells being accumulated in the cytoplasm (Figures 3 and S1).

According to their emission spectra, compounds **2-4** were detected in the range of green fluorescence, compounds **10** and **11** in the range of far-red (NIR region, which is outside the visible spectra of human eye), and compound **13** shows a width emission range, from red to far-red of the spectral region. To visualize the far-red light emitted by compounds **9-11** and **13**, we arbitrarily assigned the grey color.

The percentage of the laser power used (usually between 10-20% of its maximum) was in accordance to the quantum yield and brightness calculated for each compound. Higher percentages (50, 30 and 7%) were needed to detect internalization of compounds **10**, **11** and **3**, respectively, whereas only 1% of the laser power was sufficient to easily detect compounds **2**, **4** and **13**, which show an exceptional fluorescence intensity. The orthogonal projections (Figure 3), optical sections in the XZ and YZ axis of the merged images from each sample, definitively demonstrated that the compounds were located inside the cells and not adhere to the cell surface.

As the absorption and emission maxima of aza-BODIPY derivatives (**9**, **10** and **11**) are almost identical, they were excited using the same laser wavelength. Compounds **10** and **11** were successfully detected, but compound **9**, despite showing the highest brightness among the aza-BODIPY derivatives was not detected; no fluorescence signal was observed even after increasing the laser power to 65%. This lack of signal is probably due to the incapacity of cells to internalize compound **9** and cannot be attributed to the Me-*o*-carborane moiety, as its counterpart **10** was easily observed. The difference of the fluorescence intensities observed after cell incubation by confocal microscopy for compounds derived from the same type of BODIPY indicates that carboranes are tagged to the (aza)BODIPY during the cell cutures, since if the clusters were not linked to the (aza)BODIPY, all the cell cultures would show the same fluorescence intensity due to the (aza)BODIPY itself, but this is not the case.

Conclusions

A set of new carborane-BODIPY dyads has been successfully synthesized by a versatile Heck coupling, starting from a styrenyl-

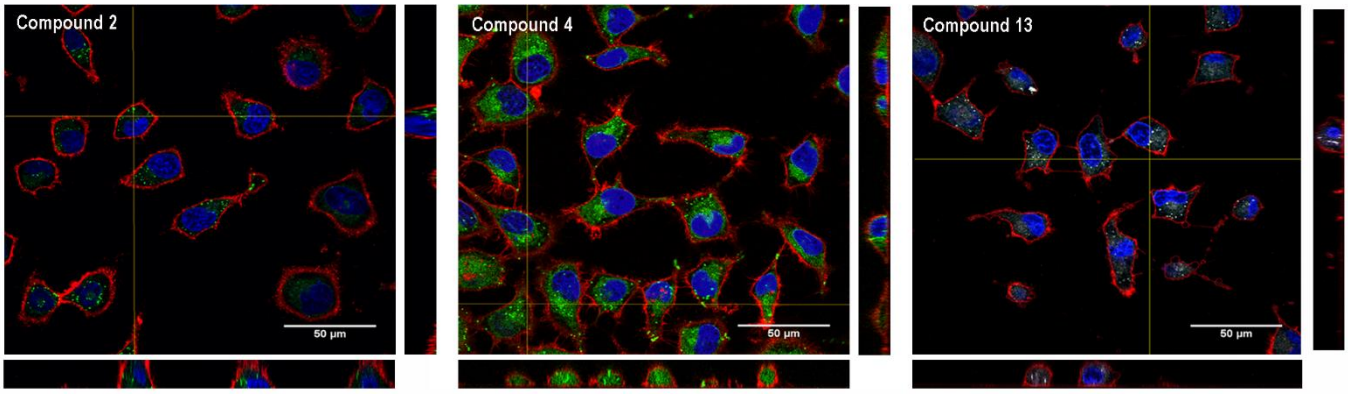


Figure 3. Cellular uptake of BODIPY-derivatives by confocal microscopy. Orthogonal projections of compounds **2**, **4** and **13** demonstrating their cytoplasmic localization. (Scale bar: 50 µm). Plasma membrane (red); nucleus (blue); compounds **2** and **4** (green); compound **13** (grey).

containing carborane and a brominated (aza)dipyrromethene fluorophore. The procedure has been fruitfully applied to different types of carborane derivatives and dyes finely tuned in their spectroscopic properties. The reaction showed moderate yields with the BODIPYs and high yields using the aza-BODIPY as precursor. The final compounds have been fully characterized and their photophysical behaviour investigated. After functionalization with the carborane cage, the absorption and emission patterns of the fluorophore are preserved. Noticeably, a bathochromic shift of the aza-BODIPY derivatives is observed because of the effective extension of conjugation, while for all the compounds a considerable decrease of fluorescence quantum yield was observed. Moreover, substitution of (aza)BODIPYs with **styrenyl-CBs** produces an increase of their Stokes shifts with respect to the non-substituted parents. However, despite the decrease in the quantum yield values, the compounds preserve an appreciable fluorescence which allows their use as fluorescent probes for confocal microscopy preliminary studies. All the compounds were successfully internalized by HeLa cells except ***o*-Me-CB** aza-BODIPY dyad **9**. Moreover, compounds **2**, **4** and **13** possess the best fluorescence characteristics for cell imaging

purposes, being **2** and **4** (and **13** when detected in the visible red wavelength) the first choice when a simple or double labelling is necessary. NIR emission of compound **13** could also be very useful to avoid overlapping emission, mainly when multiple fluorochromes are used in the same sample.

Experimental Section

General procedure for Heck coupling reaction

A round-bottomed flask equipped with a condenser was charged with 3 mL of dry 1,4-dioxane, and the solvent was degassed with nitrogen for 15 minutes. The appropriate carborane (1 equiv.) and (BO)DIPY (1.1 equiv.) derivatives were added, followed by $Pd_2(dba)_3$ (1.2 mol%), $Pd(P(t\text{-}Bu)_3)_2$ (1.6 mol%) and Cy_2NMe (1.34 equiv.). The reaction mixture was heated at reflux overnight. After complete conversion of the starting material (as monitored by TLC analysis), the mixture was filtered over celite, washed with THF and concentrated to dryness. The crude residue was purified by flash column chromatography on silica gel.

Biological assays

Products **2-4, 9-11** and **13** were first dissolved in pure DMSO (Sigma/Aldrich) and then, diluted in 2 ml of Minimum Essential Medium (MEM) supplemented with 10% of Fetal Bovine Serum (FBS) (both from Gibco) and 1% (200 mM) of L-glutamine (Biowest), obtaining a final compound concentration of 10 µM and 0.5% of DMSO. Compounds were sterilized through a syringe filter (0.2 µm diameter. Fisher Scientific) to maintain sterile conditions and kept at 4 ºC until use. HeLa cells were routinely cultured using MEM + 10% FBS + 1% L-glutamine as culture medium.

Cellular uptake

Cell internalization of the compounds was assessed by confocal laser scanning microscopy. HeLa cells ($1x10^5$ cell/ml) were seeded into glass bottom culture dishes (MatTek) and after 24 h in standard culture conditions (37ºC and 5%CO_2) to allow cell attachment, were exposed to 1 ml of each compound for 4 h. Then, compounds were removed, and the cell cultures were rinsed twice with sterile 1X phosphate buffered solution. Finally, nuclei and plasma membrane were counterstained with 1 µl/ml of Hoescht (10 mg/ml. Thermo Fisher) and Cell Mask (5 mg/ml. Thermo Fisher), respectively. Cell membrane of cultures incubated with compounds **9-11** and **13** (emission spectra in far red) were counterstained with Cell Mask Orange, whereas Cell Mask Deep Red was used in cell cultures exposed to compounds with green emission (**2-4**) to avoid signal overlapping. Serial images of each sample (20-32 optical sections of 1µm) were obtained by confocal laser scanning microscope (CLSM, Olympus) and the 3D orthogonal projections were generated using the ImageJ software. Experiments were performed in triplicate for compound **9** and in duplicate for the rest of compounds.

Supporting Information Available

Electronic Supporting Information (ESI) including the synthesis of compounds, as well as ^1H, $^1H\{^{11}B\}$, $^{13}C\{^1H\}$, ^{11}B NMR, and ESI-HR MS is available free of charge on the WWW under http http://www.chemeurj.org/ or from the author.

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Conflict of interest

The authors declare not competing finantial interest

Keywords: Carborane • BODIPY• bioimaging • photoluminescent material• Heck coupling

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