Conference paper

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Carbohydrates and BODIPYs: access to bioconjugatable and water-soluble BODIPYs

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Abstract: Fluorescent difluoroboron dipyrromethenes (BODIPYs), have been accessed in a one-pot synthetic operation from phthalides and pyrroles, a process that involves *O*-ethylation of phthalides with Meerwein's reagent (Et_3OBF_4) and reaction of the ensuing tetrafluoroborate salts with pyrrole, followed by treatment with $BF_3 \cdot OEt_2$. These derivatives are endowed with a *ortho*-hydroxymethyl 8-*C*-aryl group for further derivatization and/or conjugation to, among others, carbohydrates. The new conjugate derivatives benefit from the optimal characteristics of BODIPYs as fluorescent dyes, including in some instances water-solubility (in the case of conjugation to unprotected carbohydrates). The different kinds of BODIPY-carbohydrate derivatives are compounds of potential interest for biological studies.

Keywords: BODIPY; carbohydrate-BODIPYs; carbohydrates; fluorescent dyes; glycosylation; ICS-29.

Introduction

The last few decades have witnessed a growing awareness on the importance of carbohydrates in biological processes [1]. For instance, it has now became clear that intercellular carbohydrate-receptor interactions are crucial for physiological events, e.g. cell-cell adhesion and cell differentiation, as well as in pathological processes, e.g. cancer metastasis and bacterial infection [2, 3]. On the other hand, the use of small fluorescent molecules has enabled significant advances in chemical biology and biomedicine when combined with fluorescence spectroscopy or microscopy, detection techniques [4, 5]. Opposite to proteins and nucleic acids, fluorescent labeling of carbohydrates has received far less attention, and early work have focused on the study of glycosidase activities with the help of fluorescent glycosides [6]. More recent examples of fluorescently-labeled carbohydrates have already shown the usefulness of small-molecule carbohydrate fluorophores in the investigation of biological processes [7–11].

Our research group has focused, over the last two decades, in the study of carbohydrates with particular interest in their synthetic transformations, including glycosylation studies [12–14]. Very recently, we have turned our attention to the preparation of fluorophores aiming at the development of novel fluorescent labels for carbohydrates. In this manuscript, we include details of our efforts in that direction.

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BODIPY fluorophores

The most representative small-molecule fluorescent probes used in the labeling of biomolecules are coumarin, fluorescein, rhodamine, and cyanine and BODIPY dyes (Fig. 1) [15–18]. We were initially inclined to use BODIPY (boron dipyrromethene or 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dyes [19, 20]. These dyes present a series of features that make them very appealing as potential fluorescent labels for biomolecules, these include: (i) relatively high photostability, (ii) neutral total charge, (iii) sharp absorption and emission spectra, (iv) strong-UV-vis absorption spectra, (v) high fluorescence quantum yield (ϕ), (vi) reasonable stability under physiological conditions, (vii) negligible triplet-state formation, and (viii) photophysical properties, relatively insensitive to solvent polarity. Conversely, two general drawbacks have also been associated to BODIPY dyes: their small Stokes shifts, which may cause re-absorption effects, and the poor water-solubility associated to most of these derivatives [21].

Synthesis of conjugatable BODIPY fluorophores. Access to water-soluble carbohydrate-BODIPY hybrids

At the beginning of our studies, only a few examples on the preparation of carbohydrate-BODIPY hybrids existed in the literature, [22], and a key factor to the success on the investigations compiled in this manuscript was the launching of a collaboration with Prof. Eduardo Peña-Cabrera's group at the University of Guanajuato (Mexico). Accordingly, we developed two complementary routes to monosaccharide-BODIPY hybrids based on copper(I)-catalyzed azide alkyne cycloaddition (CuAAC) [23–26], of glycosyl derived alkynes, i.e. **6**, or azides, i.e. **7–9**, with BODIPY molecules containing azido, i.e. **4**, or alkyne, i.e. **5**, moieties, respectively (Scheme 1).

The Peña-Cabrera's approach to BODIPYs

Azido and alkyne BODIPYs **4** and **5**, respectively, were obtained according to methodologies previously described in Prof. Peña-Cabrera laboratories. Thus, Liebesking-Srögl cross-coupling reaction (LSCCR) [27] between Biellmann's BODIPY (**1**) [28] and *o*-azidobenzyl boronic acid **2**, according to Peña-Cabrera's procedure [29], produced rotationally restricted, *vide infra*, BODIPY **4**, as a reddish crystalline solid, whereas blue-emitting 8-propargylamino BODIPY **5**, was easily prepared upon treatment of BODIPY **1** with propargyl amine in methylene chloride [30]. Subsequent application of the CuAAC process to BODIPYs **4** and **5** in combination with their sugar-counterparts, propargyl-mannoside **6** and 2-azidoethyl glycosides **7–9** (*manno- gluco-* and *galacto*-configured), permitted the preparation of carbohydrate-BODIPY hybrids **10**, and **11–13**, respectively (Scheme 1). However, a further refinement came about when it was noted that both processes (LSCCR and CuAAC) in each approach, could be carried out as one-pot operations.

Subsequent saponification (NEt_3/MeOH, 4:1; reflux) of carbohydrate-BODIPY hybrids **11a–13a**, led to the desired sugar tetraols **11b–13b** (Scheme 1). These compounds, as well as tetraacetyl BODIPY-mannose derivative **10**, proved to be water-soluble, the latter to a lesser extent and most likely due to the presence of the triazole moiety. The spectral bands of these derivatives spanned from the blue to yellow owing to the changes on the spacer, amino or aryl, respectively (see Table 1). Compound **10**, where the triazole was linked to the C-8

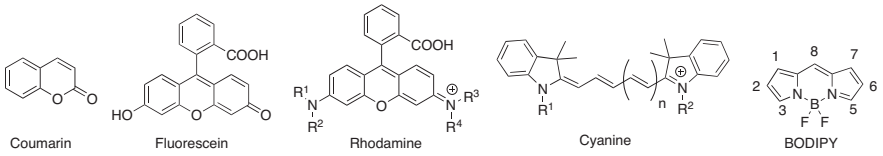
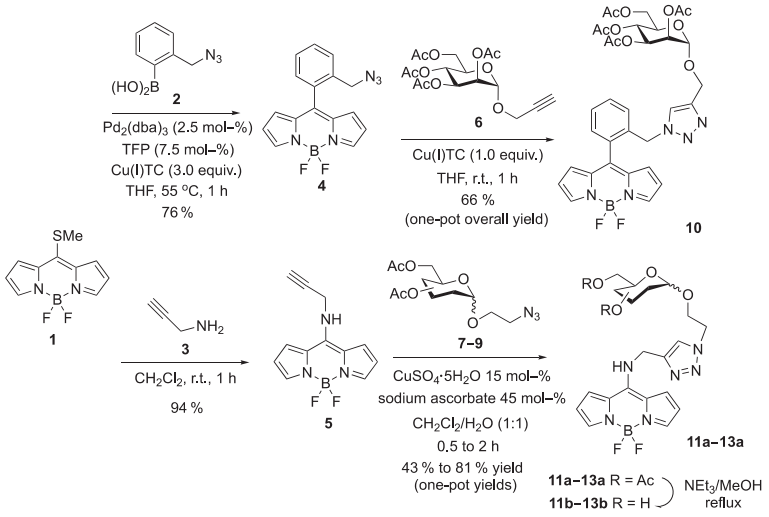


Fig. 1: Commonly used fluorescent dyes.



Scheme 1: Synthesis of carbohydrate-BODIPY hybrids **10–13** from Biellmann's BODIPY (**1**) by a (one-pot) sequence involving LSSCC and CuAAC reactions.

Table 1: Photophysical data of carbohydrate-BODIPYs **10**, **11–13b** in water.[a]

Entry	Compound	λ_{ab} [nm]	λ_{fl} [nm]	% ϕ
i	**10**	503.5	517.0	91
ii	**11b**	400.5	477.0	19
iii	**12b**	400.5	475.5	16
iv	**13b**	400	478.5	16

[a]λ_{ab}, Absorption wavelength; λ_{fl}, fluorescence wavelength; ϕ, fluorescence quantum yield.

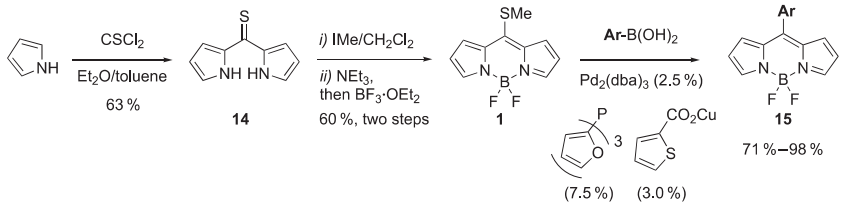
aryl group through its *ortho* position, displayed a very high fluorescent quantum yield ($\phi = 0.91$, Table 1, entry (i) compared to that of its C-8 amino analogs **11b–13b** ($\phi \approx 0.16$, see Table 1, entries (ii–iv). This phenomenon is due to the steric hindrance of the *ortho*-substituent at the C-8 phenyl ring with the hydrogen atoms at C-1 and C-7, which hampers free-rotation and therefore minimizes non-radiative relaxation processes [31].

An expeditious approach to rotationally restricted, conjugatable, BODIPY derivatives from phthalide

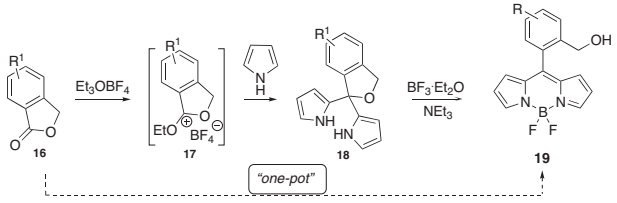
Based on the aforementioned findings, we decided to focus our investigations on *ortho*-substituted C8-aryl derivatives, e.g. **10**, rather than C-8 amino substituted BODIPYs, e.g. **11**, due to the improved fluorescent quantum yields displayed by the former compounds. In this context, and despite the efficiency and versatility of Peña-Cabrera's LSCC approach to 8-aryl substituted BODIPYs [29], we were concerned with the multi-step route to 8-thiomethyl BODIPY **1** (Scheme 2). Thus, access to Biellmann's BODIPY (**1**) from pyrrole took place in three steps, one of them involving the use of thiophosgene.

Synthesis of BODIPYs from phthalides

Accordingly, we devised a straightforward method based on the use of phthalide(s), e.g. **16**, as the 8-*C*-aryl *ortho*-substituted-component precursors of the targeted BODIPY derivatives, i.e. **19** (Scheme 3) [32]. Our



Scheme 2: Sequential synthesis of C-8 aryl BODIPYs (**15**) from pyrrole and thiophosgene, *via* 2,2′-dipyrrolyl thioketone (**14**) and Bielmann's BODIPY (**1**) followed by Peña-Cabrera LSSCC reaction.

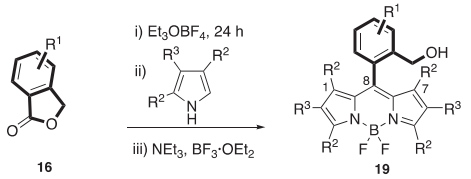


Scheme 3: Synthesis of ortho-substituted C-8 aryl BODIPYs (**19**) by *O*-ethylation of phthalide(s) (**16**) with Meerwein's reagent followed by reaction of the ensuing salts (**17**) with pyrrole.

approach made use of the unprecedented and mild reaction of salt **17** with pyrrole that, *via* the intermediacy of bis-pyrrolyl phthalan **18**, led ultimately to *ortho*-hydroxymethyl substituted C-8 aryl BODIPYs, i.e. **19**. The reaction pathway proposed for this transformation (Scheme 3) was indeed supported by the isolation of intermediate **18** ($R^1 = H$), which upon treatment with $BF_3 \cdot OEt_2$ and NEt_3, led to BODIPY **19a** ($R^1 = H$) [33]. Salt **17**, in its turn, was uneventfully generated upon treatment of phthatlide (**16**) with triethyloxonium tetrafluoroborate (Meerwein's reagent) [34]. Interestingly, the three-step process displayed in Scheme 3, gave better yields when it was carried out as a one-pot operation, probably due to the lability of the intermediate bis-pyrrolyl phthalans (**18**).

Accordingly, from a practical standpoint, the synthetic protocol (Scheme 4) involves: (i) treatment of the corresponding phthalide (**16**) in anhydrous dichloromethane, in the presence of 4 Å molecular sieves, with triethyloxonium tetrafluoroborate for 24 h at room temperature (r.t.); (ii) subsequent addition of the desired pyrrole at 0 °C (3.0 equiv. of 2-alkyl pyrroles, and 10.0 equiv. of pyrrole) and keeping of the reaction mixture for 3 h, at r.t., and (iii) cooling to 0 °C, and final addition of triethylamine (6.0 equiv.) and borontrifluoride diethyl etherate complex (9.0 equiv.) to the reaction mixture (2 h).

This synthetic methodology proved to be fairly general, and it was applied to the preparation of a series of substituted BODIPYs by combining differently substituted pyrroles and phthalides (Fig. 2). In general, the reaction proceeded well with substituted pyrroles and either electron-rich or electron-deficient phthalides. In each case the expected BODIPY could be isolated in moderate to good yields, even in gram-scale reactions (Fig. 2). This phthalide coupling reaction, unlike the Peña-Cabrera's approach more sensitive to steric factors [29], gave better BODIPY yields when alkyl-substituted pyrroles, rather than pyrrole itself, were employed (compare the yields obtained in the preparation of compounds 19a–c, Fig. 2).



Scheme 4: Detailed synthetic protocol to *ortho*-hydroxymethyl C-8 aryl BODIPYs from phthalides and pyrroles.

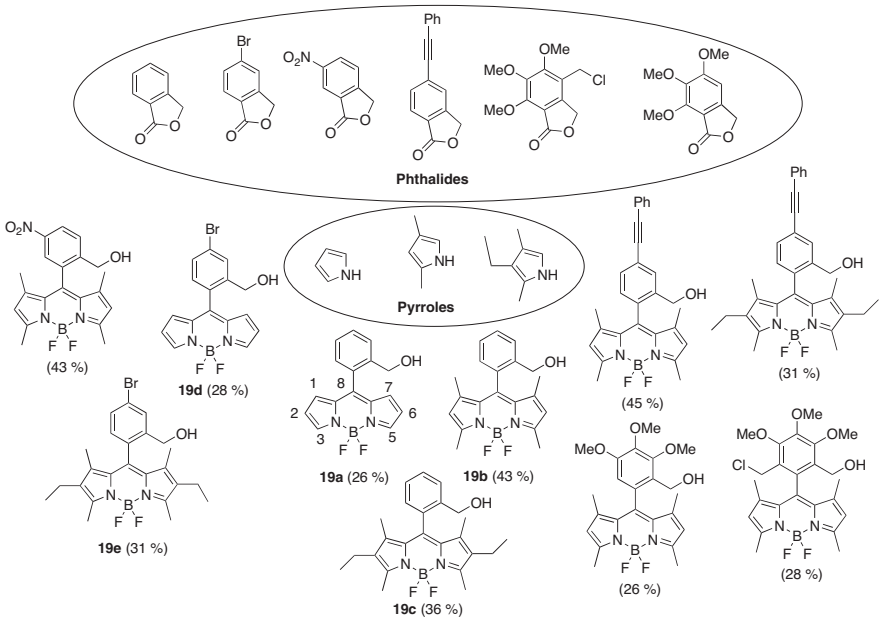


Fig. 2: Collection of BODIPYs obtained by reaction of phthalides, activated by the Meerweein's reagent, with pyrroles in a one-pot process. The isolated yields of BODIPYs are displayed.

On the role of the ortho-hydroxymethyl substituent

Our interest in *ortho*-substituted 8-*C*-hydroxymethyl BODIPYs was associated with several aspects of the *ortho*-hydroxymethyl group [33]: (i) the *ortho*-nature of the substituent prevents the rotation of the aryl moiety around the 8*C*-aryl bond, which ultimately results in much higher fluorescence quantum yield; (ii) the hydroxyl moiety, as such or after functional group modification, could provide a handle for conjugation to different molecules; and (iii) the incorporation of a bulky apical group in the fluorophore avoids aggregation, a phenomenon that is known to diminish its fluorescence quantum yield [35].

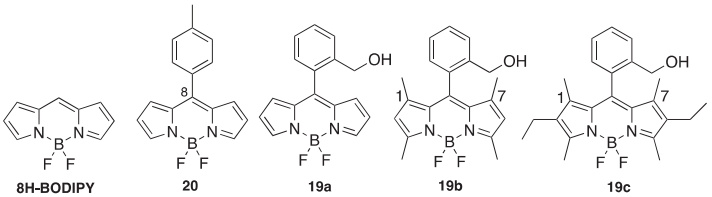
In relation with the first aspect, even though arylation at the C-8 (*meso*) position has hardly any effect on the absorption and emission wavelengths of the BODIPYs (Table 2), the quantum yield is appreciably reduced when free rotation of the *meso*-aryl group is possible, as in compound **20** (compare % ϕ, for compounds **19a** and **20**, Table 2). Consistent with this, introduction of the *ortho*-substituent and methyl groups at C-1 and C-7, also increased the quantum yields in compounds **19b–c** (see % ϕ, Table 2).

An interesting additional aspect of BODIPYs relates to their use as laser dyes with outstanding lasing efficiency upon laser irradiation [36, 37]. Thus the lasing behavior of compounds **19a–c** was studied, and it showed good correlation with their photophysical properties, in particular with the Stokes shift. In general, an increase in the Stokes shift enhances the laser action [Eff (%), Table 2] and it might outweigh the decrease in the fluorescence quantum yield [e.g. compare Eff (%) in compounds **8H-BODIPY** and **19a**, Table 2].

From the standpoint of photostability, a key feature in fluorescent dyes, photodecomposition studies were performed on derivatives **19b** and **19c**, which were shown to display high photostability when submitted to drastic pumping conditions.

In connection with the second issue, the *ortho*-hydroxymethyl group in compound **19b** could be uneventfully transformed into formyl, isothiocyanylmethyl and azidomethyl derivatives **21a–c**, respectively. The easiness in the conjugation of these derivatives with carbohydrates was illustrated by the preparation of β-glucosides **22** and **23** from **19b** and **21a**, respectively (Fig. 3). Accordingly, glycosylation of **19b** with D-glucose pentaacetate provided BODIPY-glucoside **22a**, whereas reaction of isothiocyanate **21a** with 2-aminoethyl-2,3,4-tetra-*O*-acetyl-β-D-galactopyranose, provided thiourea derivative **23**. On the other hand, conjugation of BODIPY-aldehyde **21b** to amino-containing molecules could be carried out under reductive amination

Table 2: Photophysical[a] and lasing properties[b] of BODIPYs **19a–c**, **20** [38] and unsubstituted (8H)-BODIPY.



Entry	Compound	λ_{ab} [nm]	λ_{fl} [nm]	% ϕ	$\Delta\upsilon_{st}$ (cm^{-1})	Eff (%)
i	8H-BODIPY	498	508	90	385	55
ii	**20**	500	516	3.6	–	–
iii	**19a**	499.5	513	74	527	60
iv	**19b**	505.5	510	76	370	19
v	**19c**	524.5	541	72	580	42

[a]Dye concentration: 2 μM. λ_{ab}, absorption wavelength; λ_{fl}, fluorescence wavelength; ϕ, fluorescence quantum yield; $\Delta\upsilon_{st}$, stokes shift; [b]dye concentration: 2 mM. Eff (%): lasing efficiency, as the ratio between the energy of the laser output and the pump energy incident on the cell surface.

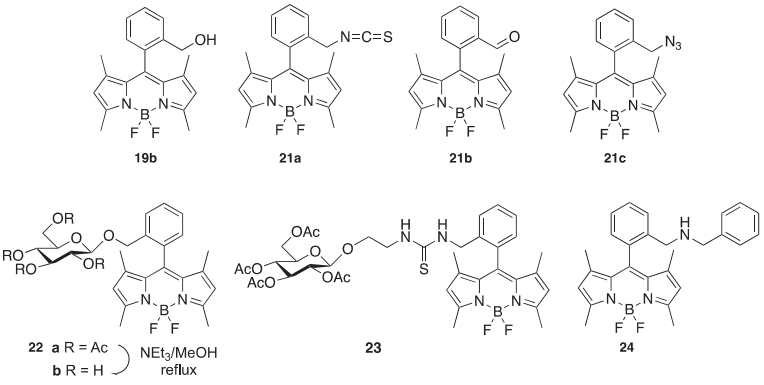


Fig. 3: Collection of BODIPYs with different anchoring functionalities (**19b**, **21a–c**) and BODIPY conjugates obtained therefrom (**22–24**).

conditions, as it was demonstrated in its reaction with benzylamine to give benzylamino derivative **24**. Azidomethyl derivative **21c**, could be used in CuAAC reactions with alkyne-containing molecules, as was previously shown with related BODIPY **4** (Scheme 1).

Structural modifications on the BODIPY core

An additional facet of general interest in the design of fluorescent probes, has been the search for organic chromophores with strong absorption in the near infrared (NIR) region (650–900 nm). These NIR-fluorophores, compared to those with absorption and fluorescence bands in the ultraviolet/visible (UV/Vis) region, will display minimum interference from background autofluorescence by biomolecules, causing less photodamage, and improved tissue penetration [39, 40]. In this context, borodipyrromethene dyes have been considered privileged platforms since, well-documented, synthetic postmodifications on the dipyrromethene core might led to NIR-fluorescent BODIPY dyes [41].

Along this line, we have performed synthetic modifications compatible with the *ortho*-hydroxymethyl group, aimed at extending the conjugation of the BODIPY core and resulting in red-shifted BODIPY fluorophores. Accordingly, di-iodo derivative **25**, readily accessible from **19b** after treatment with N-Iodosuccinide (NIS), was

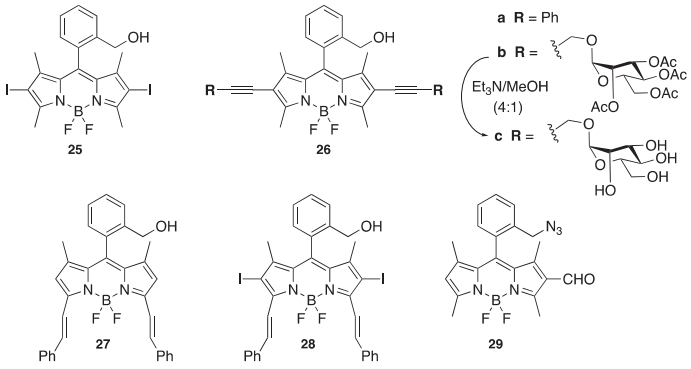


Fig. 4: Synthetic postmodifications on hydroxymethyl *ortho*-substituted BODIPY **19b**, leading to 2,6-diiodo-BODIPY **25**, and π-extended BODIPY derivatives (**26–29**).

transformed into 2,6-dialkynyl BODIPYs **26a–c** by Sonogashira cross-coupling reaction with the corresponding alkynes (Fig. 4) [42]. Interestingly, BODIPY-carbohydrate derivative **26b** could be accessed by a Sonogashira cross-coupling reaction of **25** with propargyl α-D-mannopyranoside tetraacetate, in moderate yield[1]. The former could be uneventfully deprotected to yield bis-mannopyranoside derivative **26c**. On the other hand, the π-extension of the conjugation at positions C-3 and C-5, can uneventfully be attained by a Knoevenagel-type condensation [43] of either **19b** or **25**, leading to styryl derivatives **27** and **28**, respectively (Fig. 4). Alternatively, Vilsmeier-Haak formylation of **25**, allows the synthesis of mono-formyl derivative **29** (Fig. 4) [44].

A one-pot entry to urea-bridged bis-BODIPYs dimers from a serendipitous discovery

As a continuation of our studies on conjugatable BODIPY derivatives, we had obtained azidomethyl compounds **4**, **21c**, and **29–31**, from the corresponding hydroxymethyl derivatives (Fig. 5). Thus, even though these derivatives could be engaged in CuAAC reactions for conjugation, we were interested in their transformation to *ortho*-aminomethyl BODIPY derivatives, to explore their conjugation with formyl-containing compounds, via reductive amination protocols.

In this context, we first examined the well-known Staudinger *azido→amino* transformation reaction (PPh_3, aq. NaOH) [45, 46] on azide **31**. Contrary to our expectations, no traces of the expected aminomethyl derivative **32** could be observed in the Staudinger reaction of **31**, and instead a dimeric urea derivative **33** was isolated in 75 % yield (Scheme 5) [47].

From the results shown in Scheme 5, it was clear that formation of **33** from azidomethyl derivative **31**, required the presence of an external CO_2 source in the reaction media, to account for the observed "carbonyl" bridge. Thus, on the assumption that "CO_2" was present in the reaction media, we postulated a pertinent reaction pathway for this transformation (Scheme 6). Accordingly, reaction of **31** with PPh_3 would provide iminophosphorane **34** [48], whose reaction with "CO_2" could lead to isocyanate **36** by way of an intermolecular aza-Wittig reaction [49]. The latter species already accounted for the additional carbonyl bridge in urea

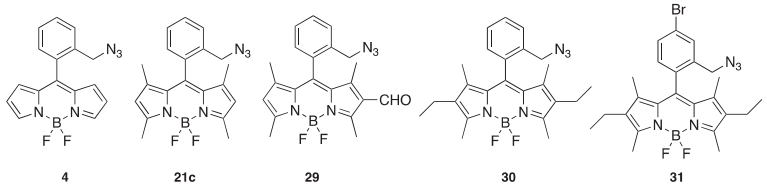
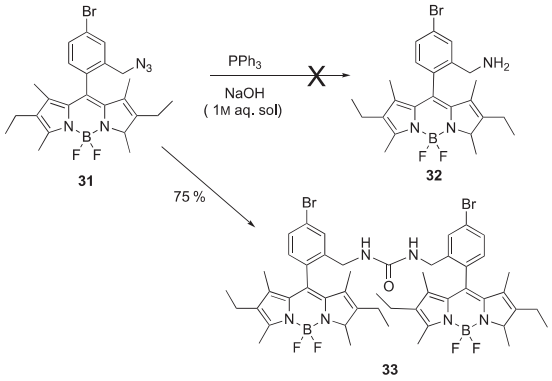
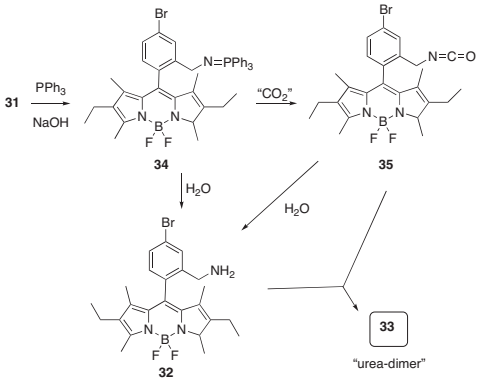


Fig. 5: *Ortho*-azidomethyl *meso*-aryl BODIPYs.

1 Unpublished results from: L. Diaz-Casado. Masters Thesis, Universidad Complutense, Madrid (2017).



Scheme 5: Staudinger reaction of compound **31**, leading to urea-bridged bis-BODIPY **33**, rather than to aminomethyl BODIPY **32**.



Scheme 6: Proposed reaction pathway from azido BODIPY **31** to urea-bridged bis-BODIPY **33**, via isocyanate intermediate **36**.

33 [50]. Finally, reaction of **36** with a postulated aminomethyl derivative intermediate **32**, will give rise to dimer **33**. Formation of amine **32**, in its turn, could be visualized by hydrolysis of either iminophosphorane **34** or isocyanate **35**, which in either case will have to be understood as the rate limiting step of the overall transformation, since no amine **32** could be detected in the reaction media. We visualized the addition of amine **32** to isocyanate **35**, leading to **33**, as a very rapid and efficient process.

Since BODIPY dimers have become a topic of interest [51, 52], we decided to search for reaction conditions leading to the reliable preparation of urea-bridged dimers. We had hypothesized that the origin of the required carbon dioxide might have been CO_2 absorbed in the aqueous NaOH solution employed [53]. Subsequent experiments were directed to find a consistent CO_2 source and to that end we drew our attention to triethylammonium hydrogen carbonate buffer (TEAB), a reagent recommended by Azhayev and co-workers for related transformations [54]. Along this line, the reaction of azidomethyl BODIPYs in the presence of PPh_3 and TEAB in 1,4-dioxane at r.t., paved the way to dimeric BODIPYs **33** and **36a–d** (Fig. 6).

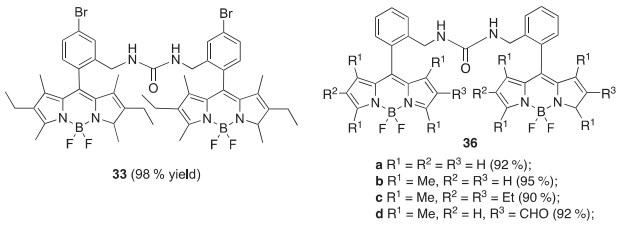
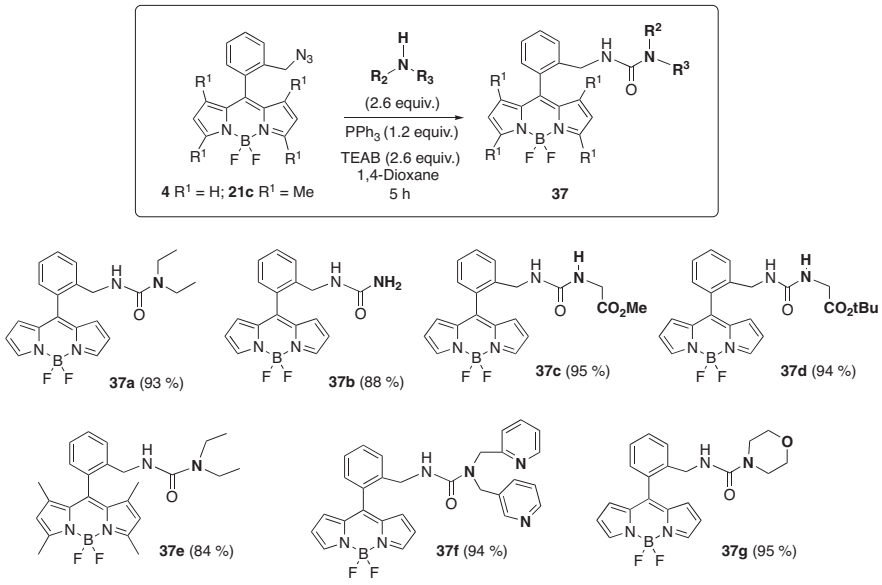


Fig. 6: Urea-bridged BODIPYs **33** and **36**, obtained from the corresponding azidomethyl BODIPYs by reaction with PPh_3 and TEAB, in 1,4-dioxane (room temperature).



Scheme 7: Conjugation of azidomethyl BODIPYs with amino-containing compounds leading to non-symmetric ureas.

Access to urea-BODIPY conjugates from azidomethyl BODIPYs

On the other hand, mindful of the interest in BODIPY species amenable to conjugation, we have also found that BODIPY azides can react with amine-containing derivatives leading to the non-symmetric BODIPY ureas, e.g. **37** (Scheme 7). This novel approach for conjugation was inspired on our proposed reaction pathway, depicted in Scheme 6, provided that amine **32**, could be replaced with an "external" amine-containing compound. From a practical standpoint, reaction of azidomethyl BODIPYs with either ammonia, primary, or secondary amines, in the presence of PPh_3 and TEAB, in dioxane at r.t. resulted in the formation of non-symmetric ureas **37** (Scheme 7), in good to excellent yields [47].

The study of the photophysical properties of these new derivatives was also carried out, displaying excellent fluorescence and laser emission properties in less polar media. This emission, however, decreased in more polar media, owing to a light induced charge transfer from the urea linker to the dipyrromethene core.

Conclusions

In summary, we have shown that borondipyrromethene fluorophores (BODIPYs) are useful dyes for conjugation with carbohydrates, which might help in the solubilization of the former, aimed at their use in biological studies. In this context, we have developed a one-pot, efficient, protocol for the synthesis of *ortho*-hydroxymethyl 8-*C*-aryl BODIPYs based in the coupling of phthalides with pyrrole derivatives. The ensuing BODIPYs possess an anchoring point that can be used as such, or after functional group modification, in conjugation reactions with a variety of partners, including: alkynes, amino derivatives, glycosyl derivatives and isocyanates. The photophysical properties of the conjugates retain the good characteristics of the BODIPY derivatives and, therefore, are promising derivatives with potential use in biological studies containing carbohydrates.

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