Postfunctionalization of the BODIPY Core: Synthesis and Spectroscopy

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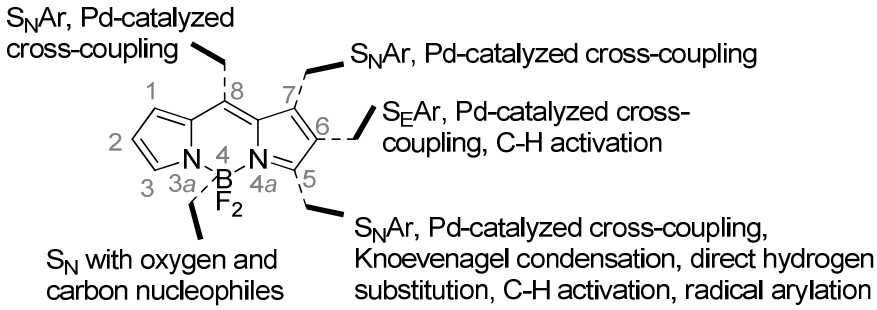

In this micro review, the various, synthetic postmodification methodologies to functionalize the BODIPY framework, as designed and developed by our research groups, are comprehensively discussed together with the electronic spectroscopic properties of the resulting dyes. Using these novel synthetic methodologies all the pyrrole C-ring positions and the *meso*-position can be readily substituted.

Keywords: BODIPY, Dyes, Photophysics, Synthetic methods, Functionalization

Abstract: In this review, we describe the various, novel synthetic postmodification methodologies of the BODIPY core designed and developed by our research groups as well as their electronic spectroscopic properties. We discuss the different strategies created for functionalization of the BODIPY framework at the pyrrole C-ring positions and the *meso*-position. Halogenated boron dipyrrins are substrates for nucleophilic substitution or Pd-catalyzed cross-coupling reactions. α-Unsubstituted BODIPYs can be functionalized with N and C nucleophiles via oxidative or vicarious nucleophilic substitution of the α-hydrogens. Combining this methodology with a

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reversible Michael addition on nitrostyrenes provides an entry to 3-styrylated BODIPYs. Furthermore, the one-step, Pd-catalyzed C–H arylation of 3,5-unsubstituted BODIPYs leads to 3- and 3,5-arylated dyes. Finally, radical C–H arylation at the 3,5-positions of α-unsubstituted BODIPYs provides an additional synthesis route to arylated dyes.

Introduction

Fluorescence spectroscopy and imaging are nowadays essential tools for the noninvasive study of matter or living systems in material and life sciences, medicine, and (bio)technology.[1–3] Fluorescence is an ultra-sensitive method for investigating with high spatiotemporal resolution the structure and dynamics of organic and inorganic materials, biopolymers, living cells and tissues in ensembles and at the single-molecule level. Among the multitude of highly fluorescent dyes available, those based on 4-bora-3*a*,4*a*-diaza-*s*-indacene (commonly known as BODIPY,[4] *bo*ron *dipy*rrin or *bo*ron *dipy*rromethene, Fig. 1) show perhaps the highest potential and have risen immensely in popularity. The first member of this class was reported in 1968 by Treibs and Kreuzer.[5] However, it is only relatively recently that the possible uses and applications of BODIPY-based dyes[6–9] – such as fluorescent indicators,[10] biological labels,[11] probes for bioimaging,[12] tunable laser dyes,[13,14] potential photodynamic therapy agents,[15,16] solar light harvesting antennas or solar cells[17–19] – have been fully recognized. The ever increasing success of boron complexes of dipyrromethenes can be credited to their many outstanding properties, including the generally bright fluorescence [due to high fluorescence quantum yields Φ combined with large molar absorption coefficients ε(λ)][20] with excitation (absorption) / emission spectra located in the visible spectral range, narrow emission bandwidths with high peak intensities, robustness against light and chemicals,

remarkable redox characteristics, good solubility, resistance toward self-aggregation in solution, fluorescence lifetimes τ in the nanosecond range, and negligible triplet-state population. Moreover, their spectroscopic and photophysical properties can be fine-tuned by attachment of suitable groups at the right positions of the boradiaza-*s*-indacene core. From a synthesis point of view, the other major reason for the attractiveness of boron dipyrrin dyes is their vast scope for functionalization (at the pyrrole C-ring positions (1, 2, 3, 5, 6, 7), the central 8- or *meso*-position, and the boron atom (position 4)). The wide versatility of synthetic pathways to the BODIPY family of fluorophores allows the creation of a perfect fit between the structure of the dye and its desired spectroscopic, (photo)physical, and chemical characteristics.

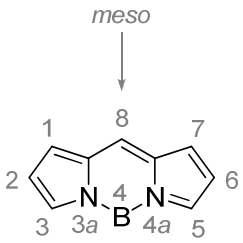
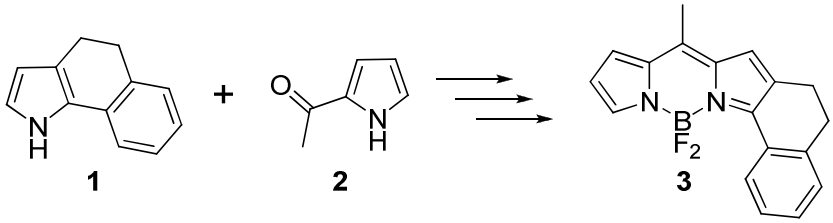


Figure 1 Representation of the "BODIPY core" and its IUPAC numbering system. The 8-position is often specified by *meso*. The 3,5-positions are sometimes referred to by α. Common BODIPYs have two fluorine atoms bound to the boron atom (4-position). Positions 1–8 are possible sites for functionalization.

There are two main synthesis paths to substituted BODIPY derivatives: either one starts from suitably functionalized pyrroles, which are used as precursors of the desired BODIPY after final boron complexation (i.e., prefunctionalization), or one postderivatizes the BODY core (i.e., postfunctionalization). In this review, we shall demonstrate that, with limited synthetic efforts, a large number of functional groups can be introduced through well-documented synthetic approaches to the BODIPY scaffold, allowing the preparation of sophisticated dyes with a nearly unlimited molecular structural variation and concomitant fine-tuned optical, (photo)physical, and chemical properties. The postfunctionalization methodology is highly attractive

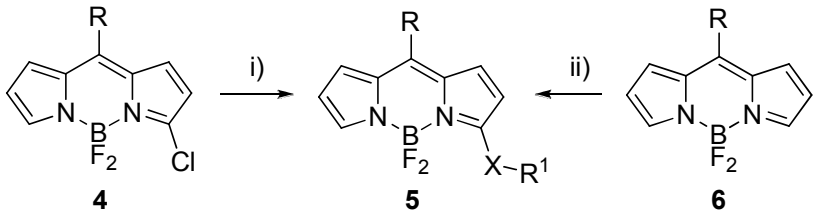
for expanding the diversity of the BODIPY family, especially for some typologies, which are difficult to access via conventional prefunctionalization methods.

Although pre- and postfunctionalization can be competitive approaches for modifying the boron dipyrrin framework, in many cases they are rather complementary. Some BODIPY derivatives are easier to synthesize starting from appropriately substituted pyrroles. An example hereof is compound **3**, which is a challenge to prepare via postmodification (Scheme 1).[21]



Scheme 1 Synthesis of **3** starts from suitably prefunctionalized pyrroles **1** and **2**.

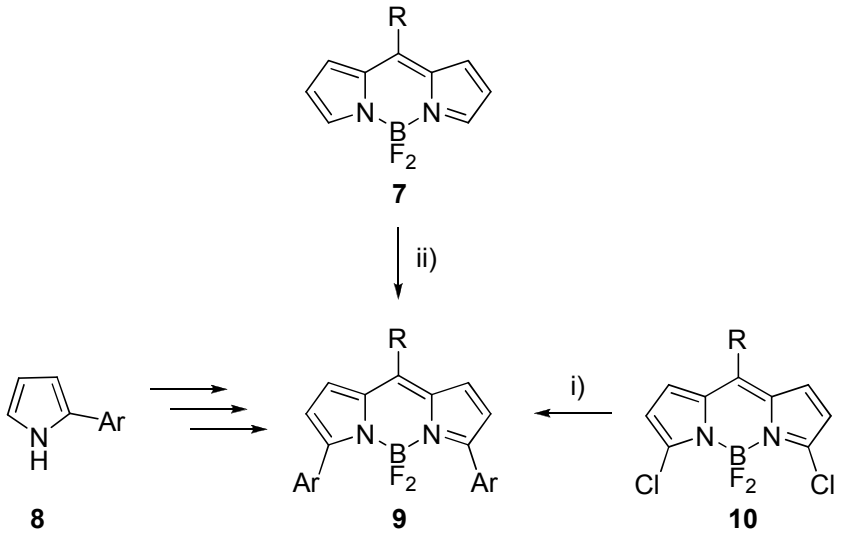
Conversely, derivatives such as **5** (Scheme 2), bearing electron-donating heteroatoms at the 3-position, are difficult to obtain via the conventional prefunctionalization approach. The synthesis of this type of compounds can be achieved via two synthetic postmodifications: either via nucleophilic substitution of 3-chloroBODIPY **4**[22,23,55] or via oxidative nucleophilic hydrogen substitution of a 3(,5)-(di)unsubstituted boron dipyrrin **6**.[24]



Scheme 2 Synthesis of **5** is possible via two postderivatization protocols: i) nucleophilic substitution of **4** and ii) oxidative nucleophilic hydrogen substitution of **6**. R = alkyl or aryl, R^1 = alkyl or aryl. Conditions: i) R^1XH (X = R^2N, O, S). ii) R^1R^2NH, O_2.

Still other BODIPY dyes can be synthesized via both methodologies. For instance, 3,5-diarylBODIPYs **9** (Scheme 3) can be made starting from 2-arylpyrrole building blocks **8** (prefunctionalization)[25–27] and via (at least) two postfunctionalization

methods: from 3,5-dihaloBODIPYs **10** in a Pd-catalyzed Suzuki reaction[23,28,29] or via a radical reaction using aryl diazonium salts and 3,5-unsubstituted BODIPYs **7**.[30] The choice of method (pre- *vs* postfunctionalization) depends on the efficiency of the synthesis with which the target molecule can be obtained.



Scheme 3 Synthesis of BODIPY derivatives **9** via pre- (starting from **8**) and postfunctionalization approaches (Pd-catalyzed Suzuki reaction using **10**, and radical reaction with **7** and aryl diazonium salts). Conditions: i) $Pd(PPh_3)_4$, Na_2CO_3, 1,2-dimethoxyethane, microwave irradiation, 150 °C. ii) ArN_2BF_4, ferrocene, acetone, rt.

Our research groups have been instrumental in the design and development of novel, synthetic postfunctionalization methodologies of the boradiaza-*s*-indacene scaffold and in the investigation of the UV–vis spectroscopy of the resulting dyes. This review deals exclusively with our pioneering contributions to this stimulating research area. However, other research groups also provided valuable input into this field. In a forthcoming extensive review, all reports of the synthetic postmodification approach of the BODIPY core will be discussed in detail. Here, we limit ourselves to citing those important papers of other scientists. Among the various synthetic methods available for derivatization of the boron dipyrrin framework (Fig. 2) are electrophilic aromatic substitution (S_EAr),[6,31,32] Knoevenagel-type condensation reactions,[33] substitution of the fluorine atoms on boron,[7,8,34–39] direct substitution of hydrogen atoms (oxidizer-free vicarious nucleophilic substitution,[40] oxidative

nucleophilic hydrogen substitution,[24] and radical aryl substitution of hydrogen[30]), direct styrylation,[40] Liebeskind cross-coupling,[41] nucleophilic aromatic substitution (S_NAr)[22,42] and transition-metal-catalyzed C–C coupling reactions[29,43] through the use of halogenated and thioether boron dipyrrins or *via* C–H activation of unsubstituted boron dipyrrins.[44–47] Figure 2 gives an overview of the various synthetic methods for postmodification at the different positions of the BODIPY core.

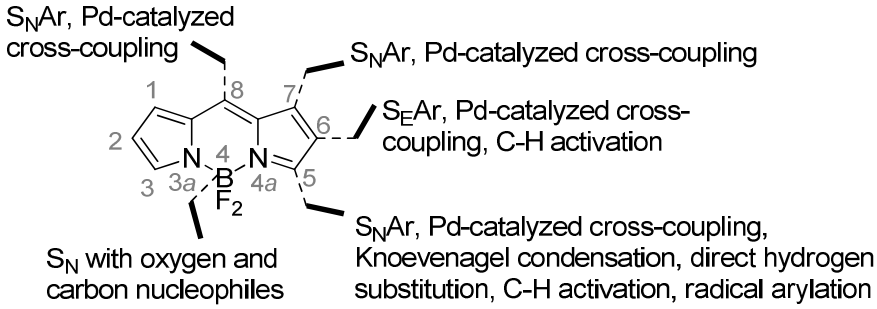


Figure 2 Overview of the different BODIPY postfunctionalization methods at their preferential site(s) of attack. For clarity, reactions on only one pyrrole ring (positions 5, 6, 7) are indicated. Disubstitution of the corresponding positions on the second pyrrole (3, 2, 1) is often possible: see text for details.

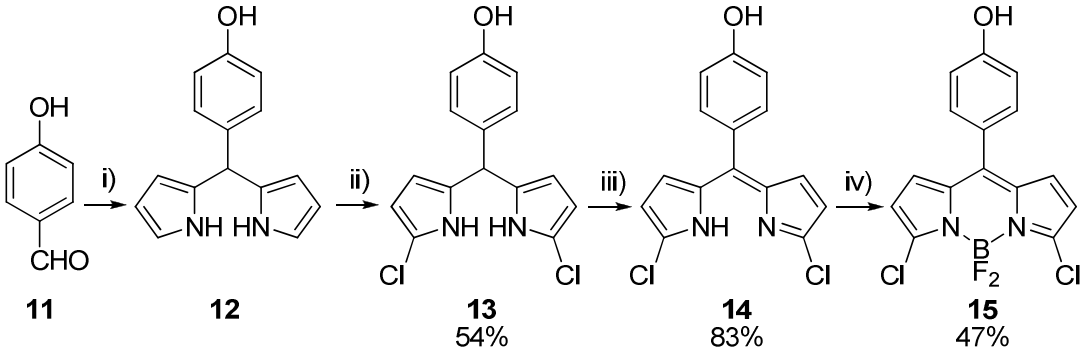
Next, we describe the different synthetic postmodification methods of the BODIPY core developed by us and the associated electronic spectroscopic properties of the obtained derivatives according to the positions of the boron dipyrrin framework (see Fig. 1 for the IUPAC numbering scheme), where the functionalization takes place.

Functionalization at the 3- and 3,5-positions

3-Halo- and 3,5-dihaloBODIPYs as starting materials

Many of the most important BODIPY functionalization reactions are based on the use of boron dipyrrins containing halogen(s) at the pyrrole carbons.[48] Halogenated BODIPYs are useful precursors to prepare a wide variety of interesting BODIPY derived compounds with properties suitable for applications in various fields. Indeed, these haloBODIPYs can undergo facile nucleophilic substitution (S_NAr) as well as transition-metal-catalyzed C–C coupling reactions. Since halogens can be introduced

at all pyrrole carbons of the boradiaza-*s*-indacene framework selectively and regiospecifically (see further), the use of halogenated boron dipyrromethenes has opened a wide avenue to a range of derivatives that are difficult to access otherwise.[48] Specifically, 3,5-dihaloBODIPYs[22,28,49,65] have been extensively used, because they can be easily prepared starting from dipyrromethane precursors. Our first paper in the field of boron dipyrrins describes the synthesis of 3,5-dichloro-4,4-difluoro-8-(4-hydroxyphenyl)-4-bora-3*a*,4*a*-diaza-*s*-indacene **15** (Scheme 4), the first reported (3,5-di)haloBODIPY derivative. 5-(4-Hydroxyphenyl) dipyrromethane **12** [prepared following the method of Lindsey *et al.*[50] by condensation of aldehyde **11** with neat excess pyrrole catalyzed by trifluoroacetic acid (TFA) at room temperature] was halogenated using *N*-chlorosuccinimide (NCS) in tetrahydrofuran (THF) at –78 ºC. The obtained dichlorodipyrromethane **13** was then oxidized to dichlorodipyrromethene **14** and further reacted with triethylamine and BF_3•OEt_2, according to standard procedures,[6,25,51,52] to afford **15**.



Scheme 4 Synthesis of **15**. Conditions: i) 25 equiv. pyrrole, 0.1 equiv. Et_3N, rt, 10 min. ii) 2 equiv. NCS / THF, –78 ºC, 2 h. iii) 1 equiv. *p*-choranil / CH_2Cl_2, rt, 1 h. iv) toluene, Et_3N / BF_3•OEt_2, 70 ºC, 2.5 h.[49]

3,5-DichloroBODIPY **15** displays the characteristic absorption features of classic boradiaza-*s*-indacene dyes: that is, a narrow, main absorption band – assigned to the $S_1 \leftarrow S_0$ transition – with the maximum λ_{abs}(max) positioned within a very narrow range (506–515 nm) and which is slightly red-shifted with increasing solvent

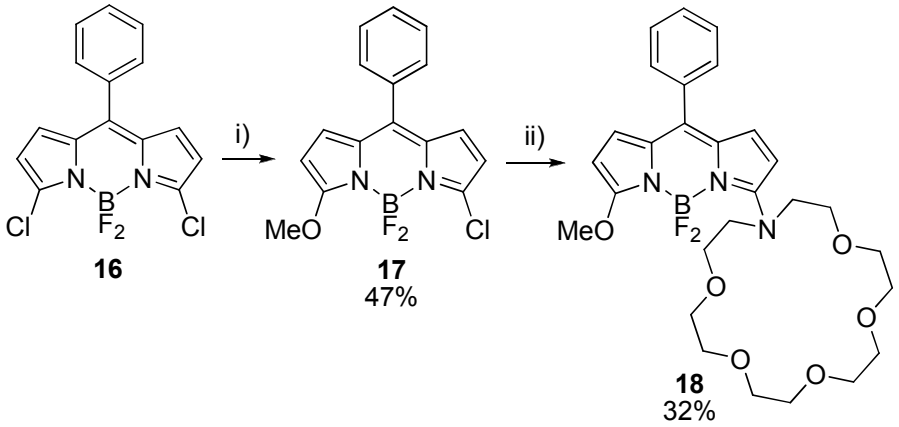
polarizability. Derivative **15** also shows the usual fluorescence emission features of difluoroboron dipyrromethenes: i.e., a narrow, slightly Stokes-shifted band of mirror image shape, which is bathochromically shifted with increasing solvent polarizability [the emission maximum λ_{em}(max) shifts from 517 nm in methanol and ethyl acetate to 527 nm in toluene].[49,53] In toluene, the fluorescence lifetime τ and quantum yield Φ are 3.44 ns and 0.63. In aqueous, nonbuffered solution, pH indicator **15** undergoes a reversible protonation-deprotonation in the near-neutral to basic pH range, producing fluorescence intensity increases with decreasing pH. The highest Φ value (0.01, λ_{ex} = 480 nm) is found at low pH (6.50). The pK_a of **15** in aqueous, nonbuffered solution is 8.41.[53]

A modified synthesis of 3,5-dichloro-4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacenes was reported by Burgess *et al*.[54,55] Moreover, 3,5-dibromo[56,57] and 3,5-diiodo[58] substituted BODIPYs have been also described.[48]

3-Halogenated and 3,5-dihalogenated boron dipyrrins are valuable starting materials for postfunctionalization of the BODIPY core, because, afterwards, they can be subjected to nucleophilic substitution with amines, alkoxides, phenoxides, thiolates, or enolates to give rise to the corresponding substituted BODIPYs with substitution patterns that are difficult to realize otherwise. Furthermore, 3-halo and 3,5-dihaloBODIPYs are versatile building blocks to synthesize novel carbon-substituted BODIPYs using palladium-catalyzed C–C coupling reactions.

The first BODIPY synthesized from a 3,5-dichloroBODIPY via nucleophilic aromatic substitution (S_NAr) is the ratiometric, fluorescent indicator **18** with high selectivity for potassium over other alkali metal ions in acetonitrile (Scheme 5).[59] The ion-free K^+-selective indicator **18** with an azacrown ether ligand absorbs and emits in the visible spectral range [λ_{abs}(max) = 529 nm and λ_{em}(max) = 565 nm in

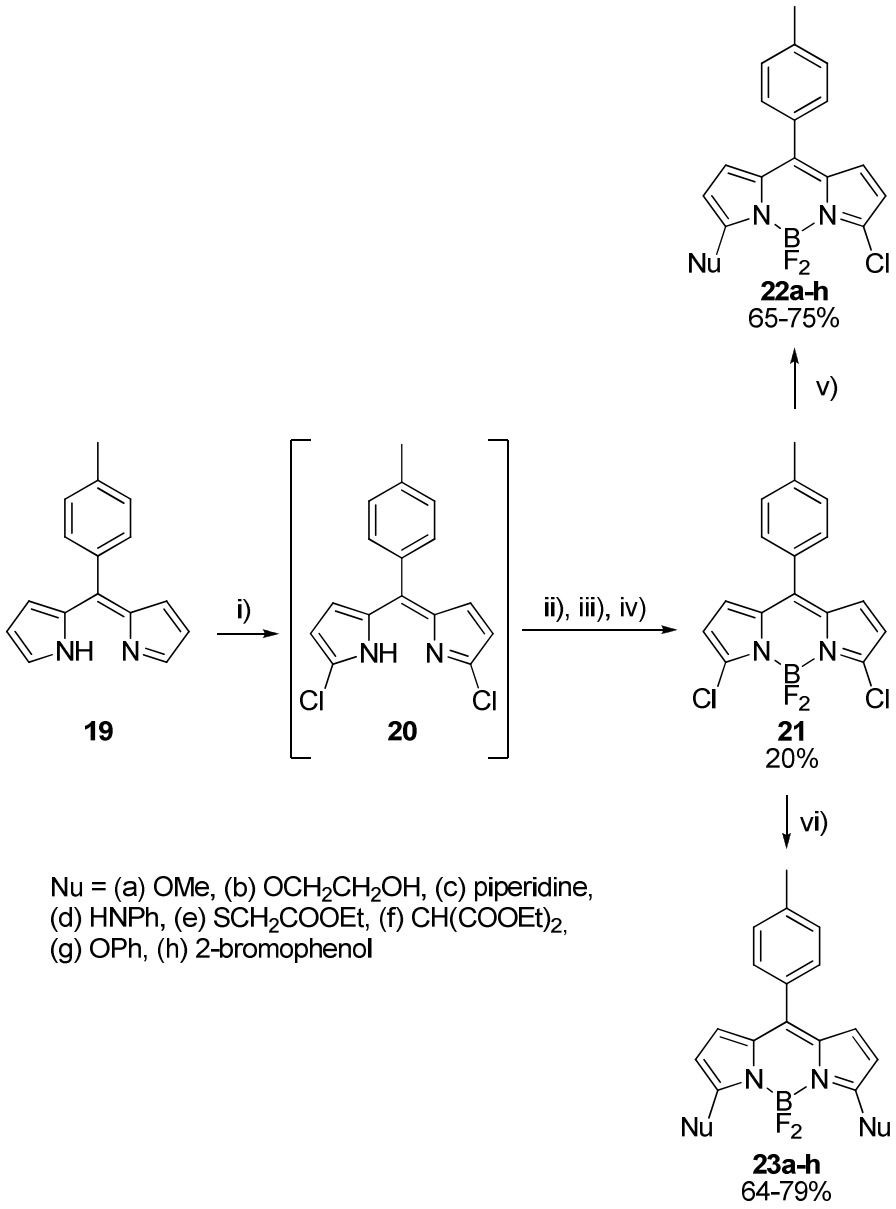
acetonitrile] with a low fluorescence quantum yield (Φ = 0.006). Upon binding K^+, the absorption and emission bands are blue-shifted [λ_{abs}(max) = 505 nm and λ_{em}(max) = 520 nm in acetonitrile] and are accompanied by isosbestic and pseudoemissive points, respectively. The fluorescence intensity increases in the presence of K^+, with Φ = 0.04 at 6 mM potassium. The dissociation constant K_d for the 1:1 complex between **18** and K^+ is 0.5 mM in acetonitrile. Quantum-chemical calculations indicate that addition of K^+ induces a marked reorganization of the indicator, with the ion-including azacrown ether ring 'folding' onto the BODIPY core. This structural rearrangement allows for the potassium ion to be coordinated not only to the nitrogen and oxygen atoms of the azacrown ring, but also to the oxygen of the methoxy group at position 5 as well as to the fluorine atoms bound to boron, as reported in ref [59].



Scheme 5 Synthesis of **18**. Conditions: i) 1 equiv. NaOMe, MeOH, rt, 30 min. ii) Et_3N, aza-18-crown-6 (1,4,7,10,13-pentaoxa-16-azacyclooctadecane), acetonitrile, reflux, 16 h.[59]

The synthetic modification of the BODIPY fluorophore by nucleophilic aromatic substitution (S_NAr) of 3,5-dichloro-4,4-difluoro-8-(4-tolyl)-4-bora-3*a*,4*a*-diaza-*s*-indacene **21** with oxygen, nitrogen, sulfur, and carbon nucleophiles has been studied in systematic way.[22,60,61] The nucleophiles investigated were amines (piperidine, aniline, 1,10-diaza-18-crown-6) and anions derived from alcohols (methanol, ethane-1,2-diol), hydroxyarenes (phenol, 2-bromophenol), thiols (ethyl 2-thioacetate), and β-diesters (diethyl malonate). By changing the reaction conditions (temperature,

nucleophile concentration, reaction time) either unsymmetrical, 3-monosubstituted **22** or symmetrical, 3,5-disubstituted products **23** are formed (Scheme 6). The compounds synthesized with O- and C-substituents at the 3(,5)-position(s) show the spectroscopic properties typical of common difluoroboron dipyrrins, represented by the starting 3,5-dichloroBODIPY derivatives **21** (Scheme 6) and **15** (Scheme 4). Indeed, these dyes have narrow absorption and emission bands with maxima in the 500–540 nm bounds, with small Stokes shifts $\Delta\bar{\nu}$ [= $1/\lambda_{abs}(max) - 1/\lambda_{em}(max)$]. The slight, solvent-dependent shifts of the spectral maxima $\lambda_{abs}(max)$ and $\lambda_{em}(max)$ reflect the polarizability of the solvent. The fluorescence rate constants k_f are in the $(1.5–2.0) \times 10^8$ s^{-1} range. Conversely, BODIPY derivatives with N- and S-substituents at the 3- and 3,5-positions have spectra that are batchochromically shifted compared to **21**.



Scheme 6 Nucleophilic substitution of 3,5-dichloroBODIPY **21**. Conditions: i) 2 equiv. NCS / THF, –78 ºC, 2 h. ii) *p*-chloranil. iii) Et_3N. iv) BF_3•OEt_2. v) Nucleophile Nu^-, CH_3CN, rt. vi) Nucleophile Nu^-, CH_3CN, reflux.[22,60,61,62]

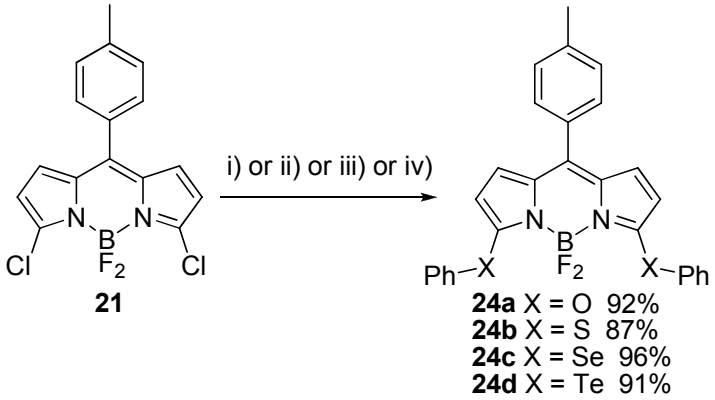
The unsymmetrically substituted BODIPY dye **22d** with a phenylamino group at the 3-position was synthesized by nucleophilic substitution of **21** at room temperature (14 h in acetonitrile, 69%, Scheme 6).[62] By changing the reaction conditions (neat aniline as both solvent and nucleophile, 140 ºC, 4 h), the symmetrical analogue **23d** with phenylamino functions at the 3,5-positions was obtained (81%, Scheme 6).[63]

In a series of organic solvents, the absorption and emission bandwidths and Stokes shifts of the mono-anilino compound **22d** are much larger than those of common,

symmetrical difluoroboron dipyrrins, whereas the λ_{abs}(max) values are very similar to those of typical BODPYs. The emission maxima λ_{em}(max) of **22d** are red-shifted by approximately 50 nm compared to classic BODIPY derivatives. Compound **22d** has low fluorescence quantum yields ($\Phi < 0.05$) in all but the nonpolar solvents cyclohexane, toluene, and chloroform. In comparison to the nonsymmetrical compound **22d**, the symmetrical analogue **23d** has higher Φ (0.45–0.86) and longer τ (3.4–4.0 ns) values, and its λ_{abs}(max) and λ_{em}(max) are shifted to the red by 65–90 nm and 44–49 nm, respectively. Moreover, the absorption bandwidths and Stokes shifts of **23d** are much smaller than those of nonsymmetrical **22d**. The larger absorption bandwidth of **22d** is due to the fact that **22d** has a relatively strong bond alternation in the ground state which changes upon excitation, a typical "merocyanine" behavior. Analysis of the solvent-dependent absorption and emission maxima of **22d** and **23d** according to the generalized treatment of the solvent effect based on a set of four mutually independent, empirical solvent scales (dipolarity, polarizability, acidity, and basicity of the medium)[64] shows that solvent dipolarity and definitely polarizability are the main factors influencing the measured shifts. For both dyes, the fluorescence rate constant k_f (1.7×10^8 s^{-1}) does not depend much on the solvent tested.

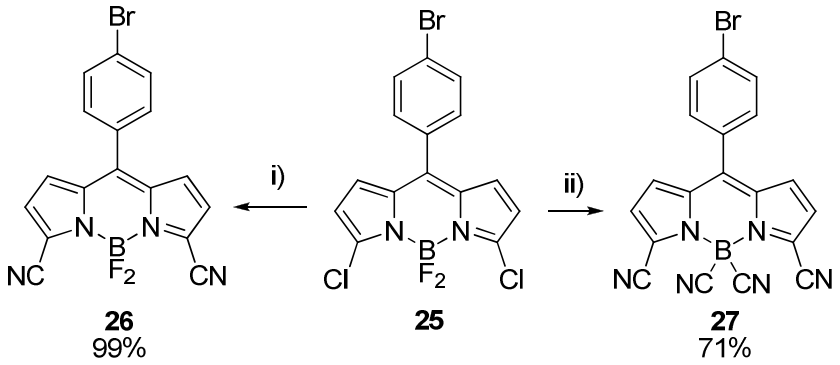
A systematic study was carried out in which chalcogen substituted BODIPY dyes **24** were prepared from 3,5-dichloroBODIPY **21** by nucleophilic disubstitution with phenol and its sulfur (i.e., thiophenol), selenium, and tellurium analogues (Scheme 7). By moving from oxygen (**24a**) to tellurium (**24d**), a gradual bathochromic shift of the absorption and emission spectra was observed going all the way to the near-infrared for the ditellurium analogue **24d**. The latter has only weak fluorescence, perhaps as a result of efficient intersystem crossing. An additional weak emission band observed

for **24d** between 820 and 1100 nm at 77 K in methyltetrahydrofuran is probably attributable to phosphorescence.[65]



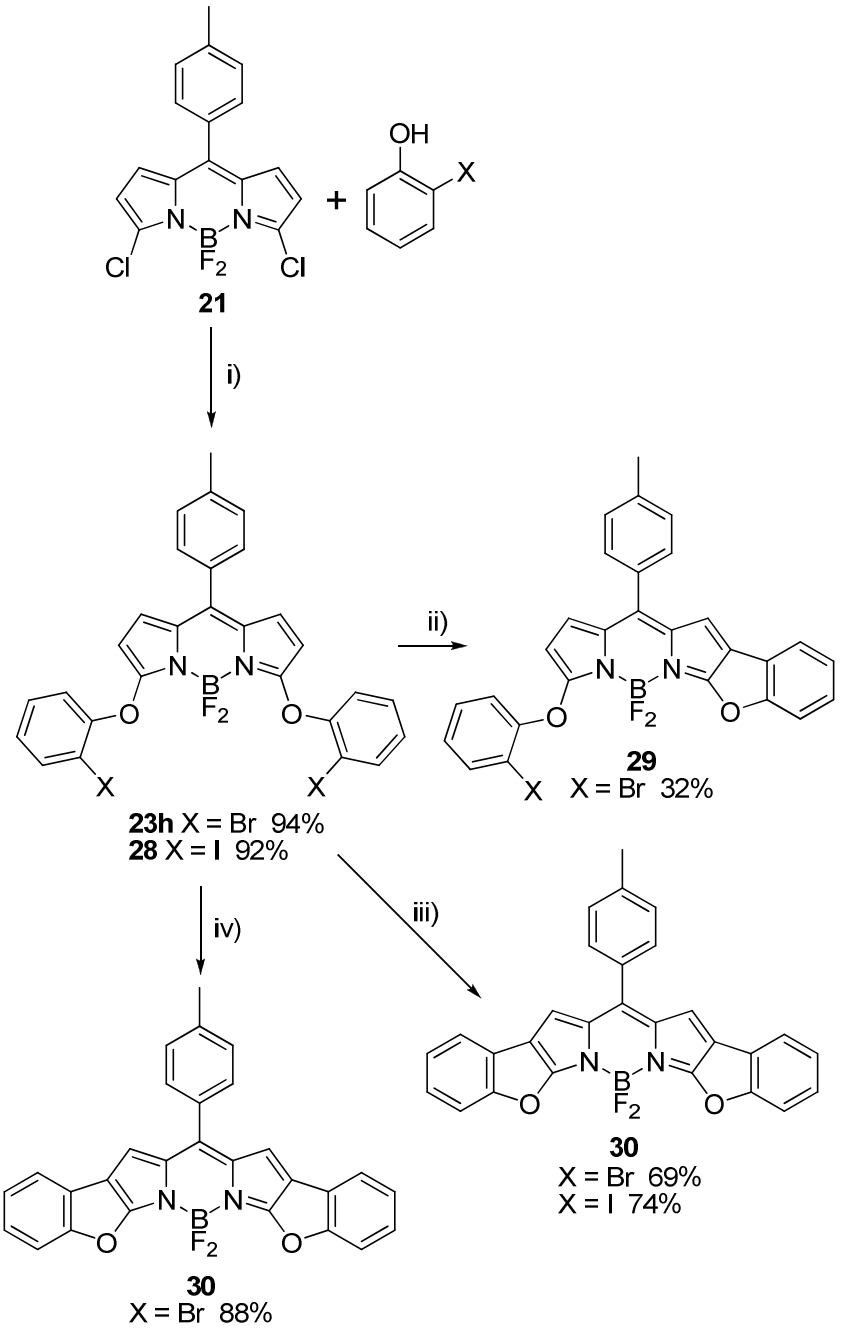
Scheme 7 Nucleophilic substitution of 3,5-dichloroBODIPY **21** with phenol and its sulfur, selenium, and tellurium analogues. Conditions: i) PhOH, K_2CO_3, CH_3CN, reflux, 4 h. ii) PhSH, K_2CO_3, DMF = *N*,*N*-dimethylformamide, 50 °C, 12 h. iii) PhSeSePh, $NaBH_4$, THF, rt, 12 h. iv) PhTeTePh, $NaBH_4$, THF, rt, 12 h.[65]

Two boron dipyrrins with cyano-substituents (**26** and **27**) were synthesized by Burgess *et al*.[55] (Scheme 8) and subsequently characterized photophysically by us.[66] The two analogues have comparable photophysical properties, implying that displacement of F by CN at boron has a negligible effect; e.g., both dyes have high Φ values (0.6–0.9) and display mono-exponential fluorescence decay profiles in nonprotic solvents. The generalized treatment of the solvent effect, proposed by Catalán,[64] indicates that solvent polarizability and, to a lesser extent, solvent dipolarity are the decisive factors influencing the solvent-dependent shifts of the absorption and emission bands. Cyano-substituted BODIPYs are rather unstable and the kinetics of decomposition of **26** and **27** in polar nonprotic solvents (acetone, acetonitrile, and *N*,*N*-dimethylformamide) is complex.



Scheme 8 Synthesis of cyano-substituted BODIPY **26** and **27** by nucleophilic substitution of 3,5-dichloroBODIPY **25**. Conditions: i) $(CH_3)_3SiCN$, $SnCl_4$, CH_2Cl_2, 25 ºC, 2 h. ii) $(CH_3)_3SiCN$, $BF_3{\bullet}OEt_2$, CH_2Cl_2, 25 ºC, 2 h.[55,66]

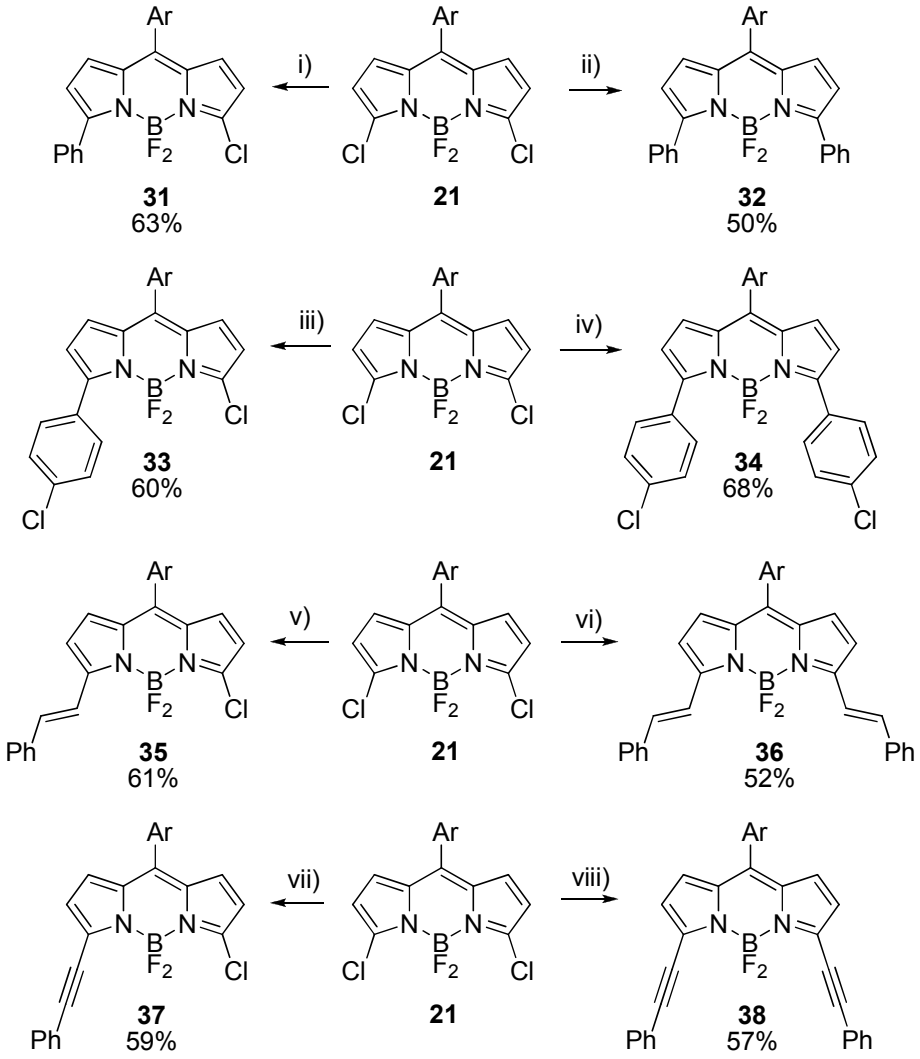
Nucleophilic aromatic substitution of **21** with 2-bromophenol and 2-iodophenol leads to the conformationally unconstrained 3,5-di(2-bromophenoxy)BODIPY **23h** (Schemes 6 and 9)[61] and its iodated analogue 3,5-di(2-iodophenoxy)BODIPY **28**, respectively (Scheme 9).[67] Palladium-catalyzed, intramolecular benzofuran formation is a straightforward method for the formation of two BODIPY dyes (**29** and **30**) with increasingly rigid conformations (Scheme 9).[67] Restricted bond rotation of the phenoxy fragments results in dyes **29** and **30**, which absorb and emit fluorescence more intensely at longer wavelengths compared to the conformationally unconstrained dye **23h**. The values of the molar absorption coefficients ε(λ), oscillator strengths *f*,[1,2] and fluorescence quantum yields Φ of **29** and **30** are considerably higher than those of **23h**. The progressively more extended planarity of the chromophore in the series **23h** → **29** → **30**, in line with the concomitant reduced conformational flexibility, accounts for the increasingly larger red shifts of the absorption and emission bands in that series. The small solvent-dependent shifts of λ_{abs}(max) and λ_{em}(max) of **23h**, **29**, and **30** were analyzed by means of the general treatment of the solvent effect[64] and are shown to be primarily determined by solvent polarizability.



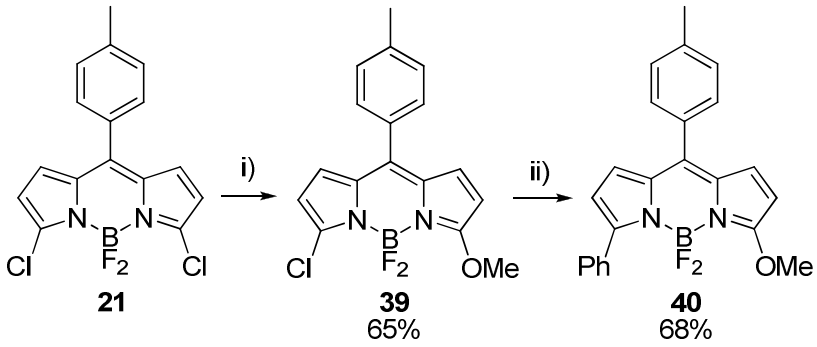
Scheme 9 Synthesis of BODIPY dyes with increasing conformational restriction. Conditions: i) Na_2CO_3, acetonitrile, reflux, 1 h. ii) $Pd(OAc)_2$, triphenylphosphine, K_2CO_3, dioxane, reflux, 96 h. iii) $Pd(OAc)_2$, triphenylphosphine, K_2CO_3, toluene, reflux, 48 h. iv) $Pd(OAc)_2$, triphenylphosphine, K_2CO_3, toluene, microwave irradiation, 130 °C, 8 h.[67]

The BODIPY scaffold can simply be functionalized at the 3- (and 5-) position(s) with one or two aryl, arylethenyl, and arylethynyl moieties by palladium-catalyzed C–C coupling reactions of 3,5-dichloroBODIPY derivative **21** using the Stille, Suzuki, Heck, and Sonogashira reactions (Scheme 10).[28] The 3-chloro derivatives **31**, **33**, **35**, and **37**, bearing one substituent at their 5-positions, can be modified further because

the imidoyl chloride can be exchanged for another (O, N, S, or C) nucleophile or aryl, arylethenyl, and arylethynyl group by respectively nucleophilic substitution or transition-metal-catalyzed coupling reactions. Examples hereof are the K^+-selective probe **18** (Scheme 5) and dye **40** (Scheme 11). These novel BODIPY derivatives display λ_{abs}(max) and λ_{em}(max) ranging from green to near-infrared.



Scheme 10 Palladium-catalyzed coupling reactions of 3,5-dichloroBODIPY **21**. Ar = *p*-tolyl. Conditions: i) 1 equiv. $SnPh_4$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux, 30 min. ii) 2 equiv. $SnPh_4$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux, 24 h. iii) 1 equiv. 4-$ClC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1,2-dimethoxyethane, microwave irradiation, 150 ºC, 5 min. iv) 2 equiv. 4-$ClC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1,2-dimethoxyethane, microwave irradiation, 150 ºC, 20 min. v) 1.5 equiv. styrene, $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 100 ºC, 1 h. vi) 2.5 equiv. styrene, $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 100 ºC, 8 h. vii) 1 equiv. phenylacetylene, $Pd(OAc)_2$ / PPh_3 / CuI, DMF / Et_3N (1:1 v/v), 80 ºC, 1 h. viii). 2.2 equiv. phenylacetylene, $Pd(OAc)_2$ / PPh_3 / CuI, DMF / Et_3N (1:1 v/v), 80 ºC, 3 h.[28]



Scheme 11 Synthesis of the BODIPY dyes **39** and **40**. Conditions: i) 2 equiv. NaOMe, MeOH, rt, 30 min. ii) $C_6H_5B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1,2-dimethoxyethane, microwave irradiation, 150 °C, 20 min.[68]

The absorption spectra of the 3,5-disubstituted derivatives **32**, **34**, **36**, and **38** are red-shifted (by 20 to 50 nm) compared to the corresponding monosubstituted compounds **31**, **33**, **35**, and **37** (with Cl at the 3-position), respectively. The emission maxima λ_{em}(max) of the symmetrically 3,5-disubstituted dyes are shifted to longer wavelengths (by 30 to 60 nm) compared to the unsymmetrically 3,5-disubstituted counterparts (with Cl at 3-position). Introduction of phenylethenyl groups causes the largest bathochromic shift in both the absorption and emission spectra. Derivatives with phenylethynyl substituents also shift λ_{abs}(max) and λ_{em}(max) to longer wavelengths compared to phenyl-substituted ones but to a lesser degree than the phenylethenyl compounds. Figure 3 displays the absorption and fluorescence emission spectra of **31**, **35**, **36**, and **38**. The Φ values of the phenylethenyl and phenylethynyl analogues are significantly higher than those of the phenyl-substituted dyes.

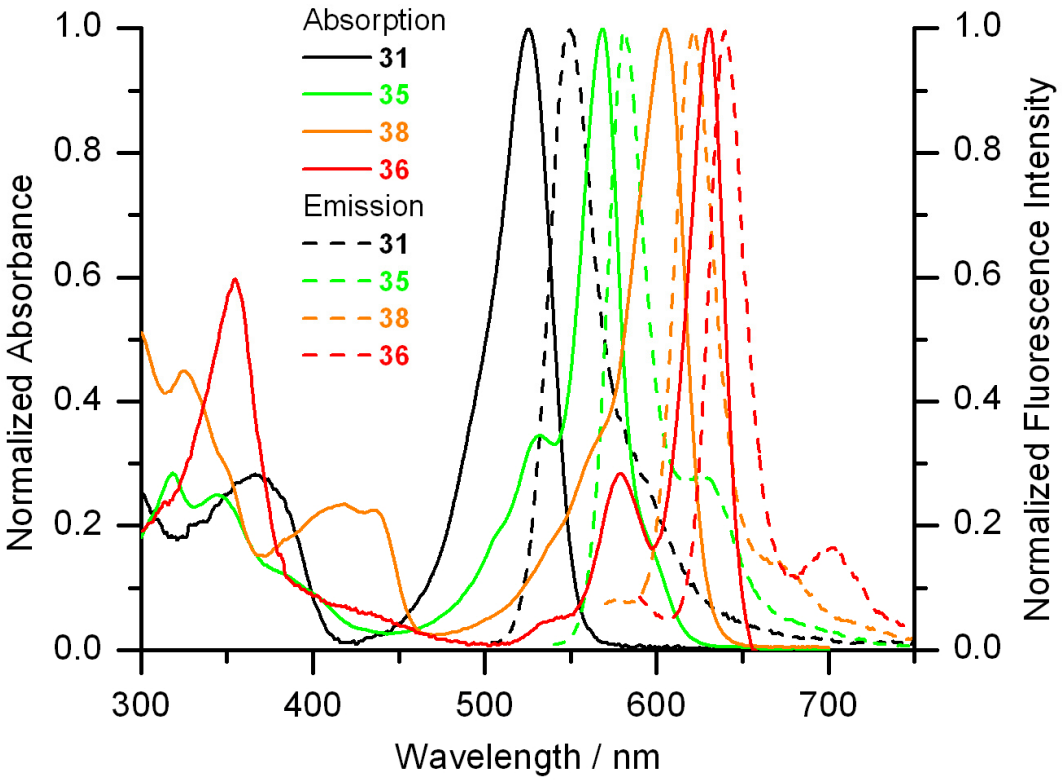


Figure 3 Normalized absorption and fluorescence emission spectra of 3-chloro-5-phenyl (**31**, in methanol: black), 3-chloro-5-phenylethenyl (**35**, in cyclohexane: green), 3,5-diphenylethenyl (**36**, in cyclohexane: red), and 3,5-diphenylethynyl (**38**, in methanol: orange) substituted BODIPY derivatives. The bathochromic shifts in going from a 5-phenyl substituent (in **31**) to a 5-phenylethenyl group (in **35**) are clearly visible. Also evident are the red shifts in going from a 3,5-diphenylethynyl substituent (in **36**) to a 3,5-diphenylethenyl group (in **38**) and the effect of disubstitution (**35** *vs* **36**). The main absorption band (assigned to the $S_1 \leftarrow S_0$ transition) as well as the weaker, blue-shifted absorption band (attributed to the $S_2 \leftarrow S_0$ transition) are shown.

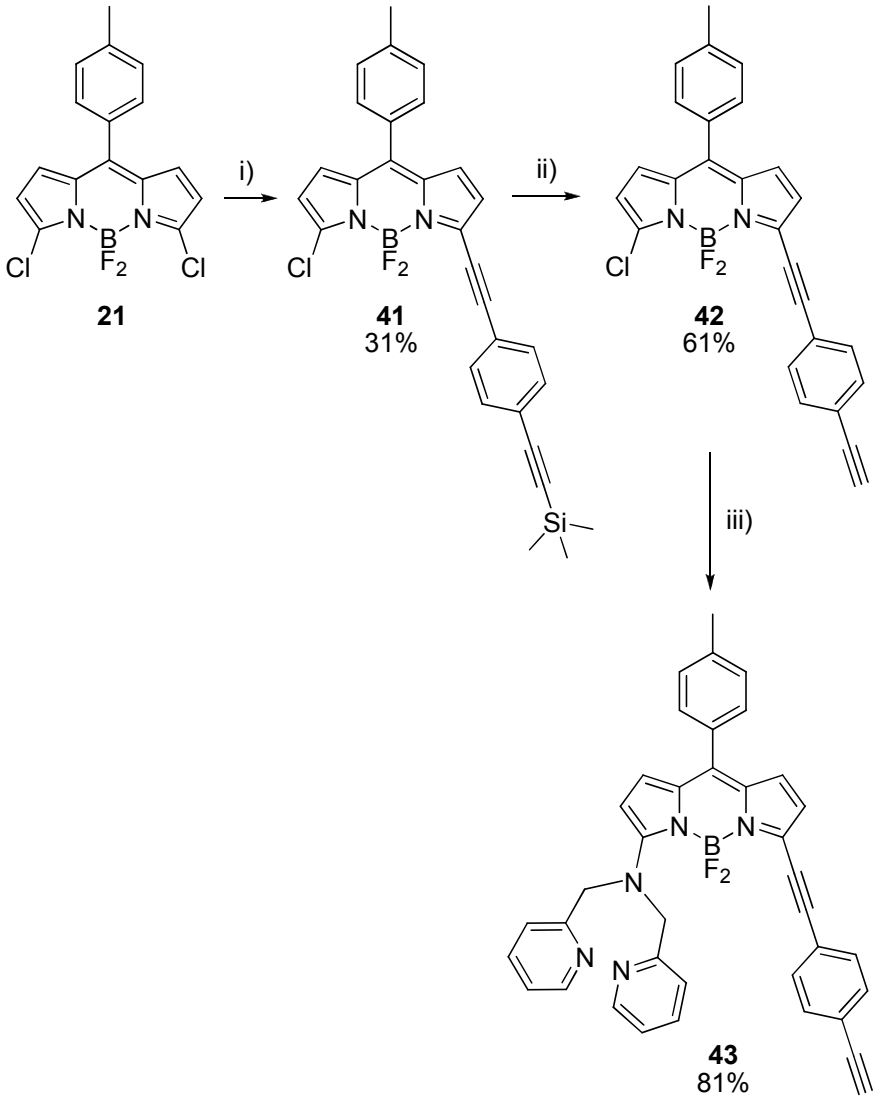
Some fundamental spectroscopic and photophysical data of representative 3-chloro-5-phenyl (**31**), 3-chloro-5-phenylethenyl (**35**), 3-chloro-5-phenylethynyl (**37**), 3,5-diphenyl (**32**), 3,5-diphenylethenyl (**36**), 3,5-diphenylethynyl (**38**), and 3-methoxy-5-phenyl (**40**) substituted BODIPY dyes in tetrahydrofuran, methanol and cyclohexane are compiled in Table 1.[68]

Table 1 Absorption and fluorescence emission spectroscopic data of **31**, **32**, **35**–**38**, and **40** in tetrahydrofuran (THF), methanol (MeOH), and cyclohexane. $\Delta\bar{\nu}$ denotes the Stokes shift, k_f and k_{nr} stand for the rate constants of fluorescence and nonradiative decay, respectively.

BODIPY	Solvent	λ_{abs}(max) / nm	λ_{em}(max) / nm	$\Delta\bar{\nu}$ / cm^{-1}	Φ	τ / ns	k_f / 10^8 s^{-1}	k_{nr} / 10^8 s^{-1}
31	THF	530	555	850	0.084			
	MeOH	525	549	833	0.037			
	cyclohexane	530	553	785	0.076			
32	THF	553	586	1018	0.22	1.40	1.6	5.6
	MeOH	547	582	1100	0.21	1.22	1.7	6.5
	cyclohexane	553	585	989	0.31	1.56	2.0	4.4
35	THF	568	581	394	0.56	3.45	1.6	1.3
	MeOH	564	579	459	0.55	3.16	1.7	1.4
	cyclohexane	569	581	363	0.72	3.64	2.0	0.8
36	THF	632	645	319	0.82	4.09	2.0	0.4
	MeOH	626	639	325	0.92	4.54	2.0	0.2
	cylohexane	630	642	297	0.96	4.37	2.2	0.1
37	THF	560	573	405	0.84	4.24	2.0	0.4
	MeOH	556	569	411	0.98	4.25	2.3	0
	cyclohexane	564	575	339	1.00	4.31	2.3	0
38	THF	610	625	393	0.99	6.62	1.5	0
	MeOH	605	622	452	1.00	6.51	1.5	0
	cyclohexane	615	626	286	1.00	6.58	1.5	0
40	THF	528	555	921	0.30	1.78	1.7	3.9
	MeOH	523	550	939	0.23	1.54	1.5	4.9

Another example of combining a palladium-catalyzed coupling reaction (i.c., Sonogashira reaction) with nucleophilic substitution [using di(2-picolyl)amine] of 3,5-dichloroBODIPY derivative **21**, is represented by the 3,5-difunctionalized, colorimetric and near-infrared, fluorescent turn-on indicator **43** for Cu^{2+} (Scheme

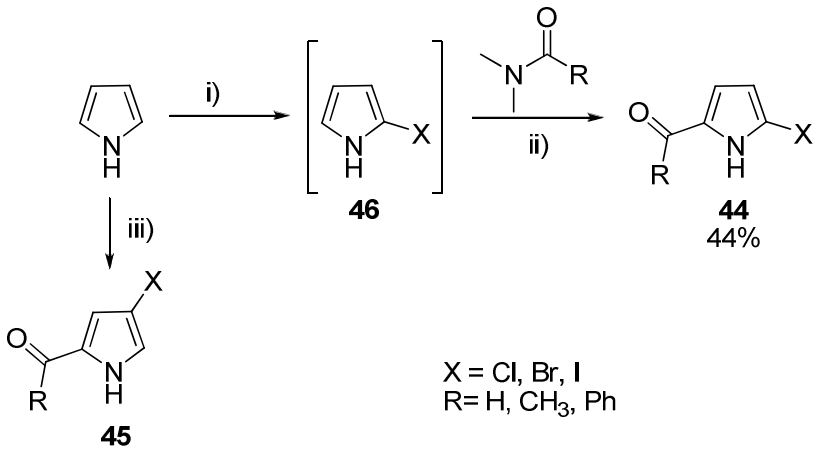
12).[69] Upon excitation at 620 nm in acetonitrile, indicator **43** displays a significant fluorescence amplification in the presence of Cu^{2+} (Φ increases from 0.09 for **43** in the absence of metal ions to 0.72 for the 1:1 complex **43**–Cu^{2+} between **43** and Cu^{2+}) and a high selectivity toward Cu^{2+} among various metal ions (K_d = 8.7 μM for **43**–Cu^{2+} in acetonitrile).



Scheme 12 Synthesis of indicator **43**. Conditions: i) 1 equiv. of silylated alkyne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, 60 ºC. ii) Bu_4NF, THF, –78 ºC. iii) Di(2-picolyl)amine, acetonitrile, rt.[69]

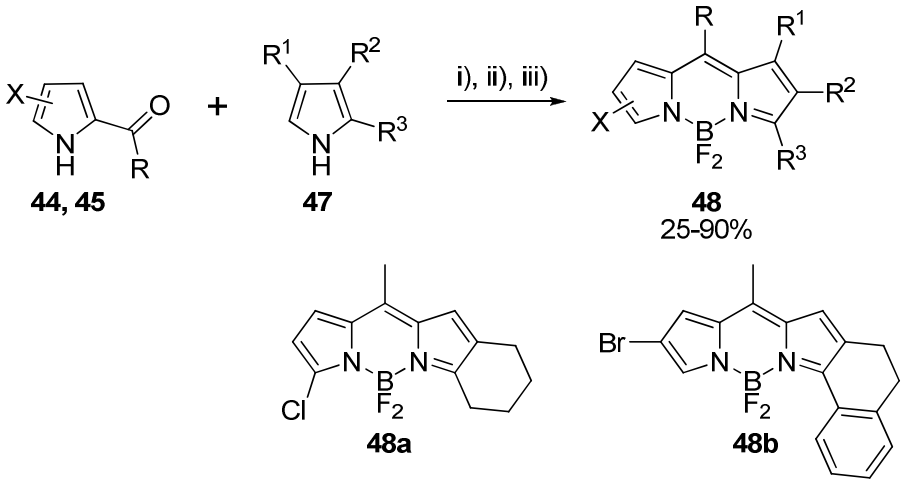
As described above, 3,5-dihaloBODIPYs allow both mono- and disubstitution by changing the reaction conditions. Because selectivity (mono *vs* di) is sometimes low (e.g., particularly in the Sonogashira reaction), exploring the synthesis of monohalogenated BODIPYs is a worthwhile endeavor. 2-Acyl-5-halopyrroles **44** and

2-acyl-4-halopyrroles **45** (Scheme 13) are valuable precursors of 3-haloBODIPYs and 2-haloBODIPYs, respectively (Scheme 14).[29] Whereas 2-acyl-4-halopyrroles **45** are well known,[70] we had to devise a versatile, one-pot synthetic procedure for their isomeric 2-acyl-5-halopyrrole **44** counterparts (Scheme 13). Thus, the notoriously unstable 2-halopyrroles **46** were formed *in situ* at low temperatures and reacted directly further by Vilmeier-Haack reaction or trifluoroacetylation.



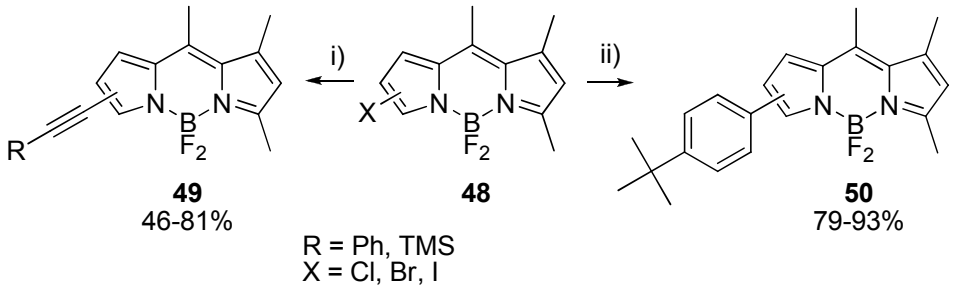
Scheme 13 Synthesis of 5-halogenated 2-acylpyrroles **44** and 4-halogenated 2-acylpyrroles **45**.[29] Conditions: i) NXS, THF. ii) Vilsmeier–Haack reaction: $POCl_3$. iii) ref [70].

The combination of a series of widely available pyrroles **47** with the monohalogenated 2-acylpyrroles **44** and **45**, as the second moiety of the target BODIPY, influences the properties of the resulting dyes **48** (Scheme 14). Selection of the halogen X (Cl, Br, I) allows tuning the reactivity of the ensuing compounds **48**. The *meso*-substituent R in **48** results from the standard Vilsmeier–Haack reaction of pyrroles and allows for a large number of substituents to be introduced.[29]



Scheme 14 Synthesis of 3-haloBODIPYs (exemplified by **48a**) and 2-haloBODIPYs (exemplified by **48b**). Conditions: i) $POCl_3$. ii) Et_3N. iii) $BF_3 \bullet OEt_2$.[29]

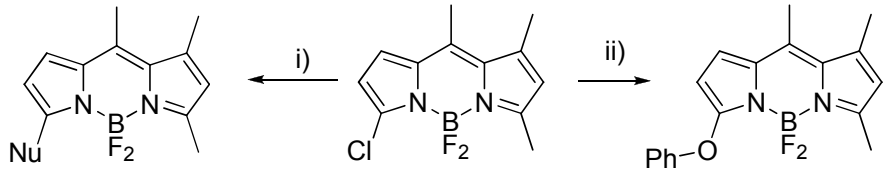
The monohalogenated difluoroboron dipyrrins **48** can be readily substituted by several nucleophiles and can be used in palladium-catalyzed cross-coupling reactions, such as Suzuki and Sonogashira reactions (Scheme 15). The 3-alkynyl dyes (**49** with R = Ph, TMS) have very high Φ values (0.8–0.9), which decrease slightly upon increasing solvent polarity. (In comparison, the 2-alkynyl counterparts have lower Φ, which decrease significantly with increasing solvent polarity.) The absorption maxima λ_{abs}(max) of the 3-alkynyl dyes are red-shifted compared to those of the 2-alkynyl analogues. In contrast, λ_{em}(max) of the 3-alkynyl derivatives are blue-shifted in relation to those of the 2-alkynyl dyes, resulting in small Stokes shifts for the 3-alkynyl isomers.



Scheme 15 Suzuki and Sonogashira reactions of 2-halo and 3-haloBODIPYs **48**. Conditions: i) 1.3 equiv. terminal alkyne, $Pd(PPh_3)_4$, CuI, THF / *i*Pr_2NH (2:1 v/v), reflux, 3 h. ii) 1.3 equiv. 4-*t*-Butyl-benzeneboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux 3 h.[29]

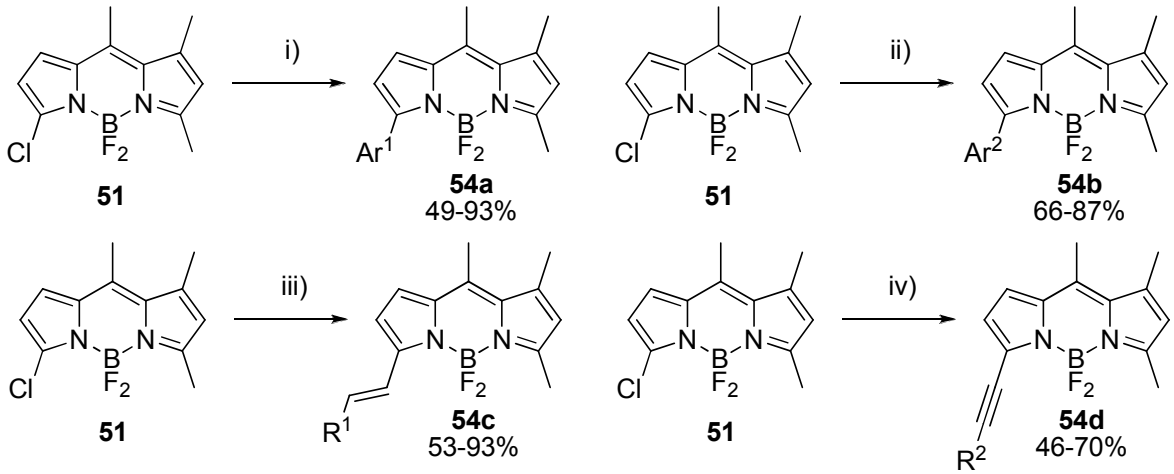
In the original procedure (Scheme 13),[29] pyrrole was halogenated using *N*-halosuccinimide NXS (X = Cl, Br). In the optimized procedure, sulfuryl chloride (SO_2Cl_2) rather than NCS is used.[23] As reported in ref [29] (Scheme 14), condensation of acylpyrrole **45** (X = Cl) with another pyrrole **47** leads to a dipyrrin salt intermediate, which is deprotonated and complexed to afford the 3-chloroBODIPY **48**.[23]

The 3-monochloro dye **51** can be substituted by nitrogen, sulfur, and oxygen nucleophiles (Scheme 16), and be subjected to Pd-catalyzed C–C coupling reactions (Scheme 17).[23]



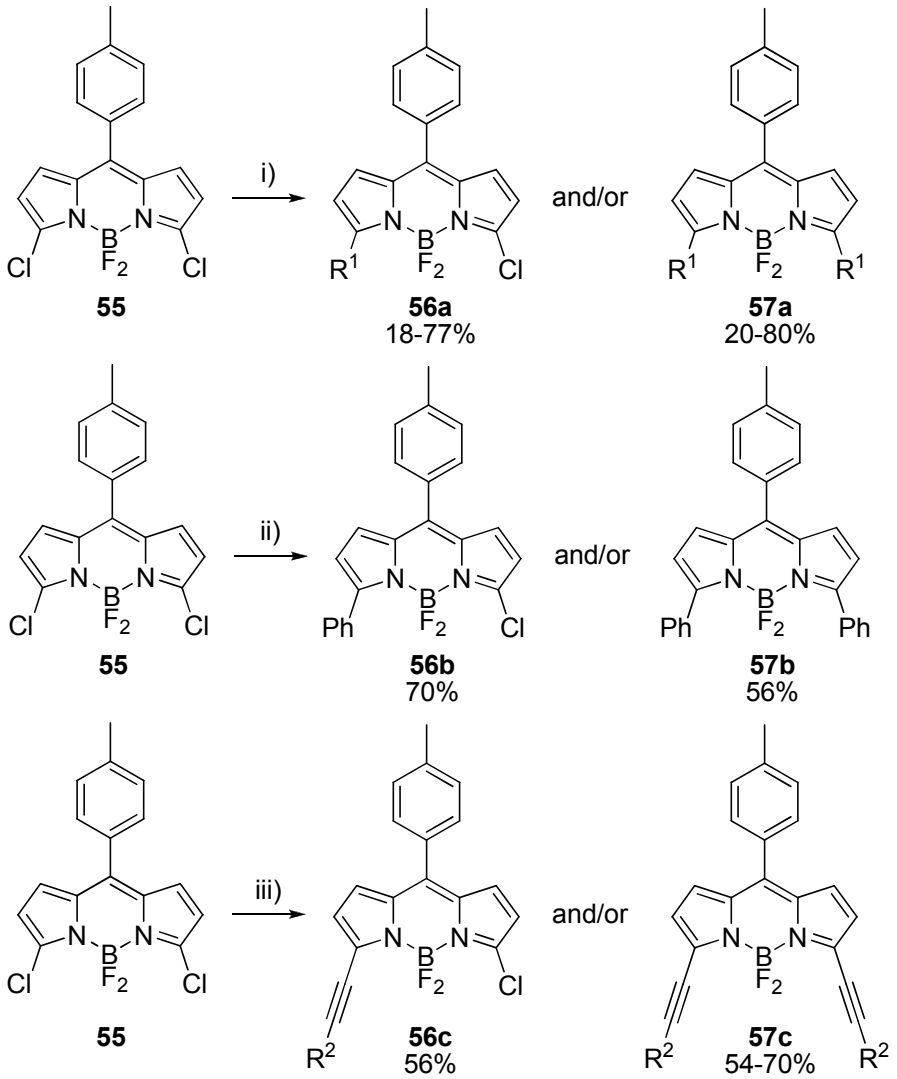
Scheme 16 Substitution of 3-chloroBODIPY **51** with heteroatom-containing nucleophiles. Conditions: i) Nucleophile NuH, base, acetonitrile, 80 ºC. ii) Phenol, K_3PO_4, THF, copper(I)-thiophene-2-carboxylate, 66 ºC.[23]

Compared with the starting compound **51**, the 3-oxygen substituent in **53** does not lead to the large bathochromic shifts observed for dyes **52a**–**c** with 3-sulfur and 3-nitrogen substituents. The 3-(N,O,S) substituted dyes **52** and **53** (Scheme 16) all have rather high quantum yields Φ (0.6–0.9).[23]



Scheme 17 Reactivity of 3-chloroBODIPY **51** in palladium-catalyzed cross-coupling reactions. Conditions: i) Suzuki: toluene, Na_2CO_3(aq), $Pd(PPh_3)_4$, boronic acid $RB(OH)_2$, reflux. Ar = Ph, 4-*t*BuPh, 4-MeO-Ph, 4-F-Ph or 2-thienyl. ii) Stille: 1,4-dioxane, $Pd(PPh_3)_4$, tributylphenyltin or 2-(tributylstannyl)thiophene or 2-(tributylstannyl)furan, reflux. Ar = Ph, 2-thienyl or 2-furyl. iii) Heck: xylene, $Pd_2(dba)_3$, Na_2CO_3, trifurylphosphine, alkene, 130 ºC. R^1 = Ph or COOBu. iv) Sonogashira: 1,4-dioxane / *i*Pr_2NEt, $Pd(PPh_3)_4$, CuI, alkyne, 100 ºC. R^2 = Ph, TMS or TIPS. [23]

As a final palladium-catalyzed C–C coupling reaction, the Negishi reaction of 3-halogen and 3,5-dihalogen substituted boradiaza-*s*-indacenes with different organozinc reagents was investigated (Scheme 18).[71] AlkylBODIPYs, which up to now have been prepared mainly through complicated prefunctionalization routes, now become accessible via postfunctionalization. Arylations and alkynylations by Negishi reactions are also possible and are alternatives to the Suzuki, Stille, and Sonogashira reactions. The Negishi reaction also provides an entry to unsymmetrically 3,5-dialkylated BODIPYs.



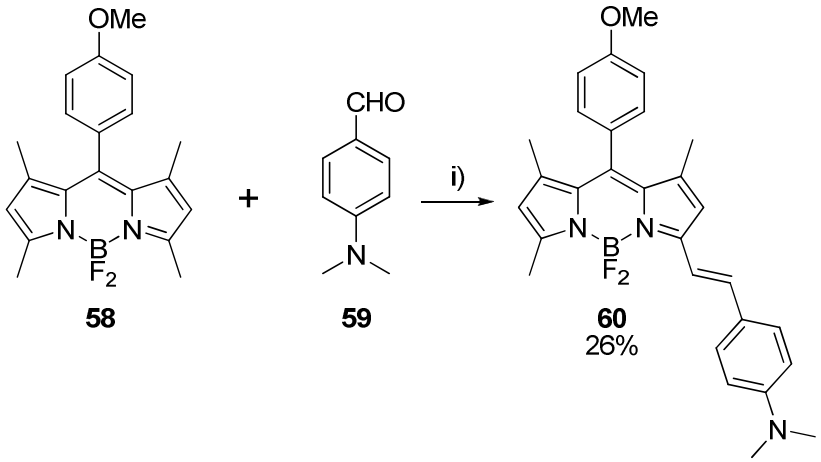
Scheme 18 Negishi reaction of haloBODIPYs **55a-c**. Conditions: i) [R^1-Zn], $Pd(PPh_3)_2Cl_2$, toluene, rt (R^1 = alkyl). ii) PhZnBr, $Pd(PPh_3)_2Cl_2$, toluene, rt. iii) R^2-C≡CZnBr, $Pd(PPh_3)_2Cl_2$, toluene, rt (R^2 = Ph or TMS).[71]

3,5-DimethylBODIPYs as starting materials

In 1988, Haugland and Kang described the piperidine catalyzed Knoevenagel type condensation of 1,3,5,7-tetramethyl substituted BODIPY with 4-dimethylaminobenzaldehyde **59** in isopropyl alcohol at reflux, leading to the 3-monostyryl derivative.[72a] Since then, this Knoevenagel type condensation between BODIPY derivatives with (at least) a 3-methyl substituent and (substituted) aromatic aldehydes has become a popular method for introducing styryl functionalities.[25,72] In this way, boron dipyrrin dyes can be synthesized with one (3-substituted[74] or 8-

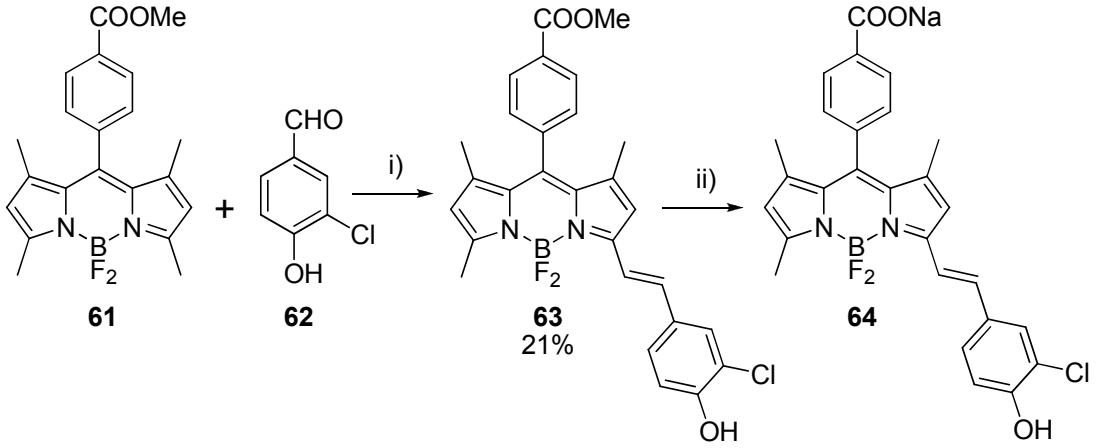
substituted[73]), two (3,5-disubstituted)[74], three (3,5,1-trisubstituted)[75] or four (3,5,1,7-tetrasubstituted)[75] alkenyl substituents.

The pH dependent BODIPY dye **60** with a dimethylaminostyryl group at the 3-position was synthesized via microwave-assisted condensation of the appropriate, 1,3,5,7-tetramethyl substituted difluoroboron dipyrrin **58** with 4-*N*,*N*-dimethylaminobenzaldehyde **59** (Scheme 19).[76] The fluorescence emission properties of **60** are strongly solvent dependent: increasing the solvent polarity leads to lower Φ and τ values, and red shifts of λ_{em}(max). The occurrence of an intramolecular charge transfer process may be responsible for the prominent solvent sensitivity. Analysis of the solvatochromic shifts of the fluorescence emission using the Catalán scales[64] indicates that polarity / polarizability effects are decisive, as corroborated by semiempirical quantum-chemical calculations performed in the dielectric continuum approximation. The small solvent-dependent variation of the absorption maxima may reflect just a slight change in polarizability on the environment of the chromophore. Dye **60** undergoes a reversible protonation–deprotonation reaction (ammonium–amine) in the acidic pH range with a pK_a of 2.25 in acetonitrile solution and with fluorescence enhancement at lower pH (Φ = 0.91 at pH 0.38). The fluorescence excitation spectra show a blue shift from 597 nm for the neutral amine to 552 nm for the ammonium form, permitting ratiometric fluorometric pH measurements.



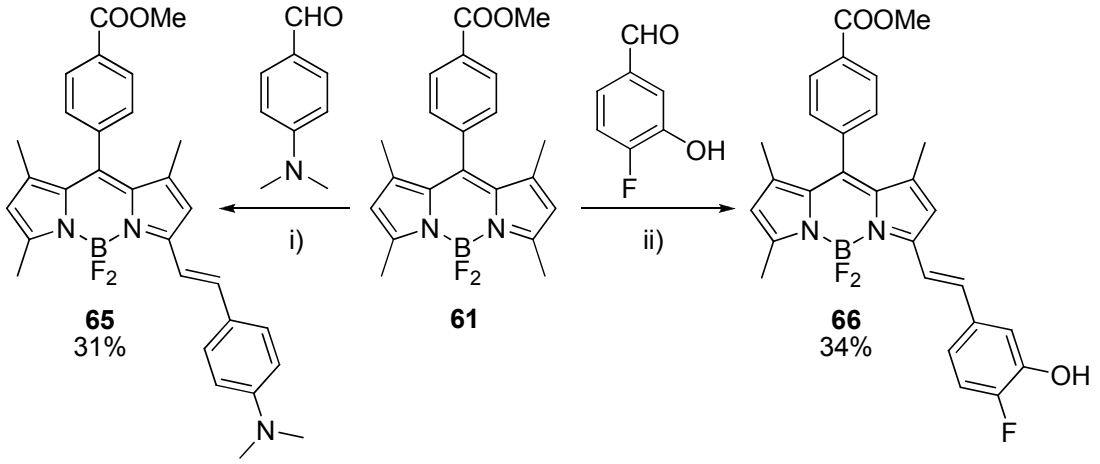
Scheme 19 Synthesis of solvent and pH dependent dye **60**. Conditions: i) toluene, piperidine, AcOH (acetic acid), molecular sieves 4 Å, microwave irradiation, 15 min.[76]

A BODIPY-based on / off pH indicator (available as methyl ester **63** and sodium salt **64**) for the near-neutral pH range with ultra bright, orange fluorescence was synthesized by linking *o*-chlorophenol to the 3-position of a BODIPY derivative via a vinyl bridge (Scheme 20).[77a] The methyl ester **63** has fluorescence lifetimes τ (3.8 ns), fluorescence rate constants k_f (2.6×10^8 s^{-1}), and quantum yields Φ (close to 1.0) that are nearly solvent independent. λ_{abs}(max) of the narrow $S_1 \leftarrow S_0$ absorption band is located between 564 nm (in acetonitrile) and 576 nm (in dimethyl sulfoxide). The emission maxima λ_{em}(max) are in the 577–595 nm range. The small solvatochromic shifts of λ_{abs}(max) and λ_{em}(max) reflect the polarizability of the solvent. In aqueous solution, the water-soluble sodium salt **64** undergoes a reversible protonation–deprotonation reaction (phenol–phenoxide) in the near-neutral pH range with a pK_a of 7.60 and with fluorescence amplification at lower pH (Φ = 0.75 at pH 6.5). The phenoxide form of **64** is nonemissive.



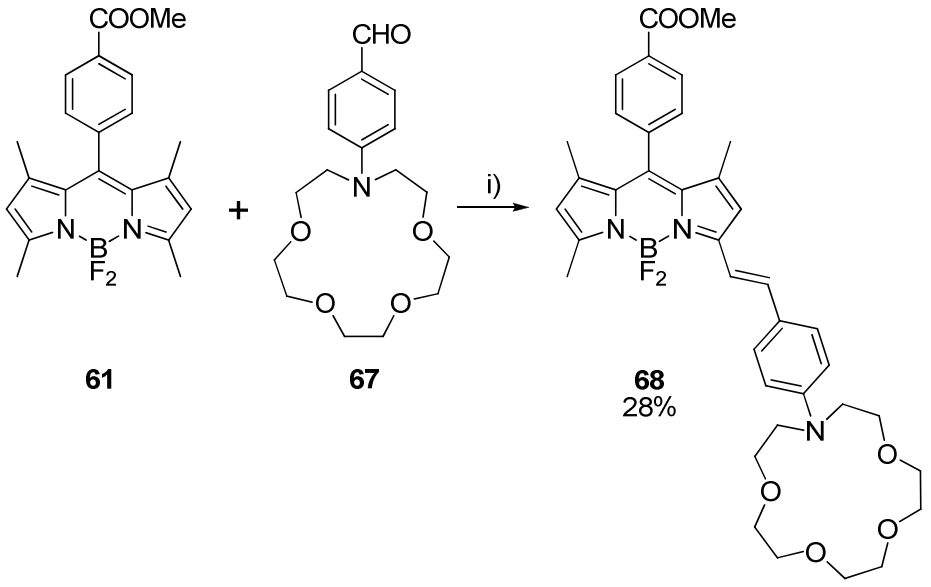
Scheme 20 Synthesis of pH indicator **64**.[77a] Conditions: i) toluene, piperidine, AcOH, molecular sieves 4 Å, microwave irradiation, 15 min. ii) $NaOH_{aq}$, ref [78].

Compounds **65** and **66** (Scheme 21) – related to **60** and **63**, respectively – were synthesized, starting from **61**, with the purpose of investigating the solvent dependency of their spectroscopic and photophysical characteristics.[77b] The generalized treatment of the solvent effect was found to be the most appropriate for analyzing the solvatochromic effects.[64] Solvent dipolarity and polarizability are the important sources for the solvatochromism of **65**. The fluorescence properties of **65** are very sensitive to the solvent: upon increasing the solvent dipolarity, the fluorescence quantum yields Φ and the fluorescence rate constants k_f decrease, and the emission maxima $\lambda_{em}(max)$ become more red-shifted. Conversely, the absorption and fluorescence emission maxima [$\lambda_{abs}(max)$ and $\lambda_{em}(max)$] of **61** and **66** are hardly dependent on the solvent: the small changes point primarily to the polarizability of the solvent surrounding the dye. The k_f values of **61** and **66** are essentially insensitive to the solvent properties.



Scheme 21 Synthesis of **65** and **66**. Conditions: i) toluene, piperidine, AcOH, molecular sieves 4 Å, microwave irradiation, 15 min. ii) toluene, piperidine, AcOH, molecular sieves 4 Å, microwave irradiation, 20 min.[77b]

The pH-sensitive and metal ion-responsive, ratiometric, fluorescent probe **68** with azacrown ether functionality was synthesized by condensation of 1,3,5,7-tetramethyl substituted **61** with 4-(1,4,7,10-tetraoxa-13-aza-cyclopentadec-13-yl)-benzaldehyde **67** (Scheme 22).[79]



Scheme 22 Synthesis of pH and metal ion-sensitive indicator **68**. Conditions: i) toluene, piperidine, AcOH, molecular sieves 4 Å, reflux, 20 h.[79]

Analysis of the small solvatochromism of the absorption spectra of **68** indicates that λ_{abs}(max) depends only on the change of polarizability of the environment of the chromophore. Conversely, solvent polarity / polarizability is the most important factor determining the spectral position and the shift of the fluorescence emission band. In

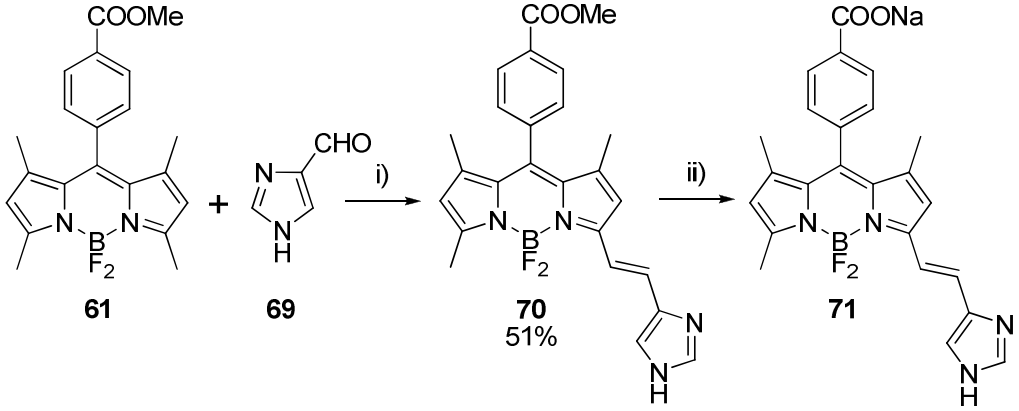
acetonitrile, **68** undergoes a reversible protonation–deprotonation reaction (pK_a = 0.09) and shows a ~50 nm blue shift in the excitation spectra and a 10-fold fluorescence enhancement upon protonation. The probe also forms 1:1 complexes with several metal ions (Table 2), producing large blue spectral shifts and significant cation-induced fluorescence amplifications. The alkali ions Li^+ and Na^+ form the most stable 1:1 complexes with **68** (K_d = 0.92 and 4.4 mM, respectively) with the smallest blue shifts in relation to **68** [λ_{abs}(max) = 594 and 579 nm, respectively; λ_{em}(max) = 700 and 708 nm, respectively], the largest Stokes shifts (> 2500 cm^{-1}) and the lowest fluorescence enhancement (Φ = 0.18 and 0.16, respectively, *vs* Φ = 0.08 for **68**). Among the divalent ions Mg^{2+}, Ca^{2+}, Ba^{2+}, Zn^{2+}, the barium complex with **68** is the most stable (K_d = 0.45 mM) with the largest fluorescence amplification (Φ = 0.92). Upon addition of K^+, Cs^+, Ni^{2+}, Cu^{2+}, and Cd^{2+} to **68** in acetonitrile, no change in the absorption and fluorescence spectra could be found, presumably because no binding takes place. Representative spectral characteristics of **68** in the absence and presence of various cations in acetonitrile are listed in Table 2.[79]

Table 2 Spectral of characteristics of **68** in the absence and presence of various cations in acetonitrile. $\Delta\bar{\nu}$ denotes the Stokes shift and K_d represents the dissociation constant of the 1:1 complex between **68** and the cation.

Dye or Complex	λ_{abs}(max) / nm	λ_{em}(max) / nm	$\Delta\bar{\nu}$ / cm^{-1}	K_d / mM	Φ
68	608	723	2616		0.08
68–H^+	555	565	319	850	0.80
68–Li^+	594	700	2549	0.919	0.18
68–Na^+	579	708	3147	4.4	0.16
68–Mg^{2+}	562	573	342	71	0.80
68–Ca^{2+}	563	569	187	10.1	0.24
68–Ba^{2+}	556	567	349	0.45	0.92

68–Zn^{2+}	558	565	222	5	0.59

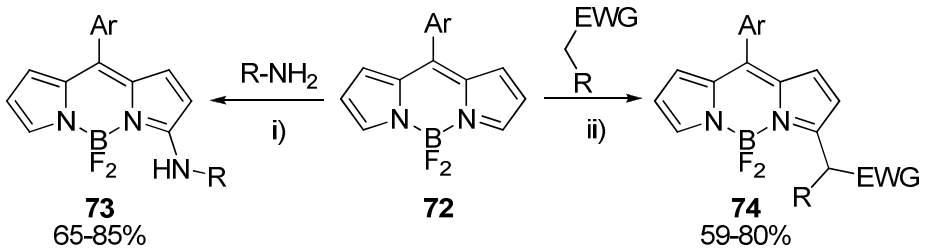
The visible-light-excitable, ratiometric, brightly fluorescent indicator **71** for near-neutral pH was synthesized starting from 1,3,5,7-tetramethylBODIPY **61** by condensation with 1*H*-imidazole-4-carbaldehyde **69**, followed by saponification with NaOH (Scheme 23).[80] The water-soluble dye **71** exhibits two acid–base equilibria in aqueous solution, characterized by pK_a values of 6.0 and 12.6. The apparent pK_a of the near-neutral acid–base equilibrium is practically independent of the added buffer and salt concentration. The Φ value of **71** in aqueous solution is high: 0.6 for the cationic and anionic forms of the imidazole ligand, and 0.8 for neutral imidazole. On protonation–deprotonation in the near-neutral pH range, spectral shifts of the fluorescence excitation and emission spectra are observed (i.e., dual excitation and dual emission). The fluorescence color changes from intense green-yellow at lower pH to intense orange at higher pH. In aqueous solution in the absence of buffer and in the pH range 5.20–7.45, biexponential fluorescence decays are measured with decay times τ_1 = 4.3 ns for the cationic and τ_2 = 3.3 ns for the neutral form of **71**. In organic solvents, the methyl ester **70** is highly fluorescent (Φ = 0.8–1.0) and has a solvent-independent fluorescence lifetime τ (ca. 4 ns). Probe is **70** readily loaded in the cytosol of biological cells, where it is highly fluorescent and adequately photostable.



Scheme 23 Synthesis of pH indicator **70**.[80] Conditions: i) toluene, piperidine, AcOH, molecular sieves 4 Å, reflux, 30 min. ii) $NaOH_{aq}$, ref [77].

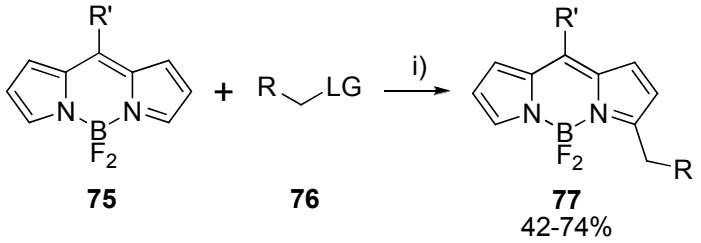
3,5-Unsubstituted BODIPYs as starting materials

Functional group interconversion of halogen containing organic compounds is a textbook reaction. Hence, it is expected that halogenated BODIPYs will display similar reactivity, as is evidenced by the highly versatile derivatization of 3-halo and 3,5-dihaloBODIPYs (see above). However, boron dipyrrins without reactive halogens can also be directly functionalized. Indeed, α-unsubstituted BODIPY dyes (**72**) are highly reactive toward the oxidative nucleophilic substitution of the α-hydrogen(s) [i.e., at the spectroscopically interesting 3(,5)- position(s)], introducing nitrogen (**73**) and carbon (**74**) nucleophiles in a single step (Scheme 24).[24a] Oxygen as oxidizing reagent in *N*,*N*-dimethylformamide (DMF) was found to give the highest yields. Both primary and secondary aliphatic amines readily participate in the oxidative nucleophilic substitution of hydrogen, yielding 3-substituted BODIPYs; no disubstituted product is formed. An aromatic amine (aniline) fails to substitute, presumably because of its lowered nucleophilicity. Carbon nucleophiles (malonate, enolates of ketones and esters) also show excellent reactivity. In contrast, oxygen and sulfur centered nucleophiles do not lead to product formation using this reaction condition. However, Pannell *et al.* recently reported a similar methodology in THF where the 3,5-hydrogens of a *meso*-(phenylthio)-BODIPY could be substituted with thiophenol.[24b]



Scheme 24 Direct functionalization of the BODIPY core at the 3- (and 3,5-) position(s) by oxidative nucleophilic substitution of hydrogen. EWG denotes an electron-withdrawing group. Conditions: i) O_2, DMF, rt. ii) O_2, DMF, base, rt.[24]

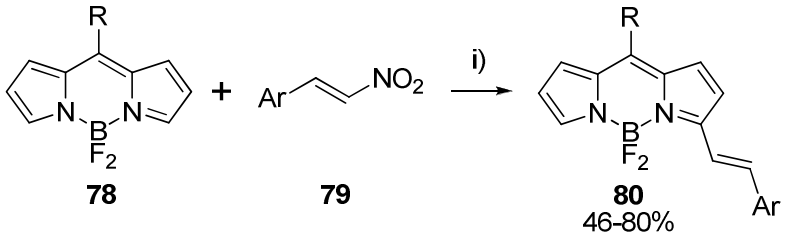
An alternative to the oxidative nucleophilic substitution of the 3,5-hydrogens of α-unsubstituted BODIPY derivatives **75**, is the oxidizer-free substitution of the 3-hydrogen through a vicarious nucleophilic substitution procedure (Scheme 25).[40] This second reaction type can take place if the nucleophile carries a leaving group (LG). The placement of a leaving group on the carbon nucleophile (anions derived from RCH_2LG **76** or R_2CHLG) favors a base-mediated elimination and rearomatization to substitution product **77**. The use of such carbon nucleophiles leads to acetate esters (R = CO_2Me, R = CO_2tBu), malonate ester, and ketones (R = COPh, COMe) in a single step. The leaving group can be varied, and even thioethers (derived from thiophenol and 2-mercaptobenzothiazole) act as leaving groups.



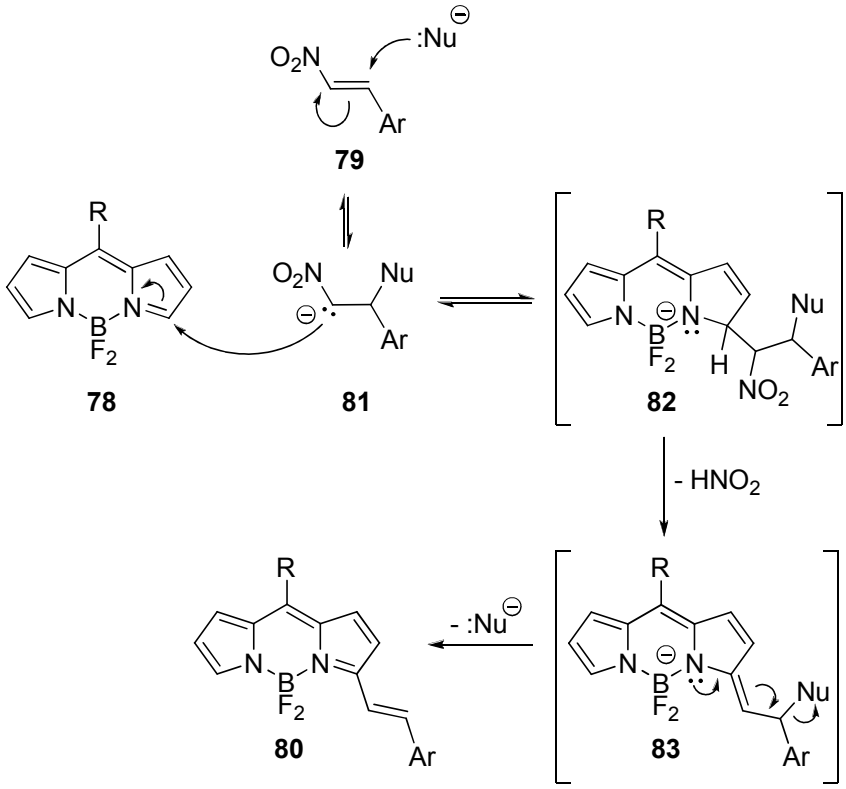
Scheme 25 Vicarious nucleophilic substitution of α-hydrogen of BODIPY **75**. LG (leaving group) = Br, Cl, SPh, etc.; R' = 2,6-dichlorophen-1-yl, phenyl, or SMe. Conditions: i) DMF, rt, base.[40]

Styrylated BODIPY dyes can be prepared either via prefunctionalization of adequately substituted pyrroles,[73,81–83] or via postfunctionalization through transition-metal-catalyzed cross-coupling reactions on halogenated[23,28,84] and borylated[46] BODIPY compounds, or through a Knoevenagel type reaction (see above). The use of nitronate nucleophiles, in the presence of a catalytic amount of thiophenol, leads to BODIPY dyes **80** with a (substituted) styryl group at the 3-position via a tandem reversible Michael addition / vicarious nucleophilic substitution of α-hydrogen (Scheme 26). The nitronate anion **81** – formed through a reversible nucleophilic Michael addition of thiophenol to nitrostyrene starting materials **79** – attacks the BODIPY core at the unsubstituted 3-position. Vicarious nucleophilic

substitution of 3-hydrogen with elimination of HNO_2 and final removal of the nucleophile from **83** with rearomatization lead to the styrylated product **80** (Scheme 27). Like vicarious nucleophilic substitution, the tandem reaction is selective for monosubstitution. As shown previously, introduction of styryl groups at the 3- (and 3,5-) position(s) produces very large bathochromic shifts of λ_{abs}(max) and λ_{em}(max) compared to the starting materials.

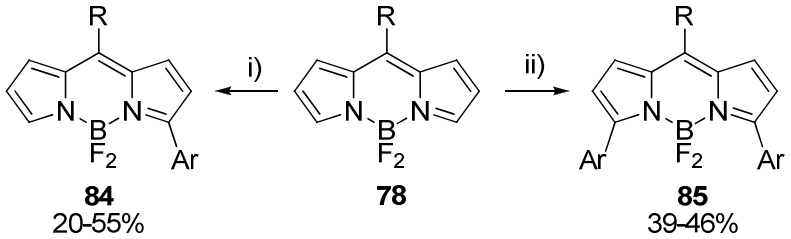


Scheme 26 Reversible Michael addition on nitrostyrenes in tandem with vicarious nucleophilic substitution of 3-hydrogen of BODIPY **78**. Ar = (un)substituted and 2-naphthyl; R = 2,6-dichlorophen-1-yl. Conditions: i) DMF, rt, PhSH (10 mol%) as activating nucleophilic organocatalyst, 18-crown-6 (cat.), K_2CO_3.[40]



Scheme 27 Proposed mechanism for a tandem reversible Michael addition / VNS of hydrogen with nitrostyrene at the 3-position of BODIPY, resulting in the 3-styrylated product.[40]

3-Arylated (**84**) and 3,5-diarylated (**85**) BODIPY dyes can be synthesized via a one-step, palladium-catalyzed C–H arylation of 3,5-unsubstituted boron dipyrrins **78** with arylbromides (Scheme 28).[44] This direct, transition-metal-catalyzed C–H functionalization is a much shorter synthetic protocol and a valuable alternative to the use of halogenated BODIPYs in traditional Suzuki and Stille cross-coupling reactions[28] or arylated pyrrole building blocks[85–87] for constructing such BODIPY derivatives. $Pd(OAc)_2$ and tricyclohexylphoshine are the superior catalyst / ligand combination. K_2CO_3 is the best base and bromoarenes in toluene or *o*-xylene give the best results. Due to the identical reactivity of the C–H bonds at the 3- and 5-positions, diarylation usually competes with monoarylation.

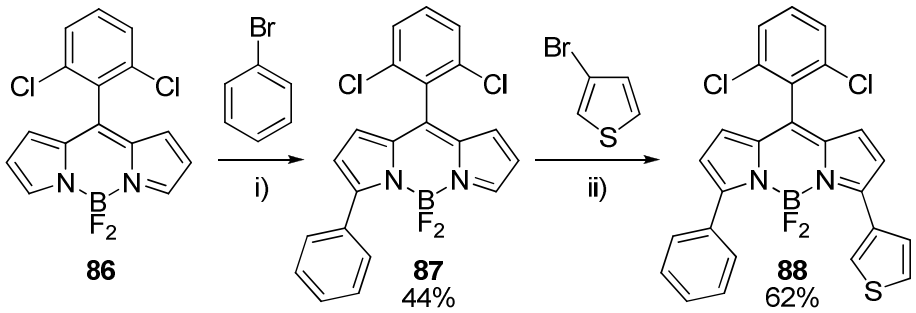


Scheme 28 Direct Pd-catalyzed C–H arylation of *meso*-substituted BODIPYs **78** with different bromoarenes. R = 2,6-dichlorophen-1-yl, phenyl, or *p*-nitrophenyl. Conditions: i) 1.1 equiv. ArBr, 5 mol% $Pd(OAc)_2$, 10 mol% $HPCy_3BF_4$, 30 mol% pivalic acid (2,2-dimethylpropanoic acid), 3 equiv. K_2CO_3, toluene or *o*-xylene, 110 ºC, 24-48 h. ii) 2.2 equiv. ArBr, 5 mol% $Pd(OAc)_2$, 10 mol% $HPCy_3BF_4$, 30 mol% pivalic acid (2,2-dimethylpropanoic acid), 3 equiv. K_2CO_3, toluene or *o*-xylene, 110 ºC, 4 days.[44]

The arylated derivatives **84** and **85** display the characteristic narrow absorption and fluorescence emission bands and the generally quite small Stokes shifts characteristic of classic difluoroboron dipyrrins. Most of the dyes **84** and **85** have high fluorescence quantum yields ($\Phi > 0.85$), except the analogues with *meso*-phenyl and *meso*-(*p*-nitrophenyl) substituents. Free rotation of the *meso*-aryl group in the latter dyes enhances nonradiative deactivation of the S_1 excited state, yielding low Φ values, whereas restricted rotation of the *meso*-(2,6-dichlorophen-1-yl) group leads to high Φ values.[88] The presence of a nitro group in the *meso*-*p*-nitrophenyl substituent contributes extra to fluorescence quenching through oxidative PeT. As a function of

the solvent, λ_{abs}(max) and λ_{em}(max) are located within a narrow wavelength range and are slightly red-shifted with increasing solvent polarizability, which is by far the most decisive parameter affecting the wavelength position of these maxima. Introduction of one phenyl group at the 3-position (in **84**) produces bathochromic shifts of λ_{abs}(max) and λ_{em}(max) of approximately 30 nm compared to the starting compound **78**. The extended π-conjugation of the 3,5-diaryl products **85** is shown in the red-shifted absorption and fluorescence emission spectra compared to those of the 3-substituted analogues **84**. The nature of the *meso*-aryl has only a small effect on the spectral positions but affects the Φ values.[89]

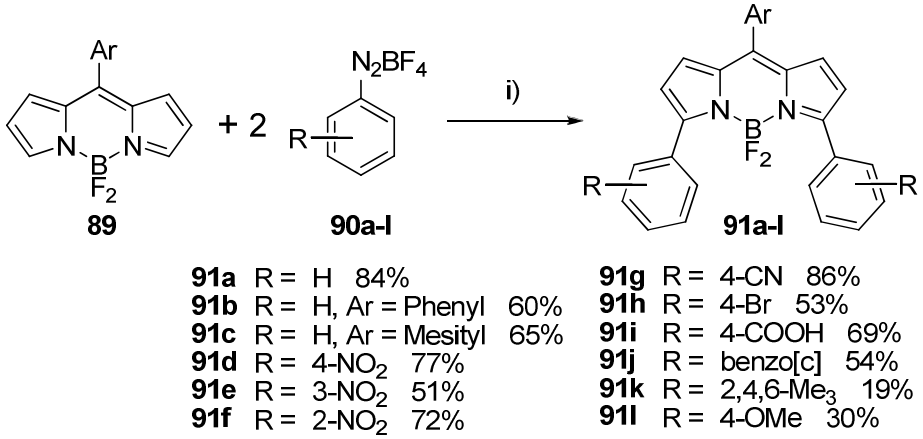
To illustrate the possibilities of this direct Pd-catalyzed C–H arylation of 3,5-unsubstituted boron dipyrrins, unsymmetrical dye **88** was prepared (Scheme 29). This compound was synthesized by performing two sequential C–H arylations, the first with bromobenzene, the second with 3-bromothiophene.[44]



Scheme 29 Synthesis of unsymmetrical BODIPY **88** using the direct C–H arylation method. Conditions: i) 5 mol% $Pd(OAc)_2$, 10 mol% $HPCy_3BF_4$, 30 mol% pivalic acid, 3 equiv. K_2CO_3, *o*-xylene, 110 ºC, 24 h. ii) 5 mol% $Pd(OAc)_2$, 10 mol% $HPCy_3BF_4$, 30 mol% pivalic acid, 3 equiv. K_2CO_3, *o*-xylene, 110 ºC, 48 h.[44]

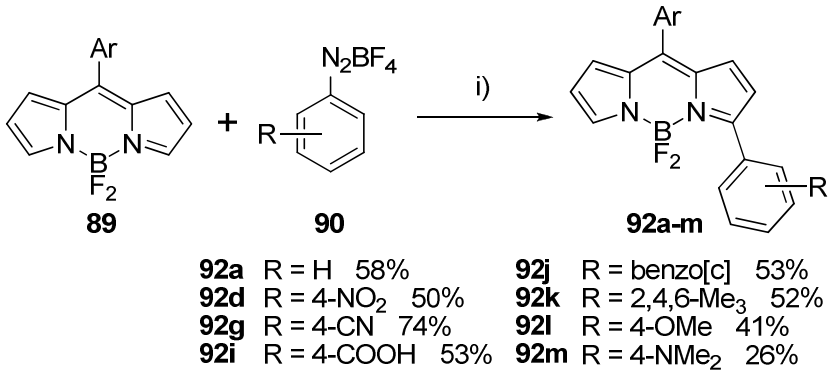
We recently showed that BODIPY dyes are excellent substrates for aryl radicals, allowing an easy synthesis of 3-arylated **92** and 3,5-diarylated **91** boron dipyrrins (Scheme 30).[30] The aryl radicals required for this reaction are formed by ferrocene-catalyzed reduction of aryldiazonium salts at room temperature in the presence of 3,5-unsubstituted BODIPY **89**. This proves to be a mild and fast functionalization strategy

to arylate these boron compounds, in contrast to our developed Pd-catalyzed C–H arylation (see above), where forcing reaction conditions were needed to overcome the inertness of the C–H bond. The mildness of this radical reaction allows an excellent yield for diarylation when an excess of diazonium salt is used. Furthermore, this functionalization strategy shows a broad scope: electron-poor, electron-rich, and sterically hindered diazonium salts all react with BODIPY at its 3,5-positions. However, it should be mentioned that in the case of electron-rich diazonium salts the resulting yields were lower than for the other examples.



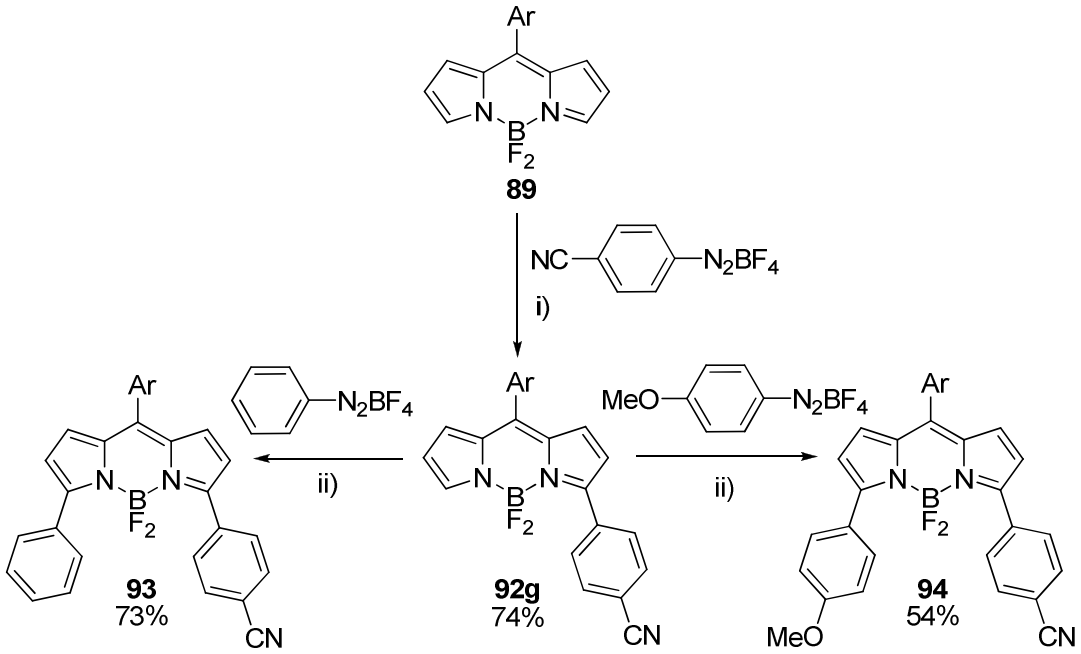
Scheme 30 Radical C–H diarylation of 3,5-unsubstituted BODIPY dyes **89** with an excess of various aryldiazonium salts **90**. Ar = 2,6-dichlorophen-1-yl (unless stated otherwise). Conditions: i) 2.5 equiv. aryldiazonium tetrafluoroborate **90**, ferrocene, acetone, rt.[30]

The procedure developed for diarylation can be modified to allow radical C–H monoarylation (Scheme 31). This is achieved by using one equivalent of diazonium salt **90** instead of a surplus and reducing simultaneously the amount of ferrocene. Hence, 3-arylBODIPYs **92** can be synthesized in good yields. However, due to the identical reactivity of the 3- and the 5-hydrogens some overarylation occurs in this case, producing the diarylated compound **91** as a side product.



Scheme 31 Radical C–H monoarylation of 3,5-unsubstituted BODIPY dyes with one equivalent of various aryldiazonium salts. Ar = 2,6-dichlorophen-1-yl. Conditions: i) 1 equiv. aryldiazonium tetrafluoroborate **90**, ferrocene, acetone, rt.[30]

To illustrate the potential of this novel radical reaction, two unsymmetrically substituted dyes (**93** and **94**) were synthesized using two sequential radical C–H arylations (Scheme 32). The first reaction was performed with 4-cyanobenzenediazonium tetrafluoroborate, while the second step was done with either benzenediazonium tetrafluoroborate or 4-methoxybenzenediazonium tetrafluoroborate. Another interesting possibility of this radical reaction is the synthesis of 3,5-bis(4'-carboxyphenyl)-BODIPY **91i** and its mono analogue **92i**. Both dyes are water-soluble fluorophores in their deprotonated form with moderate to good Φ values. Moreover, the carboxy functional group allows further functionalization *via* esterification / amidation reactions making these compounds promising candidates as the basis for constructing fluorescent biolabeling reagents.



Scheme 32 Synthesis of unsymmetrical 3,5-diarylated BODIPY dyes **93** and **94** using two sequential radical C–H arylations. Ar = 2,6-dichlorophen-1-yl. Conditions: i) 1 equiv. 4-cyanobenzenediazonium tetrafluoroborate **90g**, ferrocene, acetone, rt. ii) 1.5 equiv. aryldiazonium tetrafluoroborate **90a** (for **93**) or **90l** (for **94**), ferrocene, acetone, rt.[30]

As expected, the arylated compounds **91** and **92**, made via this radical reaction, display similar spectroscopic properties as those made by the Pd-catalyzed C–H arylation (see above). Figure 4 displays the visible absorption and fluorescence emission spectra of a selection of 3-monoarylated (**92**) and 3,5-diarylated (**91** and **93**) BODIPY analogues in acetonitrile. The symmetrically 3,5-disubstituted products **91** have red-shifted absorption and emission spectra compared to their unsymmetrically 3-substituted counterparts **92**, reflecting the better π–conjugation in the 3,5-diaryl dyes compared to their 3-aryl analogues and evidently to the starting material **89**. Electron-rich aryl groups introduce larger red shifts compared to a phenyl group, whereas electron-withdrawing groups generate smaller spectroscopic shifts in the final compound. Compound **92m** shows no fluorescence in more polar solvents; it is quenched by the electron-rich 3-[4-(dimethylamino)-phenyl] substituent. Addition of acid blocks the lone electron pair of the nitrogen donor and hence decreases the electron-donating ability of the amine. This leads to inhibition of the quenching

process, resulting in the “switching on” of the fluorescence, which renders this molecule a sensitive pH probe.

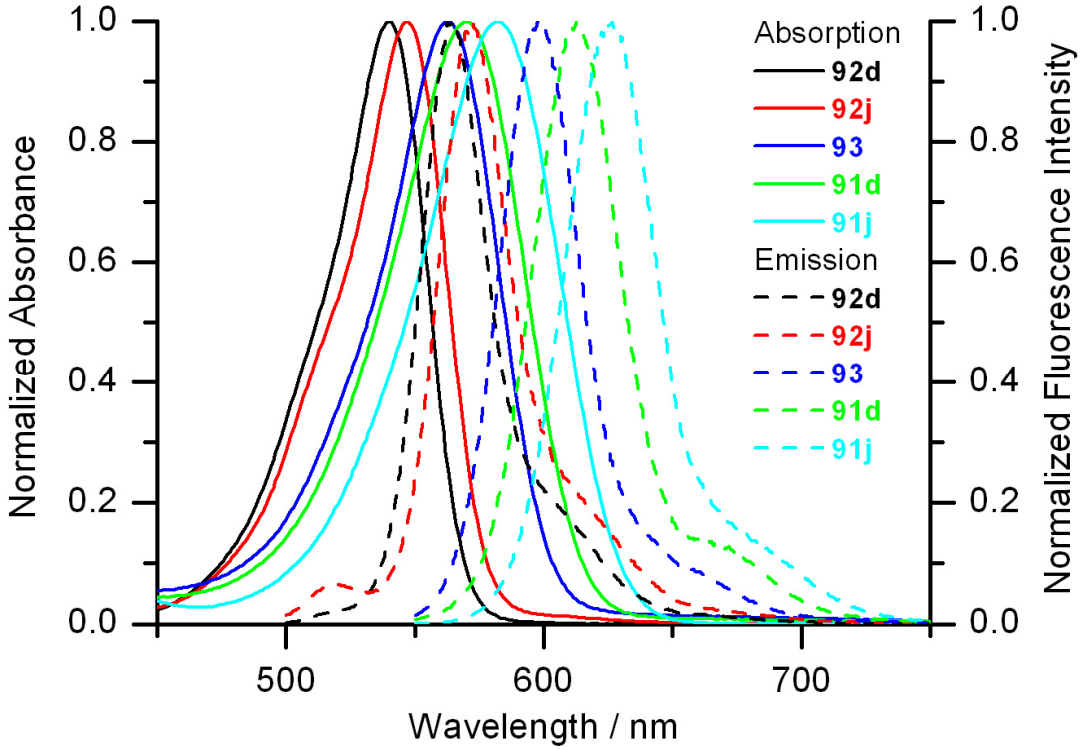
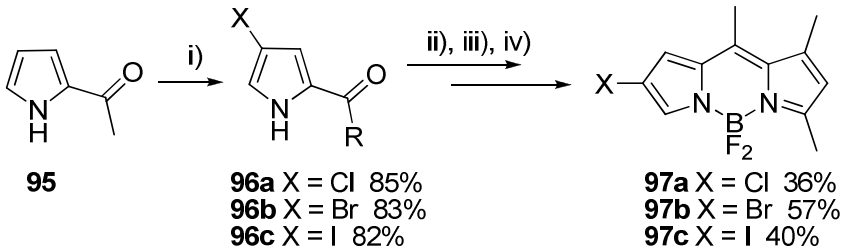


Figure 4 Normalized, visible absorption spectra and corresponding normalized fluorescence emission spectra in acetonitrile of a selection of 3-monoarylated (**92**) and 3,5-diarylated (**91** and **93**) *meso*-(2,6-dichlorophen-1-yl) substituted BODIPY dyes synthesized via radical arylation of 3,5-unsubstituted starting materials. The bathochromic shifts in going from monosubstitution (**92d** and **92j**) to disubstitution (**91d** and **91j**, respectively) are clearly seen.

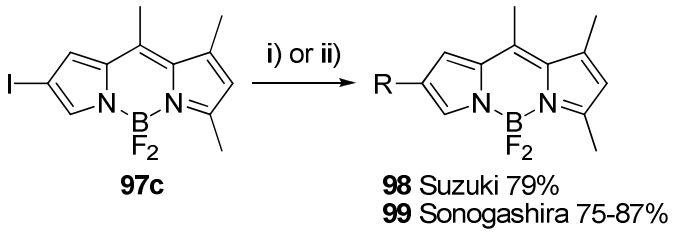
Functionalization at the 2-position

The position of the halogen atom on the BODIPY dye depends on the selection of corresponding halogenated acylpyrroles. 4-Halogenated 2-acylpyrroles **96a** (X = Cl), **96b** (X = Br), and **96c** (X = I) are prepared from 2-acylpyrrole **95**, by using oxone® and NaX (X = Cl, Br, I) in methanol / water mixtures (Scheme 33).[23] 4-Halogenated 2-acylpyrroles **96a**–**c** are converted into the corresponding 2-haloBODIPYs **97a**–**c** by application of the standard condensation–complexation sequence, as described for 3-halogenated boron diaza-*s*-indacenes (Scheme 14).



Scheme 33 Synthesis of 2-monohalogenated BODIPY dyes **97**. Conditions: i) NaX (X = Cl, Br, I), oxone, MeOH / H_2O. ii) $POCl_3$. iii) Et_3N. iv) $BF_3 \bullet OEt_2$.[23]

2-IodoBODIPY **97c** can be arylated and alkynylated (Scheme 34). However, Heck cross-coupling and copper-catalyzed etherification of 2-haloBODIPYs were unsuccessful.[23]



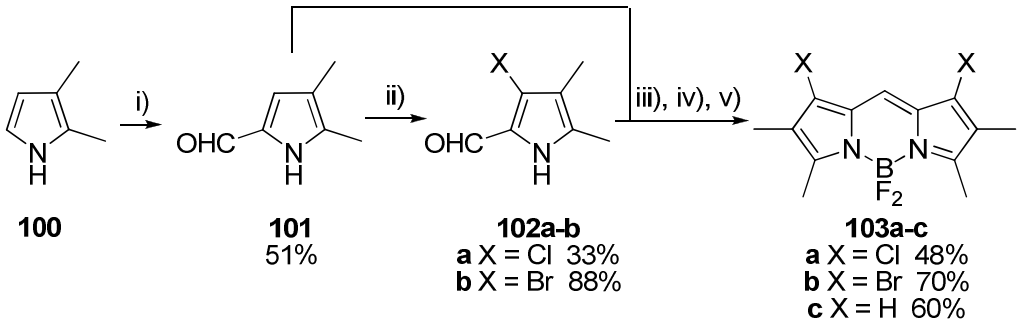
Scheme 34 Reactivity of 2-iodoBODIPY **97c** in palladium-catalyzed cross-coupling reactions (Suzuki, Sonogashira). Conditions: i) Suzuki: **98** with R = *p*-C_6H_4-*t*Bu; $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux. ii) Sonogashira: **99** with R = C≡CPh, C≡CTMS (TMS = trimethylsilyl), C≡CTIPS (TIPS = triisopropylsilyl); *i*Pr_2NH, $Pd(PPh_3)_4$, CuI, 80 °C.[23]

Compound **99** with a phenylethynyl group at the 2-position (Scheme 34) absorbs at shorter wavelengths than its 3-alkynyl constitutional isomer, but nonetheless emits at longer wavelengths. Hence, the Stokes shift is three times larger for the 2-alkynyl isomer. The Φ values for the 2-alkynyl isomer **99** are lower (0.25–0.61) than for the 3-alkynyl counterpart (0.77–0.93). Combined with the lower molar absorption coefficients ε(λ) of the 2-alkynyl isomer, the brightness of 2-phenylethynyl derivative **99** is significantly reduced compared to the 3-alkynyl isomer. The full widths at half of the maximum of the absorption and emission bands of the 3-alkynyl dye are about half that of the 2-alkynyl isomer **99**.[23]

Functionalization at the 1,7-positions

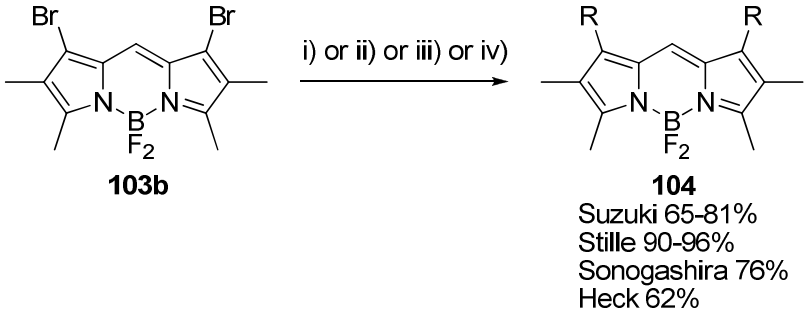
Direct halogenation at the 1,7-positions is only possible if the other positions are blocked with substituents. 1,7-DihaloBODIPY derivatives **103a–b** with a hydrogen at

the 8-position were prepared from 3-halogenated pyrrole carbaldehydes **102a**–**b** with alkyl groups at the 4,5-positions (Scheme 35).[90] Vilsmeier-Haack formylation of 2,3-dimethylpyrrole **100**, followed by halogenation afforded the starting materials **102** for BODIPY formation via dipyrromethenes. Using aldehyde **101** directly leads to 1,7,8-unsubstituted BODIPY **103c**.



Scheme 35 Halogenation–condensation approach of pyrroles carbaldehydes to 1,7-dihaloBODIPYs **103**. Conditions: i) $POCl_3$, DMF. ii) NXS (X = Cl, Br), DMF / CH_2Cl_2. iii) $POCl_3$. iv) Et_3N. v) $BF_3 \bullet OEt_2$.[90]

The bromo derivative **103b** displays excellent reactivity in Pd-catalyzed reactions (Stille, Suzuki, Heck, Sonogashira), leading to doubly substituted products **104** (Scheme 36). Unsymmetrically 1,7-substituted products can be formed through sequential Pd-catalyzed C–C coupling reactions (e.g., Suzuki followed by Sonogashira). Only strongly nucleophilic thiolate anions are able to cause substitution at the 1,7-positions; nitrogen, oxygen, and carbon nucleophiles fail.

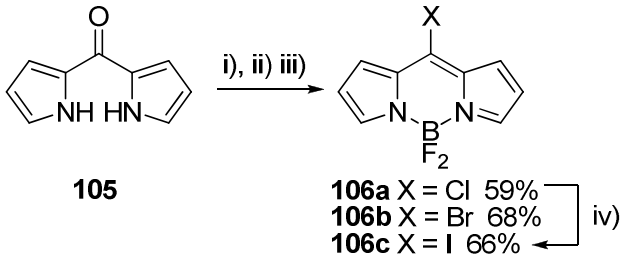


Scheme 36 Palladium-catalyzed derivation of 1,7-dibromoBODIPY **103b**. Conditions: i) Suzuki: toluene / Na_2CO_3(aq), $Pd(PPh_3)_4$, boronic acid, 100 °C. ii) Stille: 1,4-dioxane, $Pd_2(dba)_3$, trifurylphosphine, $RSnBu_3$, Na_2CO_3, 100 °C. iii) Sonogashira: DMF / Et_3N, $Pd_2(dba)_3$, trifurylphosphine, CuI, PhC≡CH, 60 °C. iv) Heck: DMF / Et_3N, styrene, $Pd(PPh_3)_4$, 65 °C.[90]

Introducing new substituents directly on the BODIPY scaffold has a dramatic effect on the spectroscopic properties of the dye. The red-shifts of the visible absorption and fluorescence emission spectra induced by the extended π-conjugation are not as large as observed for the corresponding 3,5-disubstituted analogues. Quantum-chemical calculations indicate that the smaller effect of 1,7-substituents *vs* 3,5-substituents may be due to the fact the HOMO has smaller coefficients at the 1,7-positions compared to the 3,5-positions. Phenylethenyl substituents produce the largest bathochromic shifts of λ_{abs}(max) and λ_{em}(max), followed by phenylethynyl substituents, whereas phenyl groups generate the smallest shifts. The same red-shift trend (phenylethenyl > phenylethynyl > phenyl) was observed before for these functionalities at the 3,5-positions (see above). The Stokes shifts of all the 1,7-disubstituted dyes are rather small, being in the normal range for classic BODIPYs.

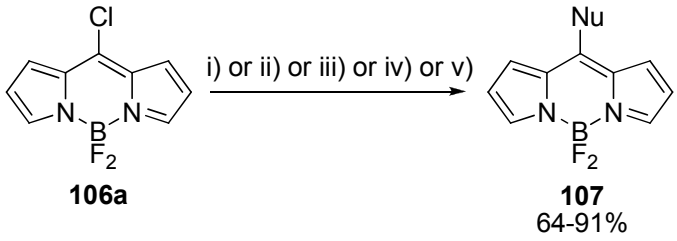
Functionalization at the 8-position

Derivatization at the 8-position (or *meso*-position) is straightforward when starting from aromatic aldehydes or acylium equivalents.[6–8] 8-MethylthioBODIPYs, introduced by Biellmann *et al.*,[91] undergo nucleophilic aromatic substitution (S_NAr) reactions with a variety of nucleophiles.[24b, 92–98] However, 8-halogenated (Cl, Br, I) boradiaza-*s*-indacenes **106a**–**c** provide an excellent alternative as they can be substituted under mild reaction conditions. 8-HaloBODIPYs can be efficiently prepared from dipyrrylketones **105** (Scheme 37).[99] The halogen is introduced through deoxygenative substitution on dipyrrylketone **105**. *In situ* deprotonation and subsequent complexation result in the *meso*-halogenated (Cl, Br) target compounds **106a,b**. *Meso*-iodinated dye **106c** is prepared from chlorinated derivative **106a** by halogen exchange (in acetone in the presence of NaI).

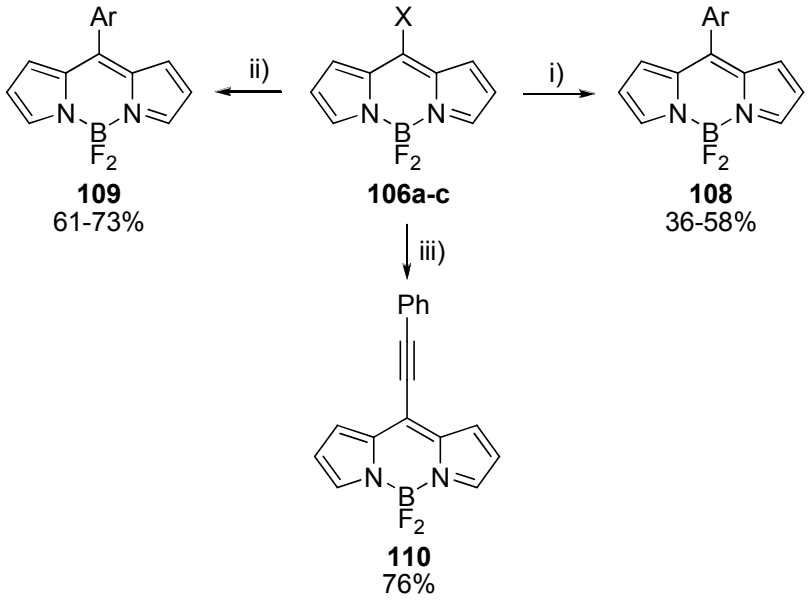


Scheme 37 Synthesis of 8-halogenated BODIPY dyes **106**. Conditions: i) POX_3 (X = Cl, Br). ii) Et_3N. iii) $BF_3 \bullet OEt_2$. iv) Me_2CO, NaI.[99]

8-Halogenated boron dipyrrins are interesting compounds because of their reactive halogen, which can be replaced by nucleophiles through S_NAr (Scheme 38)[99] or transition-metal-catalyzed transformations[99,100,101] (Scheme 39).



Scheme 38 Nucleophilic displacement of chlorine on 8-chloroBODIPY **106a**. Conditions: i) NuH = $PhNH_2$. ii) PhSH. iii) CH_3SH. iv) PhOH. v) CH_3OH.[99]



Scheme 39 Palladium-catalyzed cross-coupling reactions (Suzuki, Stille, Sonogashira) of 8-haloBODIPY **106**. Conditions: i) Suzuki: boronic acid $ArB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 60 °C (X = Cl, Br, I). ii) Stille: tributylphenyltin or 2-(tributylstannyl)thiophene, $Pd(PPh_3)_4$, Na_2CO_3, dioxane, 90 °C (X = Br). iii) Sonogashira: HC≡CPh, $Pd(PPh_3)_2Cl_2$, CuI, THF / Et_3N (1:1 v/v), 0 °C (X = Cl).[99]

The rich variety of groups introducible at the 8-position leads to a set of dyes with absorption and fluorescence emission spectra covering the major part of the visible spectrum.[102] The dyes with 8-N (8-phenylamino, 8-benzylamino; Scheme 38, i) and 8-O (8-methoxy, 8-phenoxy; Scheme 38, iv–v) substituents have blue-shifted absorption and fluorescence emission spectra and larger Stokes shifts with respect to unsubstituted BODIPY.[103,104] This hypsochromic shift is related to the electron-donating character of the heteroatom and is markedly larger for N than for O. In contrast, the halogens (Cl, Br, I) in the starting 8-halogenated compounds **106a**–**c** have a negligible effect on λ_{abs}(max) and λ_{em}(max). Conversely, the 8-phenylethynyl group in **110** leads to red-shifted absorption and fluorescence emission spectra compared to unsubstituted and classic boradiaza-*s*-indacenes, indicating that this 8-functionality extends the π-conjugation. The *meso*-O derivatives have very high fluorescence quantum yields Φ, whereas the 8-phenylamino and 8-phenylthio analogues are practically nonfluorescent. Variable temperature ^{1}H NMR reveals restricted rotation about the C8–N bond in 8-phenylaminoBODIPY and 8-benzylaminoBODIPY and unhindered rotation around the C8–O bond in 8-phenoxyBODIPY. The heavy atom effect on Φ is clearly seen in the series of 8-halo dyes **106a**–**c**.

Functionalization at the 4-position (boron atom)

Whereas all possible pyrrole carbon positions of the BODIPY framework have been functionalized by us via postderivatization, there are no examples from our own work on the substitution of the fluorine atom(s) at boron. Using hard nucleophiles these fluorines can be substituted with aryl,[34] alkyn[35] and alkyl[36] groups as well as with alkoxides[37] and carboxylates.[38,39] The papers published largely by the research team of Ziessel provide an entry point into this fascinating field.[7,8,34–39]

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