BODIPY Dyes and Their Derivatives: Syntheses and Spectroscopic Properties

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Received May 7, 2007

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1. Introduction

Advances in imaging techniques now make it feasible to do things that were not previously possible. Experiments in which interacting proteins are observed inside living cells are now common for dynamically averaged systems,[1−3] and the field is close to observation of similar events on a single molecule level.[4−8] Labels can be attached to proteins, for example, antibodies, which accumulate in specific organs for imaging in animals and human subjects.[9] The technological advances in this area are remarkable. However, there is a growing realization that imaging events in cells and whole organisms by fluorescence is limited by the probes available. For instance, there are few that emit at 800 nm or above, yet living tissues are most transparent to light at and above this wavelength.

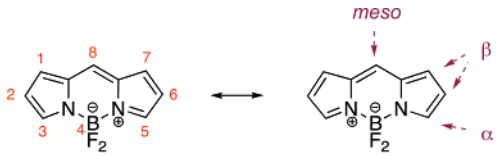
4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (hereafter abbreviated to BODIPY) dyes tend to be strongly UV-absorbing small molecules that emit relatively sharp fluorescence peaks with high quantum yields. They are relatively insensitive to the polarity and pH of their environment and are reasonably stable to physiological conditions. Small modifications to their structures enable tuning of their fluorescence characteristics; consequently, these dyes are widely used to label proteins[10−14] and DNA.[15] However, these compounds also have some undesirable characteristics for many applications in biotechnology. For instance, most emit at less than 600 nm, and only a handful of water-soluble derivatives have been made. Thus, there is the potential that

10.1021/cr078381n CCC: $65.00
Published on Web 10/09/2007

Aurore Loudet was born in France. She received her B.S. degree in biochemistry and M.S. degree in chemistry at Université Paul Sabatier in Toulouse, France. In 2000, she came to Texas A & M University and joined Kevin Burgess' group. Her research focused on the synthesis of near-IR aza-BODIPY dyes.

Kevin Burgess is a professor at Texas A & M University, where he has been since September 1992. His research interest focuses on peptidomimetics for mimicking or disrupting protein–protein interactions, asymmetric organometallic catalysis, and fluorescent dyes for multiplexing in biotechnology. The latter project involves much chemistry that centers around the BODIPY dyes. We choose to write this review to organize the literature in that field for ourselves and others in the field.

modifications to the BODIPY framework will lead to probes that can be used more effectively for imaging in living cells and whole organisms, but that is largely unrealized.



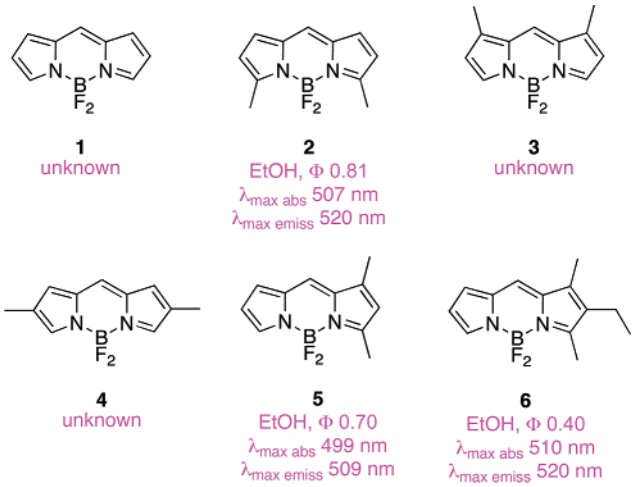
Our research group is interested in making BODIPY-related probes that will realize some of their potential for intracellular imaging. This review is intended to facilitate this process by summarizing the basic chemistry and spectroscopic properties of common BODIPY-derivatives, and highlighting ways in which other interesting probes could be prepared. Readers particularly interested in applications of BODIPY dyes as labeling reagents,[11,13,16−43] fluorescent switches,[44,45] chemosensors,[46−83] and as laser dyes[84] may be interested in this review as a guide to synthesis and spectroscopic properties, but details on use of the dyes in those ways are not included here. Readers interested in small amounts of commercially available dyes for labeling should also consult the Invitrogen (formerly Molecular Probes) catalog.[11,85]

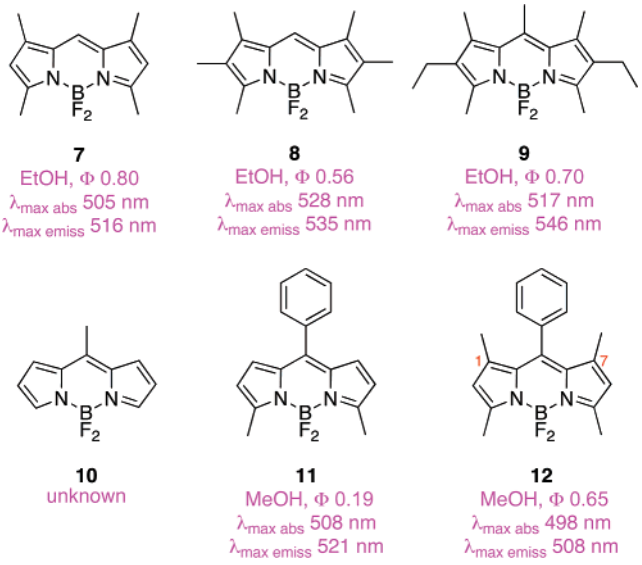
2. The BODIPY Core

The IUPAC numbering system for BODIPY dyes is different to that used for dipyrromethenes,[86] and this can lead to confusion. However, the terms α-, β-positions, and *meso*- are used in just the same way for both systems.

2.1. Fundamental Properties

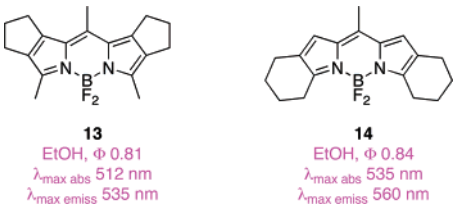
BODIPY dyes were first discovered in 1968 by Treibs and Kreuzer.[87] BODIPY **1**, which has no substituents, has not been reported in the literature. This may be because of synthetic difficulties obtaining this compound related to the fact that none of the pyrrole-based carbons are blocked from electrophilic attack. Synthesis of the corresponding dipyrromethene precursor has been reported, but this compound is unstable and decomposes above −30 to −40 °C.[88] The symmetrical, dimethyl-substituted compound **2** has been prepared[89] and could be considered as a reference to which other simple alkylated BODIPYs can be compared. The symmetrically substituted systems **3** and **4** have apparently not been reported, reflecting synthetic limitations for even some simple BODIPY systems. However, the unsymmetrically substituted BODIPYs **5** and **6** have been prepared.[90] There are relatively minor differences in the reported UV-absorption maxima, fluorescence emission maxima, and quantum yields of these compounds, and these should not be over-interpreted because small calibrations errors are common in these types of experiments. However, when the symmetrically-, tetra-, hexa-, and hepta-alkylated systems **7**,[90,91] **8**, and **9** are included in the comparison, then an unambiguous trend toward red-shifted absorption and emission maxima with increased substitution becomes apparent.





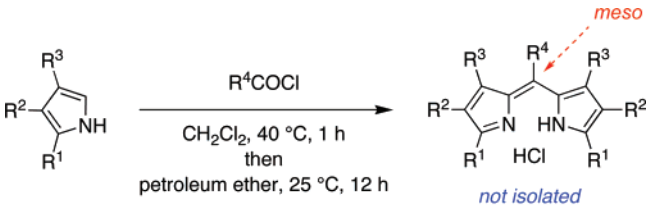
Alkylation or arylation at the *meso* position has no special effect on the absorption and emission wavelengths (compare **2** with **11**, and **7** with **12**) even though this substitution position is structurally unique. However, the quantum yield of the *meso*-phenyl compound **11** is appreciably less than the more substituted analogue **12**. Such differences are widely attributed to 1,7-substituents preventing free rotation of the phenyl group reducing loss of energy from the excited states via non-irradiative molecular motions. Consistent with this, introduction of *ortho*-substituents on the phenyl ring has been observed to increase quantum yields, and similar explanations have been invoked.

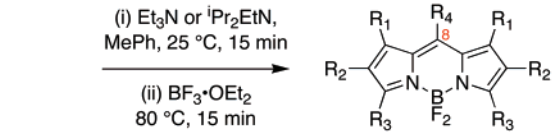
BODIPY derivatives in which aliphatic rings have been fused to the pyrrole fragments are perhaps more constrained than ones bearing acyclic aliphatic substituents. Nevertheless, the effects on their emission maxima are not always easily rationalized. Compound **13** has a shorter emission wavelength maximum than **9** even though both have three substituents on the pyrrole rings. On the other hand, **14** has only two such attachments, yet it has the longest wavelength fluorescence emission.



2.2. Syntheses from Pyrroles and Acid Chlorides or Anhydrides

8-Substituted BODIPY dyes **A** (i.e., ones with substituents in the *meso* position) tend to be relatively easy to prepare via condensation of acyl chlorides with pyrroles (reaction 1).[92,93] These transformations involve unstable dipyrromethene hydrochloride salt intermediates. The intermediate dipyrromethene hydrochlorides are easier to handle and purify as C-substitution increases, but even so, these are not generally isolated in syntheses of BODIPY dyes.

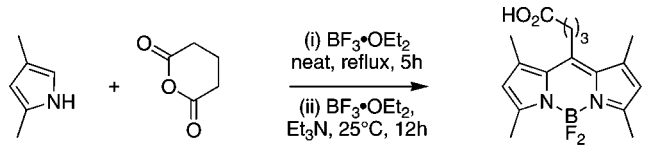




reaction 1

A
R^4 = alkyl, aryl

Other activated carboxylic acid derivatives could be used in place of acid chlorides in reaction 1. In the particular case of acid anhydrides, this concept has been reduced to practice. Reaction 2 shows how the BODIPY derivative **15** was prepared from glutaric anhydride.[37] An attractive feature of this chemistry is that a free carboxylic acid is produced, and this may later be used to attach the probe to target molecules.

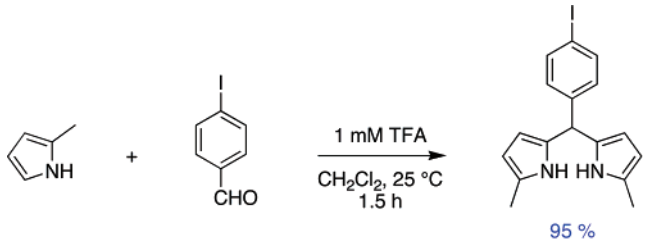


reaction 2

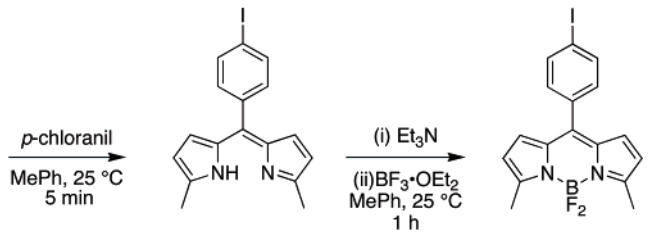
15 16 %

2.3. From Pyrroles and Aldehydes

Syntheses similar to those depicted in reactions 1 and 2 but which use aromatic aldehydes[14] (to the best of our knowledge, *aliphatic* aldehydes have not been reported in this reaction) require oxidation steps. The reagents for these oxidations can introduce experimental complications. Thus, in reaction 3, the oxidant used was *p*-chloranil, and eventually, the byproducts from this had to be removed (in fact, this was done after complexation with the boron).



95 %

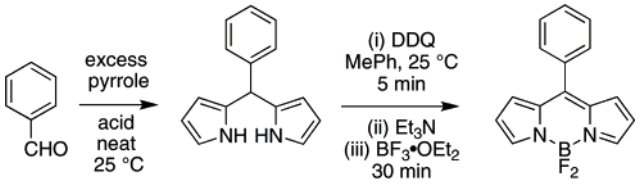


reaction 3

not isolated

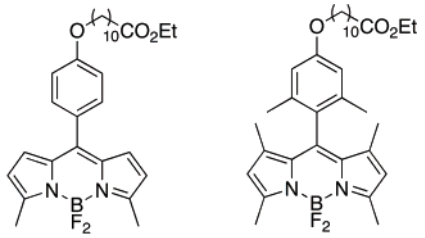
16 15 %

α,β-Unsubstituted BODIPYs, for example, **17** can also be prepared from aldehydes using neat conditions.[14] The aldehyde was dissolved in excess pyrrole at room temperature, and the dipyrromethane intermediate (the reduced form of the dipyrromethene) was formed and isolated. The BODIPY dye was obtained after oxidation with DDQ and complexation with boron (reaction 4). Acid chlorides probably would be too reactive to use with pyrrole (since it is unsubstituted and more reactive), so this aldehyde-based approach is the method of choice.



reaction 4 45-80 % **17** 22 %

Use of, for instance, halogenated benzaldehydes (or halogenated acid chlorides above) broadens the scope of the reaction by offering the potential for elaboration of these groups in compounds like **16**. In another example, systems **18** and **19** were prepared from benzaldehyde derivatives that have long chain acid substituents. These probes were used to investigate dynamic effects in membranes.[2] Presumably, *ortho*-substituents were included on the *meso*-aromatic group to restrict rotation of that ring and increase quantum yields.

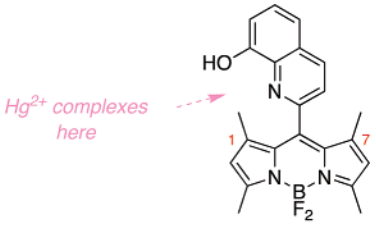


18
CH_2Cl_2, Φ 0.36
$\lambda_{max\ abs}$ 508 nm
$\lambda_{max\ emiss}$ 524 nm

19
CH_2Cl_2, Φ 0.94
$\lambda_{max\ abs}$ 501 nm
$\lambda_{max\ emiss}$ 512 nm

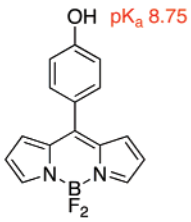
The fact that a diverse set of aldehydes could be used to prepare *meso*-substituted BODIPYs provides a means to introduce more sophisticated functionalities for specialized purposes. For instance, 8-hydroxyquinoline-2-carboxaldehyde was used to prepare the Hg^{2+}-selective chromo- and fluoroionophore **20**.[60] This probe is highly fluorescent in the presence of transition-metal ions (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}) and heavy-metal ions (Pb^{2+}, Cd^{2+}), but 5 equiv of mercuric ions reduced its emission by more than 98% (the color of the solution also changed from light amber to red, enabling the progress of the complexation event to be visualized). A 1:1 complex with Hg^{2+} is formed in which the dipyrromethene core of **20** adopts a nearly orthogonal conformation with the 8-hydroxyquinoline moiety because of the methyl groups in positions 1- and 7- on the BODIPY core. This particular arrangement displays the binding site of 8-hydroxyquinoline for complexation of metal ions. The shape of these BODIPY-based ligand is such that 2:1 L−M complexes are sterically disfavored.

Fluorescent pH probes **21**−**24** have been prepared from phenolic benzaldehydes (a case where the acid chloride approach would have raised chemoselectivity issues).[68] These compounds are weakly fluorescent in the phenolate form

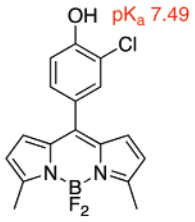


20

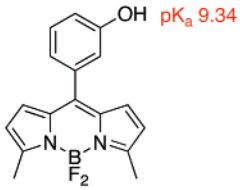
presumably due to charge transfer from the phenolate donor to the excited-state indacene moiety. The pK_a of the different derivatives was tuned by varying the aromatic substituent.



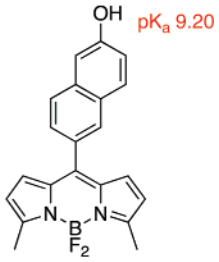
21
MeOH, Φ 0.28
$\lambda_{max\ abs}$ 505 nm
$\lambda_{max\ emiss}$ 517 nm



22
MeOH, Φ 0.16
$\lambda_{max\ abs}$ 507 nm
$\lambda_{max\ emiss}$ 520 nm

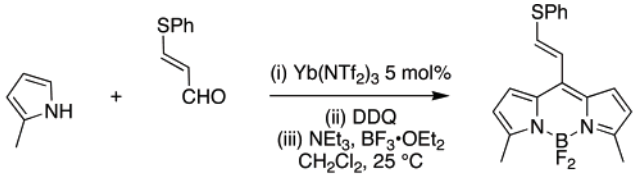


23
MeOH, Φ 0.19
$\lambda_{max\ abs}$ 508 nm
$\lambda_{max\ emiss}$ 521 nm



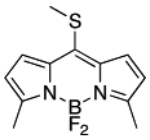
24
MeOH, Φ 0.025
$\lambda_{max\ abs}$ 508 nm
$\lambda_{max\ emiss}$ 522 nm

It is unusual to use any aldehydes that are not aromatic to prepare BODIPY derivatives. In this sense, the vinylic thioether probe **25** (reaction 5) is exceptional. A catalytic amount of ytterbium(III) trifluoromethane sulfonamide was used to mediate the condensation process, the intermediate dipyrromethane was oxidized with DDQ, and complexation with boron trifluoride gave the product, though in very poor yield.[94] The fluorescence emission of compound **25** was red-shifted relative to dyes with a phenyl group at the *meso* position (e.g., **11**). Compound **26** has a sulfide in conjugation with the BODIPY core, just as **25** does. The fluorescence emission maximum of **25** is 26 nm red-shifted compared to **26**, indicating that electron donating groups in this position tend to have that effect.



reaction 5

25 2 %
MeOH, Φ na
$\lambda_{max\ abs}$ 528 nm
$\lambda_{max\ abs}$ 580 nm



26
MeOH, Φ 0.37
$\lambda_{max\ abs}$ 530 nm
$\lambda_{max\ abs}$ 554 nm

2.4. From Ketopyrroles

Condensations of pyrroles with acid chlorides or with benzaldehyde derivatives, as outlined above, are direct and convenient methods to access symmetrically substituted BODIPY dyes. However, another approach is required to form unsymmetrically substituted ones. Generally, this is achieved via preparations of ketopyrrole intermediates, followed by a Lewis acid mediated condensation of these with another pyrrole fragment.

Scheme 1a,b shows reactions of magnesium anions of pyrroles with activated carboxylic acid derivatives to give the corresponding 2-ketopyrroles.[95,96] In part c, one such ketopyrrole is condensed with another pyrrole unit to give a BODIPY framework. That example gives a symmetrical product, but the method is particularly valuable for unsymmetrical ones, as in Scheme 1d.

3. Modifications to *meso*-Aromatic Substituents on the BODIPY Core

The BODIPY core is robust enough to withstand a range of chemical transformations, and a variety of aromatic groups

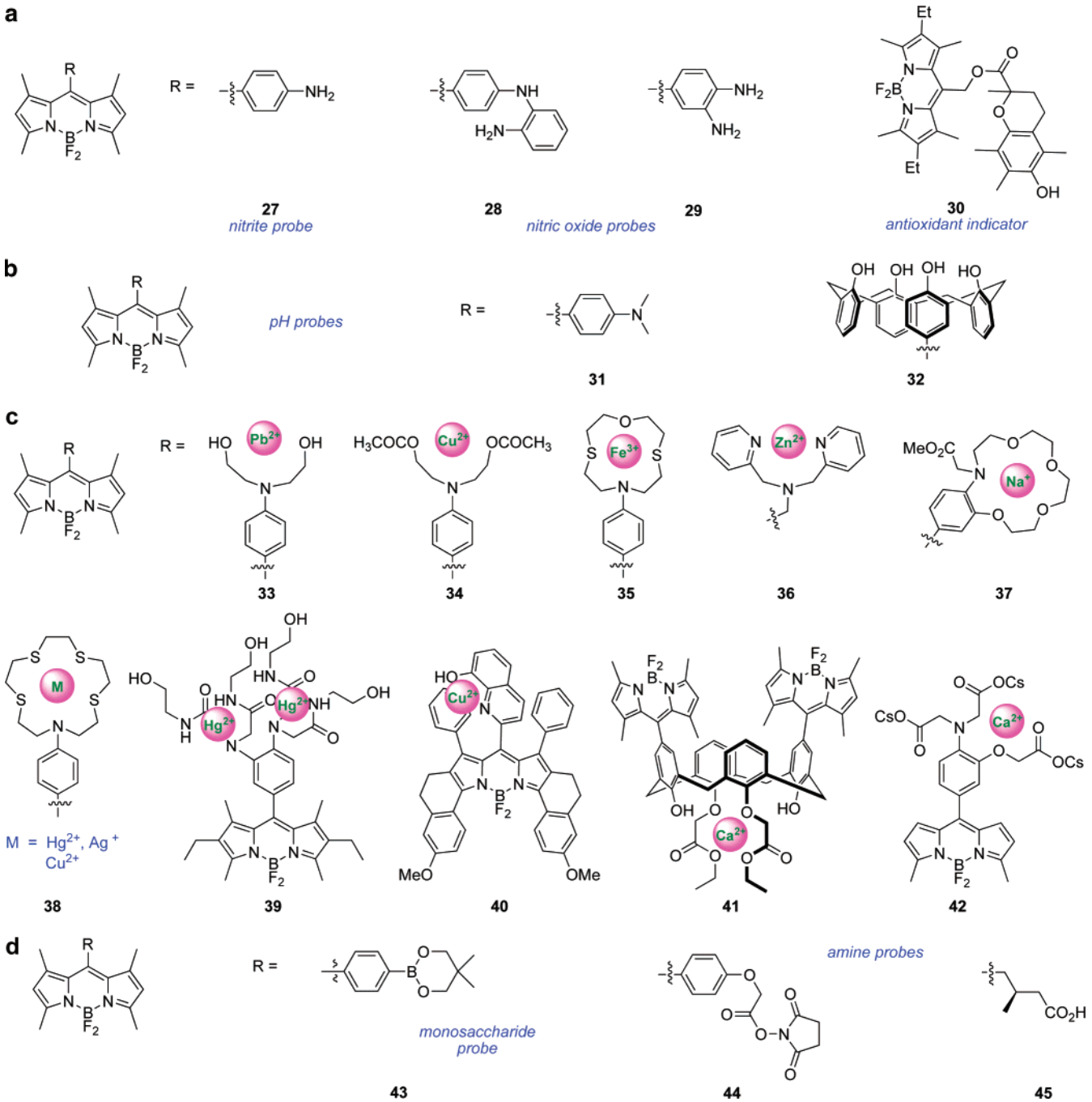
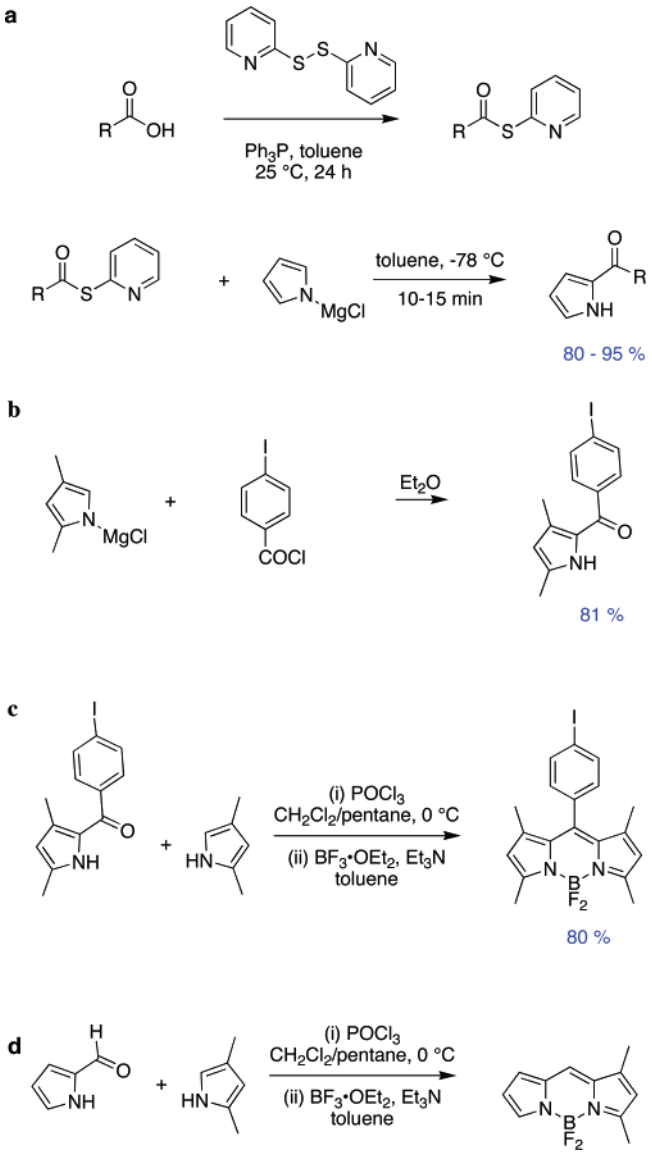


Figure 1. Selected BODIPYs with *meso*-modifications to give (a) selective sensors of particular redox active molecules, (b) pH probes, (c) metal-chelators, and (d) biomolecule conjugating groups.

Scheme 1[a]



[a] (a and b) Two different methods for production of ketopyrroles from magnesium derivatives of pyrrole, and application of these starting materials in the production of (c) symmetrical, and (d) unsymmetrical dyes.

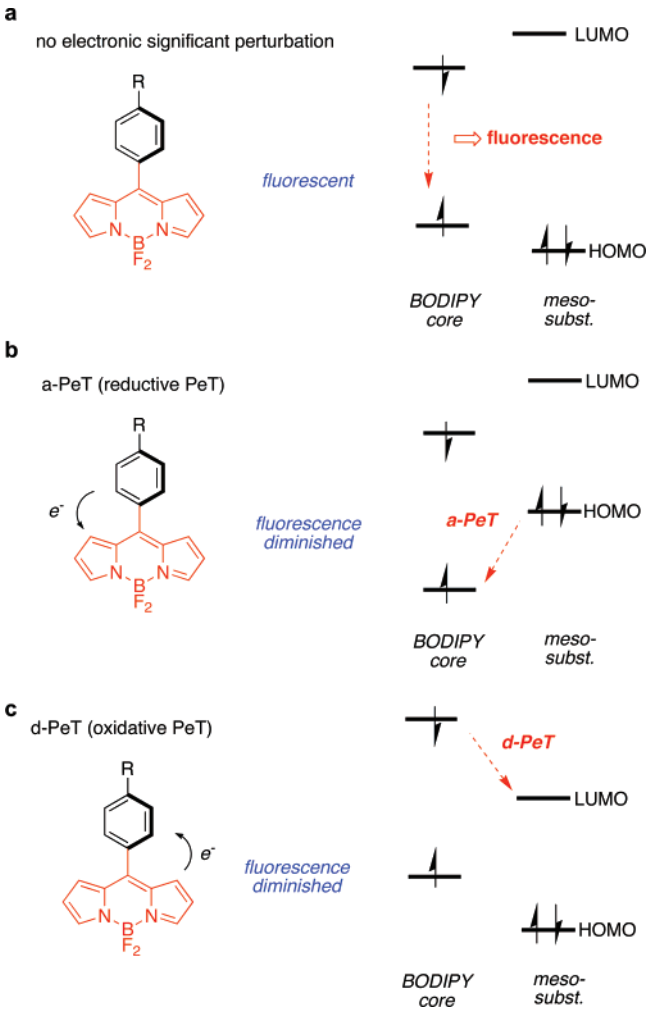


Figure 2. The *meso*-substituent provides (a) no significant electronic perturbation, (b) electrons to the excited state, and (c) a low lying LUMO to accept electrons from the excited state.

can be introduced at the *meso*-position for appropriately functionalized BODIPY dyes. Alternatively, dyes with special *meso*-groups can be produced via *in vivo* synthesis. These strategies have been used to produce several dyes for many different applications; just a few illustrative ones are shown in Figure 1. For instance, derivatives of this type have been formed as selective sensors of particular redox active molecules (**27**,[62] **28**,[65] **29**,[48] and **30**,[97] Figure 1a), pH probes (**31**[55] and **32**[51], Figure 1b), metal-chelators (**33**,[79] **34**,[79] **35**,[74] **36**,[67] **37**,[66] **38**,[53] **39**,[80] **40**,[78] **41**,[82] and **42**,[71] Figure 1c), and as biomolecule conjugating groups (**43**,[49] **44**,[81] and **45**,[98] Figure 1d).

Here, we intend to restrict the discussion to the general concepts that influence the fluorescence properties of *meso*-modified BODIPY dyes; this review does not attempt to give a comprehensive list of all the compounds made. Without exception, the chemosensors operate by perturbing the reduction potential of the *meso*-substituent. The next section discusses the electronic effects of these perturbations on fluorescence.

3.1. Fluorescence Control via Photoinduced Electron Transfer

Transfer of electrons between nonplanar parts of fluorescent molecules modifies their fluorescence intensities.[99] This has been known for sometime, but Nagano, Ueno, and coworkers have skillfully applied calculated orbital energy levels and experimentally determined electrochemical data to rationalize quantum yields. Their initial work with fluorescein derivatives[100,101] was later expanded to encompass BODIPY systems as described here.[102]

Some nonplanar fluorescent molecules can be regarded as a highly fluorescent group with non- (or significantly less) fluorescent substituents (Figure 2a). Some such substituents, depending on their oxidation potentials relative to the excited-state of the BODIPY core, can act as electron donors or acceptors. If electron transfer occurs, then the fluorescence is diminished when the fluorescent group in its excited-state is reduced. In this situation, the fluorescent group is acting as an acceptor; consequently, this may be called

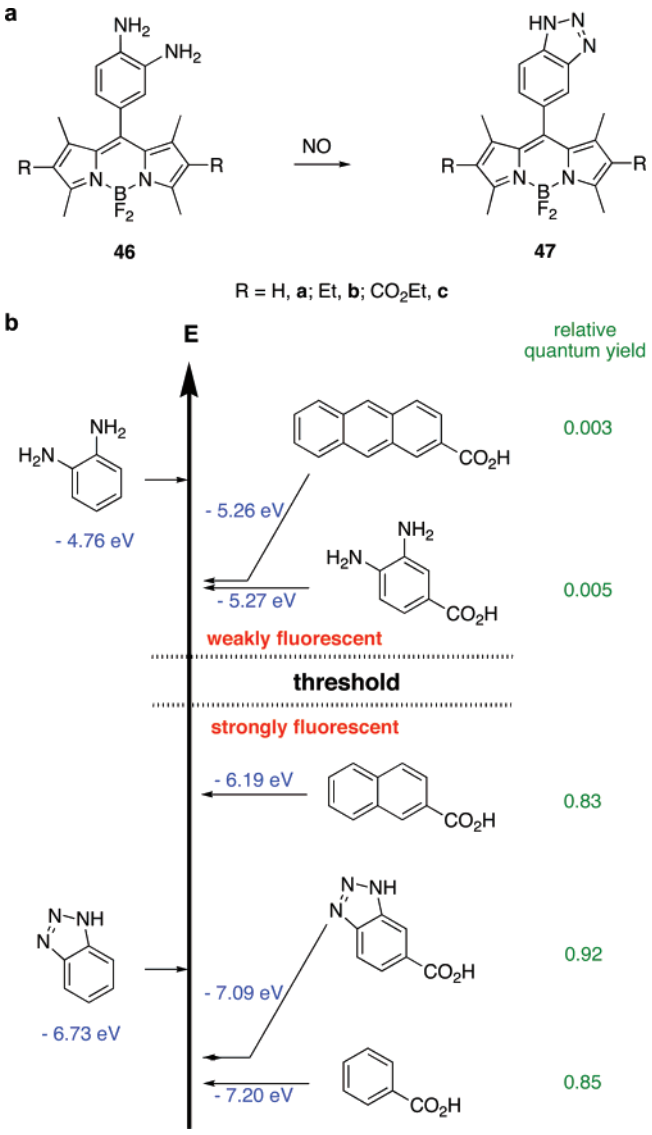


Figure 3. (a) Calculated HOMO energy levels of *meso*-substituents for BODIPY **46** and **47**; (b) reductive PeT occurs above the threshold indicated.

reductive-PeT or a-PeT ("a" for acceptor; Figure 2b). However, if the energy states are such that the excited-state of the fluorescent group can donate electrons to the substituent LUMO, then oxidative-PeT, d-PeT, occurs ("d" for donor; Figure 2c). Indirectly, solvent polarity has an effect on this process. This is because photoexcitation and oxidation processes involve modification of ground state dipoles, and solvents may stabilize or destabilize these changes according to polarity.

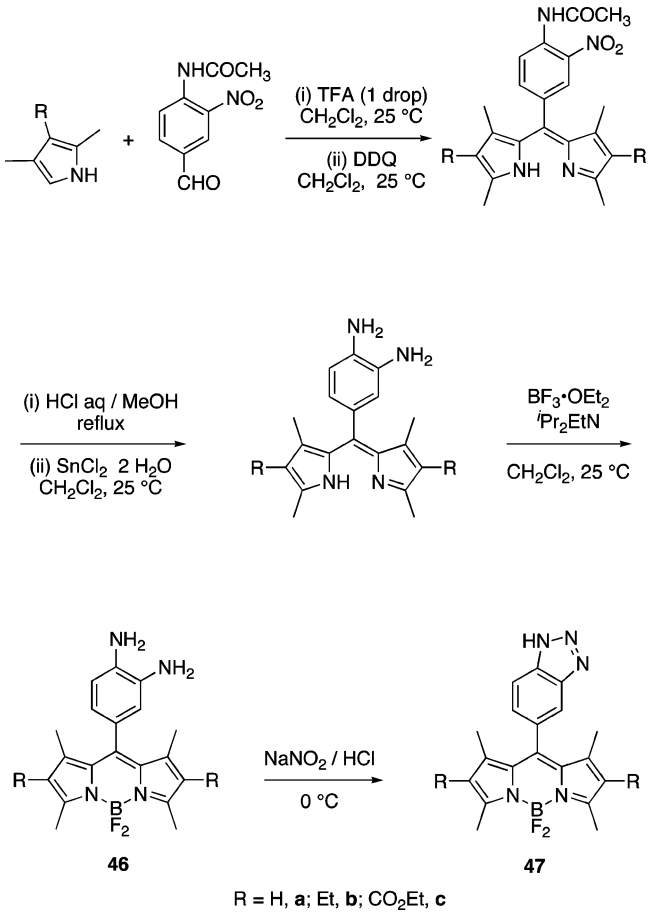
The feasibility of electron transfer can be judged from the change in free energy (ΔG_{PeT}), as described by the Rehm–Weller equation:[103]

$$\Delta G_{PeT} = E_{1/2}(D^+/D) - E_{1/2}(A/A^-) - \Delta E_{00} - C$$

where $E_{1/2}$ (D^+/D) is the ground-state oxidation potential of the donor, $E_{1/2}$ (A/A^-) is the ground-state reduction potential of the acceptor, ΔE_{00} is the excitation energy, and C is an electrostatic interaction term.

Nagano and co-workers applied these principles to the triazole-BODIPY derivative **47** (Figure 3) to develop a nitric

Scheme 2. Synthesis of Diaminobenzene- and Triazole-BODIPY Derivatives 46 and 47



oxide probe.[61] The low fluorescence of the diamine **46** was explained in terms of reductive PeT. When nitric oxide converts the diamine into the benzotriazole **47**, then reductive PeT does *not* occur and fluorescence is observed. Scheme 2 outlines the synthesis of the probe and the oxidized product.

A refinement of the ideas presented above was used to explain the observation that fluorescence for the compounds **47** decreased in the order **b** > **a** > **c** (Figure 4). This is because the nature of the substituent impacts the reduction potential of the BODIPY core in that order (**b** is the most negative).

Fluorescence of the Zn^{2+} and NO_2^+ chemosensors **48**[63] and **49**[104] has been explained using reductive PeT concepts outlined above. Chelation or nitration, respectively, makes the reduction potential of the *meso*-substituent more

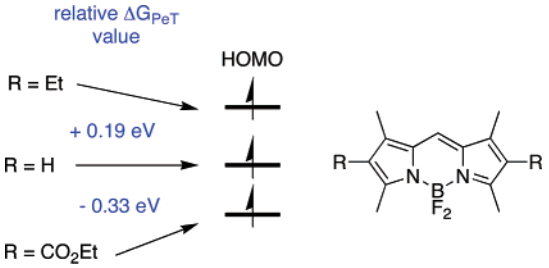
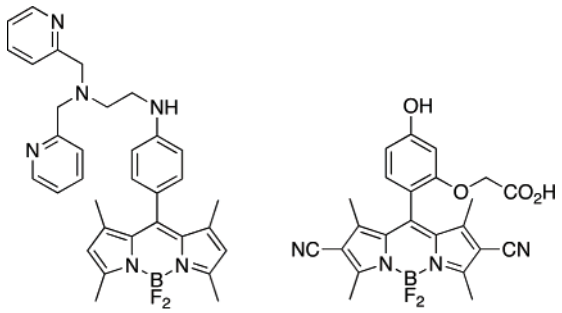


Figure 4. Reductive PeT increases in the order Et < H < CO_2Et.

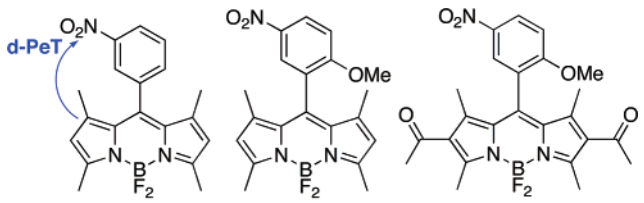
negative, PeT is switched-off, and the probes become fluorescent.



48 **49**

$\lambda_{max\ abs}$ 499 nm
$\lambda_{max\ emiss}$ 509 nm
Φ 0.003 (without Zn^{2+})
Φ 0.058 (with Zn^{2+})

Strongly electron withdrawing substituents on aromatic *meso*-substituents lower the LUMO of the aromatic system to the level where it might accept electrons from the orbital containing the promoted electron in the BODIPY core (Figure 2c). In such cases, *oxidative* PeT comes into play. Evidence for this is seen in the quantum yields of **50**−**52**.[104] For dye **52**, oxidative PeT is diminished because the ketones lower the energy of the BODIPY orbital containing the promoted electron.



	50	**51**	**52**
Φ	0.004	0.023	0.529
ΔG_{PeT} (eV)	0	+ 0.15	+ 0.42

There are at least two weaknesses associated with combining theoretical calculations and electrochemical data to rationalize quantum yields. First, the reduction potentials for the two components are calculated on isolated systems: the fact that they are attached to each other must perturb the actual orbital levels. Second, energies of excited states are notoriously difficult to calculate. Nevertheless, the approach emphasized by Nagano and co-workers helps dispel dogmas that surround fluorescent probes. For instance, the assertion that nitro groups or heavy atom substituents always quench fluorescence is simply not true. The reality is that they tend to do so but only if their orbital energy levels interact with the fluorescent chromophore in a way that facilitates PeT.

4. BODIPYs with Heteroatom Substituents

4.1. From Electrophilic Substitution Reactions

Simple considerations of mesomeric structures reveal that the 2- and 6-positions of the BODIPY core bear the least positive charge, so they should be most susceptible to electrophilic attack (Figure 5). However, there is no definitive study of regioselectivities in these reactions for BODIPYs without pyrrole substituents; almost invariably, some of the other positions are blocked by substituents.

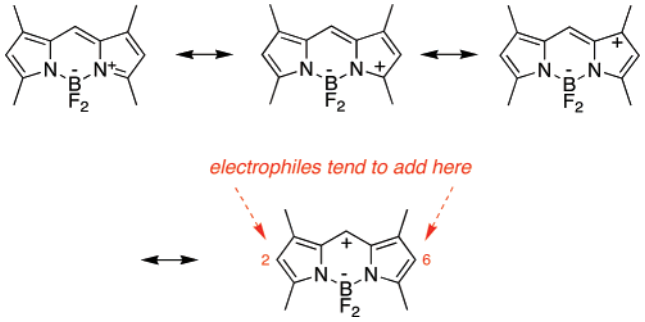
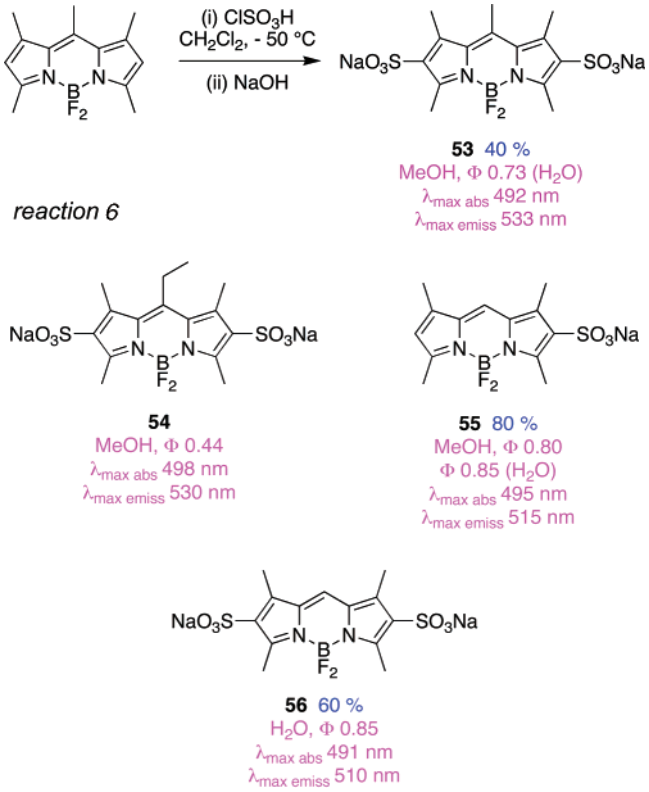


Figure 5. Electrophilic attack on tetramethyl-BODIPY.

4.1.1. Sulfonation

To the best of our knowledge, less than a handful of sulfonated BODIPY dyes have been reported. They were obtained from tetra-, or penta-substituted BODIPYs via treatment with chlorosulfonic acid, then subsequent neutralization with a base (e.g., reaction 6). Monosulfonated systems can be obtained when only one equivalent of chlorosulfonic acid is used. Introduction of sulfonate groups do not change the absorption and fluorescence emission maxima significantly relative to the unsulfonated dye. The sulfonated BODIPY dyes **53**−**56** are strongly fluorescent in water and/or methanol, and are claimed to have even better stability than the parent dyes.[92,105−110]



reaction 6

53 40 %
MeOH, Φ 0.73 (H_2O)
$\lambda_{max\ abs}$ 492 nm
$\lambda_{max\ emiss}$ 533 nm

54
MeOH, Φ 0.44
$\lambda_{max\ abs}$ 498 nm
$\lambda_{max\ emiss}$ 530 nm

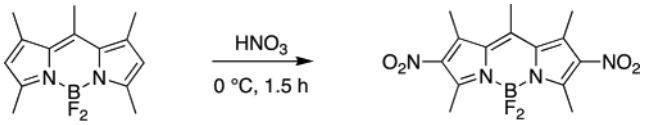
55 80 %
MeOH, Φ 0.80
Φ 0.85 (H_2O)
$\lambda_{max\ abs}$ 495 nm
$\lambda_{max\ emiss}$ 515 nm

56 60 %
H_2O, Φ 0.85
$\lambda_{max\ abs}$ 491 nm
$\lambda_{max\ emiss}$ 510 nm

4.1.2. Nitration

The 2,6-dinitro BODIPY dye **57** can be obtained via nitration with nitric acid at 0 °C (reaction 7). Introduction of the nitro groups drastically reduces the fluorescence quantum yield.[92,111−113] To the best of our knowledge, this is the only nitration of a BODIPY dye that has been reported in the literature.

2,6-Dinitro-BODIPY **58**[114] and **59**[115−119]) have also been reported in the Japanese patent literature for applications as

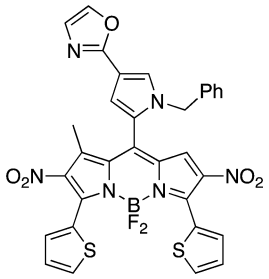


57 72 %
MeOH
Φ na
$\lambda_{max\ abs}$ 493 nm
$\lambda_{max\ emiss}$ 533 nm

reaction 7

sensitizers and inks. We were unable to find procedures for their syntheses and spectroscopic data.

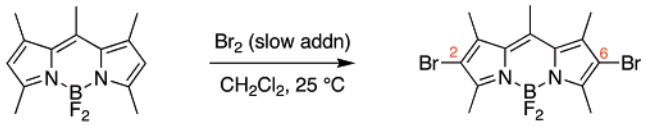
58



59

4.1.3. Halogenation

Bromination of the 1,3,5,7,8-pentamethyl-substituted BODIPY **PM 546** shown in reaction 8 gave the dibromination product **60**.[92,120] Predictably, introduction of bromo substituent onto the dipyrromethene core causes a significant red shift of both the UV-absorption and emission maxima, and it quenches the fluorescence quantum yield via the heavy atom effect.

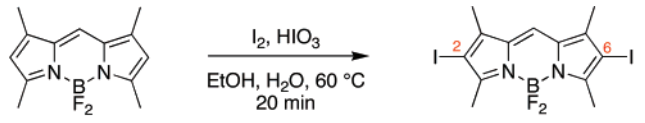


PM 546
MeOH, Φ 0.95
$\lambda_{max\ abs}$ 492 nm
$\lambda_{max\ emiss}$ 504 nm

60 50 %
9:1 MeOH:CH_2Cl_2
Φ 0.45 (CH_2Cl_2)
$\lambda_{max\ abs}$ 516 nm
$\lambda_{max\ emiss}$ 546 nm

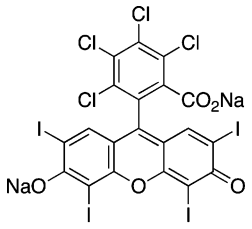
reaction 8

2,6-Diiodo-tetramethyl BODIPY **61** was obtained via the route described in reaction 9.[121] Just as for the dibromo-BODIPY **60**, iodo-substituents cause significant red shift of the UV-absorption and fluorescence emission maxima, and quench the fluorescence quantum yield via the heavy atom effect. Compound **61** is much more resistant to photobleaching than Rose Bengal; this is because the BODIPY core has a more positive oxidation potential than the xanthone unit of Rose Bengal. Compound **61** is an efficient photosensitizer.



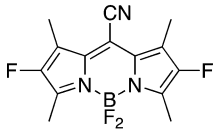
61 83 %
MeOH
Φ 0.02 (0.1 % (v/v) DMF as cosolvent)
$\lambda_{max\ abs}$ 534 nm
$\lambda_{max\ emiss}$ 548 nm

reaction 9

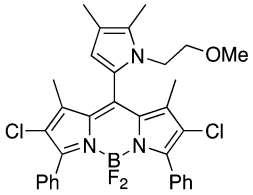


Rose Bengal

2,6-Difluoro- and 2,6-dichloro- BODIPY derivatives **62**[114] and **63**[115−119] have found applications as electroluminescent devices and sensitizers. Their synthesis has not been reported.



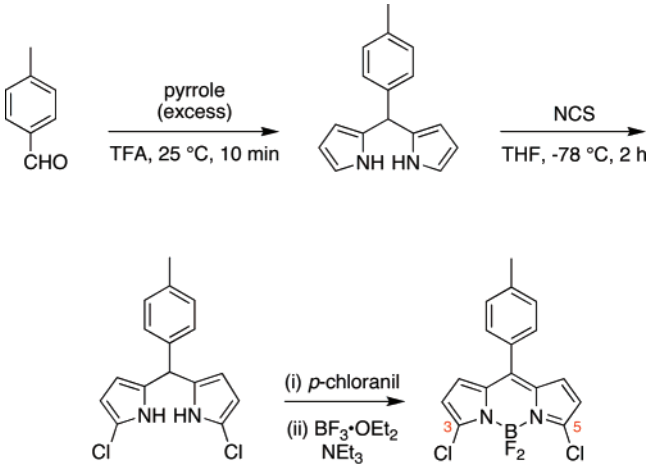
62



63

Chlorination of the unsubstituted dipyrromethane shown in Scheme 3 occurs preferentially at the α-positions. Thus, the 3,5-dichloro BODIPY derivative **64** could be obtained after oxidation with *p*-chloranil and complexation with boron trifluoride etherate. Applications of such chlorinated materials as S_NAr electrophiles are described later in this review.

Scheme 3. Preparation of 3,5-Dichloro-BODIPY via Chlorination of a Dipyrromethane Intermediate

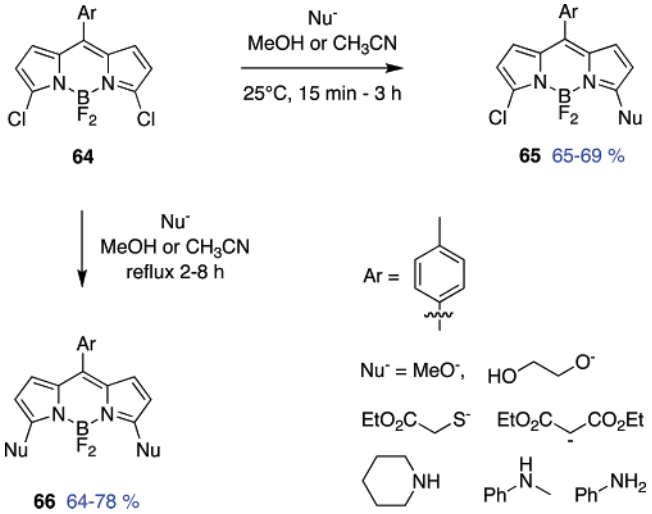


64 20 % overall
MeOH, Φ 0.27
$\lambda_{max\ abs}$ 508 nm
$\lambda_{max\ emiss}$ 519 nm

4.1.4. Potential for Other Electrophilic Substitution Reactions

BODIPY dyes are intrinsically electron rich, and the reactions shown above illustrate that they will react with electrophiles. It is therefore surprising that the reactions shown above represent the state-of-the-art in this area. There are very few sulfonation reactions despite the importance of water-soluble dyes; most of the sulfonated BODIPY compounds in the Invitrogen catalog feature carboxylic acids with sulfonated leaving groups. There are no reports of some common electrophilic addition processes like Vilsmeyer-Haack reactions, but our group has investigated this type of reaction, and the mono-formylated BODIPY dye could successfully be synthesized in excellent yield (unpublished results).

Scheme 4. BODIPY Dyes via S_NAr Reactions

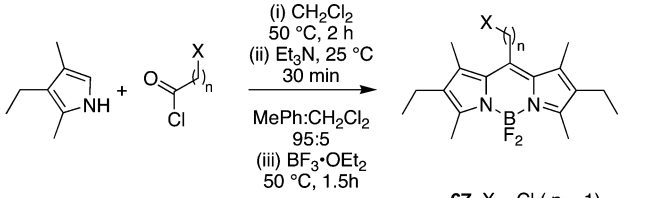


4.2. From Nucleophilic Attack on Halogenated BODIPYs

The most common approach to introduce substituents on the 3- and 5-positions of the BODIPY core involve *de novo* syntheses with appropriately substituted pyrroles, but an exciting recent development reaches the same goal via nucleophilic substitution on the 3,5-dichloro-BODIPY **64**.[122,123] The nucleophiles used so far include alkoxides, amines, thioalkoxides, and the diethyl malonate anion. These reactions can be stopped at the monosubstitution stage or forced to the disubstitution product (Scheme 4); hence, they are useful for access to asymmetric **65** and symmetric **66**, heterosubstituted BODIPY dyes, which would be difficult to obtain by other routes.

The spectroscopic effects of electron donating groups attached to the BODIPY core for the compounds in Scheme 4 were studied. The 3- and 5-substituents had significant effects, shifting both the absorption and/or emission spectra, and changing the fluorescence quantum yields. For example, introduction of an amino- or sulfur-centered nucleophiles results in a significant bathochromic shift (red shift) of both the absorption and emission.[122] Data were collected in methanol (Figure 6); the absorption and emission maxima were red-shifted in cyclohexane, but otherwise, it was quite similar to that for methanol (data not shown). The quantum yields varied widely, but generally tended to be reduced relative to unsubstituted BODIPYs.

8-(ω-Haloalkyl)-BODIPY dyes **67** and **68** are useful starting materials. These are easily synthesized by condensation of a ω-haloacyl chloride with 3-ethyl-2,4-dimethyl pyrrole (reaction 10).[124]



reaction 10

67 X = Cl (n = 1),
68 X = Br (n = 3, 5, 10, 15)

Compounds **67** and **68** can be functionalized by nucleophilic substitution reactions.[58,124] Thus, **67** and **68** are precursors to a range of compounds **B** including fluorescent electrophiles, disulfides for chemoselective labeling of cysteine residues, fluorescent amino acids, and chemosensors for metal ions.[58]

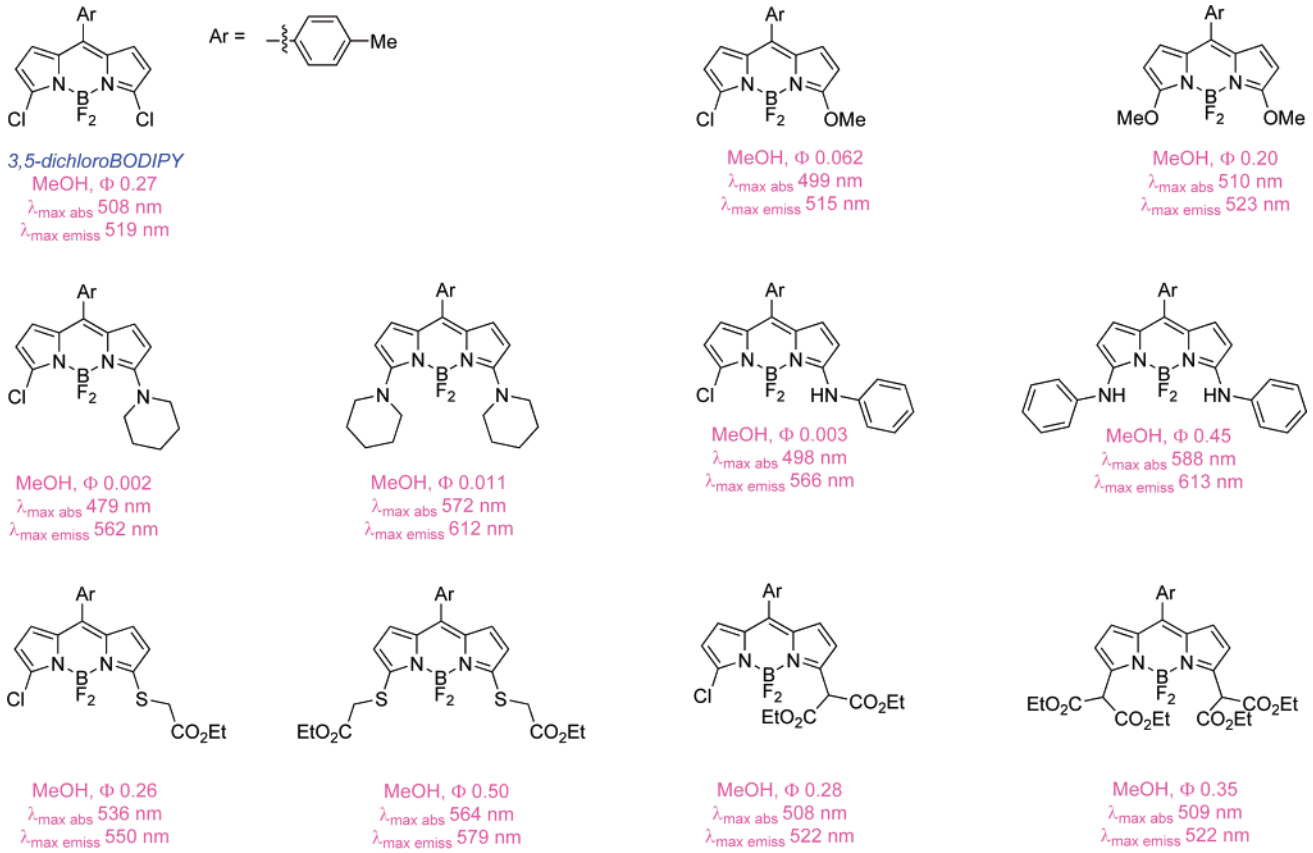
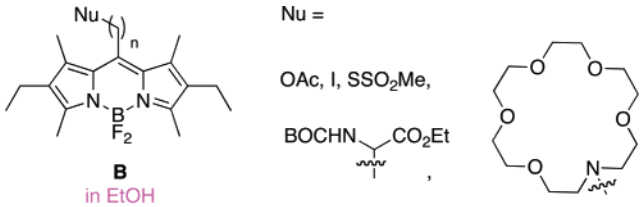


Figure 6. Spectroscopic data for some BODIPYs formed by S_NAr reactions.

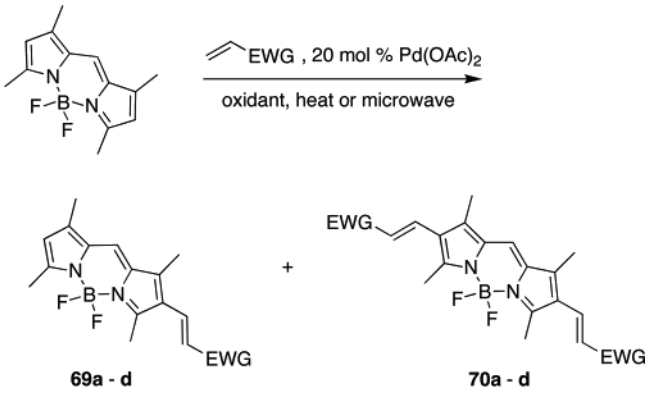


B
in EtOH
$\lambda_{max\ abs}$ 518-545 nm

4.3. From Palladium Mediated C–H Functionalization

Pyrroles can be functionalized via palladium catalyzed activation reactions.[125−127] Our group applied the same strategy to synthesize novel BODIPY dyes via palladium mediated C−H functionalization (reaction 11).[128] This route provides a direct way to extend the conjugation of the BODIPY core, without a halogenated or metalated intermediate prior to the coupling reaction. Highly fluorescent, mono- (**69**) or disubstituted (**70**) dyes can be obtained. A water-soluble, sulfonated BODIPY dye **69d** was also prepared via this route, but in low yield (2%).

The C−H functionalization process was also applied to α,β-unsaturated esters to form compounds **71** and **72**. Mono- and disubstituted products were obtained, but the alkene double bond was shifted out of conjugation with the BODIPY core.



69a - d + **70a - d**

EWG =

a CO_2Me
EtOH, Φ 0.73
$\lambda_{max\ abs}$ 527 nm
$\lambda_{max\ emiss}$ 549 nm

a CO_2Me
CH_3CO_2Et, Φ 0.51
$\lambda_{max\ abs}$ 559 nm
$\lambda_{max\ emiss}$ 580 nm

b CO_2Bu
EtOH, Φ 0.73
$\lambda_{max\ abs}$ 528 nm
$\lambda_{max\ emiss}$ 551 nm

b CO_2Bu
EtOH, Φ 0.52
$\lambda_{max\ abs}$ 560 nm
$\lambda_{max\ emiss}$ 580 nm

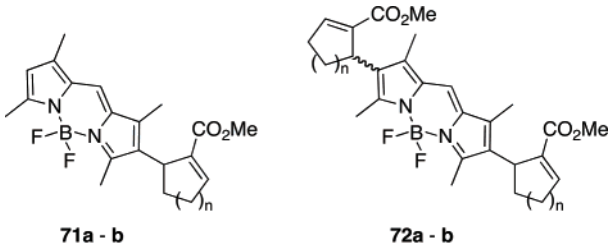
c CO_2H
EtOH, Φ 0.42
$\lambda_{max\ abs}$ 531 nm
$\lambda_{max\ emiss}$ 570 nm

c *not formed*

d SO_3H
EtOH, Φ 0.25
$\lambda_{max\ abs}$ 529 nm
$\lambda_{max\ emiss}$ 560 nm

d *not formed*

reaction 11



71a - b **72a - b**

a n = 1
EtOH, Φ 0.72
$\lambda_{max\ abs}$ 518 nm
$\lambda_{max\ emiss}$ 525 nm

a n = 1
EtOH, Φ 0.92
$\lambda_{max\ abs}$ 530nm
$\lambda_{max\ emiss}$ 539 nm

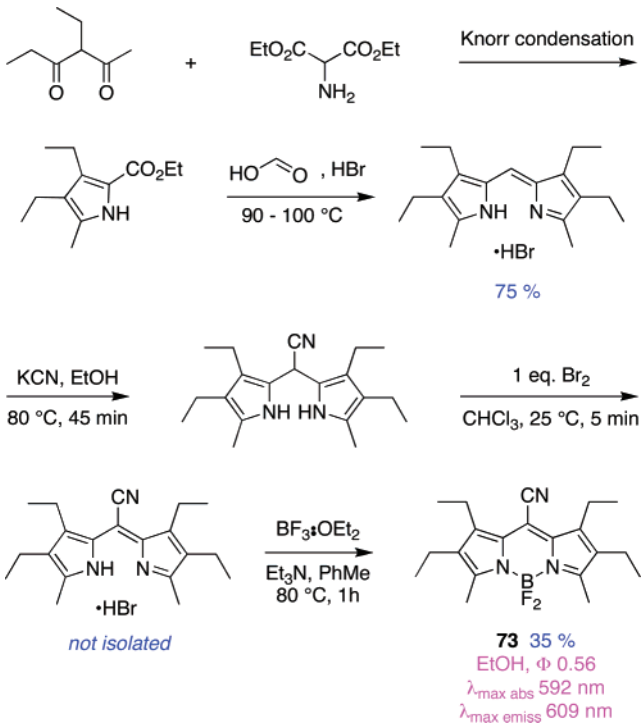
b n = 2
EtOH, Φ 0.78
$\lambda_{max\ abs}$ 517 nm
$\lambda_{max\ emiss}$ 527 nm

b n = 2
EtOH, Φ 0.89
$\lambda_{max\ abs}$ 529 nm
$\lambda_{max\ emiss}$ 540 nm

4.4. From Nucleophilic Attack at the *meso*-Position

BODIPY systems with a *meso*-cyanide substituent are special insofar as they fluoresce at significantly longer wavelengths than the unsubstituted systems.[129] Further, they can be accessed by direct addition of cyanide anion to the dipyrromethene core, followed by oxidation. The first synthetic route developed gave poor overall yields, mainly due to loss of material in forming the dipyrromethene,[93] but an improved route was developed by Boyer (Scheme 5).[130] In that work, Knorr condensation of 3-ethylhexan-2,4-dione with diethyl

Scheme 5. Cyanopyrromethene−BF_2 Complexes via Addition of Cyanide

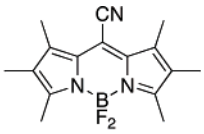


not isolated

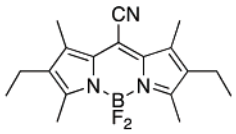
73 35 %
EtOH, Φ 0.56
$\lambda_{max\ abs}$ 592 nm
$\lambda_{max\ emiss}$ 609 nm

aminomalonate give ethyl 3,4-diethyl-5-methylpyrrole-2-carboxylate. This pyrrole is then converted to the dipyrromethene hydrobromide via the presumed intermediacy of 2-methyl-3,4-diethylpyrrole and its condensation with the α-formyl derivative that is formed *in situ*.

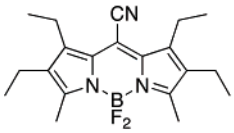
Comparison of compound **73** with other *meso*-cyano BODIPYs (e.g., **74**−**77**) shows they fluoresce and absorb at about 60 nm longer wavelengths than simple alkyl-substituted BODIPYs. This large bathochromic shift seems attributable to a net stabilization of the LUMO level due to the cyano group decreasing the energy gap. The presence of the cyano group also significantly reduces the molecular extinction coefficient. Only in the case of **77** where the core bears two ester groups is this red shift attenuated. Presumably, in this case, the esters reduce the electron density on the BODIPY core that is available for delocalization into the nitrile, and this affects the fluorescence emission wavelength.



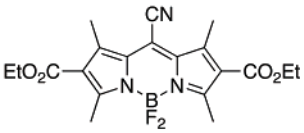
74
MeOH, Φ 0.54
$\lambda_{max\ abs}$ 588 nm
$\lambda_{max\ emiss}$ 612 nm



75
dioxane, Φ 0.55
$\lambda_{max\ abs}$ 580 nm
$\lambda_{max\ emiss}$ 620 nm

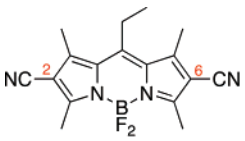


76
MeOH, Φ 0.56
$\lambda_{max\ abs}$ 592 nm
$\lambda_{max\ emiss}$ 609 nm

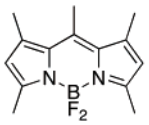


77
dioxane, Φ 0.82
$\lambda_{max\ abs}$ 556 nm
$\lambda_{max\ emiss}$ 589 nm

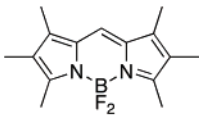
The red shift in fluorescence observed when a cyano group is added to the *meso*-position is somewhat particular to that site. 2,6-Dicyano BODIPY **78** has two cyano groups, but neither occupies the *meso*-position. Fluorescence from this compound peaks at about the same wavelength as similar BODIPYs without nitrile substituents, for example, **79** and **8**.[130] Similarly, substitution at the 2- and 6-positions with carboethoxy, acetamido, sulfonate anion, bromo, or nitro groups do not produce any red shift.[93,130,131]



78
dioxane, Φ 0.79
$\lambda_{max\ abs}$ 496 nm
$\lambda_{max\ emiss}$ 511 nm



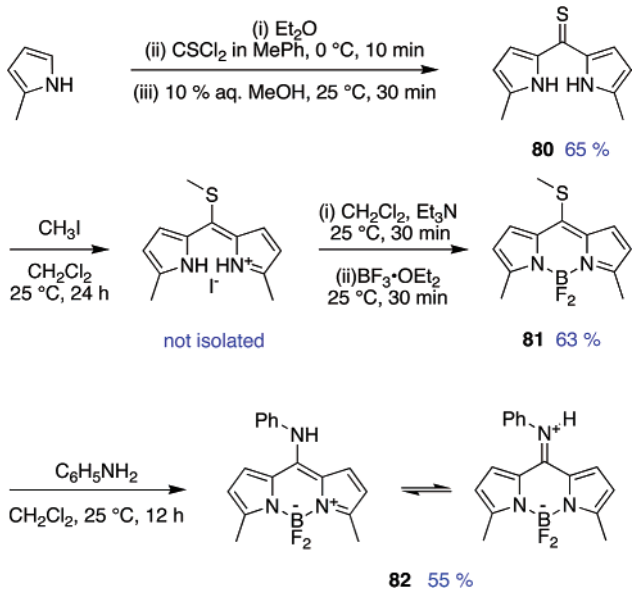
79
dioxane, Φ 0.99
$\lambda_{max\ abs}$ 493 nm
$\lambda_{max\ emiss}$ 519 nm



8
MeOH, Φ 0.56
$\lambda_{max\ abs}$ 528 nm
$\lambda_{max\ emiss}$ 552 nm

A synthesis of sulfur containing BODIPYs under mild conditions was recently achieved via reaction of thiophosgene with substituted pyrroles to give the corresponding thioketone **80**. The latter can then react with various

Scheme 6. Synthesis of Sulfur- and Anilino-BODIPY Derivatives

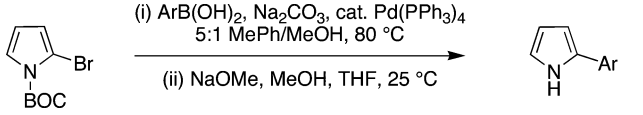


electrophiles to form the dipyrromethene intermediates that were combined with boron trifluoride in presence of base to afford the thio-BODIPY derivatives **81**. These *meso*-thioalkyl groups can be displaced by nucleophiles to give anilino-substituted BODIPY derivative **82** (Scheme 6). Amine adduct **82** was not fluorescent, presumably because of electron transfer from the amine group to the BODIPY core in the excited state.

5. Aryl-, Alkenyl-, and Alkynyl-Substituted BODIPYs

5.1. Aryl-Substituted BODIPYs from Aryl-Pyrroles

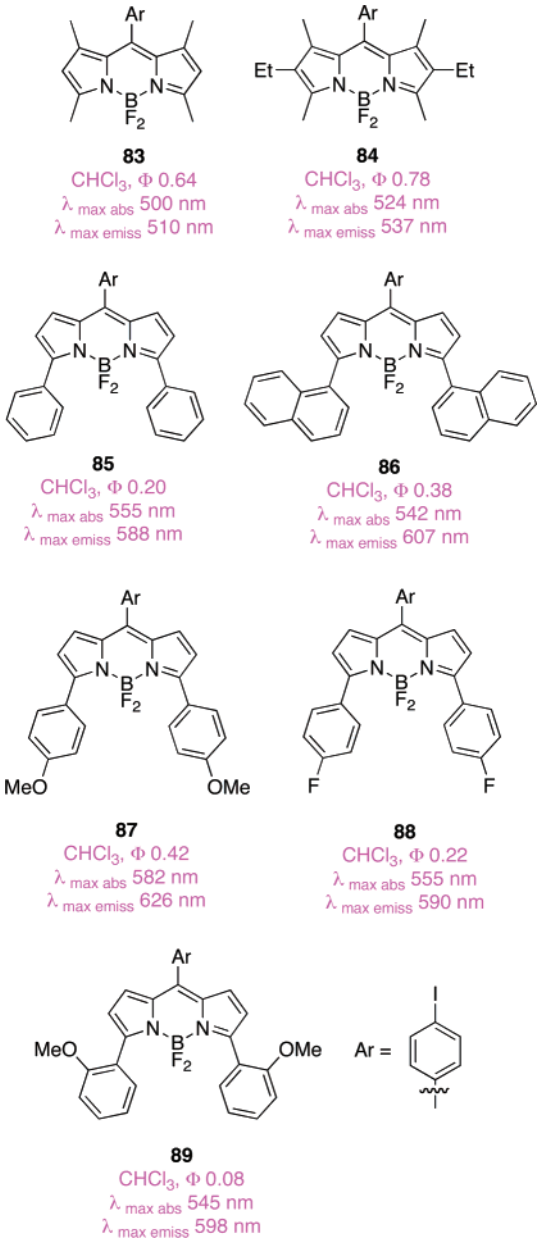
Aryl-substituted BODIPY dyes can be formed via condensation of the corresponding pyrroles with acyl chlorides.[132,133] The 2-aryl pyrroles used were prepared via Suzuki couplings[134] of *N*-*tert*-butoxycarbonyl-2-bromopyrrole (reaction 12); this was more convenient than starting with less accessible materials like 4-aryl-1-azidobutadienes[135] or *N*-tosylarylimine.[136,137] Removal of the *N*-BOC protecting group under basic conditions gave the desired aryl pyrroles. These products were found to decompose on standing, rapidly under acidic conditions, and were therefore best formed immediately before use.



reaction 12

3,5-Diaryl BODIPY dyes were obtained from the pyrroles shown above, via a one pot, two-step process featuring 4-iodobenzoyl chloride. The 3,5-aryl groups extend the conjugation of the BODIPY systems. Compared to the alkyl-substituted derivatives, for example, **83** and **84** which have green, fluorescein-like emissions ($\lambda_{max\ emis}$ = 510 nm), both

the absorption and emission maxima of 3,5-diaryl substituted BODIPYs **85**−**89** are shifted to longer wavelengths ($\lambda_{max\ emis}$ = 588−626 nm).[132,133] The *para*-electron-donating group of **87** gives a larger bathochromic shift and increased quantum yield, compared to the compound with those same substituents in the *ortho*-position **89**. Similarly, the extended aromatic substituent naphthalene of **86** red-shifted the emission maximum for this compound. However, the extinction coefficients for **85**−**89** were not markedly increased relative to the alkyl systems **83** and **84**, and their fluorescence quantum yields were significantly lower due to nonradiative loss of energy via rotation around the C−Ar bonds.[138]



83
$CHCl_3$, Φ 0.64
$\lambda_{max\ abs}$ 500 nm
$\lambda_{max\ emiss}$ 510 nm

84
$CHCl_3$, Φ 0.78
$\lambda_{max\ abs}$ 524 nm
$\lambda_{max\ emiss}$ 537 nm

85
$CHCl_3$, Φ 0.20
$\lambda_{max\ abs}$ 555 nm
$\lambda_{max\ emiss}$ 588 nm

86
$CHCl_3$, Φ 0.38
$\lambda_{max\ abs}$ 542 nm
$\lambda_{max\ emiss}$ 607 nm

87
$CHCl_3$, Φ 0.42
$\lambda_{max\ abs}$ 582 nm
$\lambda_{max\ emiss}$ 626 nm

88
$CHCl_3$, Φ 0.22
$\lambda_{max\ abs}$ 555 nm
$\lambda_{max\ emiss}$ 590 nm

89
$CHCl_3$, Φ 0.08
$\lambda_{max\ abs}$ 545 nm
$\lambda_{max\ emiss}$ 598 nm

Fluorescence of BODIPYs in solution can be reduced at elevated concentrations due to intermolecular π-stacking. BODIPY dyes can stack in two geometrically distinct forms: H- and J-dimers (Figure 7). The former is most likely a result of intramolecular dimerization, with the stacking of two BODIPY planes with almost parallel $S_0 \rightarrow S_1$ transition

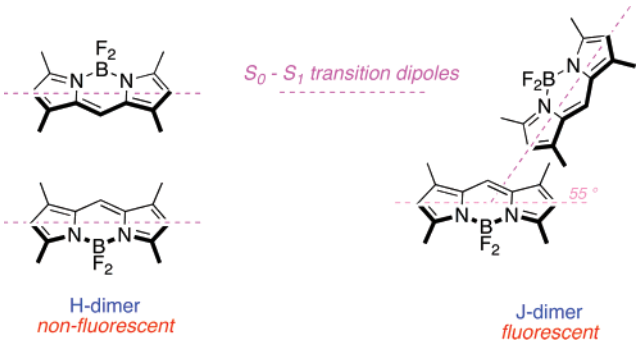
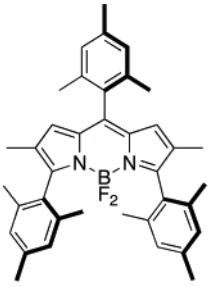


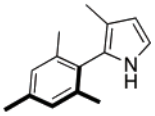
Figure 7. Structures of H-dimer and J-dimer.

dipoles, and antiparallel electric dipole moments. This dimer is practically nonfluorescent, and exhibits blue-shifted absorption relative to that of the monomer. The J-dimer, in which the $S_0 \rightarrow S_1$ transition dipoles are oriented in planes at 55°, is fluorescent and shows a red-shifted absorption relative to that of the monomer.[139−141]

Compound **90** was designed as a probe that was sterically prevented from forming dimers in solution.[142] Further, the hindered internal rotation of the mesityl rings reduces nonradiative relaxation of excited states, enhancing fluorescence quantum yields. Dye **90** was prepared from mesityl aldehyde and pyrrole **91** (made via a Trofimov reaction).[137]



90
CH_2Cl_2, Φ 0.95
$\lambda_{max\ abs}$ 543 nm
$\lambda_{max\ emiss}$ 559 nm

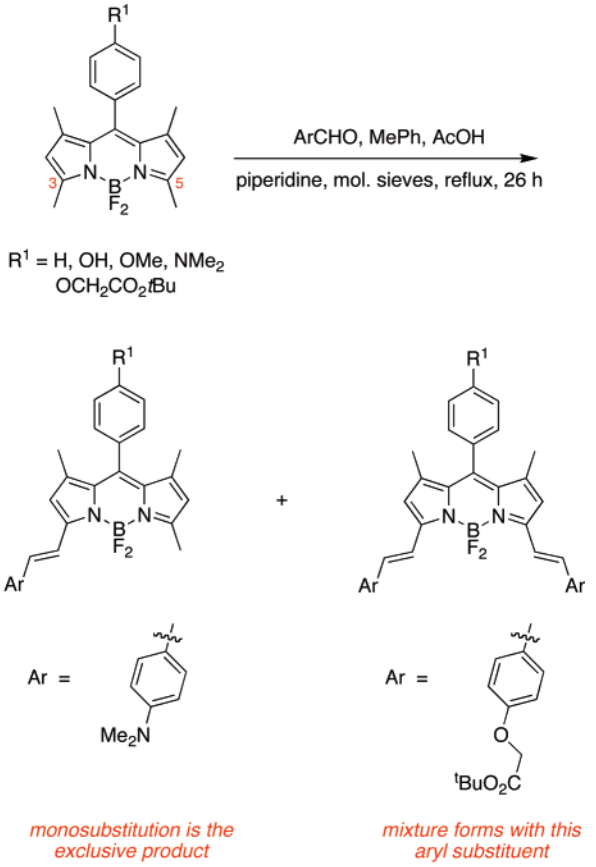


91

5.2. Condensation Reactions of the 3,5-Dimethyl Derivatives with Benzaldehyde Derivatives To Give Alkenyl Systems

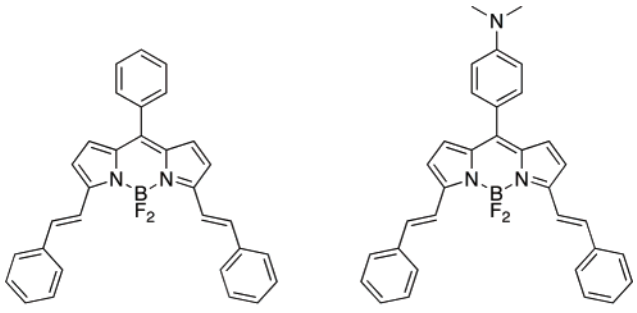
In the past few years, it has been shown that 3- and 5-methyl BODIPY-substituents are acidic enough to participate in Knoevenagel reactions. Thus, styryl-BODIPY derivatives can be obtained by condensation of 3,5-dimethyl-BODIPYs with aromatic aldehydes (reaction 13).[143,144] With *p*-dialkylaminobenzaldehyde, the reaction can be restricted to one condensation, but 4-alkoxybenzaldehydes tend to give mixtures corresponding to one and two condensations.[145] Di-(dimethylamino)styryl-substituted BODIPY dyes can be obtained with longer reaction time (7 days).[146]

The condensation processes shown in reaction 13 provide direct entry into BODIPY derivatives that have red-shifted fluorescence properties, and functional groups that can be used in sensors and molecular logic gates. UV-absorption spectra of compounds from one condensation (e.g., **94** and **95**) tend to reach a maximum around 594 nm



reaction 13

in MeOH, and their fluorescence emissions are similarly red-shifted. Both the absorption and, particularly, the fluorescence spectra are dependent upon solvent polarity.[147,148] The red shift is more pronounced in polar solvents indicating excitation of the dyes leads to more polarized excited states.

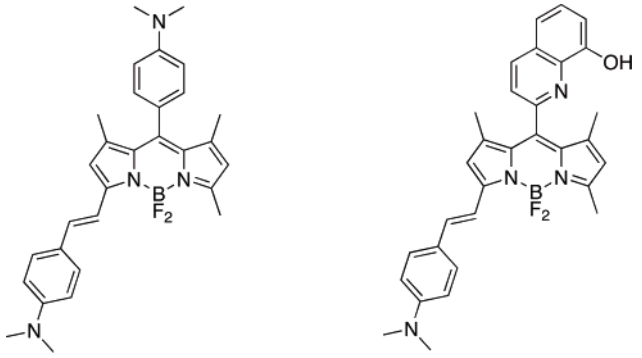


92
CH_3CN, Φ 0.84
$\lambda_{max\ abs}$ 628 nm
$\lambda_{max\ emiss}$ 642 nm

93
CH_3CN, Φ 4 x 10^{-4}
$\lambda_{max\ abs}$ 620 nm
$\lambda_{max\ emiss}$ 636 nm

$CH_3CN + H^+$, Φ 0.75
$\lambda_{max\ abs}$ 634 nm
$\lambda_{max\ emiss}$ 652 nm

Structures **93**−**97** illustrate some effects of amino substituents in these styryl systems. When the amine is directly conjugated with the styryl group, then a maximum red shift is obtained, but when it is part of the *meso*-substituent,



94
H_2O, Φ 9 x 10^{-4}
$\lambda_{max\ abs}$ 578 nm
$\lambda_{max\ emiss}$ 758 nm

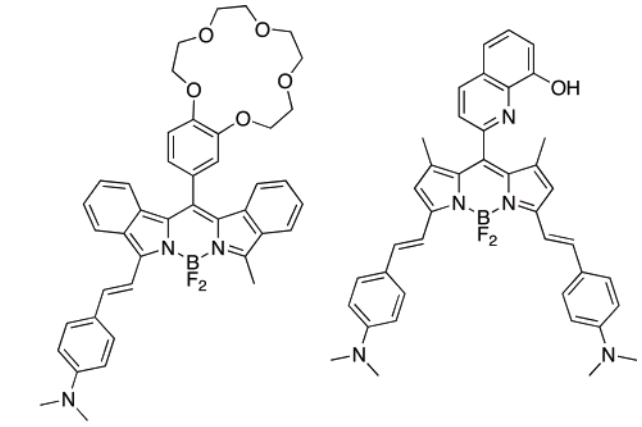
MeOH, Φ 0.10
$\lambda_{max\ abs}$ 594 nm
$\lambda_{max\ emiss}$ 699 nm

$H_2O + 2H^+$, Φ 0.55
$\lambda_{max\ abs}$ 557 nm
$\lambda_{max\ emiss}$ 565 nm

95
MeOH, Φ 0.04
$\lambda_{max\ abs}$ 608 nm
$\lambda_{max\ emiss}$ 738 nm

then the bathochromic shift is less because this *meso*-substituent is nonplanar. Quantum yields for these materials are only high when the amine is protonated disfavoring Intramolecular Charge Transfer (ICT) in the excited state.[143,148]

Structures **95**−**97** were prepared as metal sensors where complexation to ions alleviates ICT and increases the quantum yields. Comparison of the spectral data for **95** and **97** reveals a second styryl group gives a red shift in the UV absorbance of almost 100 nm, and in about 50 nm in the fluorescence spectrum.[146]



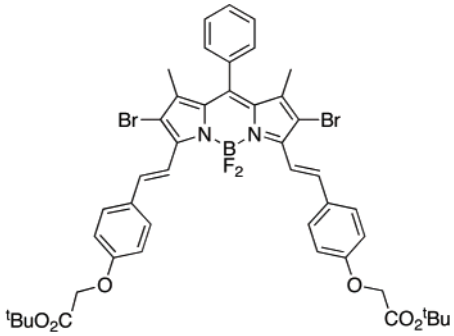
96
H_2O, Φ n.d.
$\lambda_{max\ abs}$ 722 nm
$\lambda_{max\ emiss}$ n.d. nm

MeOH, Φ 0.20
$\lambda_{max\ abs}$ 691 nm
$\lambda_{max\ emiss}$ 732 nm

$H_2O + H^+$, Φ 0.27
$\lambda_{max\ abs}$ 664 nm
$\lambda_{max\ emiss}$ 675 nm

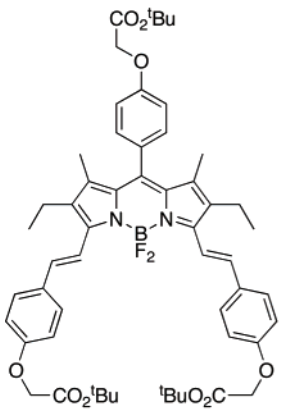
97
MeOH, Φ 0.07
$\lambda_{max\ abs}$ 705 nm
$\lambda_{max\ emiss}$ 791 nm

There is no marked pH dependence for the alkoxy-substituted systems **98** and **99**.[145] However, the aminophenol **100** has quenched fluorescence when the hydroxyl group is deprotonated, but the UV absorbance and fluorescence remain the same; fluorescence is enhanced and there is a blue shift when the amine group is protonated. This molecule has therefore been compared to a logic gate.[75]



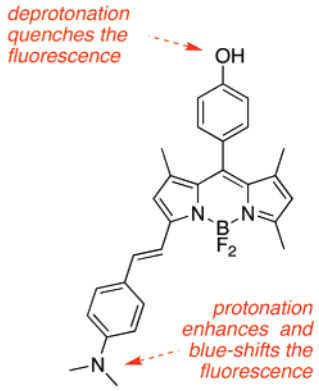
98

^{i}PrOH, Φ 0.42
$\lambda_{max\ abs}$ 657 nm
$\lambda_{max\ emiss}$ 679 nm
fwhm 41 nm



99

^{i}PrOH, Φ 0.40
$\lambda_{max\ abs}$ 657 nm
$\lambda_{max\ emiss}$ 679 nm
fwhm 43 nm



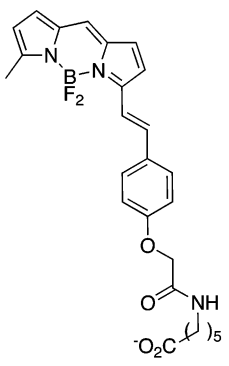
100

THF, Φ 0.25
$\lambda_{max\ abs}$ 565 nm
$\lambda_{max\ emiss}$ 660 nm

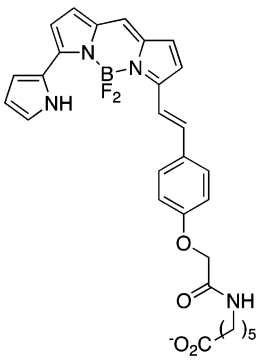
THF + H^{+}, Φ 0.85
$\lambda_{max\ abs}$ 525 nm
$\lambda_{max\ emiss}$ 560 nm

THF + OH^{-}, Φ 0.032
$\lambda_{max\ abs}$ 565 nm
$\lambda_{max\ emiss}$ 660 nm

Invitrogen's BODIPY 630/650 and BODIPY 650/665 probes are the longest-wavelength amine-reactive BODIPY fluorophores reported to date.



BODIPY 630/650



BODIPY 650/665

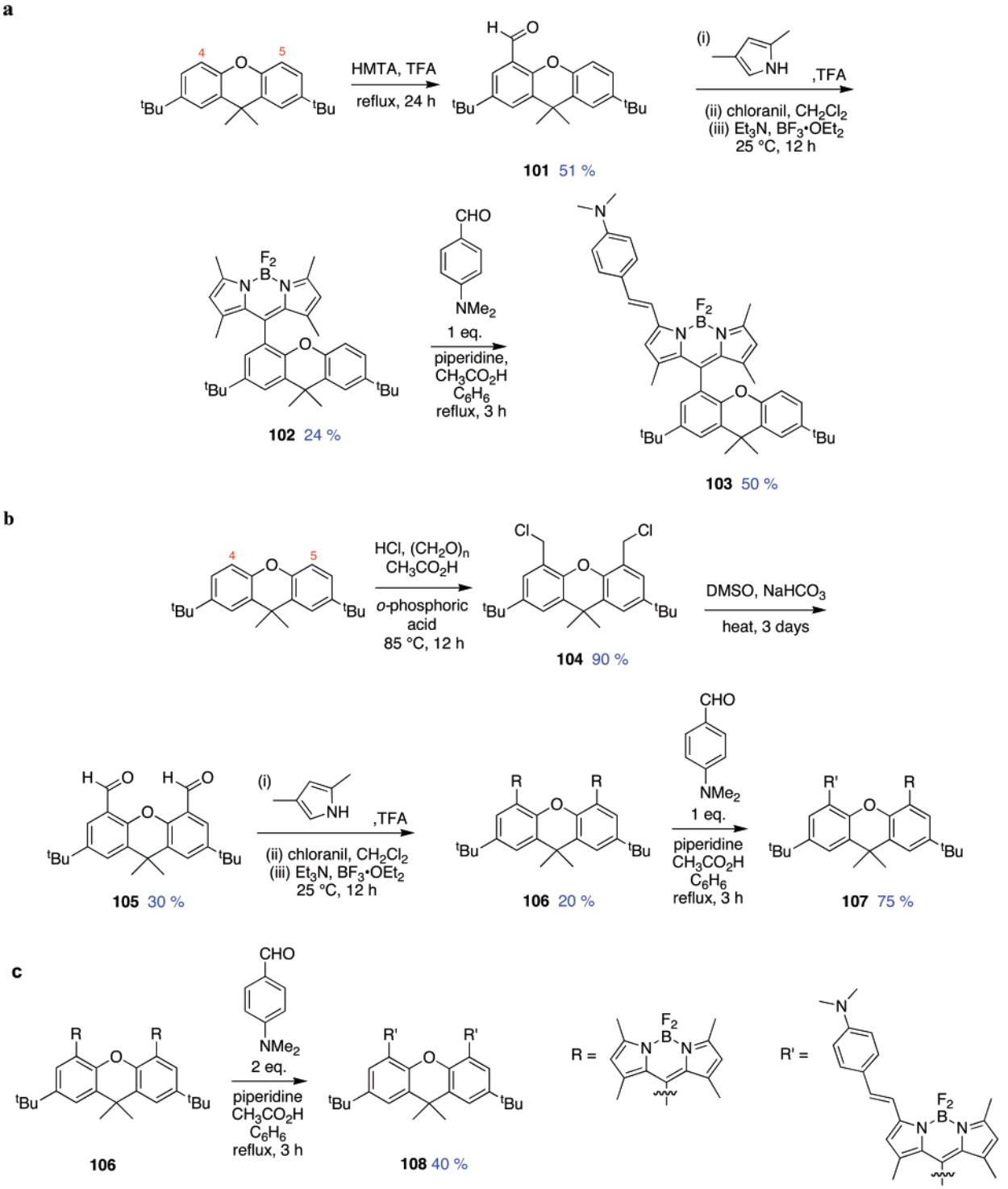
Biomolecules labeled at relatively large BODIPY/protein ratios can have diminished fluorescence due to interactions between the probes; the fluorescence can also be red-shifted for the same reason.[149] Small molecules containing two BODIPYs have been produced to test these types of effects. The first prepared were somewhat flexible being based on cyclohexane.[139,140] More recently, rigid test molecules with cofacial BODIPY dyes have been made and studied. Only one transition dipole moment is possible for these structures. The xanthane unit was chosen as a scaffold, since it can be easily functionalized on its 4- and 5-positions. Aldehyde or bis-aldehyde functionalities on the xanthane (**101** or **105**, respectively) were used to construct the BODIPY units by condensation with 2,4-dimethylpyrrole. A 3-methyl substituent on the BODIPY was then reacted with *p*-dimethylaminobenzaldehyde to extend the conjugation (Scheme 7).[150]

Compound **106** has two cofacial BODIPY groups, and the UV absorption maximum of the BODIPY part is blue-shifted (to 478 nm, with a shoulder at 504 nm) relative to 1,3,5,7-tetramethyl-BODIPY **7** and the control compound **102**. Compound **107** which has one styryl-extended BODIPY and one tetramethyl-BODIPY substituent has UV absorption peaks corresponding to both these substituents (455 and 575 nm). Upon excitation at 480 nm, the monochromophoric system **102** exhibits a very strong emission at 500 nm, while the fluorescence emission of the di-BODIPY system **106** is significantly quenched; it shows two peaks, one at 505 nm and a broader excimer-type emission at 590 nm. Efficient energy transfer from the donor (tetra-methyl BODIPY) to the acceptor (extended BODIPY) was observed for the system **107**. The cofacial chromophores are separated by approximately 4.5 Å, allowing both energy transfer and formation of an excimer-like state. Incidentally, system **107** acts as an energy transfer cassette; fluorescence emission could be observed at 650 nm from the extended BODIPY (acceptor) upon excitation of the other BODIPY (donor) at 480 nm. More discussion of energy transfer cassettes follows in section 6.

5.3. From Palladium-Catalyzed Coupling Reactions at the 3- and 5-Positions

3,5-Dichloro BODIPY derivatives such as **64** have similar reactivities to heterocyclic imidoyl chlorides; this opens a new window for derivatization using transition-metal-catalyzed reactions. Thus, new 3-, 5-aryl, ethenylaryl, and ethynylaryl compounds **109** and **110** were obtained via Stille, Suzuki, Heck, and Sonogashira couplings (reaction 14).[151] The extended conjugation, and mono-/disubstitution patterns of these dyes give dispersed fluorescence emission maxima within the series. Absorption maxima for the monosubstituted compounds **109** are blue-shifted by 20−50 nm relative to the disubstituted ones **110**. The largest red shift for both absorption and emission was observed for the styryl-substituted derivatives. The dyes with ethenyl- or ethynyl-aryl substituents gave the highest quantum yields (**110c**, 0.92; **109d**, 0.98; and **110d**, 1.00).[151] The monosubstituted BODIPY dyes can further be derivatized by nucleophilic substitution (see section above) or by another transition-metal-catalyzed coupling reaction to give unsymmetrically substituted probes.

Scheme 7. Syntheses of BODIPY Dyes Anchored on Xanthene Units To Test Self-Quenching[a]



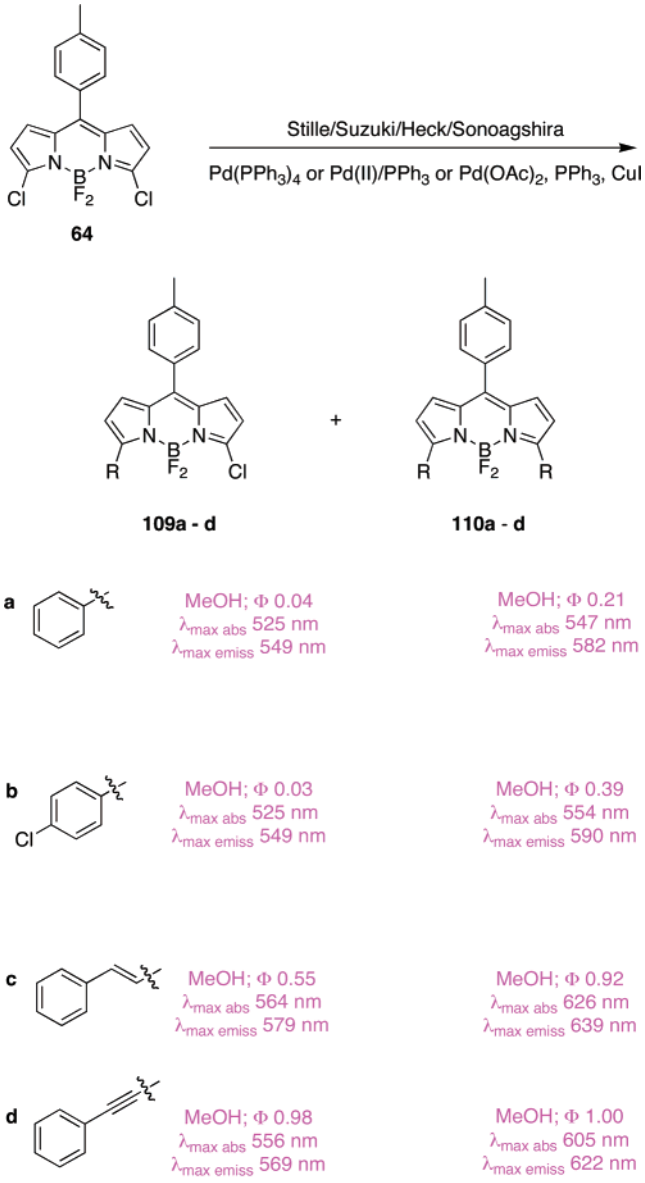
[a] (a) A system with one BODIPY dye; (b) a similar compound with two, where only one has extended conjugation; and (c) another where both have extended conjugation.

6. Energy Transfer Cassettes

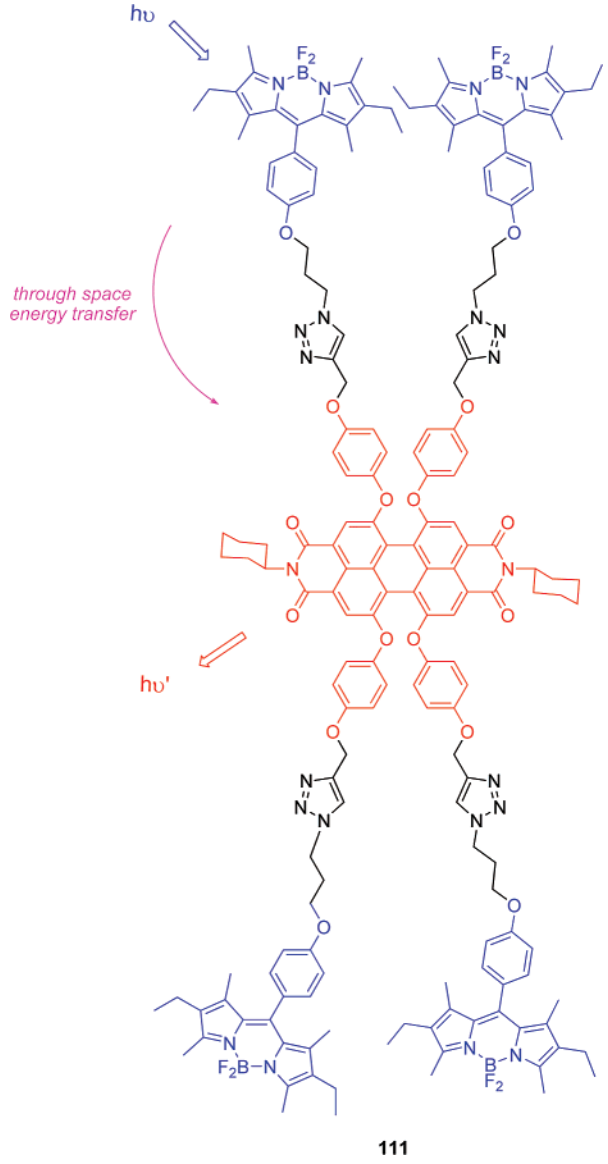
6.1. Through-Space Energy Transfer Cassettes

Two fluorescent entities may be joined in the same molecule to give a "cassette". One of these, the *donor*, may collect radiation efficiently at the excitation wavelength and pass this energy to the second fluorescent moiety that emits it at a longer wavelength. If the mechanism of energy transfer is through space, then this system might be called a through-space energy transfer cassette. Through-space energy transfer cassettes are typically used to artificially enhance the Stokes' shift of a probe. Ones featuring BODIPY dyes have been somewhat useful for DNA sequencing on a genomic scale[152] where four distinct fluorescent outputs are required, and usually only one excitation wavelength is used.

Through-space energy transfer efficiencies depend on several factors, including (i) spectral overlap of the donor emission with the acceptor absorbance, (ii) distance between the donor and the acceptor, (iii) the orientation factors, and (iv) the effectiveness of alternative de-excitation modes.



reaction *14*

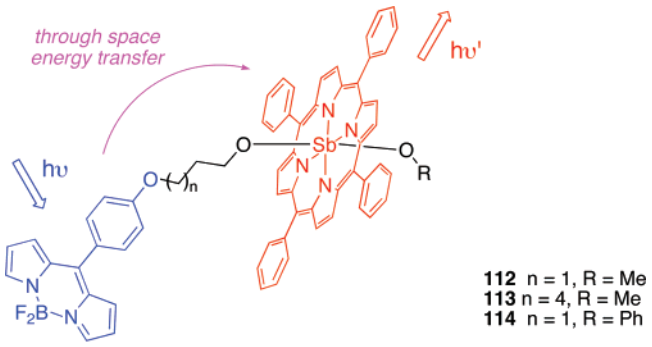


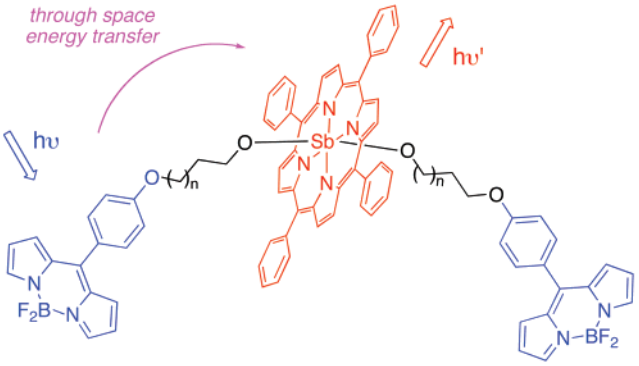
Cassettes described in this section have no obvious way to transfer energy from donors to acceptors via bonds.

The dendritic light harvesting system **111** with four BODIPY donors and a perylenediimide (PDI) acceptor was constructed via click chemistry.[153] Its UV spectrum is equal to the sum of the donor and acceptor components indicating they are not electronically perturbing each ther.[154] The extinction coefficients of **111** at 526 nm (BODIPY λ_{max}) and 582 nm (PDI λ_{max}) are 240 000 and 45 000 M^{-1} cm^{-1}, respectively; hence, the donor absorption is huge simply because four BODIPY units are involved. No green fluorescence emission from BODIPY was observed upon excitation at 526 nm, indicating efficient energy transfer (99%). On the basis of the energy transfer efficiency, the authors of this work calculated a Förster critical radius of 47 Å. An "antenna effect" {emission intensity at 618 nm when excited at 526 nm (BODIPY core) divided by that from excitation at 588 nm (at the PDI core)} gave approximately a 3.5-fold enhancement.

Most studies on energy transfer between porphyrins and other chromophores have focused on electron and energy transfer in the plane of the porphyrin. "Vertical" electron and energy transfer from axial ligands, on the other hand, have not been studied extensively, but systems **112**−**115** were synthesized to study these phenomena. An antimony porphyrin was chosen as the acceptor because this central metal can coordinate to ligands with oxygen, nitrogen, or sulfur atoms. Energy transfer from the excited singlet state of the BODIPY to the Sb(TPP) chromophore occurs for **112**, **113**, and **115**. This happens with efficiencies in the 13−40% range, decreasing as the length of the methylene bridge increases. Little or no evidence was seen for quenching of the porphyrin excited singlet state by the BODIPY. This was true even when polar solvents were used and the donor and acceptor fragments would be expected to pack against each other. However, for system **114**, which differs from **112** only at the second axial ligand (phenoxy vs methoxy), the excited singlet state of the Sb(TPP)- acceptor was quenched by the BODIPY and phenoxy ligands. The quenching by the phenoxy group occurs, at least in part, via a nonradiative electron-transfer process.[155]

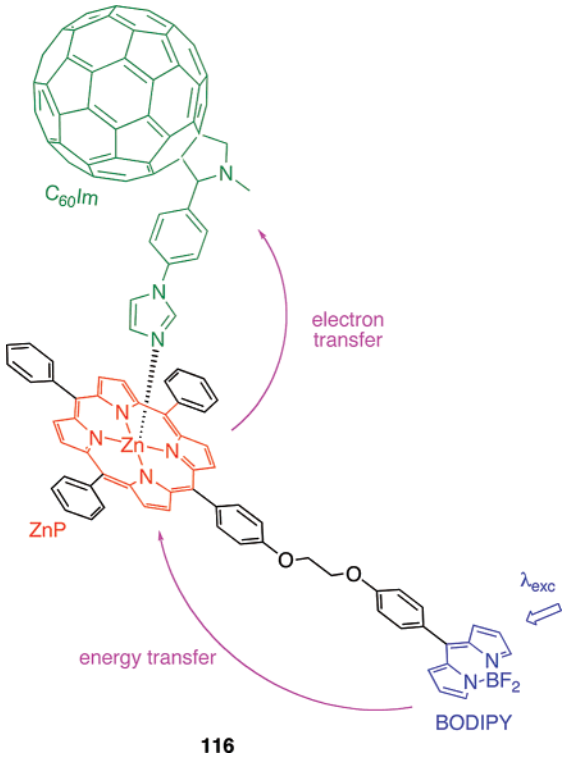
System **116** is another artificial light harvesting system with BODIPY dye donors, but here the energy is transferred to a zinc porphyrin (ZnP), then electron transfer occurs





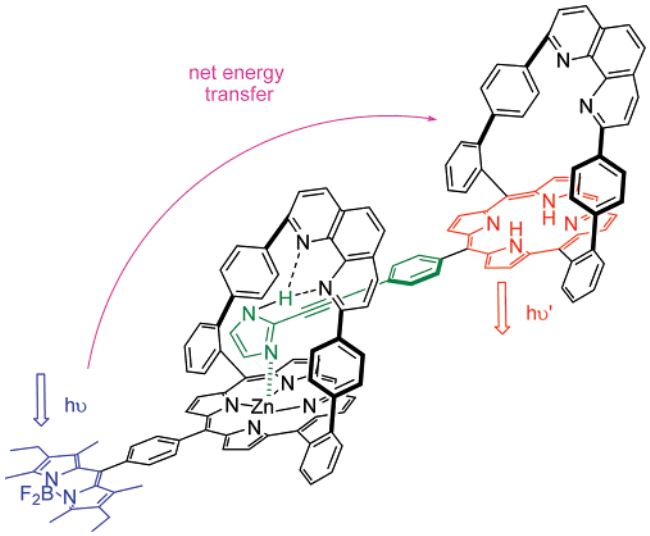
115

to a fullerene (C_{60}-Im) unit; thus, the molecule was called a "supramolecular triad". The Zn-porphyrin connects to the fullerene component via metal to axial-ligand coordination. Both steps in the process were efficient. Overall, the system was said to mimic the "combined antenna-reaction center" events in natural photosynthesis.[156]



116

Like **112**−**116**, complex **117** also features a donor and an acceptor system linked via axial coordination to a zinc porphyrin.[157] This self-assembling system is based on the exceptional affinity of phenanthroline-strapped zinc porphyrins for *N*-unsubstituted imidazoles.[158,159] Efficient net energy transfer (80%) was observed for excitation of the BODIPY at 495 nm and emission at the free porphyrin. Energy transfer from the excited ZnP−Im complex to the free porphyrin was calculated to be 85%.



117

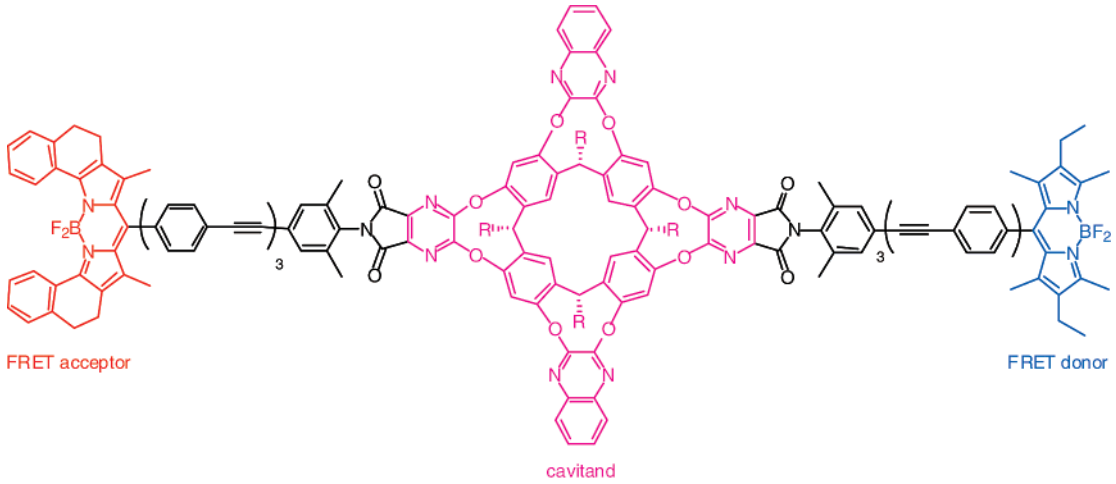
Compound **118** was designed to be a molecular switch. It has two stable conformations governed by the bridged resorcin[4]arene scaffold.[160] In the absence of protons (or perhaps other guest cations) the molecule exists in a contracted geometry maximizing FRET (fluorescence resonance energy transfer) between the two BODIPY-based probes. Decreased pH values switch the molecule to the expanded conformation, and this is evident by the reduced energy transfer. An advantage of using BODIPY dyes in this study is their low sensitivity to pH changes.

The UV spectrum of **118** displays three strong absorption bands assigned to the spacer (λ_{max} 332 nm), the donor (λ_{max} 529 nm), and the acceptor dye (λ_{max} 619 nm), respectively. Upon excitation at 490 nm, two emission bands at 542 nm (donor dye) and 630 nm (acceptor dye) are observed, in a ratio of the donor/acceptor fluorescence intensity of 45:55, indicating low FRET efficiency (possibly due to unfavorable orientations of the transition dipole moments, and/or to the dynamic behavior of the cavitand part). Upon addition of TFA, the emission from the acceptor is nearly completely quenched, whereas the donor fluorescence intensity doubles.

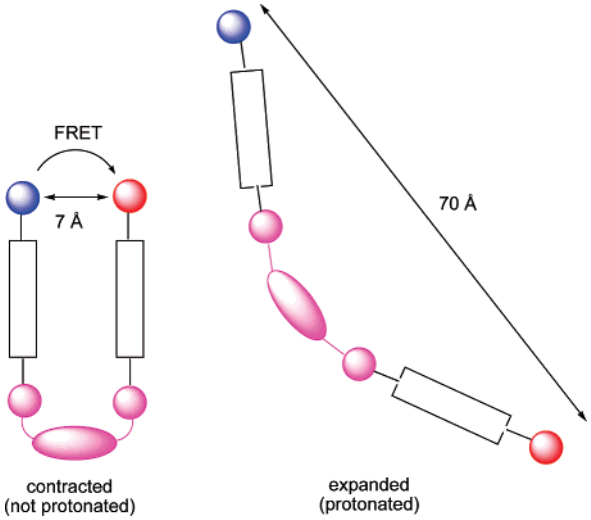
6.2. Through-Bond Energy Transfer Cassettes

6.2.1. Porphyrin-Based Systems as Models of Photosynthesis

The prevalent mechanism of through-space energy transfer is likely to be via dipolar couplings, that is, Förster energy transfer. The rate and efficiency of this is governed by, among other things, the overlap integral between the donor fluorescence and the acceptor absorbance.



118
R = *n*-C_6H_{13}

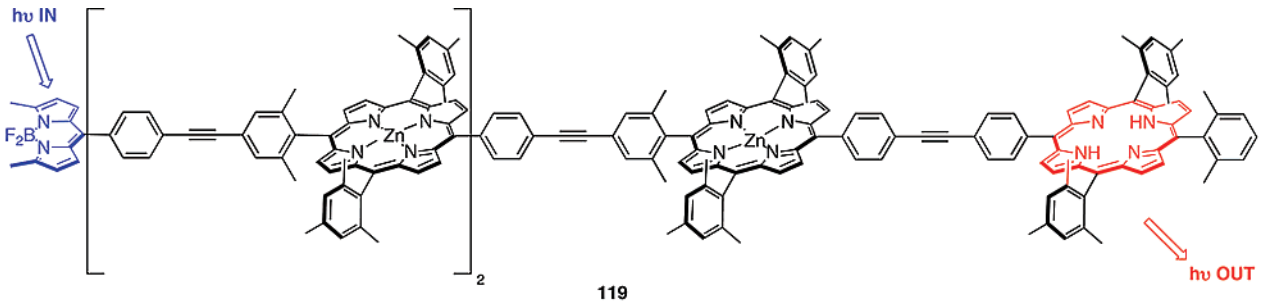


If the donor and acceptor dyes are coupled to each other via a conjugated but twisted π-system, then the prevalent mechanism of energy transfer is likely to be through bonds. Constraints on through-bond energy transfer are not well-understood, but it appears there is no requirement for a good overlap integral. This is important in the design of fluorescent cassettes because, if this is true, there is no obvious limitation on the energy gap between the donor fluorescence and the acceptor absorbance; hence, cassettes with huge "apparent Stokes' shifts" could be produced.

A pioneer of energy transfer systems featuring BODIPY donors was Lindsey who studied them in the context of model porphyrin-based systems for photosynthesis.[161] He proposed that the rates and efficiencies of through-bond energy transfer are influenced by the following factors:

- steric interactions between the donor/acceptor wherein increased torsional constraints decrease rates and efficiencies of energy transfer;
- frontier orbital characteristics for the HOMO and LUMO; and related to that,
- the site of attachment of the donor/acceptor to the linker and the nature of the linker.

Lindsey has described the through-bond energy transfer cassette **119** as a "linear molecular photonic wire". It features a BODIPY donor and a free base porphyrin acceptor.



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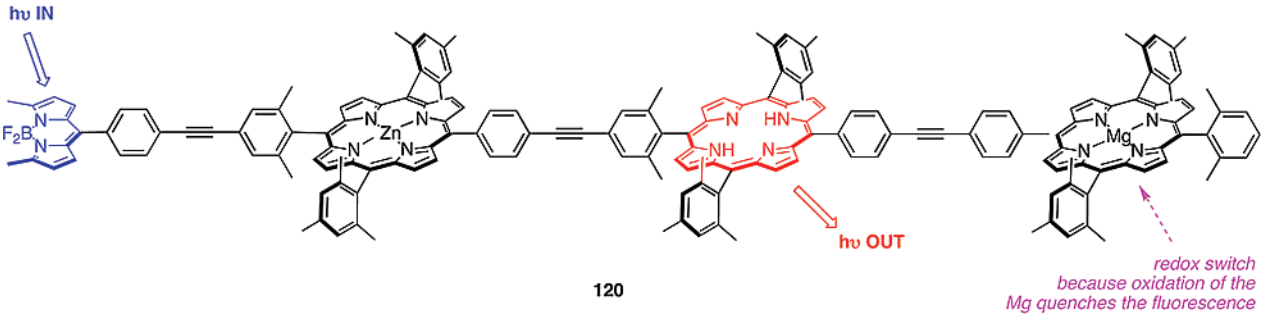
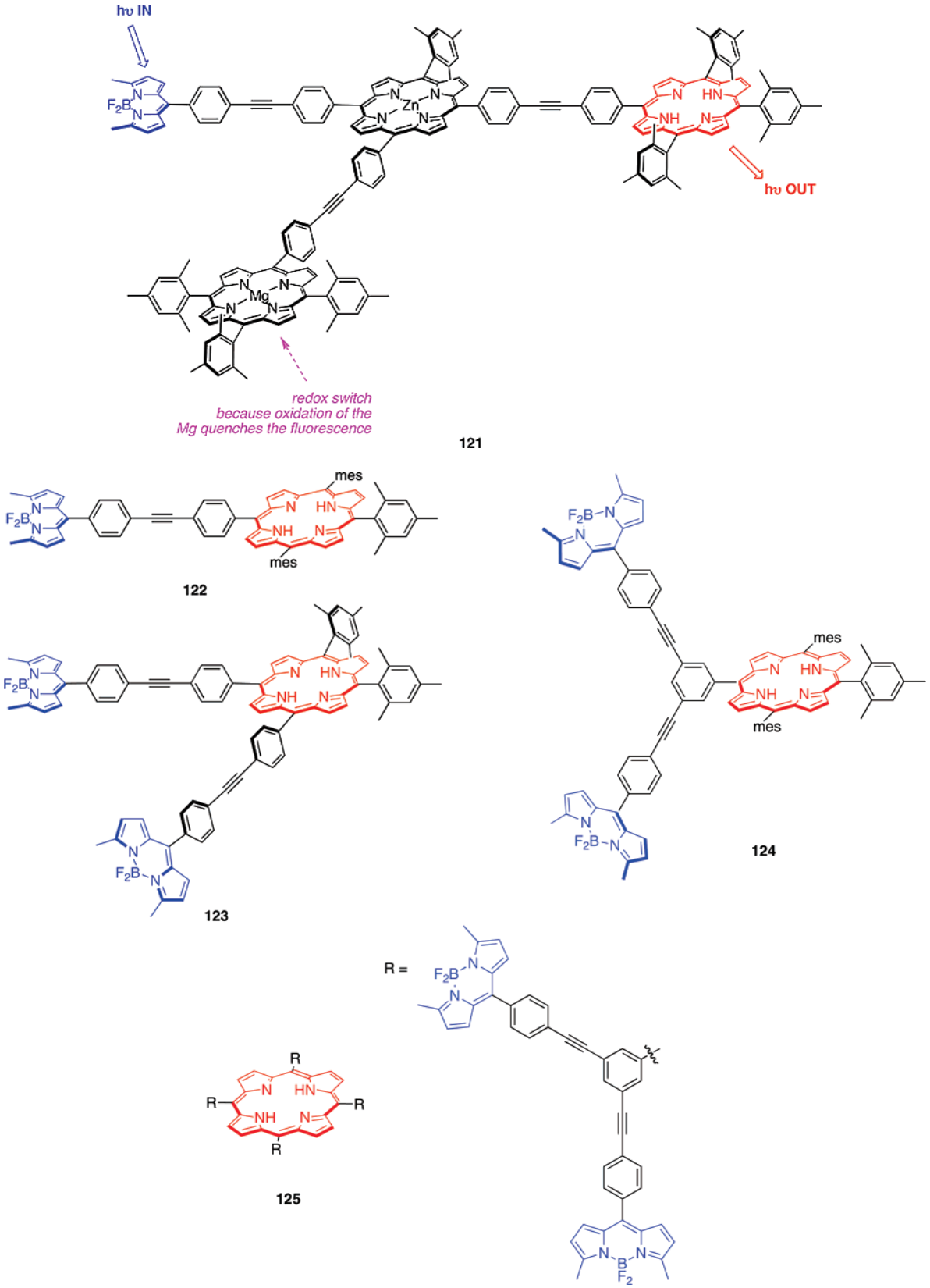


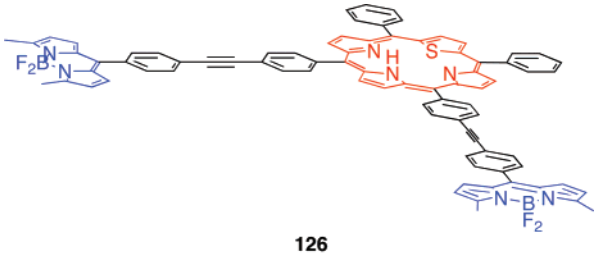
120



This donor−acceptor pair is separated by 90 Å. Efficient energy transfer (76%) from the donor to the acceptor was observed upon excitation at 485 nm (i.e., the donor $\lambda_{max\ abs}$).[162]

Systems **120** and **121** were described as "molecular optoelectronic linear- and T-gates", respectively. In these cassettes, the emission of the acceptor can be turned on or off via reduction or oxidation f the attached magnesioporphyrin; the latter in its oxidized state quenches fluorescence via ICT. For each cassette, more than 80% of energy transfer was observed upon excitation of the BODIPY donor part.[163]

Compounds **122**−**125** are light-harvesting arrays featuring one, two, or eight BODIPY donors and one porphyrin acceptor. Increasing the number of BODIPY donors from one to eight only increases the relative absorption at 516 nm from 68 to 94% (of a BODIPY standard) for the free base porphyrins **122**−**125**, and from 91 to 99% for the Zn-



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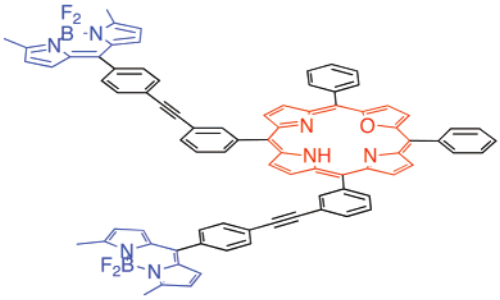

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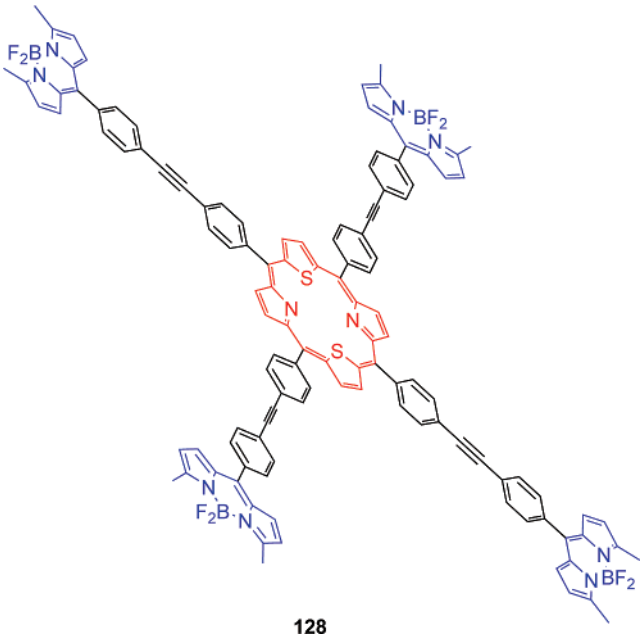


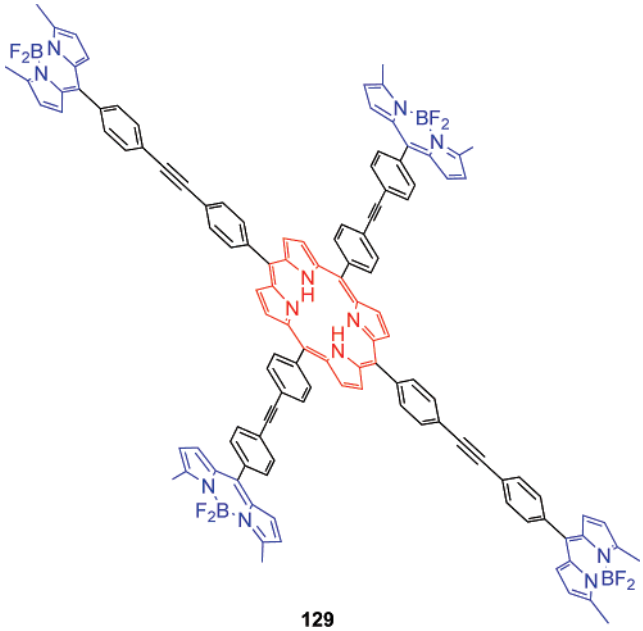
128

porphyrin (not shown). Near quantitative energy transfer was observed for the systems containing one or two BODIPY units, but 80−90% energy transfer was observed for the system bearing eight BODIPY units.[164]

Cassettes **126** and **127** were synthesized from the corresponding 21-thia and 21-oxoporphyrins by Sonogashira couplings with 8-(4-iodophenyl)-BODIPY. Excitation of the BODIPY part at 485 nm gave weak emission from the BODIPY core and strong emissions from the porphyrin units, suggesting efficient energy transfer. Direct comparison of the efficiencies of energy transfer is difficult because the separations and orientations of the donor and acceptor fragments are different.[165,166] Interestingly, the analogous system with two sulfurs, **128**, gave poor energy transfer (~11%) upon excitation at 485 nm,[167] whereas **129** which has a normal porphyrin core gave 97% energy transfer.[168]

6.2.2. Polypyridine Complexes Containing Accessory BODIPY Chromophores

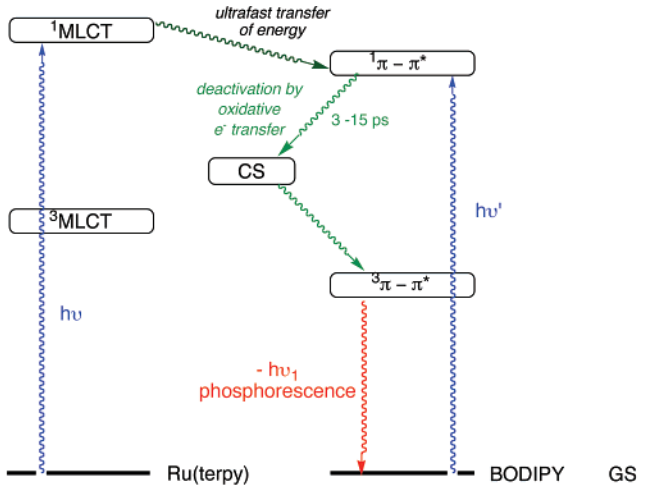
The dual-dye systems **130**−**137** featuring one or more BODIPY chromophores and a Ru(II) polypyridine complex

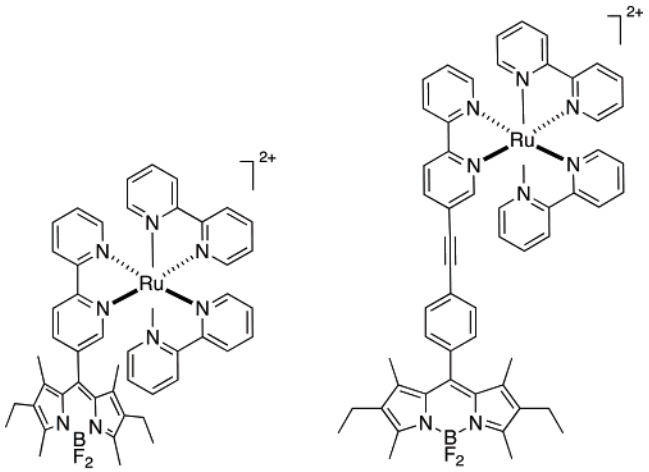


129

have been synthesized as models for solar energy conversion and storage. The BODIPY chromophore was chosen for its strong fluorescence, whereas the Ru(II) polypyridine complex was chosen for its relatively intense and long-lived triplet metal-to-ligand charge transfer (MLCT) emission. The pyridine-based BODIPY dyes were synthesized by condensation of formylpyridine with 3-ethyl-2,4-dimethylpyrrole.[169−172] The new compounds exhibit intense absorption in the visible region (acetonitrile solution), with a major sharp band at 523 nm assigned to the $\pi-\pi^*$ transition for the dipyrromethene dye and a broader band of lower intensity between 450 and 500 nm. The free ligands are strongly fluorescent both in solution at room temperature and at 77 K in a rigid matrix, but no luminescence could be observed in solution for the Ru complexes, independently of the excitation wavelength. Nanosecond transient absorption spectra, however, revealed that a relatively long-lived (ms time scale) excited-state was formed for all metal complexes. The latter was identified as the BODIPY-based triplet state, and is believed to be formed through a charge-separated level from the BODIPY-based $^1\pi-\pi^*$ state. At 77 K, all the complexes studied except for **130**, exhibit the BODIPY-based fluorescence, although with a slightly shortened lifetime compared to the free ligands. However, the surprising finding was that **133**−**135** also exhibit a phosphorescence assigned to the BODIPY subunits (emission at 774 nm of 50 ms lifetime). This is the first report of phosphorescence for BODIPY-based dyes. The authors propose that the phosphorescence is due to the presence of the heavy ruthenium metal, which facilitated intensity to be diverted into the BODIPY $^3\pi-\pi^*$ state from the closely lying metal-based ^{3}MLCT level (for which luminescence decay is highly efficient at 77 K).[170,173,174] Phosphorescence from BODIPY units is certainly unusual. It only was observed here at 77 K for a system coupled with a ruthenium complex, and the efficiency of the process was not determined.

Compounds **136** and **137** combine ruthenium polypyridine units with BODIPY fragments. The BODIPY part ensures a high molar absorption coefficient of the system in the metal-to-ligand charge-transfer region (around 500 nm). The singlet excited states of **136** and **137** are strongly quenched by the presence of ruthenium: energy transfers





130 131

to the Ru center with high efficiency (93% and 73% for **136** and **137**, respectively), where it is then dissipated via electron transfer and/or singlet to triplet intersystem crossing. The net effect is that these complexes are not fluorescent.[175]

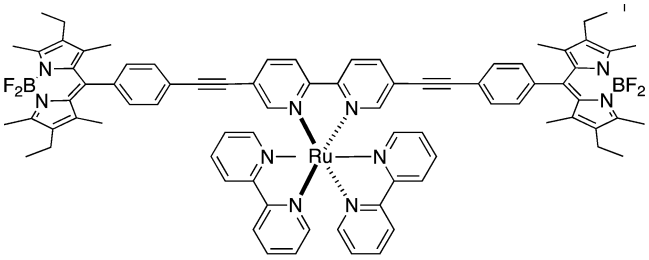
Loss of fluorescence when BODIPY dyes are conjugated with metal complexes is common. For instance complexes **138** and **139** have greatly reduced fluorescence relative to the free ligands,[171,172] presumably due to intramolecular electron transfer.[171,176]

Other complexes, for example, of platinum,[177] containing BODIPY-based ligands have been prepared, but without comment on their fluorescent properties. It is unlikely that such materials will be useful as probes.

6.2.3. Relatively Compact Systems as Potential Probes in Biotechnology

Porphyrin-based cassettes tend to be larger than is ideal for applications relating to labeling of biomolecules, but the through-bond energy transfer aspect could be very useful for applications wherein one source is used and several different outputs must be observed simultaneously. Thus, there has been interest in making smaller through-bond energy transfer cassettes.

BODIPY-based cassettes featuring simple aromatic donors can be prepared from halogenated BODIPYs, for example, **140** via palladium-mediated cross-coupling reactions.[178] Monoiodinated products can be quite useful for such syntheses. For instance, reaction 15 shows a typical stepwise BODIPY synthesis that was used for this.[178]



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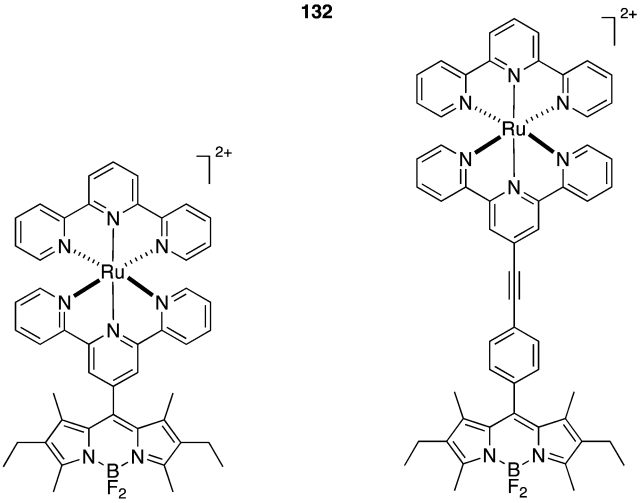
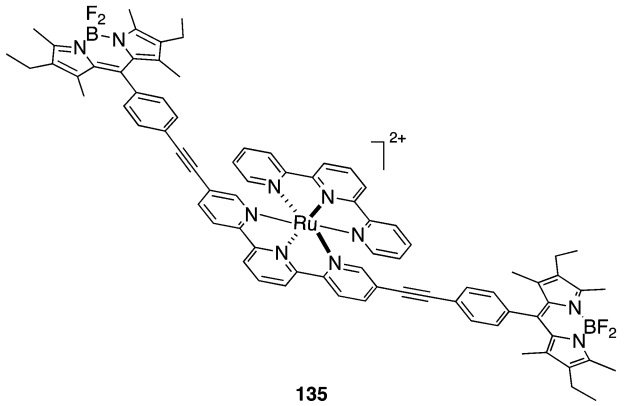
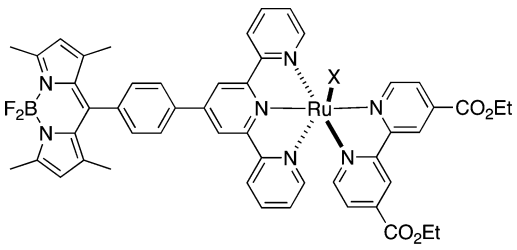


133 134

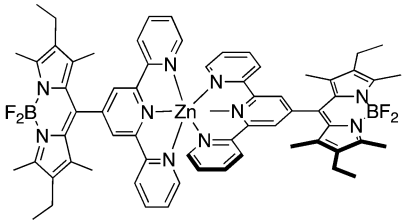


135

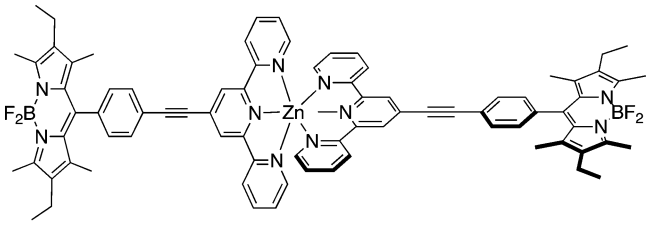


136 X = Cl
137 X = NCS

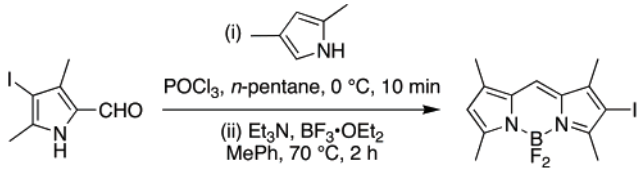
Fluorescence quantum yields of compounds **141**−**144** excited at the donor λ_{max} range from 0.02 to 0.75 (in chloroform). In compound **145**, the $S_1 \leftrightarrows S_0$ transition moments of the chromophores are mutually perpendicular in all conformations. Fast energy transfer, of the order of 0.45 ± 0.08 ps, was observed for this compound. For **141**−**144**, the donor and acceptor $S_1 \leftrightarrows S_0$ transition moments are mutually coaxial with the linker in all conformations. The transfer rate for this set of compounds was *even faster* than for



138



139



reaction 15 140 36 %

145, ~ 200 fs; in fact, this was too fast to be measured accurately.[179] Thus, it appears from this data that parallel and aligned transition moments are ideal for extremely fast energy transfer. The length of the linker in this series of compounds was also varied, but not enough derivatives were made to arrive at conclusions relating this parameter with energy-transfer rates.

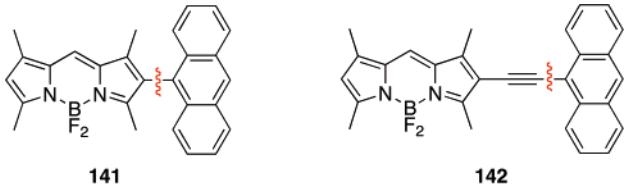
More recently, energy transfer cassettes like **145** have been prepared; these are very similar except that the *meso*-donor group is one or two pyrene units linked with alkynes. It was shown that the energy transfer efficiency is reduced when alkyne units are added. Of course, use of conjugated pyrenes as the donor increases the UV absorption at shorter wavelengths and the λ_{max} for that donor-based band; the latter effect decreases the apparent Stokes' shift observed.[180]

Energy transfer cassettes like **146**−**148**, in which two BODIPY chromophores are linked via an acetylenic linker, have been prepared.[160] As the size of the linker increases, energy transfer efficiency decreases from about 98% to ~35%. These were described as FRET cassettes, but there is a strong possibility that some of the energy transfer takes place through bonds.

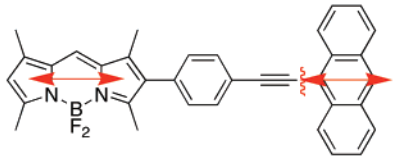
7. Substitution of Fluoride Atoms in the BF_2-Group

7.1. With Alkyl Groups

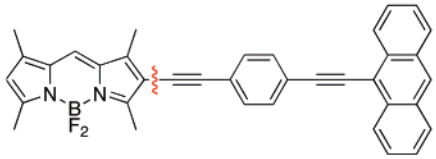
Some dialkyl-*B* BODIPY compounds have been prepared via reactions of the corresponding dipyrromethenes with bromodimethylborane, dibutylboron triflate, or 9-BBN triflate. Increased steric bulk at the boron atom along this series correlated with *decreased* fluorescence quantum yields.



141 142



143



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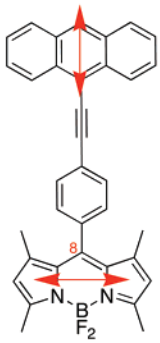
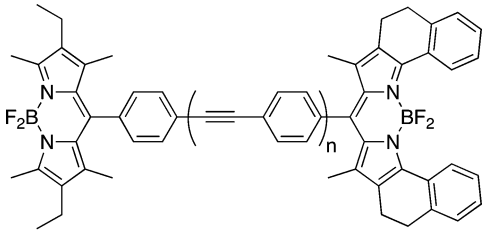


145

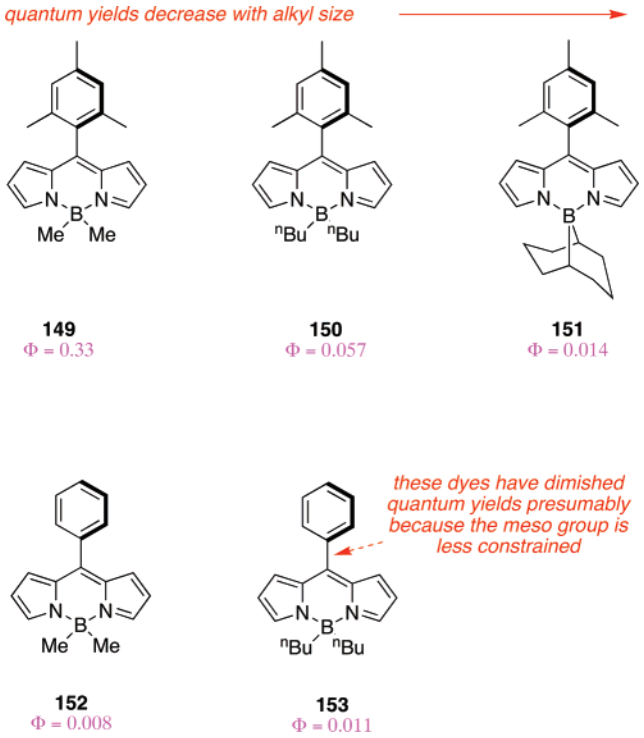


146 - 148
n = 1, 3, and 6 respectively

While the substituent at the *meso*-position has no effect on the UV absorption and emission spectra, the fluorescence quantum yields strongly depend on the nature of the aryl group. Introduction of steric constraints on the aryl ring increases the quantum yield (compare **149** and **152**, **150** and **153**)).[181]

7.2. With Aryl Groups

Aryl Grignards can displace fluoride from the boron difluoride entity of BODIPY dyes. In Scheme 8a, at 0 °C, even with excess Grignard reagent, only the monosubstituted products **154** and **155** were obtained, but the disubstituted product **156** was formed by adding the Grignard reagent at room temperature. Reaction of aryl lithium reagents was much faster; these gave only the disubstituted products **157**−**159**, even when just one equivalent of anion was added (Scheme 8b).



The new dyes **154**−**159** are highly fluorescent in solution. While the absorption maximum of the BF_2 parent dye is relatively insensitive to the solvent polarity, the *B*-Ar BODIPYs tend to undergo small red shifts in more polar solvents. The origin of this solvent dependence may be minimization of interactions of the *B*-aryl groups with more polar media. The fluorescence emission maxima of **154**−**159** are also red-shifted relative to the parent BF_2 structures.

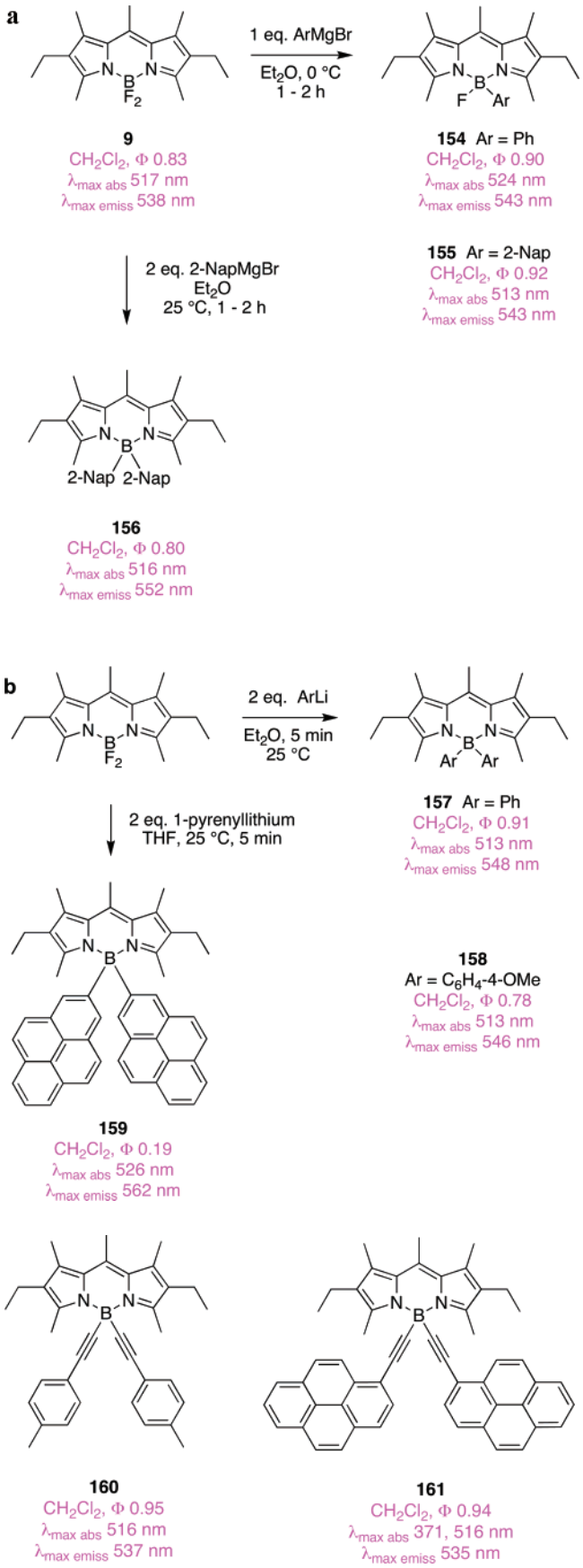
UV absorbance by the aromatic substituents means that these compounds can be regarded as energy transfer cassettes, and when the *B*-Ar groups have good extinction coefficients, then there may be some value in this aspect of their properties. The dipyrene system **159** absorbs in the range 230−317 nm corresponding to the $\pi \leftrightarrow \pi^*$ transition of the pyrene units, and emits exclusively (100% energy transfer) from the BODIPY part.[182] However, there is no immediate application of this effect.

7.3. With Alkyne Groups

Acetylide anions are also good nucleophiles for the displacement of fluoride from the borondifluoride entity of BODIPY dyes. The pyrromethene dialkynyl borane complexes **160** and **161**, for instance, were synthesized from 4-lithioethynyltoluene and 1-lithioethynylpyrene, respectively.[183−185]

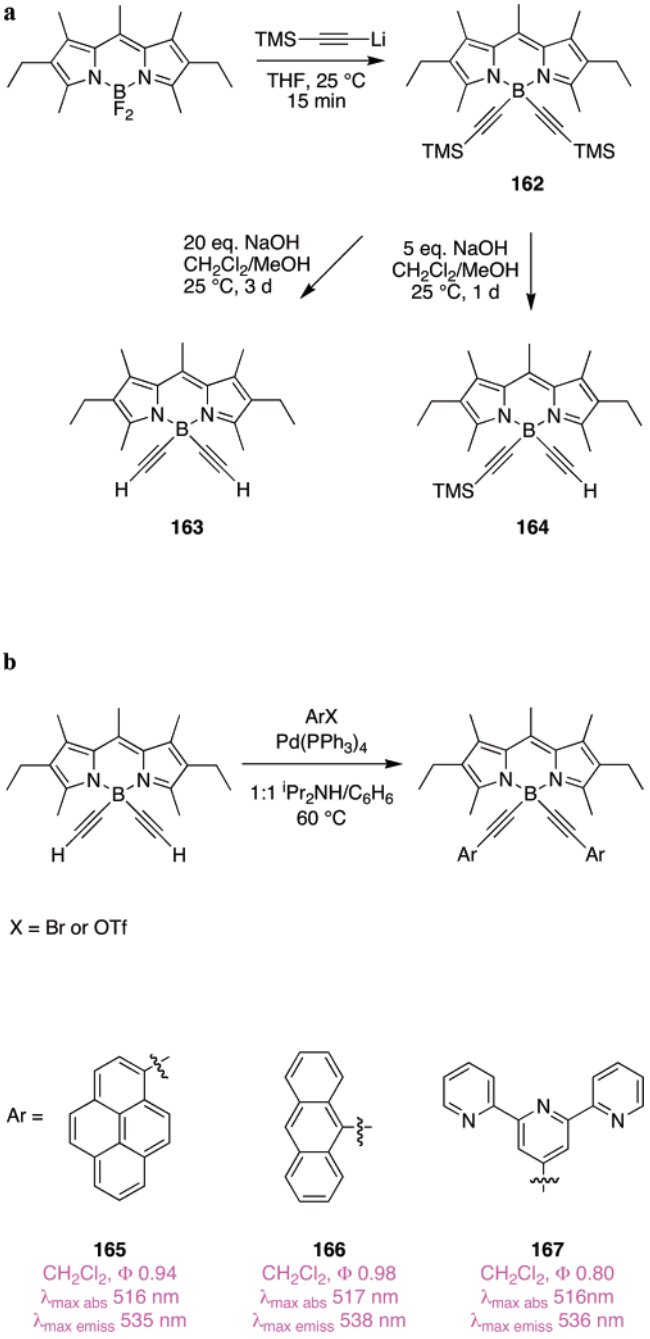
Adding groups to the boron atoms does not bring them into conjugation with the BODIPY core. Consistent with this, the absorption spectra of **160** and **161** have distinct BODIPY and ethynylaryl components. Upon excitation at 516 nm, both **160** and **161** emit strongly, with high fluorescence quantum yield, in the region 535−540 nm. For **161**, excitation at 371 nm (pyrene absorption band) did not lead to emission from the pyrene but instead to emission characteristic of the indacene core, indicating an efficient energy transfer from the pyrene to the indacene moiety.[183,184,186]

Scheme 8. Synthesis of *C*-BODIPYs Using (a) Aryl Grignard Reagents; and (b) Aryl Lithium Reagents



It is possible to add trimethylsilylacetylide to displace fluoride from BODIPYs, then desilylate under basic condi-

Scheme 9[a]

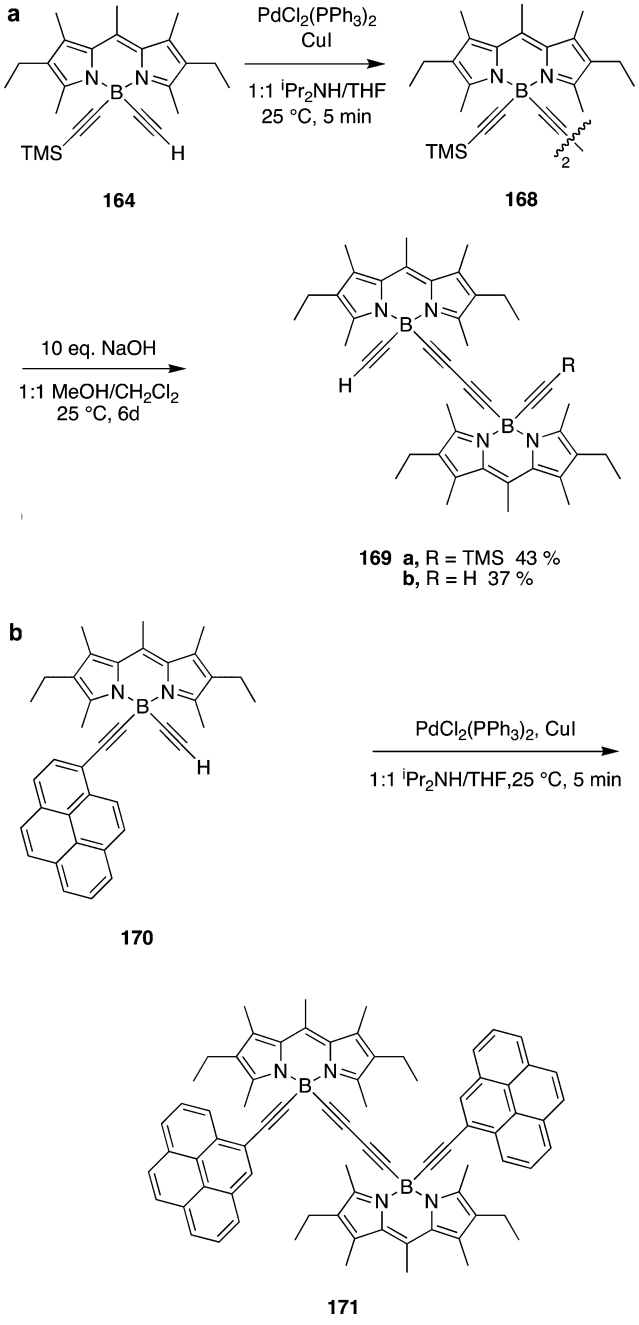


[a] (a) Two-step synthesis of bis(ethynyl)BODIPY **163**, and the monoprotected analogue **164**; and (b) some examples of compounds that have been prepared via Sonogashira coupling of **163**.

tions and Sonogashira couple with the terminal alkyne, for example, **163** (Scheme 9). Whereas use of excess sodium hydroxide in the desilylation reaction affords the bis(ethynyl)-BODIPY **163**, the monoprotected derivative **164** can be obtained using limited amounts of NaOH and shorter reaction times.[187,188] Access to the monoprotected derivative facilitates introduction of different substituents on the *B*-alkynes.[184]

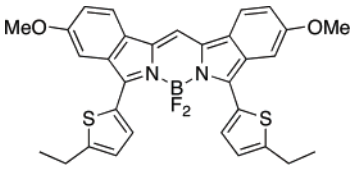
Compounds **165** and **166** can act as energy transfer cassettes, just like the *B*-aryl systems mentioned above. Irradiation of the donor (pyrene or anthracene) was observed to give only BODIPY emission, indicative of a near quantitative energy transfer.

Scheme 10. Synthesis of Homocoupled Products

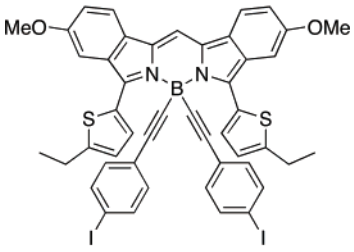


Terminal alkynes like **164** and **170** can be oxidatively dimerized (Pd(II) and CuI under aerobic conditions) to give butadiynes **168** and **171** (Scheme 10).[187] Deprotection of the product butadiyne **168** was very slow; a mixture of monodeprotected **169a** and bisdeprotected **169b** was isolated after 6 days.[187]

A very similar concept was explored by the same group but using diisoindolodithienylpyrromethene-dialkynyl borane dyes.[189] These dyes have quite long wavelength emissions (over 750 nm); the parent BF_2 dye **172** was known prior to this work.[190] Intermediate **173** was obtained by reaction of **172** with the appropriate alkynyl-Grignard reagent. Sonogashira coupling with various ethynyl-arene derivatives afforded the systems **174**−**178**. All the new dyes exhibit a UV absorption maximum at 708 nm with a molar absorptivity of ~80 000 M^{-1} cm^{-1}. Higher energy absorption bands

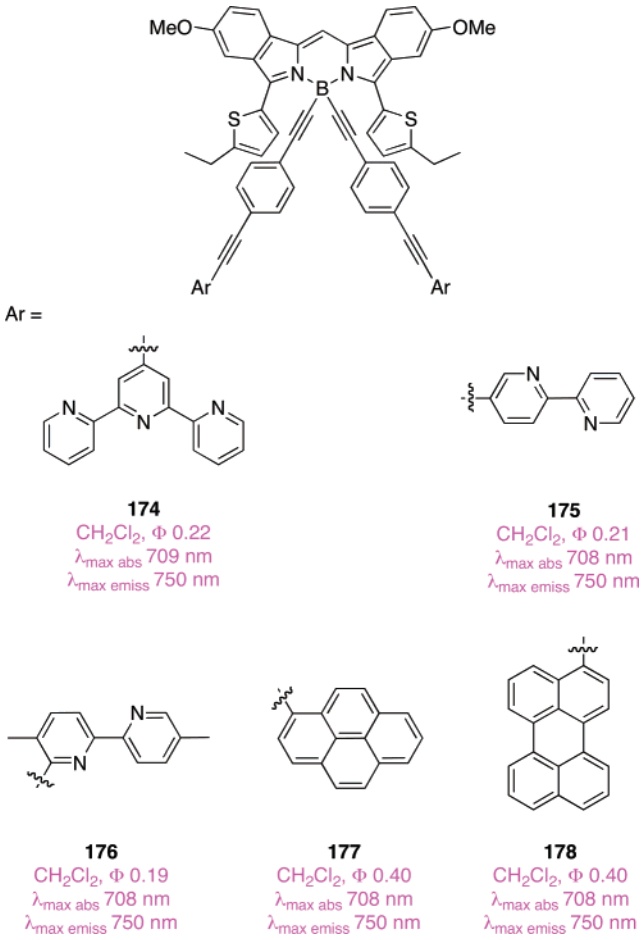


172
CH_2Cl_2, Φ 0.20
$\lambda_{max\ abs}$ 727 nm
$\lambda_{max\ emiss}$ 780 nm



173
CH_2Cl_2, Φ 0.45
$\lambda_{max\ abs}$ 709 nm
$\lambda_{max\ emiss}$ 750 nm

assigned to the pyrene, perylene, and bis- and tri-pyridine were also observed near 350 and 450 nm. Upon excitation at 708 nm, a broad emission band at 750 nm, with quantum yields between 0.19 and 0.45 was observed in all cases. Fast energy transfer to the central dipyrromethene core was observed upon irradiation of the pyrene and perylene units in **177** and **178**, giving large virtual Stokes'shifts. The efficiency of the energy transfer for compounds **177** and **178** was estimated to 58% and 38%, respectively. Formation of aggregates was observed when the dyes were dissolved at concentrations higher than 10^{-7} M.



174
CH_2Cl_2, Φ 0.22
$\lambda_{max\ abs}$ 709 nm
$\lambda_{max\ emiss}$ 750 nm

175
CH_2Cl_2, Φ 0.21
$\lambda_{max\ abs}$ 708 nm
$\lambda_{max\ emiss}$ 750 nm

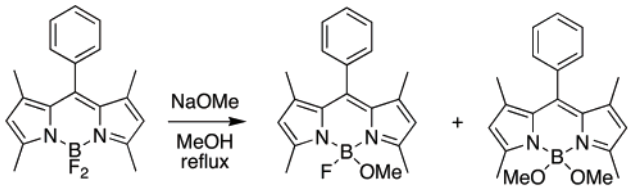
176
CH_2Cl_2, Φ 0.19
$\lambda_{max\ abs}$ 708 nm
$\lambda_{max\ emiss}$ 750 nm

177
CH_2Cl_2, Φ 0.40
$\lambda_{max\ abs}$ 708 nm
$\lambda_{max\ emiss}$ 750 nm

178
CH_2Cl_2, Φ 0.40
$\lambda_{max\ abs}$ 708 nm
$\lambda_{max\ emiss}$ 750 nm

7.4. With Alkoxide Groups

The first two *B*-methoxy BODIPYs prepared were **179**−**180**. These were made by reacting the corresponding BF_2 compound with sodium methoxide in methanol (reaction 16). The shape of the absorption and emission spectra were the same for the starting material **12** and the two products, suggesting the change in *B*-substituents had little effect on the electronic states of the boroindacene core. Interestingly, the monomethoxy and dimethoxy products were more water-soluble than the corresponding BF_2 compounds.[83]



12
MeOH, Φ 0.46
$\lambda_{max\ abs}$ 497 nm
$\lambda_{max\ emiss}$ 507 nm

179
MeOH, Φ 0.45
$\lambda_{max\ abs}$ 498 nm
$\lambda_{max\ emiss}$ 509 nm

180
MeOH, Φ 0.49
$\lambda_{max\ abs}$ 498 nm
$\lambda_{max\ emiss}$ 509 nm

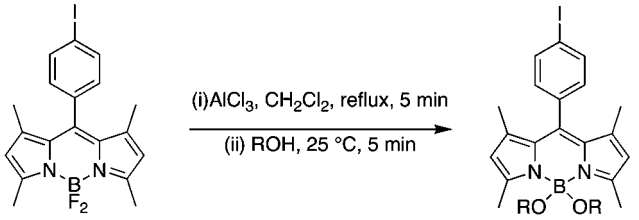
reaction 16

The only other report of *B*-OR BODIPYs systems **C** describes their syntheses via treatment of the corresponding BODIPY with various alcohols in the presence of aluminum trichloride (reaction 17).[96] This study was more expansive than the first insofar as a more diverse set of alcohols were studied. Thus, the alcohols used included simple alkoxy **181**−**183**, aryloxy **184**−**187**, and several diol-derived systems **188**−**191**. Across this series there were only minor changes in the absorbance and emission spectra. The *dialkoxy*-BODIPYs **181**−**183** appear to have higher fluorescence quantum yields than the *diaryloxy*-ones **184**−**187**, and the binaphthol- and catechol-derived systems **188** and **189** have extremely poor quantum yields.

8. Use of Metals Other than Boron

The BODIPY core features a boroindacene unit, so compounds where the boron has been substituted with other metals are, strictly speaking, beyond the scope of this review. However, there are a few dipyrromethene anion complexes of other metals that have highly fluorescent spectroscopic characteristics. These are covered here because they are clearly relevant as probes.

Free base dipyrrins react readily with a variety of metals salts to form the corresponding bis(dipyrrinato)−metal(II) or tris(dipyrrinato)−metal(III) complexes, but their fluorescence properties have rarely been studied, and they have generally been regarded as nonfluorescent.[191−214] The first report (2003) of fluorescent properties was for zinc complexes of the boraindacene fragment.[215,216] The complexes were prepared either from (i) treatment of a purified dipyrrin with zinc acetate, or (ii) a two-step, one-flask approach involving oxidation of a dipyrromethane and complexation of the resulting crude dipyrrin with a $Zn(OAc)_2$ in presence of triethylamine. Complexes **192** and **193** are weakly fluorescent, but **194** is a stronger emitter (it has a multi-nanosecond excited-state lifetime); thus, free rotation of the *meso*-phenyl is again implicated as a major pathway for nonradiative relaxation to the ground state for **192** and **193**.



reaction 17

c

R =

181
$CHCl_3$, Φ 0.55
$\lambda_{max\ abs}$ 505 nm
$\lambda_{max\ emiss}$ 519 nm

182
$CHCl_3$, Φ 0.76
$\lambda_{max\ abs}$ 504 nm
$\lambda_{max\ emiss}$ 518 nm

183
$CHCl_3$, Φ 0.65
$\lambda_{max\ abs}$ 506 nm
$\lambda_{max\ emiss}$ 522 nm

184
$CHCl_3$, Φ 0.06
$\lambda_{max\ abs}$ 506 nm
$\lambda_{max\ emiss}$ 517 nm

185
$CHCl_3$, Φ 0.004
$\lambda_{max\ abs}$ 507 nm
$\lambda_{max\ emiss}$ 518 nm

186
$CHCl_3$, Φ 0.065
$\lambda_{max\ abs}$ 506 nm
$\lambda_{max\ emiss}$ 520 nm

187
$CHCl_3$, Φ 0.54
$\lambda_{max\ abs}$ 504 nm
$\lambda_{max\ emiss}$ 516 nm

$(RO)_2$ =

188
$CHCl_3$, Φ 0.002
$\lambda_{max\ abs}$ 506 nm
$\lambda_{max\ emiss}$ 516 nm

189
$CHCl_3$, Φ 0
$\lambda_{max\ abs}$ 510 nm
$\lambda_{max\ emiss}$ na

190
$CHCl_3$, Φ 0.14
$\lambda_{max\ abs}$ 507 nm
$\lambda_{max\ emiss}$ 521 nm

191
$CHCl_3$, Φ 0.54
$\lambda_{max\ abs}$ 504 nm
$\lambda_{max\ emiss}$ 522 nm

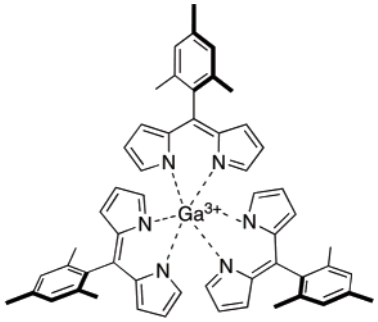
quantum yield increases as the rotation of the meso group is hindered

192
PhMe; Φ 0.006

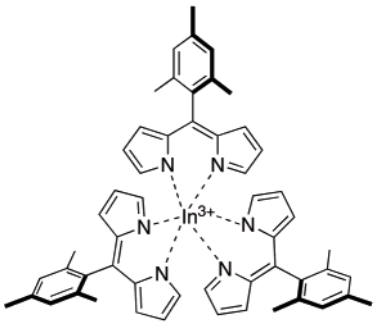
193
PhMe; Φ 0.006

194
PhMe; Φ 0.36

Porphyrin or phthalocyanine complexes of group 13 metals can be fluorescent; this inspired syntheses of two new

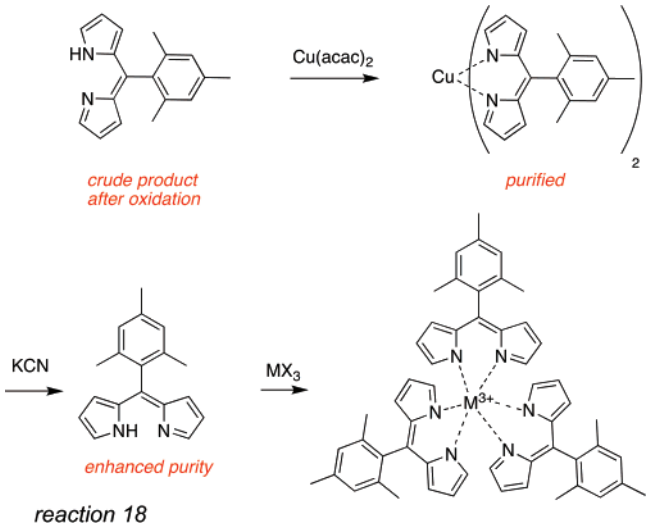


195
hexanes, Φ 0.024
$\lambda_{max\ abs}$ 448 nm
$\lambda_{max\ emiss}$ 528 nm



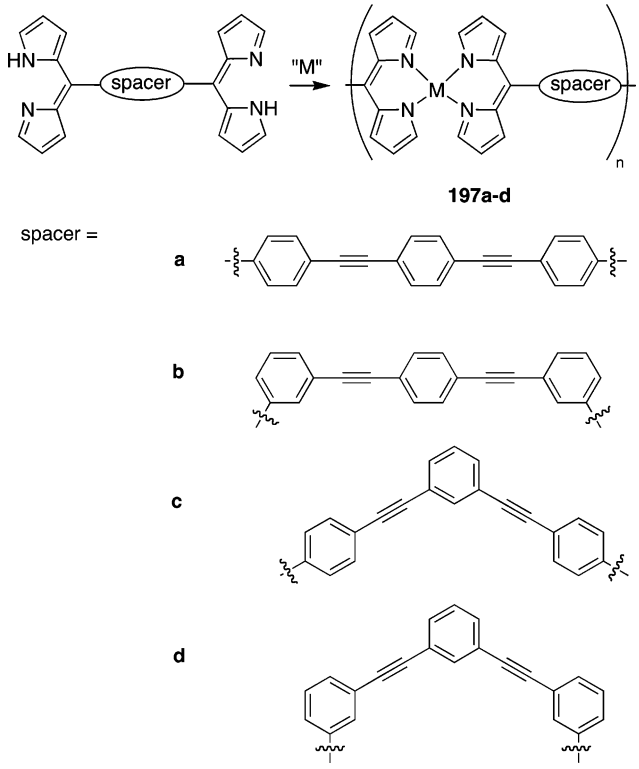
196
hexanes, Φ 0.074
$\lambda_{max\ abs}$ 444 nm
$\lambda_{max\ emiss}$ 522 nm

dipyrromethenes **195** and **196** from gallium(III) and indium(III), respectively (reaction 18). In hexanes, the new compounds fluoresce green light, with quantum yields of 0.024 and 0.074 for the gallium(III) and indium(III) complexes, respectively.[217]



reaction 18

"Nanoarchitectures" **197a**−**d** have been fabricated from Zn, Co, Ni, and Cu with dipyrromethene-based ligands, but are only strongly fluorescent with zinc.[218] The fluorescence emission maxima of the zinc complexes in THF and in the solid state are around 510−515 nm and 532−543 nm, respectively. In acetonitrile, no emission was observed

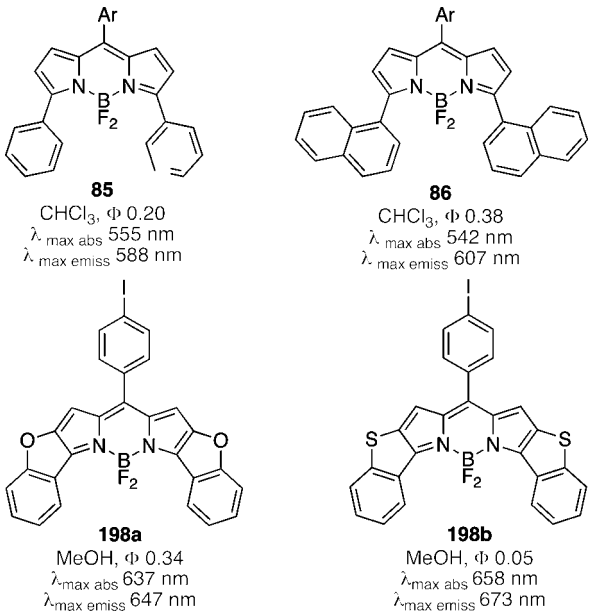


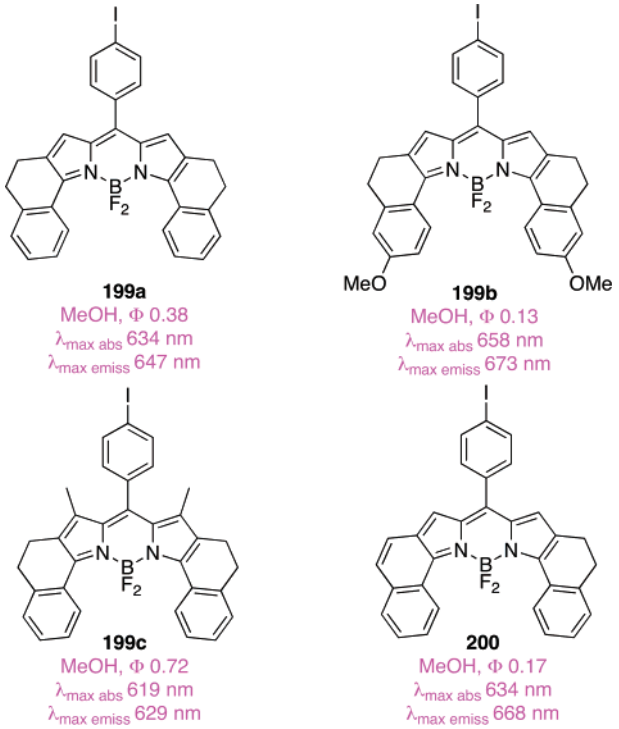
possibly because of aggregation of the particles. Fluorescence emission could be observed at submicron scale for particles derived from Zn-bridged dipyrromethene oligomers; this is significant because quantum dots formed from clusters of inorganic compounds are considerably larger.

9. BODIPY Analogues with Extended Aromatic Conjugation

9.1. Restricted Systems

As mentioned previously, aryl-substituents on the BODIPY chromophore, for example, in **85** and **86**, red-shift the absorption and emission spectra, but decrease the fluorescence intensity, presumably because of the free rotation of the aryl groups.[132,133] Consequently, more rigid systems like **198** and **199** were prepared and studied.[219] These absorb and fluoresce more intensely at longer wavelengths, and their quantum

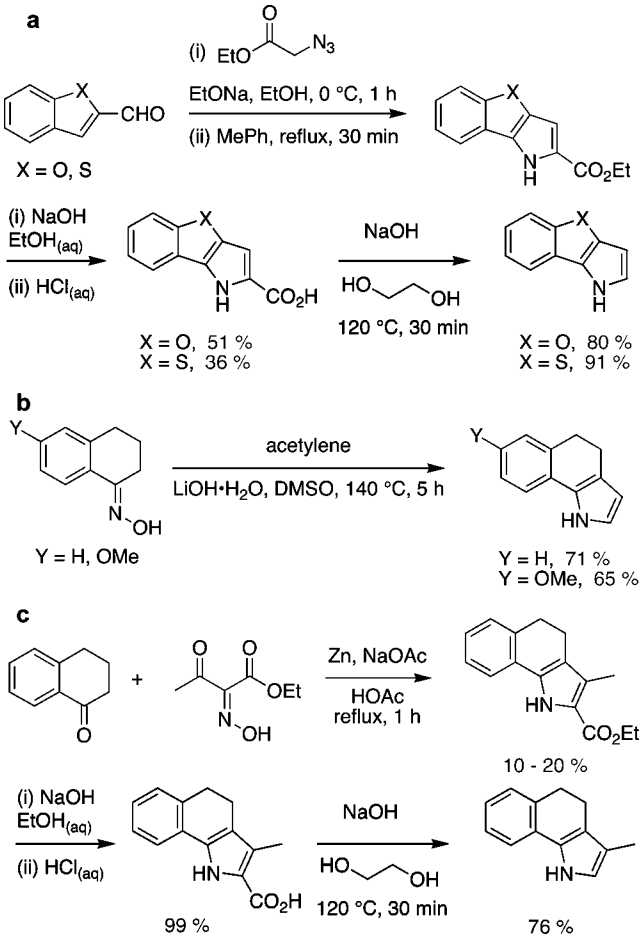




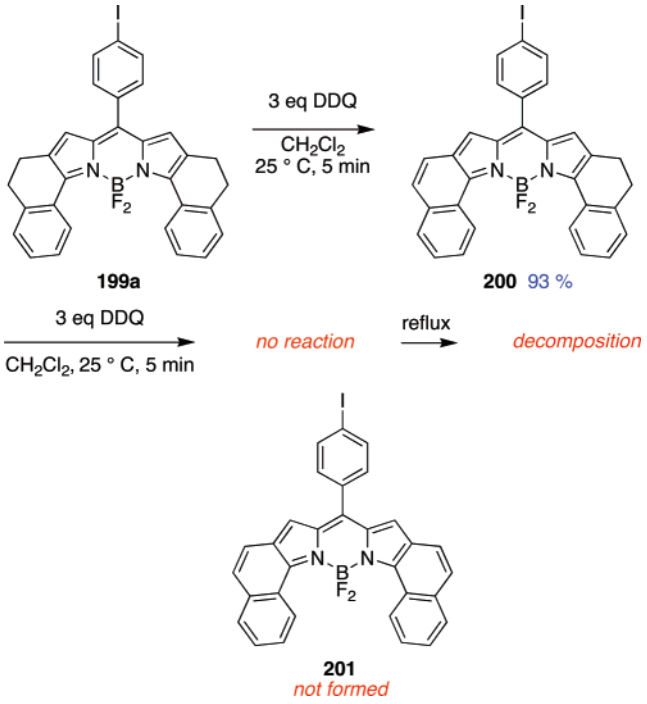
yields are generally higher, with the exception of **198b**.

The new derivatives **198** and **199** were obtained by condensation of 4-iodobenzoyl chloride with the corresponding pyrrole-based starting materials, which were prepared in several steps as described in Scheme 11. Most of the effort here

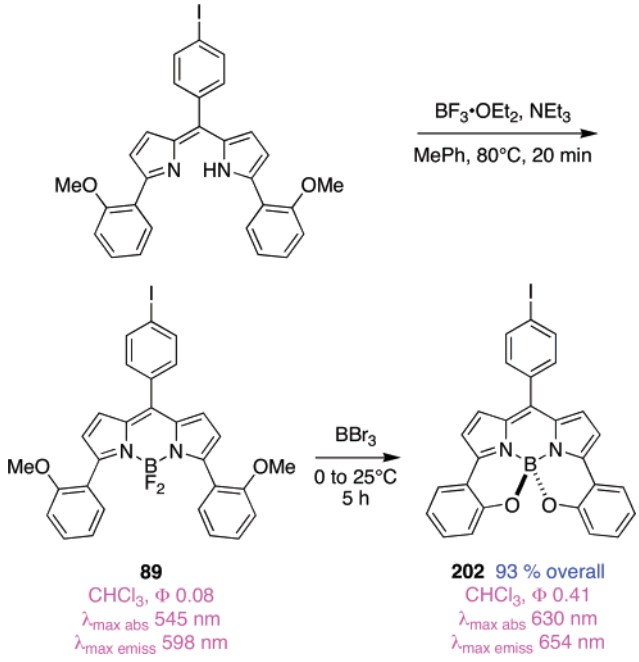
Scheme 11. Syntheses of the Pyrrole-Based Starting Materials



Scheme 12. Synthesis of More Conjugated BODIPY Derivatives



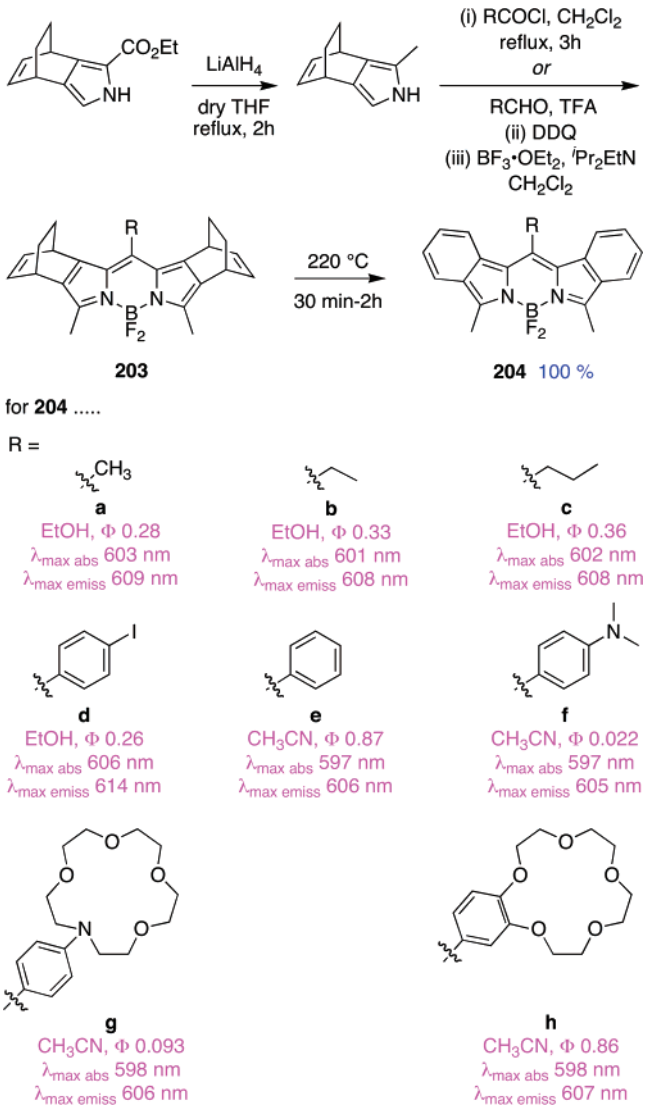
Scheme 13. Synthesis of a New NIR BODIPY Dye



is in the preparation of the pyrrole-based starting materials. Part a of Scheme 11 shows a route that featured intramolecular C−H activation by a nitrene, part b involves a Trofimov reaction,[137] and part c shows a classical condensation route.[220]

Oxidation of **199a** was attempted, but only the half-oxidized product **200** could be obtained; further treatment with excess DDQ at room temperature for overnight gave no reaction (Scheme 12). Semiempirical calculations showed that the activation energy required to form **201**was excessive compared with the half-oxidized form **200** due to steric reasons. The physical properties of the mono-oxidized product were somewhat surprising. First, the maximum absorbance was not shifted to the red relative to **199a**, only the fluorescence emission was shifted to the red by 21 nm. Second,

Scheme 14. Extended Aromatic Dyes from Retro-Diels Alder Reactions



although the conjugation of the system was extended, the extinction coefficient was 3 times smaller than the reduced form of the dye **199a** (41 000 vs 126 250, respectively); the quantum yield was also less than half that of **199a**.

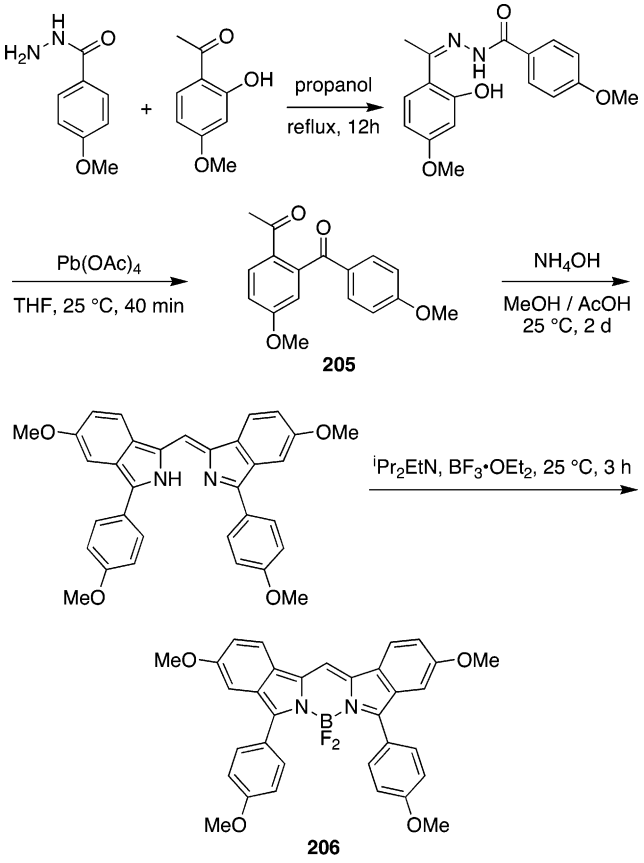
2′-Methoxy groups on α-aryl groups provide a special opportunity for syntheses of constrained BODIPY dyes. Thus, **202**, wherein rotation around a C−Ar bond was prevented by B−O bond formation, was conveniently obtained by demethylation and intramolecular cyclization of **89** (Scheme 13).[221] Dye **202** has a red-shifted, sharper fluorescence emission than the BF_2 parent dye and its quantum yield is 5.5−6.0 times larger.

9.2. Extended Aromatic Systems

9.2.1. Di(iso)indomethene Dyes

Aromatic ring-fused BODIPY derivatives, boron-di(iso)-indomethene dyes **204**, have been prepared via retro Diels−Alder reactions[222,223] featuring a norbornane-derived pyrrole (Scheme 14).[224] The spectroscopic data for the di(iso)-indomethene derivatives **204** are shown below. The nature of the substituents at the *meso* position has no influence on the absorption and emission properties of the new dyes. The new di(iso)indomethene dyes display a red-shifted absorption compared to the bicyclic-BODIPY precursors **203**. The more

Scheme 15. Synthesis of Di(iso)indomethene Dyes from 2-Acylacetophenone Derivatives

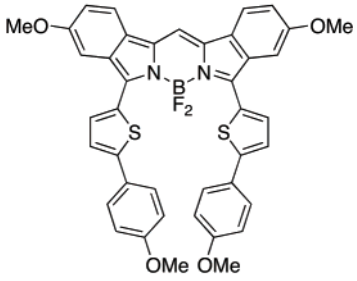


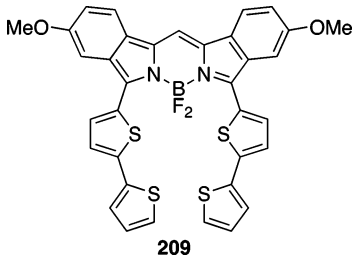
expanded, conjugated, and rigid di(iso)indomethene BODIPY dyes **204** are also characterized by a significantly higher extinction coefficient relative to the bicyclic-BODIPY dyes **203**. Because of their rigid-fused system, which prevents a nonradiative deactivation of the excited state, bicyclic-BODIPY **203** and di(iso)indomethene BODIPY dyes **204** have small Stokes' shifts. The Stokes' shifts are, however, generally larger for bicyclic-BODIPY dyes **203** than for the di(iso)indomethene derivatives **204**. The absorption and emission spectra of bicyclic-BODIPY **203** and di(iso)-indomethene BODIPY dyes **204** are independent of the solvent polarity. The fluorescence quantum yield of the bicyclic-BODIPY dyes **203** is much higher than the one for the corresponding di(iso)indomethene BODIPY dyes **204**.

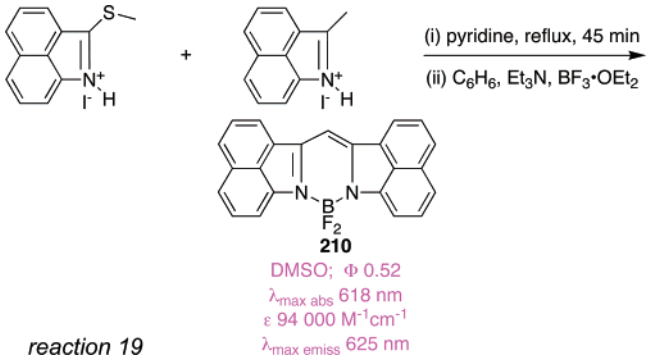
Other indomethene dyes including **172**[190] and **206**−**209**[190,225] have been prepared via a different route. Substituted 2-acylacetophenones **205**, obtained from 2-hydroxyacetophenones and hydrazines,[226] were condensed with ammonia to give the dibenzopyrromethene. These were treated with boron trifluoride to give the 3,4:3′,4′-dibenzopyrromethene boron difluoride core (Scheme 15). The new dyes exhibit very long wavelength absorption and emission bands, and are relatively stable to photobleaching.

9.2.2. Dyes Based On Benz[c,d]indole

Benz[*c,d*]indole and its derivatives have been used to form deeply colored dyes. Compound **210** (reaction 19), for instance, was obtained by condensation of 2-methylthiobenz-[*c,d*]indolium iodide and 2-methylbenz[*c,d*]indolium iodide, followed by complexation with boron trifluoride etherate. Its fixed planar structure exhibits a sharp absorption band at 618 nm, and fluoresces at 625 nm.[227,228]







reaction 19

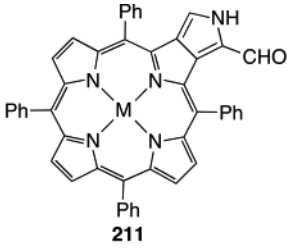
9.2.3. Porphyrin-Fused Systems

Systems **212**−**214** have edge-shared porphyrin and BODIPY parts. They were synthesized from the formylated pyrroloporphyrin **211** via acid-catalyzed condensation with 2,4-dimethylpyrrole. Their UV spectra contain four quite intense bands in the 300−750 nm region, and do not resemble the sum of the spectra of tetraphenylporphyrin (TPP) and of BODIPY. Systems **212** and **214** emit, respectively, at 693 and 714 nm upon excitation over all the 240−700 nm region with low quantum yields, and **213** did not show any significant fluorescence.[12]

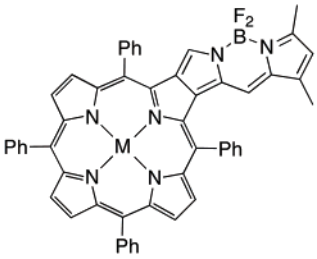
10. Aza-BODIPY Dyes

10.1. Tetraaryl Systems

Synthesis of the azadipyrromethene chromophore **215** (without boron, but with aryl substituents) was first described in the 1940s.[229−231] This, as described below, is the framework for a very interesting set of dyes called the aza-BODIPYs. Two general methods to prepare these compounds were developed. In one, 2,4-diarylpyrroles were converted into their 5-nitroso derivatives, then condensed with a second



211



M = none
212
CH_2Cl_2, Φ 0.04
$\lambda_{max\ abs}$ 388, 413, 531, 640 nm
$\lambda_{max\ emiss}$ 693 nm

M = Cu
213
CH_2Cl_2, Φ 0
$\lambda_{max\ abs}$ 390, 412, 531, 675 nm
$\lambda_{max\ emiss}$ 693 nm

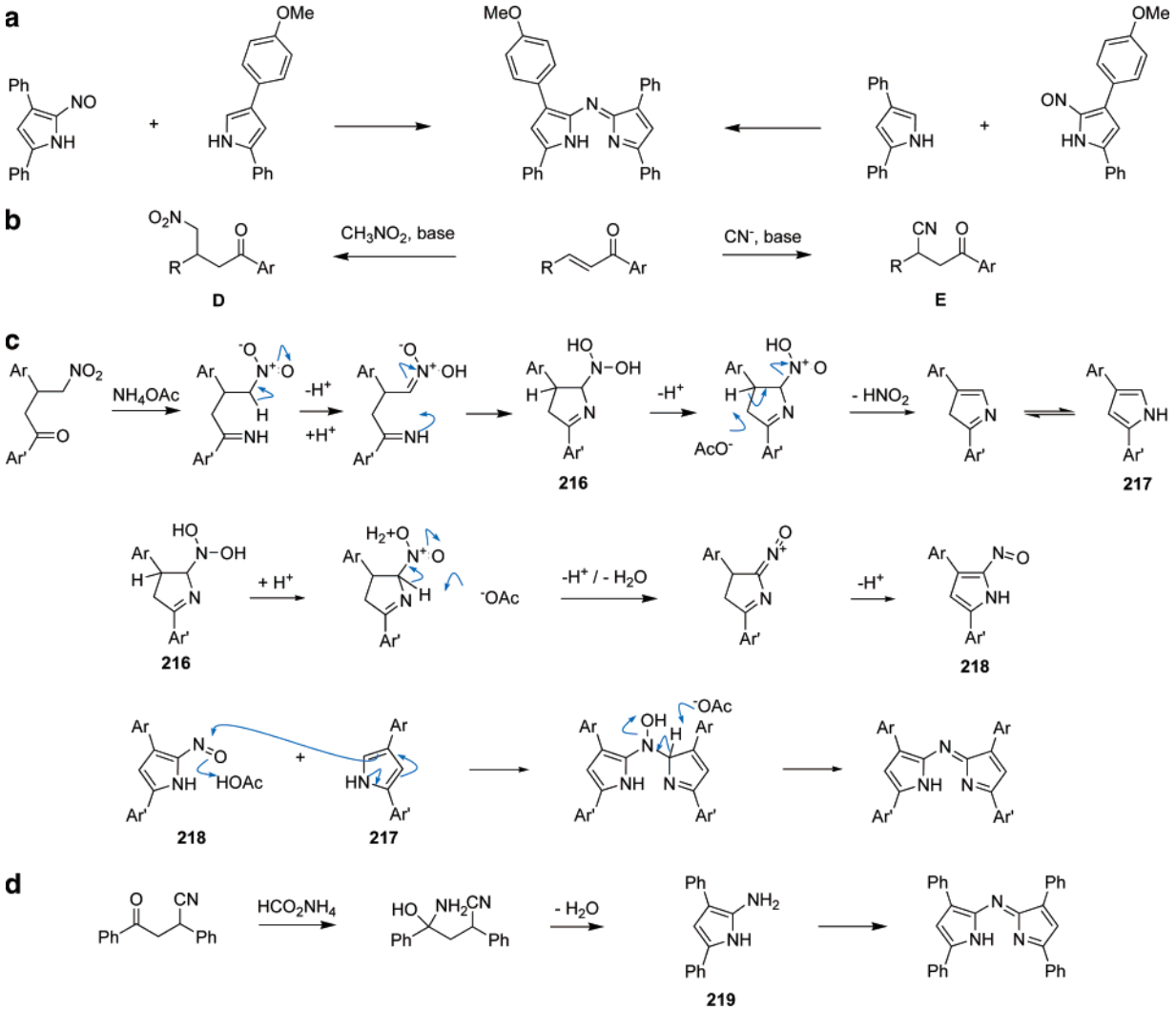
M = Zn
214
CH_2Cl_2, Φ 0.053
$\lambda_{max\ abs}$ 392, 415, 539, 676 nm
$\lambda_{max\ emiss}$ 714 nm

molecule of pyrrole (Scheme 16a). Scheme 16b shows the second method, in which Michael addition products **D** from chalcones and nitromethane,[229] or cyanide **E**,[230,231] was reacted with formamide (or other ammonia-sources) to give the core **215**. In the first instance, these reactions were performed neat, that is, without solvent. Soon after, it was realized that use of alcohol solvents usually causes the azadipyrromethenes to precipitate from the reaction mixture, thus, enhancing the ease of isolation and yields. The postulated mechanism for formation of the azadipyrromethene core from the nitromethane adducts is shown in Scheme 16c. It proceeds via pyrrole **217**, which is nitrosylated *in situ* to give **218** that then condenses with another molecule of the pyrrole.

It is also possible to prepare the azadipyrromethene chromophore from cyanide Michael addition products **E** as described in Scheme 16d. Ammonium formate serves as a source of ammonia in the pyrrole-forming condensation step. The 2-amino pyrrole intermediates **219** readily convert to the azadipyrromethene core on heating in the air. Switching from acetate to formate in the dry melt process for the synthesis of **215** nearly doubled the yield to give approximately 50%.[231] Formation of this chromophore seems to be most facile when there are four phenyl substituents, but it is possible to obtain the diphenyl products **222** (below) by slight modification of the reaction conditions.[231]

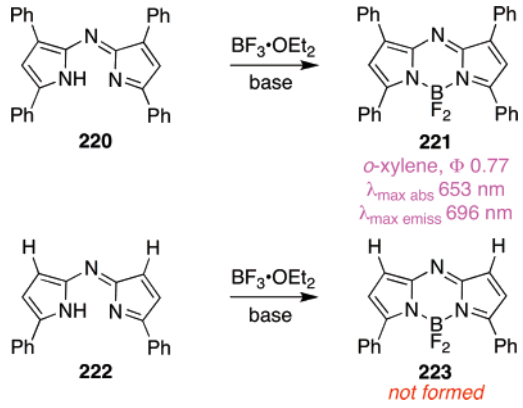
The first reactions of azadipyrromethenes with boron electrophiles were reported in the early 1990's (Scheme 17).[131,232]

Scheme 16. Formation of Azapyrromethene[a]



[a] Formation from (a) nitroso pyrrole and (b) nitrobutyrophenones **D** and keto-nitrile **E**; (c) postulated mechanism for the formation of azapyrromethene from nitrobutyrophenones **D** and (d) from keto-nitrile **E**.

Scheme 17. First Syntheses of Aza-BODIPY Dyes



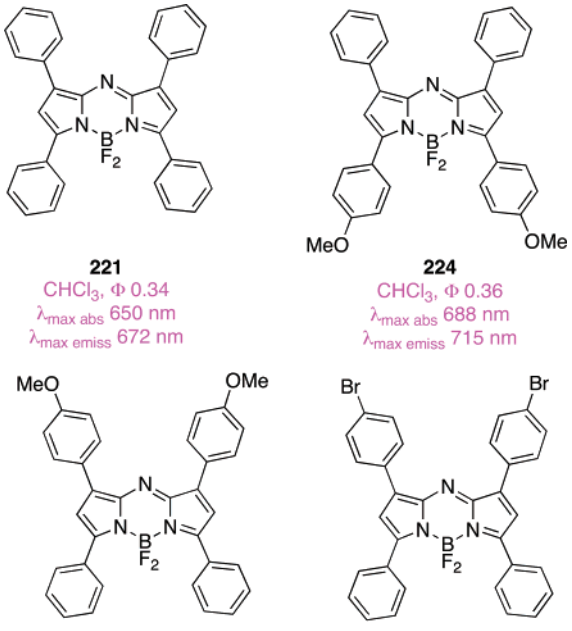
The aza-BODIPY **221** was made from the 3,5-tetraphenyl azapyrromethene **220** in that way. It was reported that the less substituted aza-BODIPY **223** could not be obtained after treatment of the corresponding aza-dipyrromethene **222** with boron trifluoride;[232] however, this might have been an artifact of the particular conditions screened.

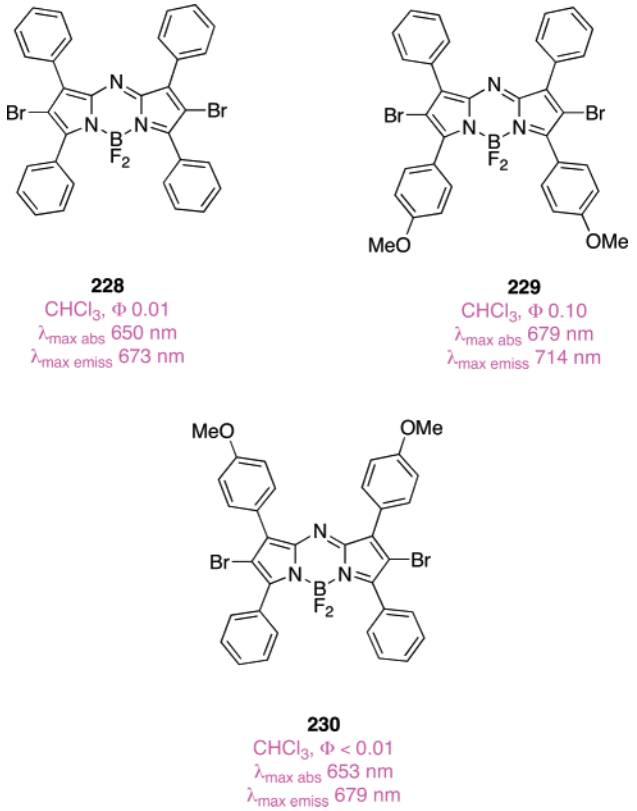
Beginning with research largely from O'Shea's group from 2002 onward, there has been a resurgence of interest in aza-BODIPY dyes, and this has resulted in syntheses of dyes like **224**−**227**.[233−235] In this latest era of the field, the azadipyrromethene skeletons are still prepared from nitromethane adducts to the corresponding chalcone according to the route described in Scheme 16c, but butanol, rather than methanol or solvent-free conditions, was the preferred medium.[234] The syntheses were completed by adding BF_3•OEt_2 at room temperature; the intermediate azadipyrromethanes precipitated out in high purities and were not purified beyond washing with ethanol.[233,234]

UV absorption maxima of the tetraarylazadipyrromethene−BF_2 chelates strongly depend on the Ar-substituents. *para*-Electron donating groups on the 5-Ar substituents give increased extinction coefficients and significant red shifts in the λ_{maxabs} (149 nm for dimethylamino vs H, cf. **227** vs **221**).[235] *para*-Substitution with an electron donating group on the 3-aryl ring has less impact, but still gives a bathochromic shift (cf. **224** vs **225**).[234]

The UV absorption maxima of the aza-BODIPY dyes are relatively insensitive to solvent polarity; only small blue shifts tend to be observed (6−9 nm) when switching solvents from toluene to ethanol. Their absorptions are sharp, with a full width at half-maximum height (fwhm) varying from 51 to 67 nm in aqueous solution with an emulsifier called Cremophor EL, and 47−57 nm in chloroform indicating that the dyes do not aggregate under those conditions. The extinction coefficients range from 75 000 to 85 000 M^{-1} cm^{-1}, which is much greater than substituted porphyrins (3000−5000 M^{-1} cm^{-1}) for instance. This strong absorbance is one of the factors that facilitate efficient singlet-oxygen generation; hence, these molecules are potentially useful photosensitizers for photodynamic therapy.[236−239]

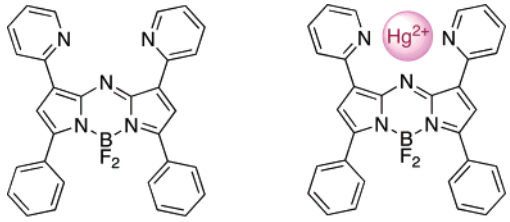
Fluorescence emission spectra of the aza-BODIPY dyes reported to date are also relatively insensitive to the solvent polarity. Compounds **221** and **224**−**226** have high fluorescence quantum yields. In the case of **226,** there is a bromine atom attached to the phenyl substituent, but no significant decrease in the quantum yield was observed.[234] On the other hand, introduction of bromine directly into the core of the dye, for example, compounds **228**−**230** results in a





significant decrease of the fluorescence quantum yields, indicating a larger heavy-atom effect and an increased singlet oxygen production.[234] A quantum yield was not reported for **227**, but the compound became much more fluorescent under acidic conditions due to variation in the internal charge transfer.[235] Upon addition of acid, the absorption band at 799 nm disappears, and a new band at 738 nm appears indicating the monoprotonated form. The later disappears with addition of more acid, and a new band characteristic of the bis-protonated species appears at 643 nm.

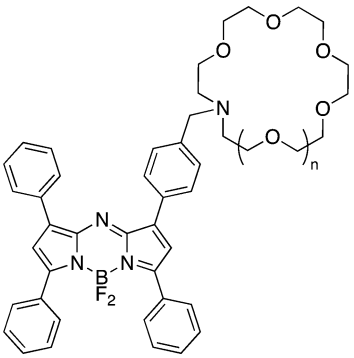
Aza-BODIPY dyes mostly have been discussed in the context of agents for photodynamic therapy, but chemosensors have also been made from these compounds. Compound **231** is highly selective for mercuric ions that become chelated between the 2′-pyridyl groups.[240] Mercuric ion complexation red-shifts both the UV-absorption and fluorescence emission maxima. The dissociation constant was determined to be 5.4 $\times$ 10^{-6} M, with a 1:1 binding stoichiometry.



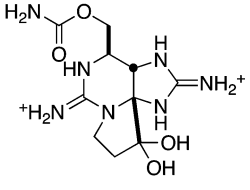
231
CH_3CN; Φ 0.19
$\lambda_{max\ abs}$ 655 nm
$\lambda_{max\ emiss}$ 682 nm

CH_3CN; Φ 0.17
$\lambda_{max\ abs}$ 696 nm
$\lambda_{max\ emiss}$ 719 nm

Compounds **232** and **233** are photoinduced electron-transfer crown ether chemosensors featuring aza-BODIPY chromophore;[241] they are used as visible sensors for the paralytic shellfish toxin Saxitoxin. Saxitoxin contains guanidine groups, and it is these functional groups that interact with the crown ether part of these molecules. In the absence of Saxitoxin, PET from the crown ether to the fluorophore quenches the fluorescence. Upon complexation of the toxin, PET can no longer happen and fluorescence is turned on. At 1:1 toxin/crown stoichiometry, the fluorescence enhancement was over 100% for compound **232**. The average binding constant for **232** to Saxitoxin, 6.2 $\times$ 10^5 M^{-1}, was among the highest observed for any chemosensor of that toxin. Compound **233**, which has a larger crown ether, bound the toxin less strongly (1.4 $\times$ 10^4 M^{-1}) and gave insignificant fluorescence enhancement. The putative PET mechanism in these systems involves π-stacking of one of the Saxitoxin's guanidiniums to the fluorophore.

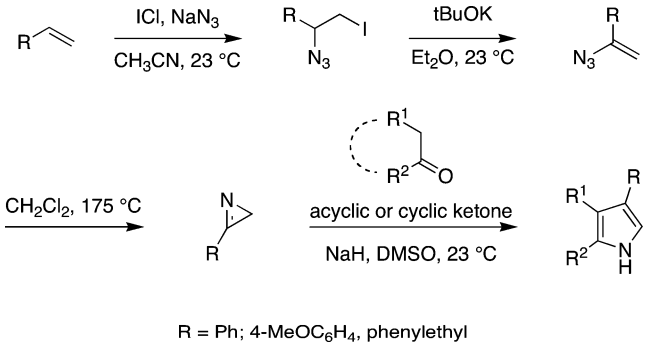


232 n = 1
233 n = 4



Saxitoxin

Scheme 18. Synthesis of Cyclized/Restricted 2,4-Diarylpyrroles



R = Ph; 4-$MeOC_6H_4$, phenylethyl

10.2. Extended Aza-BODIPY Systems

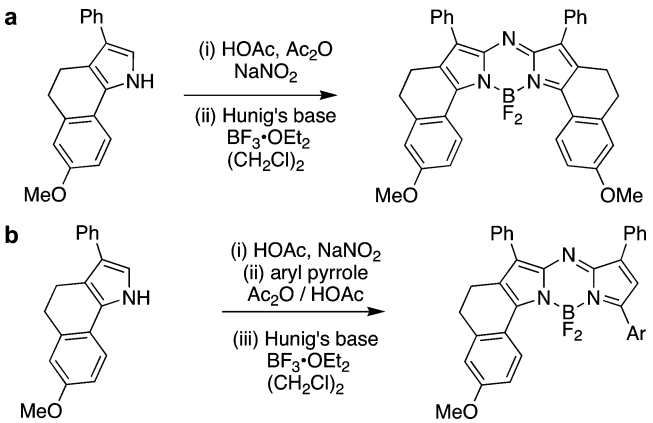
Strongly electron-donating groups, rigidifying structural modifications, and embellishments to extend the conjugation of the BODIPY dyes tend to red-shift their fluorescence emissions. Predictably then, similar modifications can be used to push the emission spectra of aza-BODIPY systems into the near-IR.

The "extended" aza-BODIPY systems **234**−**246** were synthesized from 2,4-diarylpyrroles. These starting materials were obtained in good overall yield over four steps from an alkene via (i) addition of iodo azide, (ii) dehydro-halogenation, (iii) pyrrolysis (azirine formation), and (iv) carbanion-induced pyrrole formation as shown in Scheme 18.[242,243]

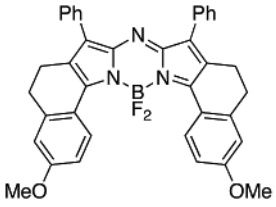
The conformationally restricted aza-BODIPY dyes were then prepared as shown in Scheme 19 via condensation of the pyrrole generated in Scheme 18 with a nitrosopyrrole gen erated *in situ*, followed by complexation with boron trifluoride. Attempts to condense 2,4-dimethylpyrrole with a nitrosated restricted 2,4-diarylpyrrole failed to give any product, suggesting that the 2-aryl substituent in the pyrrole is essential for the formation of these restricted aza-BODIPY dyes.

All the conformationally restricted systems **234**−**246** absorb over 650 nm. Dyes **234**−**236** with both sides incorporated in carbocyclic rings have narrow, intense (high ϵ) absorption bands at long wavelengths. In comparison to the "non-constrained" tetraaryl-azaBODIPY **224**, there is a bathochromic shift of up to 52 nm and a concomitant halving of the fwhm (27.1 nm for **236** vs 52.0 nm for **224**). The novel dyes were reported to possess excellent chemical and

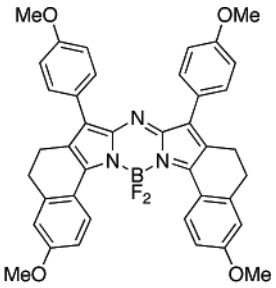
Scheme 19. Synthesis of (a) Symmetrical and (b) Asymmetrical Conformationally Restricted AzaBODIPY Dyes



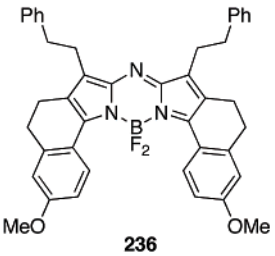
photostability. Furthermore, the fluorescence is insensitive to solvent polarity.[242,243]



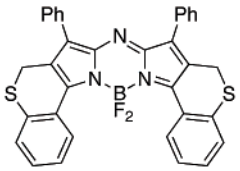
234
$CHCl_3$, Φ 0.28
$\lambda_{max\ abs}$ 740 nm
ε 159000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 752 nm



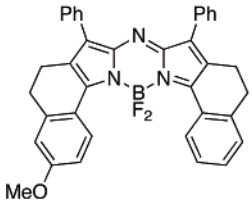
235
$CHCl_3$, Φ 0.29
$\lambda_{max\ abs}$ 736 nm
ε 157000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 748 nm



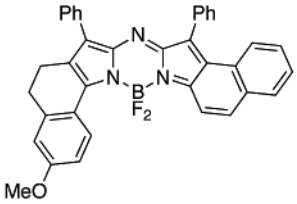
236
$CHCl_3$, Φ 0.31
$\lambda_{max\ abs}$ 721 nm
ε 162000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 732 nm



237
$CHCl_3$, Φ 0.11
$\lambda_{max\ abs}$ 706 nm
ε 115000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 730 nm

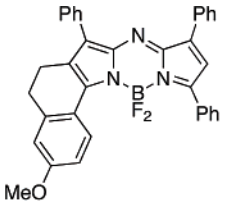


238
$CHCl_3$, Φ 0.32
$\lambda_{max\ abs}$ 723 nm
ε 157000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 734 nm

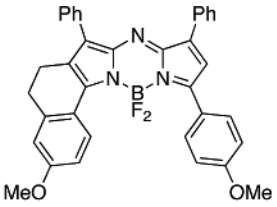


239
$CHCl_3$, Φ 0.11
$\lambda_{max\ abs}$ 715 nm
ε 141000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 730 nm

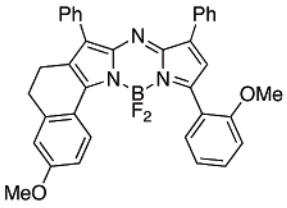
There are also several details regarding the spectral properties of the dyes in this series. Substitution at the 3-position of the core does not affect the ϵ-value of the dyes (compare **234**−**236**). Introduction of electron-donating groups results in a small blue shift and a slightly higher fluorescence quantum yield (**234** vs **235**). Shorter $\lambda_{abs,}$ lower ϵ, broader absorption band, and lower fluorescence quantum yield were associated with the sulfur-containing dye **237**. The dehydrogenated carbocyclic restricted ring in system **239** decreases its quantum yield relative to **234**. Aza-BODIPYs with only one side restricted have much lower extinction coefficients (**240**−**246** vs **234**). The quantum yields of nonsymmetric aza-BODIPY dyes are highly dependent on the substituents on the aromatic ring. Electron donating *para*-substituents give higher quantum yields (**240** and **241**), with shorter λ_{abs}, indicating that the phenyl rings are twisted. *ortho*-Electron donating groups (e.g., in **242**) result in short λ_{abs}, low ϵ, and broad absorption bands, indicating that the phenyl rings in **242** are twisted. Unexpectedly shorter λ_{abs}, low ϵ, broader absorption bands and lower quantum yields were observed when two methoxy groups were present (**243** and **244**). The sharp and intense absorption, high quantum yield obtained in the special case of **245** wherein a 2-methoxy-1-naphthyl substituent is present indicates that the naphthyl ring is distorted so that electron transfer is suppressed.



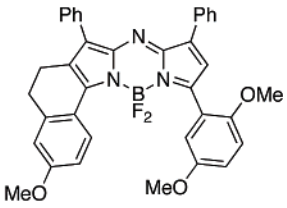
240
$CHCl_3$, Φ 0.44
$\lambda_{max\ abs}$ 688 nm
ε 108000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 710 nm



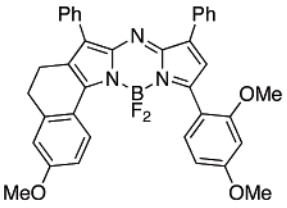
241
$CHCl_3$, Φ 0.38
$\lambda_{max\ abs}$ 708 nm
ε 96200 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 732 nm



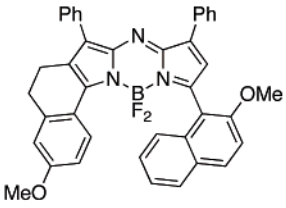
242
$CHCl_3$, Φ 0.38
$\lambda_{max\ abs}$ 678 nm
ε 83900 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 713 nm



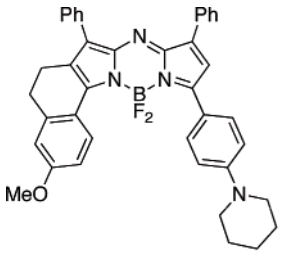
243
$CHCl_3$, Φ 0.24
$\lambda_{max\ abs}$ 681 nm
ε 66500 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 728 nm



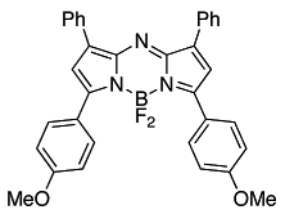
244
$CHCl_3$, Φ 0.18
$\lambda_{max\ abs}$ 707 nm
ε 78000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 735 nm



245
$CHCl_3$, Φ 0.46
$\lambda_{max\ abs}$ 668 nm
ε 113000 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 692 nm



246
$CHCl_3$, Φ 0.05
$\lambda_{max\ abs}$ 774 nm
ε 70300 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 815 nm

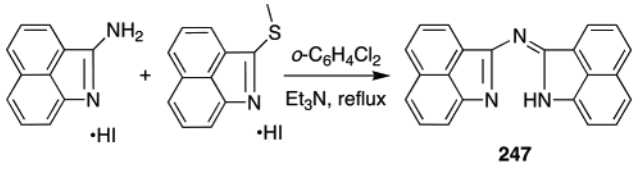


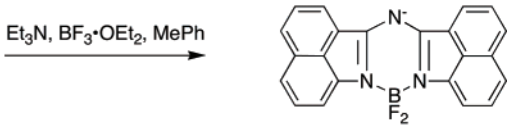
224
$CHCl_3$, Φ 0.36
$\lambda_{max\ abs}$ 688 nm
ε 78500 $M^{-1}cm^{-1}$
$\lambda_{max\ emiss}$ 715 nm

10.2.1. Dyes Based on Benz[c,d]indole

Synthesis of compound **248** involves refluxing 2-benz[*c*,*d*]indolamine hydroiodide with 2-(methylthio)benz[*c*,*d*]-indole-hydroiodide in 1,2-dichlorobenzene in presence of triethylamine, giving the amine **247**. Subsequent treatment with boron trifluoride etherate affords the desired product **248** (reaction 20).[244]

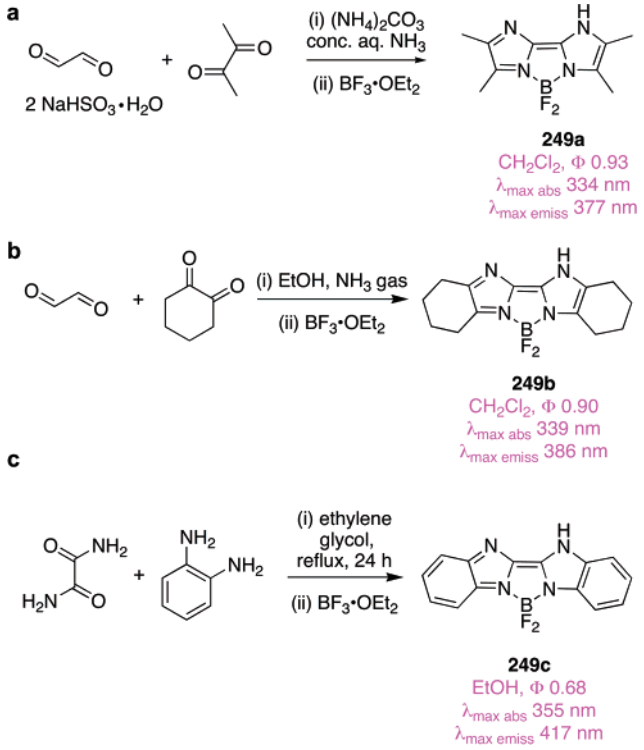
While the benz[*c*,*d*]indole-based BODIPY dye **210** displays a red-shifted absorption and fluorescence, the aza-





reaction 20

Scheme 20. Synthesis of Biimidazol-2-yls−BF_2 Complexes

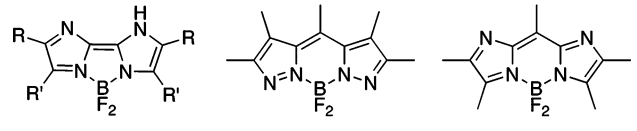


BODIPY analogue **248** shows a blue-shifted absorption at 540 nm. Unfortunately, no fluorescence properties have been reported.

11. Other Analogues of the BODIPYs

11.1. Biimidazol-2-yl–BF_2 Complexes

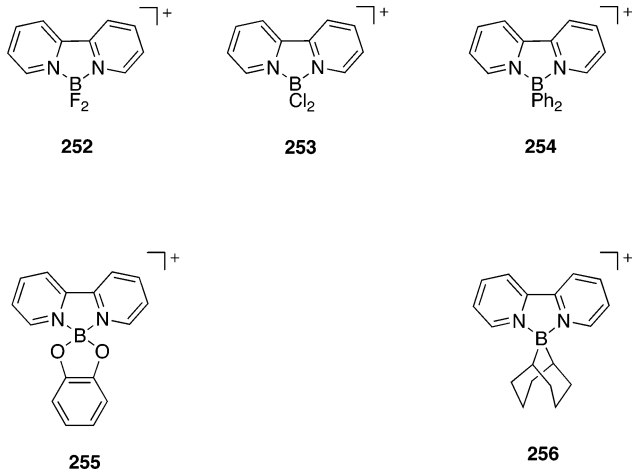
Biimidazol-2-yls difluoroborate complexes **249** have been obtained by (i) reacting glyoxal bisulfite, 2,3-butanedione, and concentrated aqueous NH_3 (Scheme 20a);[245,246] (ii) condensation of 1,2-cyclohexanedione with 40% aqueous glyoxal in ethanol saturated with dry ammonia gas;[246] and, (iii) condensation of oxamide with *o*-phenylenediamine in refluxing ethylene glycol (Scheme 20c).[247,248] It would seem logical that similar dyes of the type **250** and **251** could be prepared, but attempts to do so have been reported as unsuccessful.[249]



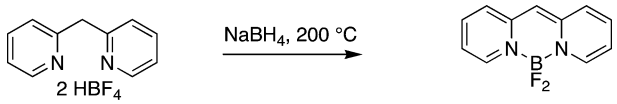
The parent, non-*B*-coordinated heterocyclic systems for molecules **249** are not significantly fluorescent, but the BF_2 complexes display strong fluorescence as shown in the diagrams. Predictably, red shifts for both the absorption and emission maxima, and increased extinction coefficients are observed with increased conjugation and rigidity.

11.2. Pyridine-Based Systems

The dipyridyl-2-yl-boron complexes **252**−**256** have been prepared from reactions of bipyridines with boron electrophiles.[250] They absorb between 302 and 322 nm, with the exception of the complex **255**, which absorbs at 371 nm. No fluorescence was detected for these complexes.

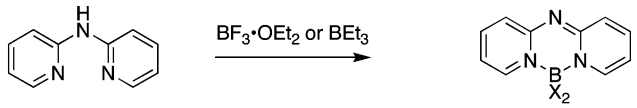


The pyridomethene−BF_2 complex **257** was synthesized as shown in reaction 21 from the 2,2′-dipyridylmethane by fusion with sodium borohydride.[251] The product shows a strong absorption at 468 nm, with a extinction coefficient of 17 783 M^{-1} cm^{-1} in chloroform, but does not fluoresce.



reaction 21

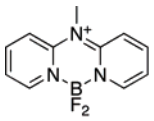
The 10-azapyridomethene−BF_2 complex **258a** was obtained via condensation between dipyrid-2-ylamine and boron trifluoride.[232] Similarly, 10-azapyridomethene-B$(Et)_2$ **258b** was obtained by condensation with triethylboron (reaction 22). Complex **258a** absorbs at 382 nm (log $\epsilon = 4.47$) in ethanol, and strongly fluoresces at 422 nm ($\Phi = 0.81$).



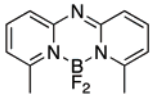
reaction 22

Treatment of dipyrid-2-ylamine with methyl iodide gives the methyldipyrid-2-ylamine, which can be converted to the 10-methyl-10-azapyridomethene−BF_2 complex **259** by treatment with boron trifluoride. The homologous complex **260**

was obtained by condensation between 2-amino-6-methylpyridine and 2-chloro-6-methylpyridine, and subsequent treatment with boron trifluoride. Both these complexes are fluorescent, but the neutral one, **260**, fluoresces at longer wavelength.



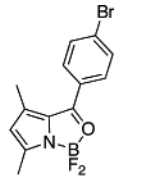
259
EtOH, Φ 0.36
$\lambda_{max\ abs}$ 325 nm
$\lambda_{max\ emiss}$ 362 nm



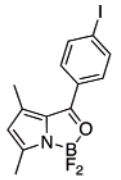
260
EtOH, Φ 0.40
$\lambda_{max\ abs}$ 396 nm
$\lambda_{max\ emiss}$ 416 nm

11.3. 2-Ketopyrrole Complexes[252]

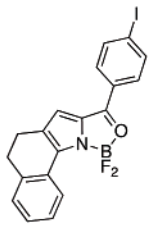
The 2-ketopyrrole complexes **261**−**265** were isolated as minor byproducts (less than 5%) in the synthesis of the corresponding BODIPY analogues.[252] The yield of **261**−**265** could be improved by increasing the amount of acid chloride used in the synthesis. 2-Ketopyrrole complexes are less conjugated than BODIPY dyes; hence, their absorption, extinction coefficients, and emission wavelengths are shorter/smaller. The Stokes' shifts for these compounds, however, are greater than for BODIPY systems (48−154 nm, cf. approximately 10−15 nm for BODIPY dyes).



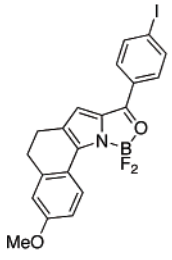
261
$CHCl_3$, Φ na
$\lambda_{max\ abs}$ 321 nm
ε 19 000
$\lambda_{max\ emiss}$ 475 nm



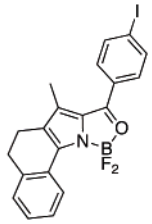
262
$CHCl_3$, Φ na
$\lambda_{max\ abs}$ 322 nm
ε 16 000
$\lambda_{max\ emiss}$ 475 nm



263
$CHCl_3$, Φ 0.89
$\lambda_{max\ abs}$ 468 nm
ε 48 000
$\lambda_{max\ emiss}$ 516 nm



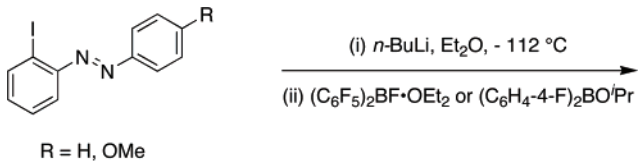
264
$CHCl_3$, Φ 0.52
$\lambda_{max\ abs}$ 488 nm
ε 43 000
$\lambda_{max\ emiss}$ 544 nm



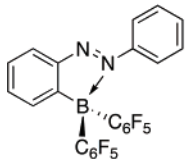
265
$CHCl_3$, Φ 0.58
$\lambda_{max\ abs}$ 445 nm
ε 46 000
$\lambda_{max\ emiss}$ 504 nm

11.4. Azobenzene Derivatives

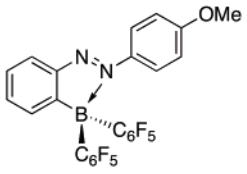
Azobenzenes are the most common chromophores in commercial dyes and, because of photoinduced isomerization, they are used as photoresponsive molecular switches. A consequence of facile photoisomerization is that quantum yields for these compounds are so low that fluorescence tends only to be observed in a rigid matrix at low temperature. A recent innovation in this field, however, is fixation of the π-conjugate systems using boryl-entities to give the fluorescent compounds **266**−**268** (reaction 23).[253]



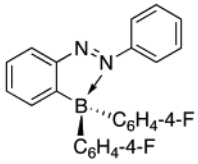
R = H, OMe



266
hexanes; Φ 0.23
$\lambda_{max\ abs}$ 386 nm
$\lambda_{max\ emiss}$ 503 nm



267
hexanes; Φ 0.76
$\lambda_{max\ abs}$ 439 nm
$\lambda_{max\ emiss}$ 524 nm



reaction 23

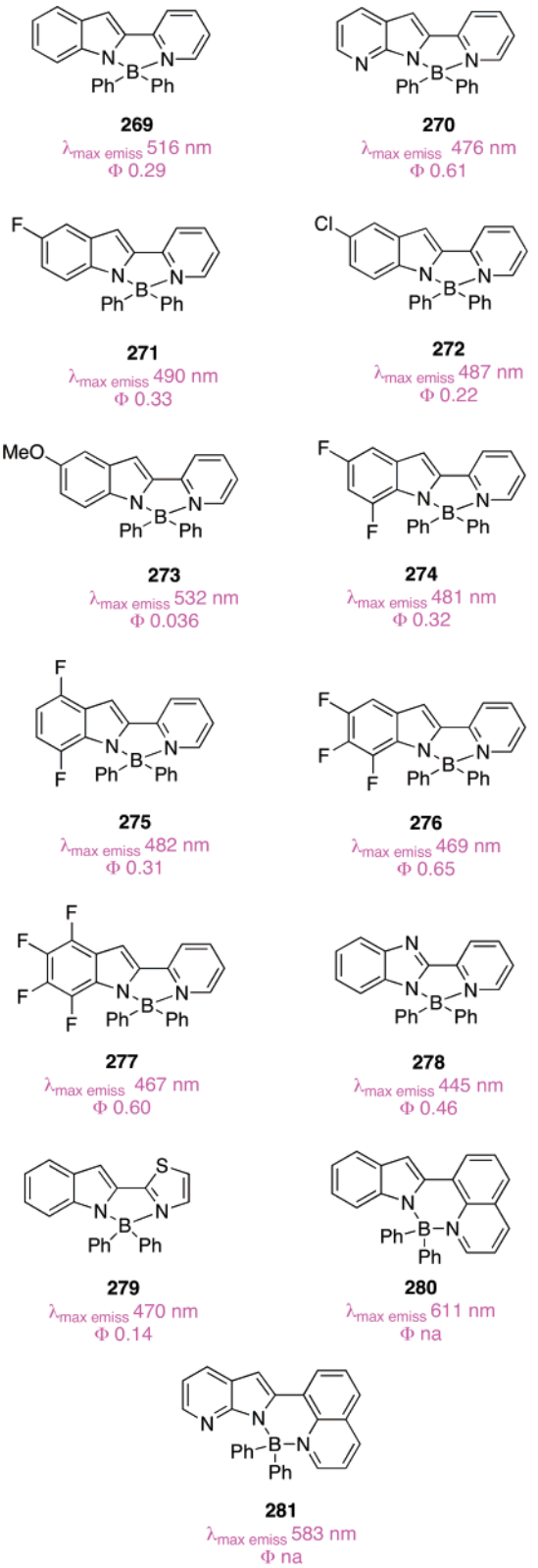
268
no fluorescence

Azobenzene dyes **266** and **267** display a remarkable red-shifted absorbance (386 and 439 nm, respectively) relative to unsubstituted (*E*)-azobenzene (λ = 315 nm). Irradiation of **266** and **267** with a super-high-pressure mercury lamp did not cause photoisomerization. The azobenzene derivative **268**, bearing a fluorinated substituent on the boron atom, showed almost no fluorescence. We speculate that this could be due to intramolecular charge transfer from the least electron rich aryl substituent into the excited-state of the complexed azobenzene system.

11.5. Miscellaneous *N,N*-Bidentate Diphenyl Boron Chelates

Luminescent *N,N*-bidentate diphenylboron chelates **269**−**281**[254,255] have emission maxima that vary with the nature of the parent organic system. Limited information was provided regarding the spectroscopic properties of these molecules, but the data presented are interesting because some of the dyes have high quantum yields and/or fluorescence emissions around 600 nm. These systems perhaps warrant further attention.

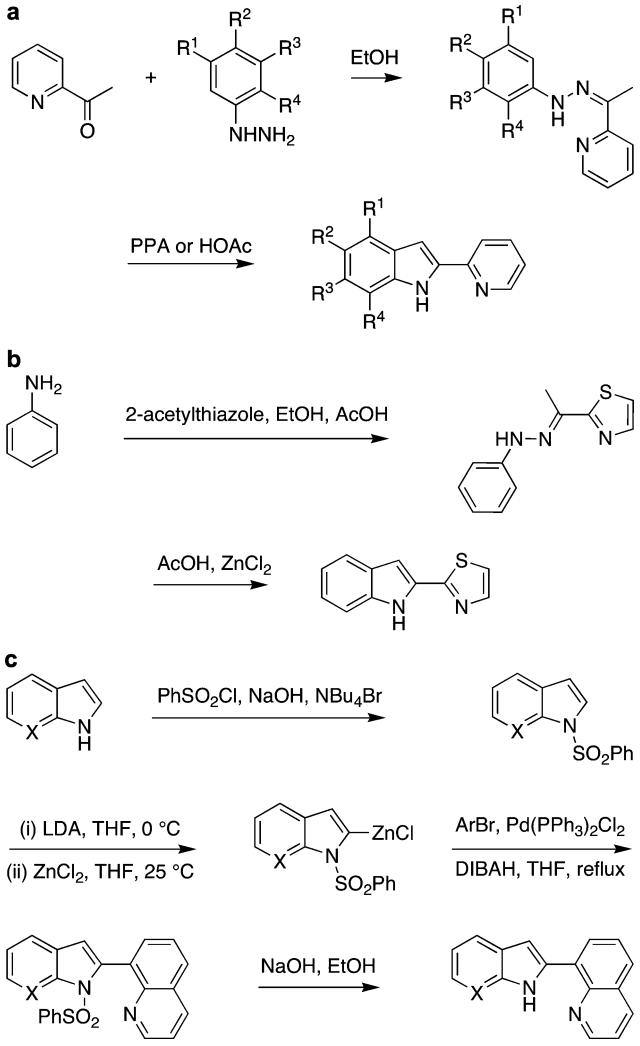
A variety of methods were used to produce the parent heterocycles for the dyes shown above (Scheme 21). The 2-(2′-pyridyl)indole- and 2-(2′-thiazolyl)indole-based ligands were synthesized by a two-step Fischer synthesis (Scheme 21, panels a and b, respectively). Scheme 21c illustrates how a Negishi coupling[256] was used for the synthesis of the 2-(8′-quinolyl)indole or -azaindole. Treatment of the product heterocycles shown in Scheme 21 with triphenylboron (1:1 ratio) in toluene afforded the boron complexes **269**−**281** in good yields.



11.6. Boryl-Substituted Thienylthiazoles

Finally, there are compounds that are even less closely related to the BODIPY core, formed by intramolecular B−N coordination in *N*-heteroaromatic systems. This new concept is illustrated for the development of new electronic materials. The interaction between the Lewis acid (boron) and Lewis base (nitrogen) not only constrain the π-conjugated framework in a coplanar fashion, but also lower the LUMO level (Figure 8). Thus, (3-boryl-2-thienyl)-2-thiazole **282** was

Scheme 21. Two-Step Fischer Synthesis of (a) 2-(2′-Pyridyl)-indole, (b) 2-(2′-Thiazolyl)indole, and (c) Synthesis of 2-(8′-Quinolyl)indole or Aza-indole via Negishi Coupling



synthesized from (3-bromo-2-thienyl)-2-thiazole as shown in Scheme 22.[257] Compound **282** can easily be functionalized to the tin **283** or iodo **284** derivatives via the lithiated intermediates. Lithiation occurs regioselectively at the 5-position of the thiazole ring.

The corresponding tin and iodo derivatives can be used as building blocks in metal-catalyzed coupling reactions to prepare extended π-electron systems such as the head-to-head (H−H), head-to-tail (H−T), and tail-to-tail (T−T) dimers **285**−**287** (Scheme 23). The dimers display red-shifted absorption and emission relative to the monomer. The boryl-substituted thienylthiazoles **282** and **285**−**287** show weak fluorescence emission in the range 452−492 nm.[257]

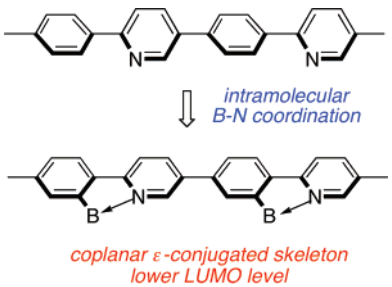
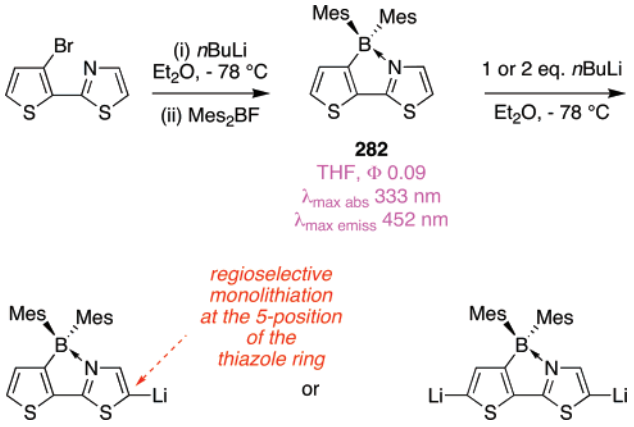
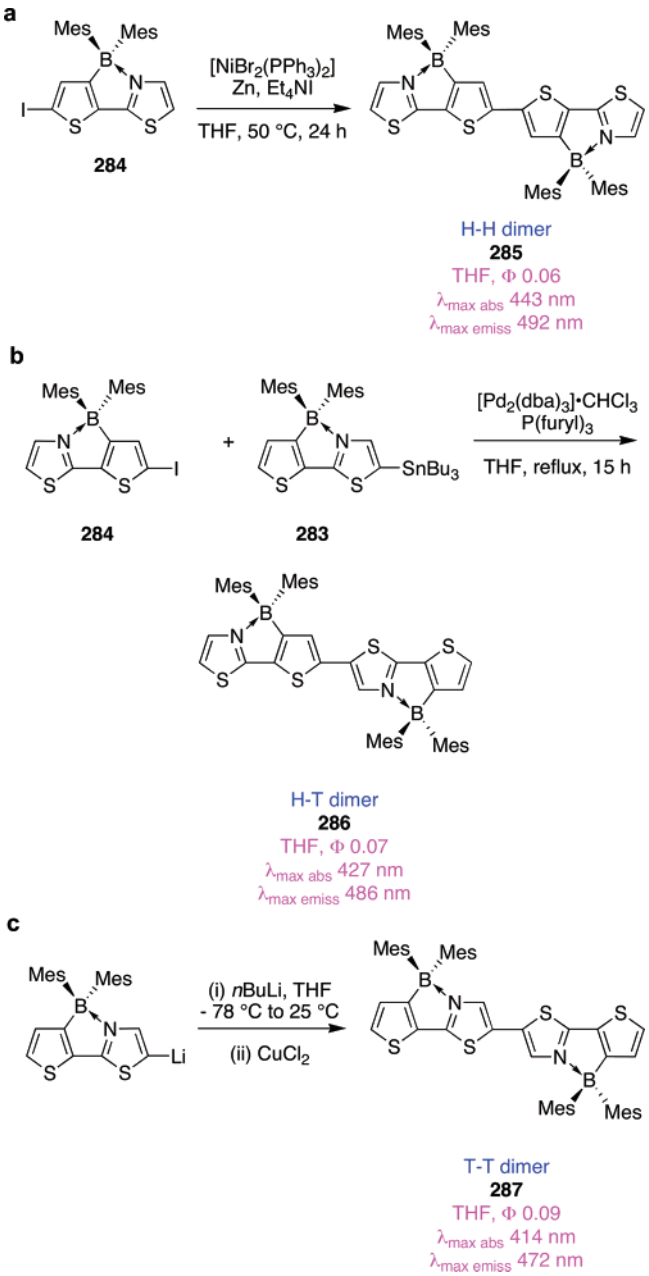


Figure 8. Intramolecular B−N Coordination of *N*-heteroaromatic systems.

Scheme 22. Synthesis of the Dimesityl-boryl Substituted Thienylthiazole 282



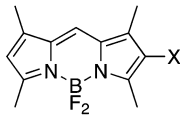
Scheme 23. Synthesis of (a) Head-to-Head, (b) Head-to-Tail, and (c) Tail-to-Tail Dimers



12. Conclusion

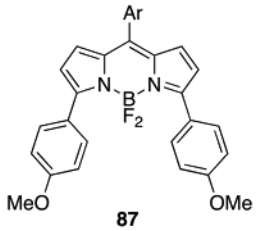
Applications of BODIPY dyes outnumber, by far, studies of their fundamental chemistry and spectroscopic properties. This is unfortunate because they are such powerful tools for imaging, chemosensors, lasing materials, and so forth. There would be even more applications if some deficiencies in the area were addressed. For instance, there are very few water-soluble BODIPY dyes. In this review, we mentioned compounds **53**−**56** and **69d**. The only other examples of water-soluble BODIPY dyes we found were lipophilic BODIPYs made water-soluble by activation with a sulfonated *N*-hydroxysuccinimide (NHS) derivative. 4-Sulfo-2,3,5,6-tetrafluorophenyl (STP) BODIPY esters derivatives have also been synthesized, and proved to be more water-soluble and more reactive with a primary amine than the corresponding *N*-hydroxysuccinimidyl esters.[258]

R = Me, **53**; Et, **54**; H, **56**

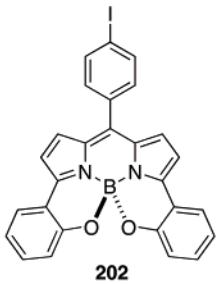


X = SO_3Na, **55**
CH=$CHSO_3H$, **69d**

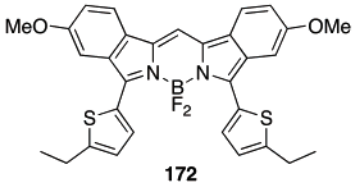
One conspicuous area for further research is the design and synthesis of BODIPY derivatives that emit further into the near-IR. Steps toward this can be taken by attaching aromatic groups, preferably with electron-donating substituents (e.g., **87**), rigidifying their structure (e.g., **202**), or producing ring-fused systems like **172**. One of the most



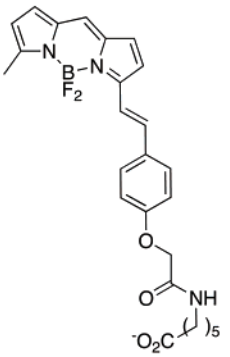
87
$CHCl_3$
λ max emiss 626 nm



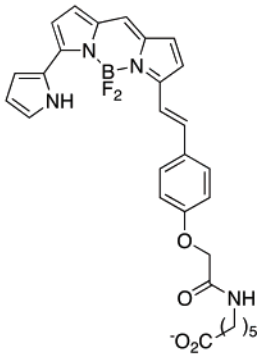
202
$CHCl_3$
λmax emiss 654 nm



172
CH_2Cl_2
λmax emiss 780 nm



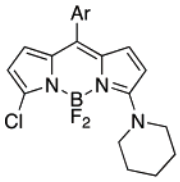
BODIPY 630/650



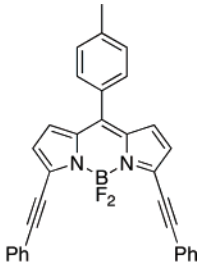
BODIPY 650/665

innovative synthetic procedures for doing this involves condensation of BODIPY methyl substituents to give dyes similar to ones that Invitrogen markets such as "BODIPY 630/650" and "BODIPY 650/665".

Another synthetic innovation is the chlorination of certain BODIPYs to give 3,5-dichloro-derivatives. These products may be functionalized via Pd-mediated couplings or S_NAr reactions to give products that tend to fluoresce at longer wavelengths. Compounds **65** and **110d** are examples of the products that can be formed by this approach.

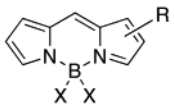


65
MeOH
$\lambda_{max\ emiss}$ 562 nm



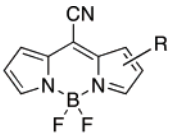
110d
MeOH
$\lambda_{max\ emiss}$ 622 nm

Many papers have been published on BODIPY-like systems in which fluorine atoms on the BODIPY dyes are replaced by a variety of *C*- or *O*-based nucleophiles to give products **F**. These modifications have proven useful as a means to make energy transfer systems. Substitutions of this kind may alter the quantum yields and fluorescence properties of the dyes, but they do not tend to shift their emissions to the red. Conversely, incorporation of a cyanide group at the *meso*-position gives a dramatic shift toward the near-IR.



F
X = alkyne, aryl, alkyl or alkoxide

no significant red shift

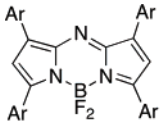


G

pronounced red shift

Substitution of the boron atom in BODIPY dyes gives fluorescent Zn, In, and Ga derivatives, but other metals tend to quench the fluorescence. Quenching in such derivatives presumably occurs via electron-trasnfer mechanisms involving the dyes in their excited states.

Replacement of C-8 in the BODIPY with a nitrogen gives the so-called "AzaBODIPYs". These are an extremely interesting set of dyes because of their long fluorescence emissions wavelength. No water-soluble derivatives of these have been prepared, and nearly all the substituted compounds feature aryl groups in the 3,5-positions.



relatively long wavelength fluorescence emissions

azaBODIPYs

Overall, an abundance of relatively straightforward applications of BODIPY dyes have been reported. Some of the most significant synthetic procedures tend to be written in cryptic styles that are so often seen in the patent literature, but there have been some recent milestones in this area. The most important future developments with respect to applications in biotechnology will involve synthesis of water-soluble, easily functionalized systems, particularly those fluorescing above 600 nm.

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