

# Functionalized boron-dipyrromethenes and their applications

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**Abstract:** Boron-dipyrromethenes/BF<sub>2</sub>-dipyrins (BODIPYs) are highly fluorescent dyes with a wide range of applications in various fields because of their attractive photophysical properties. One of the salient features of BODIPYs is that the properties of the BODIPY can be fine-tuned at will by selectively introducing the substituent(s) at the desired location(s) of the BODIPY. The BODIPYs have several potential sites where the functional groups can be introduced and the functionalized BODIPYs can be used as building blocks to synthesize the desired BODIPY derivatives with interesting features. In this review, we presented the synthesis of different types of functionalized BODIPYs where the functional group(s) were introduced directly at the meso-carbon, at the pyrrole carbons of the BODIPY core as well as at the boron center and discussed their applications toward synthesis of simple substituted BODIPYs to complex BODIPY based systems.

**Keywords:** boron-dipyrromethenes, functionalization, electronic properties, sterically crowded, fluorescence, application

## Introduction

Fluorescent dyes are very useful for visualizing biomolecules in vitro and in vivo.<sup>1-3</sup> The most important criteria for fluorescent dyes is their ability to overcome biological barriers and accumulate and localize at the subcellular targets. Accordingly, significant efforts have been made to develop fluorescent probes for bioimaging applications.<sup>4-7</sup> The most widely used fluorescent probes are coumarin, fluorescein, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins (BODIPYs), rhodamine, and cyanine dyes.<sup>8-10</sup> Among these fluorescent probes, BODIPYs<sup>11</sup> have played a pivotal role in fluorescent probe development and it is one of the most exploited fluorophores because of the following features: 1) sharp absorption and fluorescence in the visible and near-infrared region depending on substituents; 2) large absorption coefficients, high fluorescence quantum yields, and reasonably long singlet state lifetimes; 3) easy to synthesize; 4) chemical, thermal, and photostability; and 5) relative insensitivity to environmental perturbations such as solvent and pH. Besides their extensive applications as fluorescent probes in biology, the BODIPY dyes are also widely used as cation and anion sensors, drug delivery agents, fluorescent switches, electroluminescent films, laser dyes, light harvesters, and sensitizers for solar cells.<sup>12-16</sup> The wide applications of BODIPY dyes are because of their excellent physico-chemical properties combined with their ease of synthesis. Furthermore, the photophysical properties of BODIPYs can be fine-tuned by changing the substituents of different electron densities or by manipulating the conjugation length or by chemical modification at various positions of BODIPY dyes.<sup>17</sup> Such modifications can be carried out conveniently on BODIPY dyes because these dyes are amenable

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for functionalization at all positions and the functionalized BODIPYs are suitable synthons to prepare a wide variety of BODIPY derivatives with desired photophysical properties. Thus, the functional group(s) can be introduced at the various positions of BODIPYs such as at the meso-aryl group; directly at the meso group; at the pyrrole carbon(s) BODIPY core, and also at the B(III) center. In recent times, several reviews have appeared on various aspects of BODIPY dyes<sup>18–22</sup> including the reviews on BODIPY based probes for the fluorescence imaging of biomolecules in living cells; fluorescent indicators for pH, metal ions, anions, biomolecules, reactive oxygen and nitrogen species, redox potential and chemical reactions and photosensitizers for photodynamic therapy along with reviews on synthesis and properties of BODIPY dyes. Interestingly, a perusal of literature reveals that there is no dedicated review on functionalized BODIPYs and their applications to prepare novel BODIPY based complex systems having potential applications in various research fields. In this review, we focus on various functionalized BODIPYs and their applications in synthesis of selective BODIPY based complex systems. This review is limited to the synthesis of functionalized BODIPYs and how the functionalized BODIPYs were used for the synthesis of some complex BODIPY based systems but their applications in materials, biology, and medicinal fields were not discussed here. Readers interested in BODIPY applications can refer to the excellent reviews that have recently appeared in the literature.<sup>12–16</sup> Since the functional groups were introduced either on dipyrromethane I or directly on BODIPY II and the numbering of the positions for these two are different, we presented the numbering on dipyrromethane I and BODIPY II in Figure 1. The functionalized BODIPYs are classified based on the position at the BODIPY systems as discussed below.

## Meso-functionalized BODIPYs

### Meso-aryl functionalized BODIPYs

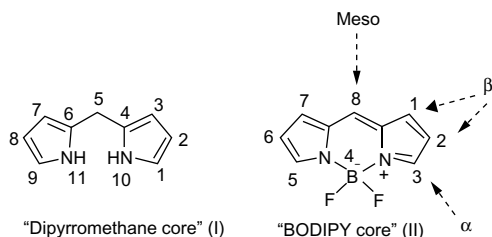
BODIPYs containing a functionalized aryl group at the meso-position is the most desirable fluorophore for the

construction of complex BODIPY fluorophores<sup>18–22</sup> because of the straightforward synthesis from functionalized aromatic aldehydes. Meso-aryl functionalized BODIPYs are highly desirable building blocks to synthesize simple BODIPY based systems<sup>18–22</sup> to complex light harvesting arrays,<sup>23</sup> photonic wires,<sup>24</sup> and opto-electronic gates.<sup>25,26</sup> The meso-aryl functionalized BODIPYs can be prepared easily by following the well-established Lindsey's<sup>27</sup> traditional Lewis acid catalyzed approach. In Lindsey's approach, the synthesis of meso-aryl functionalized BODIPYs involves the condensation reaction between  $\alpha$ -free pyrrole and functionalized aryl aldehydes in the presence of a catalytic amount of Lewis acid to obtain dipyrromethane which is on subsequent oxidation by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to dipyrromethene followed by  $\text{BF}_2$  complexation using  $\text{BF}_3 \cdot \text{OEt}_2$  under basic conditions to yield meso-aryl BODIPYs (Figure 2). The meso-aryl functionalized BODIPYs are very stable to carry out functional group inter-conversions to afford other meso-aryl functionalized BODIPYs where the functionalized aryl aldehydes are not commercially available. Thus, this synthetic protocol gives access to prepare several meso-aryl functionalized BODIPYs that have been used for the construction of several complex BODIPY based systems. There are several reviews available on BODIPY based systems using meso-aryl functionalized BODIPYs.<sup>28,29</sup> However, here we mainly focus on functionalized BODIPYs where the functional group was directly present at the meso carbon of BODIPY which was subsequently used for the synthesis of other functionalized BODIPYs and complex substituted BODIPYs.

### Meso-thiomethyl BODIPY

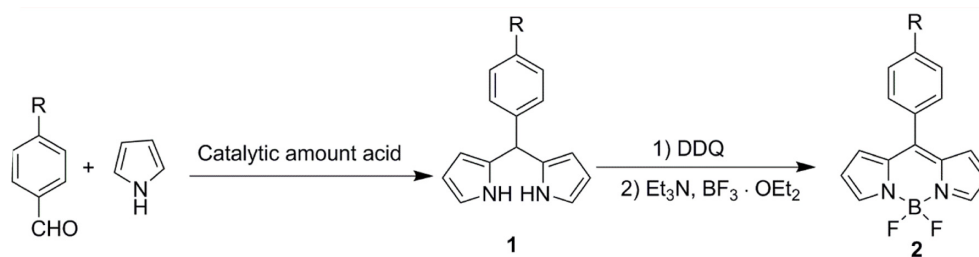
Although Lindsey's methodology<sup>27</sup> gives access to synthesize several complex BODIPY based systems, there are certain drawbacks with this approach that include laborious purifications, the separate synthesis of the starting aldehydes if aldehydes are not commercially available, and incompatibility of the functional groups on the aryl ring of the aryl aldehyde toward exposure to strong Lewis acids and DDQ oxidation. These limitations of Lindsey's protocol challenged researchers to look for alternate routes to prepare the required meso-substituted BODIPYs. In 2006, Goud et al<sup>30</sup> reported the synthesis 8-thiomethyl BODIPY 3 which acted as a key synthon to prepare different meso-substituted BODIPYs via Liebeskind–Srogl cross-coupling reaction<sup>31</sup> and an  $\text{S}_\text{N}\text{Ar}$ -like process.

The Biellmann's BODIPY was prepared in a few steps. In the first step, the pyrrole was reacted with thiophosgene (Figure 3) to produce thioketone.<sup>30</sup> In the subsequent steps,



**Figure 1** Dipyrromethane and boron-dipyrromethene skeletons and their International Union of Pure and Applied Chemistry numbering figure.

**Abbreviation:** BODIPY, boron-dipyrromethene/ $\text{BF}_2$ -dipyrin.



**Figure 2** Synthesis of meso-aryl boron-dipyrromethene complexes 2.

**Note:** R = NO<sub>2</sub>, NH<sub>2</sub>, OH, Cl, Br, I, F, CN etc.

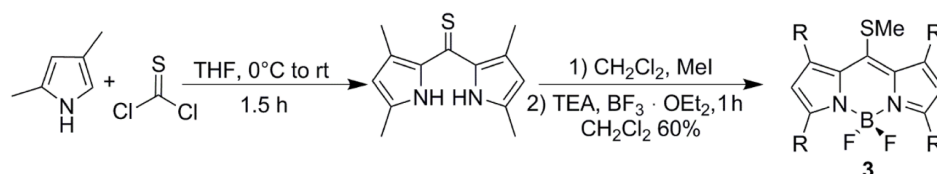
**Abbreviation:** DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone.

the thioketone was reacted with CH<sub>3</sub>I followed by treatment with tertiary amine and complexation with BF<sub>3</sub> · OEt<sub>2</sub> to produce 8-thiomethyl BODIPY 3. Peña-Cabrera et al<sup>32–37</sup> used 8-thiomethyl BODIPY 3 to prepare a series of meso-substituted BODIPYs under Liebeskind–Srogl cross-coupling reaction conditions.<sup>31</sup> The 8-thiomethyl BODIPY 3 was treated with aryl, heteroaryl, alkenyl and organometallic boronic acids (Figure 4) in the presence of a catalytic amount of Pd(0)/trifurylphosphine and a stoichiometric amount of Cu(I)-2-thienylcarboxylate under neutral conditions and prepared corresponding meso-substituted BODIPYs 4–9.<sup>32–37</sup> The reaction also works efficiently if one uses organostannanes instead of boronic acids under the same Pd(0) coupling conditions.<sup>38</sup> They have used this methodology to prepare different types of meso-aryl functionalized BODIPYs like 10 and the functionalized meso-aryl group was used as handle for additional elaboration. For example, BODIPY containing meso-bromoaryl group 8 was used to couple with different substituted boronic acids under Suzuki coupling conditions to prepare meso-polyaryl 15 or meso-polyarylamine BODIPY hybrids 15 (Figure 4) in decent yields.<sup>32</sup> BODIPY containing azido functionalized meso-aryl group 9 was used to react with propargyl α-D-mannopyranoside under Cu(I) catalyzed click reaction conditions to afford carbohydrate-BODIPY hybrid 16.<sup>33</sup> The BODIPY containing meso-alkenyl group 6 was subjected to Michael-type nucleophilic addition by treating it with dodecane-1-thiol in THF (tetrahydrofuran) under mild reaction conditions (Figure 4) to obtain the

desired adduct 12.<sup>34</sup> The meso-alkyl containing BODIPY 13 was also prepared in high yield by Pd-catalyzed reduction of corresponding meso-alkenyl BODIPY 6.<sup>34</sup>

The meso-vinylphenyl substituted BODIPY 7 was subjected to Grubbs catalyzed conditions (Figure 4) to prepare novel BODIPY dyad 14.<sup>32</sup> Thus, the meso-aryl functionalized/alkenyl containing BODIPYs open up the synthesis of a wide variety of complex BODIPY systems under mild reaction conditions. Recently the same research group developed a straightforward synthetic route<sup>39</sup> to directly incorporate 1,3-dicarbonyl nucleophiles such as acetylacetonate into the meso-position of BODIPY 11 by treating 8-(thiomethyl) BODIPY 3 (Figure 5) with 1,3-dicarbonyl derivatives in the presence of Cu(I) thiophenecarboxylate in stoichiometric amounts at room temperature.

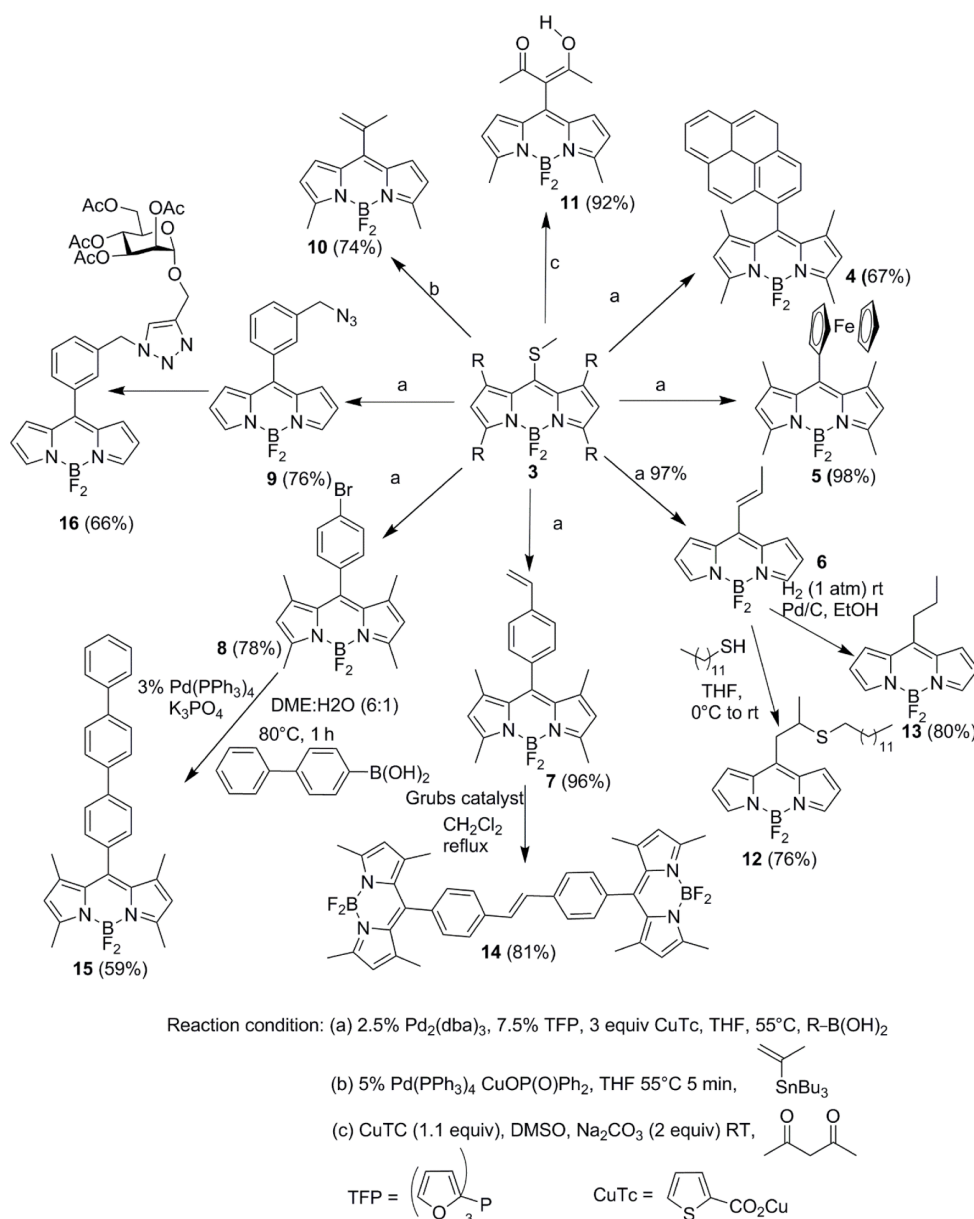
The thiomethyl (–SCH<sub>3</sub>) group at the meso-position showed not only excellent reactivity as a cross-coupled partner but also acted as simple leaving group to prepare N– and O– based nucleophiles substituted at the meso-position of BODIPY. Thus, meso-(thiomethyl) group of BODIPY 3 can be displaced in an S<sub>N</sub>Ar-like process by amines to produce meso-amine substituted BODIPYs 17–24 (Figure 5). Goud et al who first prepared meso-(thiomethyl) BODIPY 3 showed<sup>30</sup> that –SCH<sub>3</sub> group can be displaced by reacting 3 with aniline in CH<sub>2</sub>Cl<sub>2</sub> to form meso-anilino BODIPY 19. Later, Osorio-Martínez et al relouked at the reaction and prepared several meso-substituted amino BODIPYs 17–24 by treating 3 with various substituted amines.<sup>40–44</sup> The meso-amino BODIPY 23



**Figure 3** Synthesis of meso-(thiomethyl) BODIPY 3.

**Note:** R = H/CH<sub>3</sub>; 3

**Abbreviations:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrin; h, hours; THF, tetrahydrofuran; rt, room temperature.



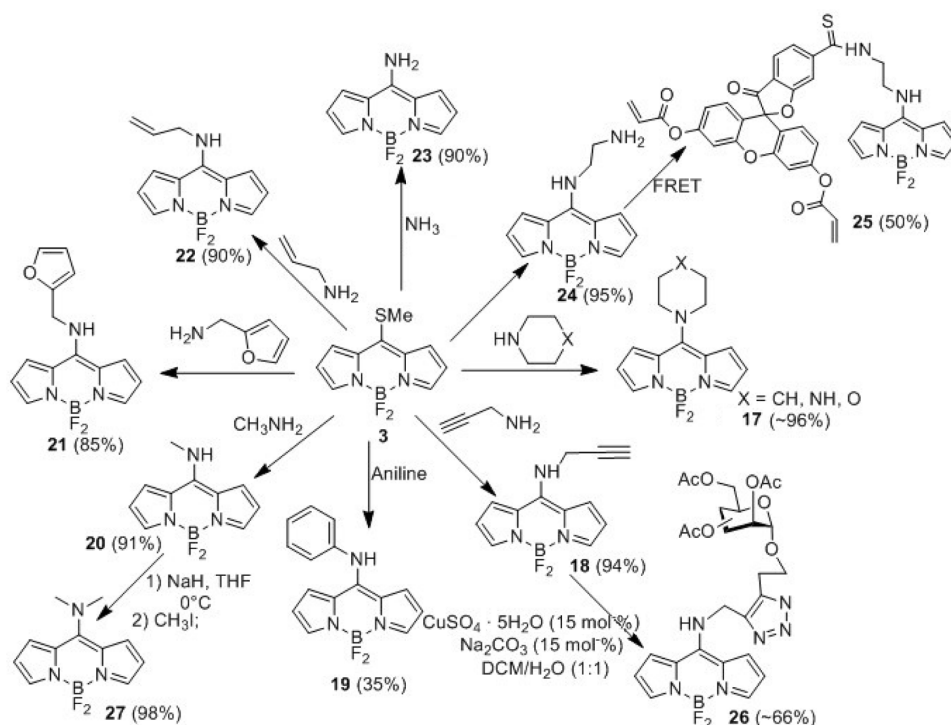
**Figure 4** Synthesis of various types of meso-substituted BODIPYs 4–16 derived from meso-(thiomethyl) BODIPY 3 under Pd catalyzed conditions.

**Abbreviations:** BODIPY, boron-dipyrromethene/ $\text{BF}_2$ -dipyrin; equiv, equivalent(s); min, minutes; DMSO, dimethyl sulfoxide; atm, atmospheric pressure; THF, tetrahydrofuran; rt, room temperature.

was prepared by treating meso-(thiomethyl) BODIPY 3 with ammonia. The other meso-amino substituted BODIPYs 17–24 (Figure 5) were prepared by treating meso-(thiomethyl) BODIPY 3 with corresponding amines. The meso-substituted amino-BODIPYs 17–24 were also used further to prepare several interesting meso-substituted BODIPY compounds. For example, meso-(propargylamino) BODIPY 18 on reaction with azido-carbohydrates under click reaction conditions (Figure 5) produced BODIPY-carbohydrate hybrid 26.<sup>33</sup> The meso-methylamino BODIPY 20 on treatment with  $\text{CH}_3\text{I}$  in the presence of NaH in THF at 0°C produced meso-(N,N'-dimethylamino) BODIPY 27.<sup>43</sup> Ma et al synthesized<sup>41</sup>

a fluorescence resonance energy transfer (FRET) donor connected BODIPY conjugate by treating meso-substituted amino BODIPY 24 with FRET such as fluorescein isothiocyanate and prepared fluorescein isothiocyanate-BODIPY FRET couple 25 (Figure 5) and used for sensing cysteine. Thus, meso-substituted amino BODIPYs gave wide access to prepare several novel meso-substituted amino BODIPYs (Figure 5). The presence of substituted amino group at the meso-position of BODIPYs alters the electronic properties significantly and these meso-amino substituted BODIPYs absorb and emit efficiently in the blue spectral region unlike other meso-aryl BODIPYs which are normally absorbed in





**Figure 5** Synthesis of various types of meso-substituted BODIPYs 17–27 derived from meso-(thiomethyl) BODIPY 3 by nucleophilic substitution.  
**Abbreviations:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrin; FRET, fluorescence resonance energy transfer; THF, tetrahydrofuran.

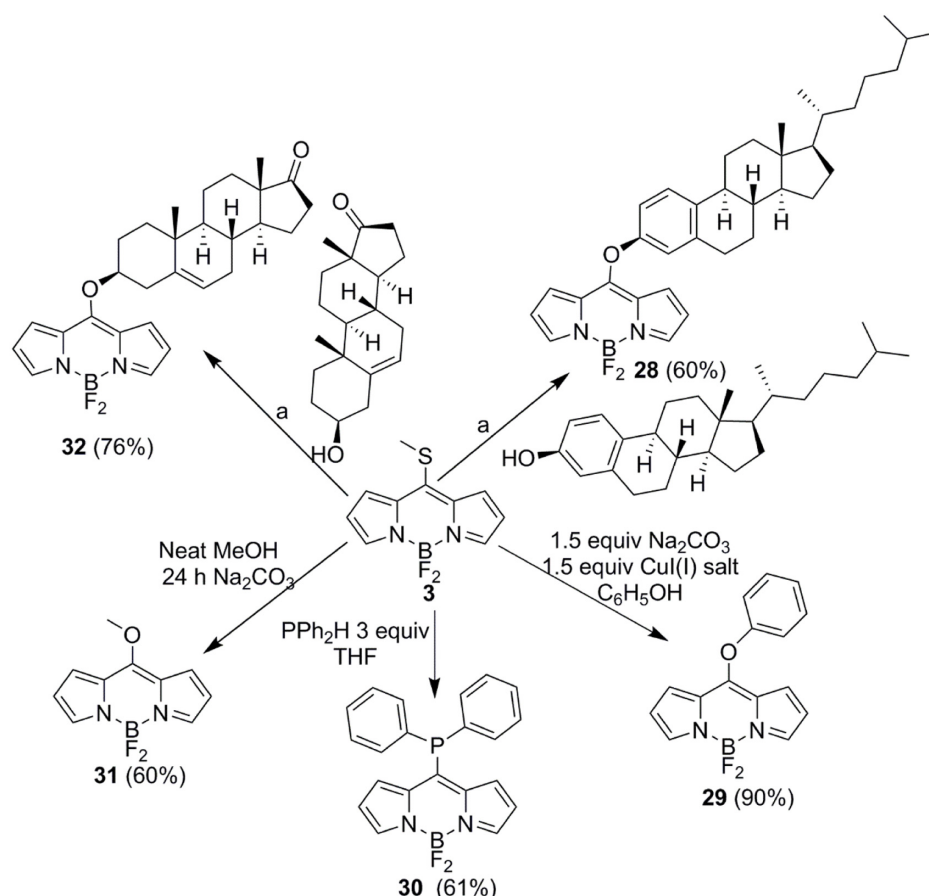
the blue-green region as well as in red and infra-red region upon slight modifications. Thus, the meso-substituted amino BODIPYs are blue emitting dyes and some of these dyes exhibit very high fluorescence quantum yields, close to unity, and large Stokes shifts, leading to highly efficient tunable laser dyes in the blue part of the spectrum.

The meso-(thiomethyl) BODIPY 3 was also used effectively to prepare meso-alkoxy 31 and meso-aryloxy BODIPYs 29 by treating it with corresponding alcohols (Figure 6) in the presence of a base and Cu(I) additive.<sup>45,46</sup> In addition to simple alcohols, they also succeeded in connecting natural products such as eugenol, menthol, cholesterol 28, and estrone 32 under simple reaction conditions (Figure 6).<sup>45</sup> These hybrids are highly fluorescent in the blue-green part of the visible region and the BODIPY bearing cholesterol at the meso-position 28 can be used as fluorescence biological marker. Esnal et al also introduced phosphorus<sup>46</sup> atom at the meso-position of the BODIPY core by treating meso-(thiomethyl) BODIPY 3 with excess of PPh<sub>2</sub>H in THF (Figure 6) and yielded 30 in 61% yield. Thus, the meso-(thiomethyl) BODIPY 3 allows the introduction of different kinds of –C, –N, and –O based nucleophiles at the meso-position via Liebeskind–Srogl coupling reaction and S<sub>N</sub>Ar-process. These dyes can absorb and emit from the blue region to visible-near-infrared region depending on the meso-substituent.

## Meso-halogenated BODIPYs

The meso-substituted BODIPYs can also be prepared by using meso-halo BODIPYs. Leen et al reported<sup>47</sup> the synthesis of meso-halogenated BODIPYs and their applications in the synthesis of meso-substituted BODIPYs via S<sub>N</sub>Ar process and palladium-catalyzed Suzuki, Stille and Sonogashira cross-coupling reactions. The meso-chloro BODIPY 35 was prepared by reacting the dipyrrolylketone with POCl<sub>3</sub> followed by in situ deprotonation by base and complexation with BF<sub>3</sub>·OEt<sub>2</sub>. Similarly, the dipyrrolylketone was reacted (Figure 7) with POBr<sub>3</sub> followed by deprotonation and complexation with BF<sub>3</sub>·OEt<sub>2</sub> in situ to afford meso-bromo BODIPY 33. However, under the same reaction conditions, PI<sub>3</sub> was unsuccessful in producing meso-iodo BODIPY 34. They were also unsuccessful to prepare meso-fluoro BODIPY. Leen et al adopted a halogen exchange approach to prepare meso-iodo BODIPY 34. In modified Finkelstein procedure, the meso-chloro BODIPY 35 was stirred in acetone in the presence of sodium iodide (Figure 7) and afforded meso-iodo BODIPY 34 in good yield.

The meso-halo BODIPYs like meso-(thiomethyl) BODIPY 3 are very useful compounds because they are very promising functionalized BODIPYs for the preparation of more complex meso-substituted BODIPY 36–44 analogs via elaboration of the reactive halogen by S<sub>N</sub>Ar or transition metal catalyzed transformations such as Suzuki, Stille, Heck,



**Figure 6** Synthesis of nucleophilic substituted BODIPYs 28–32 derived from meso-thiomethyl BODIPY 3.

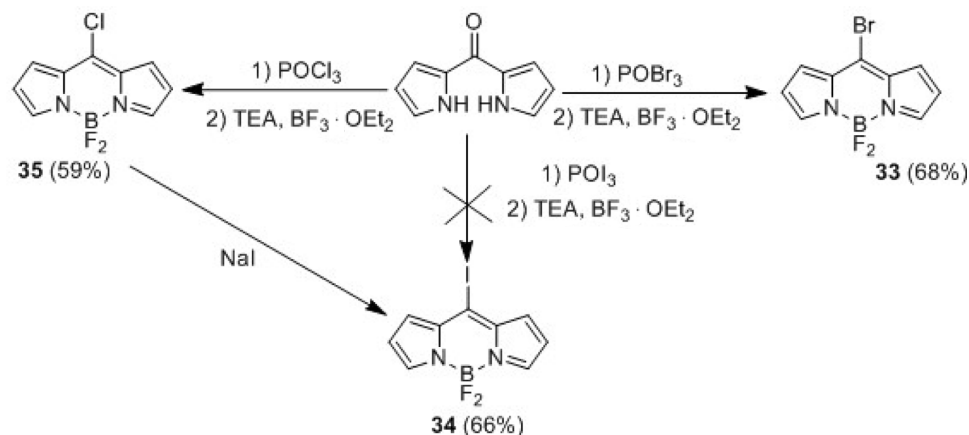
**Note:** (a) 1.5 equiv  $\text{CuTC}$ , 1.5 equiv.  $\text{Na}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ ,  $55^\circ\text{C}$ .

**Abbreviations:** BODIPY, boron-dipyrromethene/ $\text{BF}_2$ -dipyrin; equiv, equivalent(s); h, hours; THF, tetrahydrofuran.

Negishi, Sonogashira etc as shown in Figure 8. The chloride substituent at the meso-position of BODIPY is an efficient leaving group in  $\text{S}_\text{N}\text{Ar}$  reactions. Meso-chloro BODIPY 35 was also useful to prepare a wide range of heteroatom (–N, –O, and –S) meso-substituted derivatives by nucleophilic

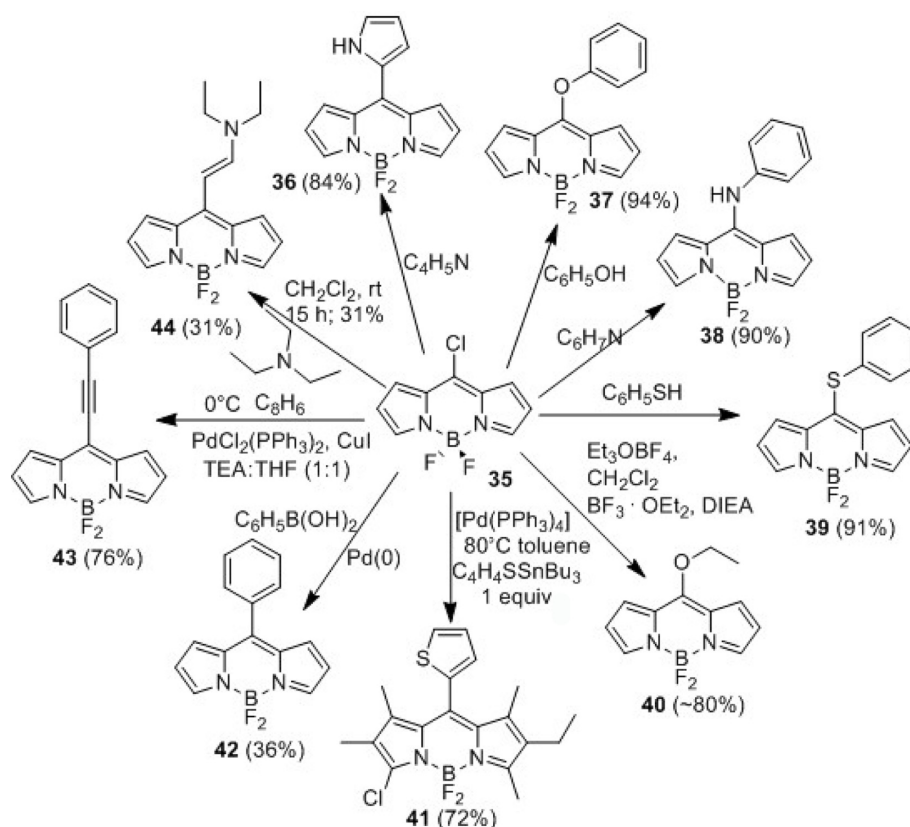
displacement of the meso-halogen substituent of BODIPY.<sup>47–49</sup>

Several meso-substituted derivatives 36–39 were prepared by stirring meso-halo BODIPY with appropriate nucleophile (N, O, and S-nucleophiles) in the presence of base. The meso-halo BODIPYs were also used to prepare several



**Figure 7** Synthesis of meso-functionalized BODIPYs 33–35.

**Abbreviation:** BODIPYs, boron-dipyrromethenes/ $\text{BF}_2$ -dipyrins.



**Figure 8** Synthesis of various meso-substituted BODIPY derivatives 36–44 from meso-chloro BODIPY 35.

**Abbreviations:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrryn; h, hours; equiv, equivalent(s); THF, tetrahydrofuran; rt, room temperature.

types of aryl, heteroaromatic and ethynyl aromatic groups at the meso-position of BODIPY under Pd(0) catalyzed Suzuki, Stille, and Sonogashira coupling reactions. They have also showed that meso-chloro BODIPY 35 is a very good synthon for the preparation of meso-aryl, meso-alkyl, and meso-vinyl substituted BODIPYs 41–43 in high yields using Pd(0)-catalyzed Stille cross-coupling reactions.<sup>50–56</sup> Misra et al also synthesized a series of meso-arylethynyl BODIPYs 43 by reacting meso-chloro BODIPY 35 with various aryethynes (Figure 8) under Pd-catalyzed Sonogashira cross-coupling reaction and studied the effect of the donor on the photophysical properties of the BODIPYs.<sup>50–52,54,56</sup> The same group also introduced<sup>57</sup> enamines at the meso-position of the BODIPY core by coupling 8-chloro BODIPY with tertiary amines and synthesized 44 via catalyst free oxidation of tertiary amines (Figure 8).

## Pyrrole functionalized BODIPYs

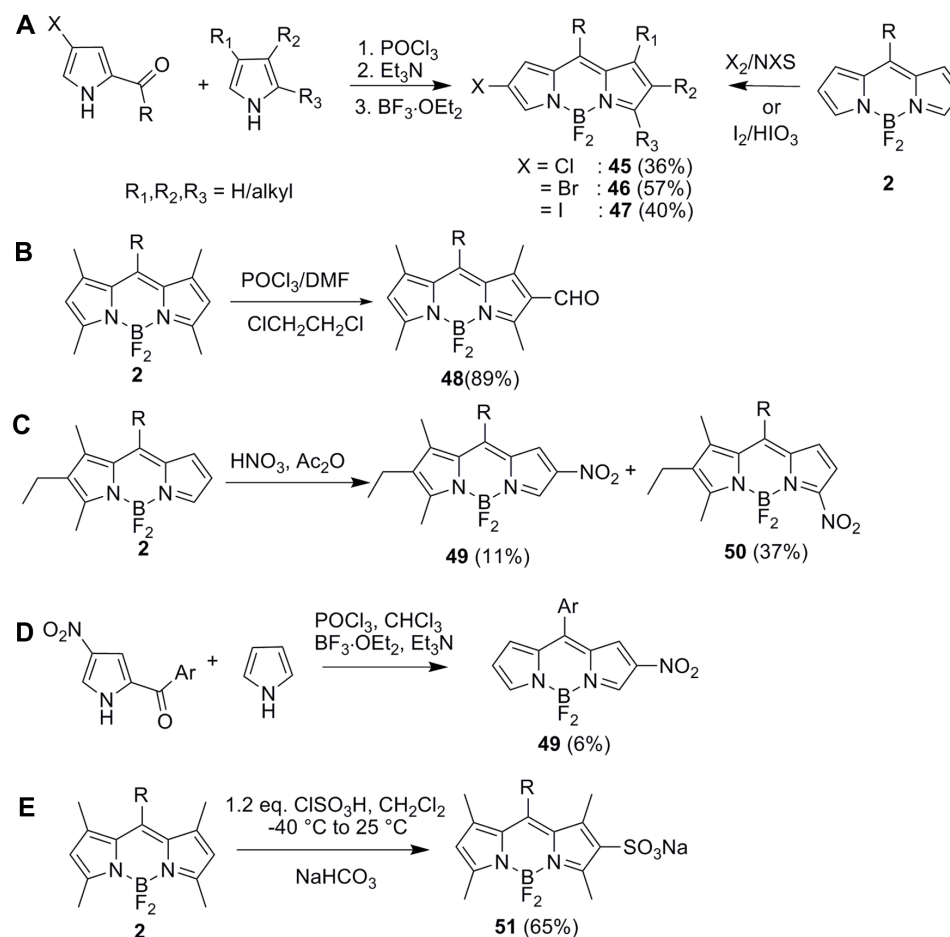
The six-pyrrole carbons of the BODIPY core is prone to functionalization and BODIPYs containing one to six functional groups were synthesized and used effectively to prepare the desired substituted BODIPYs. There are different strategies available to prepare pyrrole functionalized BODIPYs.

## Mono-functionalized BODIPYs

The functional group can be introduced either at 2- or 3-position of BODIPY to synthesize 2-functionalized and 3-functionalized BODIPYs.

### 2-functionalized BODIPYs

The functional groups such as halogens, formyl, cyano etc, were introduced at the 2-position of BODIPY by various synthetic routes. The halogens such as bromo, chloro, and iodo functional groups were introduced at the 2-position of BODIPY by two different synthetic routes as outlined in Figure 9.<sup>58–60</sup> The condensation of 4-halogenated-2-acylpyrrole with the desired substituted pyrrole in the presence of one equivalent of POCl<sub>3</sub> resulted in the formation of halogen substituted dipyrromethene which was then neutralized by adding excess of triethylamine followed by complexation with BF<sub>3</sub>·OEt<sub>2</sub> to afford 2-halogenated BODIPYs 45–47 (Figure 9A).<sup>58</sup> During this method, the halogen atom was varied from chlorine to bromine to iodine and produced all three mono-halogenated BODIPYs 45–47 in 36%–57% yields.<sup>58</sup> Alternately, 2-halogenated BODIPYs 45 and 46 were prepared by treating BODIPY 2 with one or less than one equivalent of N-halosuccinimide (NXS) in CH<sub>2</sub>Cl<sub>2</sub> in high yields since the 2-position of BODIPY 2 is more



**Figure 9** Synthesis of (A) 2-halo, (B) 2-formyl, (C) and (D) 2-nitro and (E) 2-sulfonyl functionalized BODIPYs 45–51.  
**Abbreviations:** BODIPYs, boron-dipyrromethenes/ $\text{BF}_2$ -dipyrins; NXs, N-halosuccinimide; eq, equivalent(s).

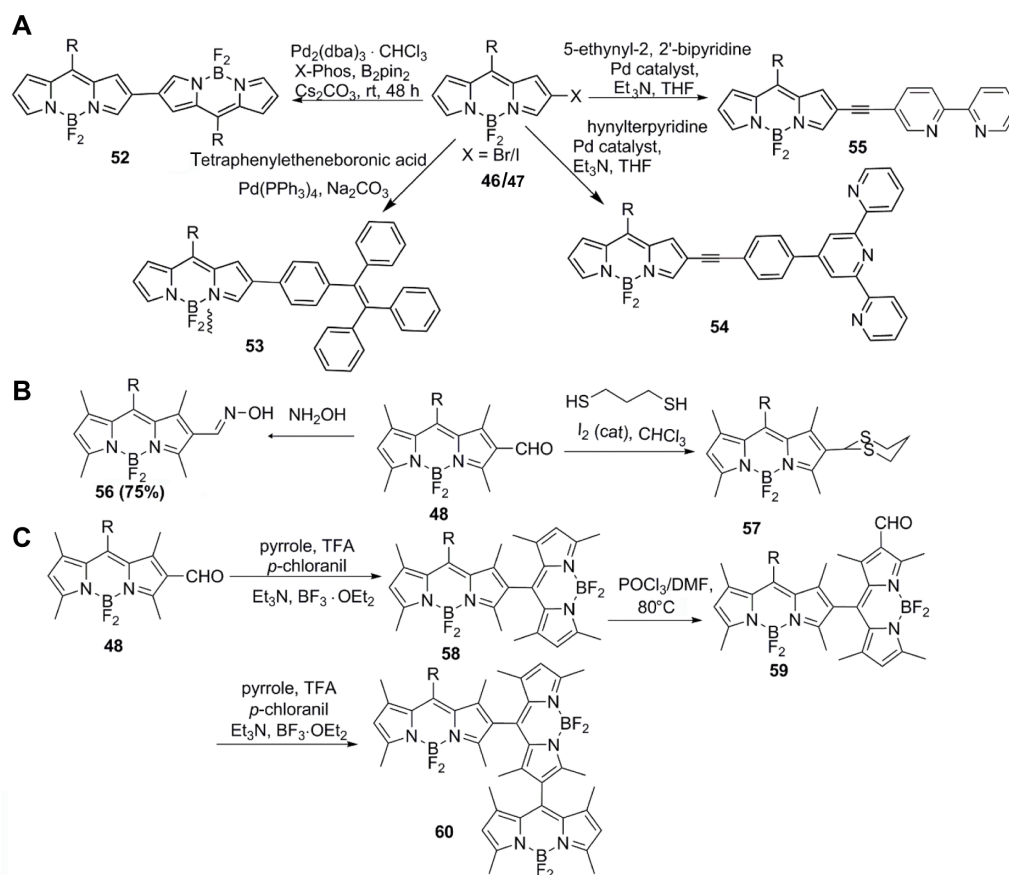
prone to electrophilic substitution reactions (Figure 9A).<sup>59,60</sup> The halogenation at 2-position of BODIPY **2** was also carried out by treating BODIPY **2** with a brominating agent<sup>61</sup> such as  $\text{Br}_2$  and iodinating agent<sup>62</sup> such as  $\text{I}_2/\text{HIO}_3$  and afforded respective 2-halogenated BODIPYs **46** and **47** in high yields (Figure 8A).

The 2-formylated BODIPY **48** was prepared under modified Vilsmeier–Haack reaction conditions by treating BODIPY **2** with Vilsmeier reagent under mild reaction conditions (Figure 9B).<sup>63</sup> Recently, Esnal et al attempted to synthesize  $\beta$ -nitro substituted BODIPY **49** by treating BODIPY **2** with two equivalents of  $\text{HNO}_3$  and  $\text{Ac}_2\text{O}$  at  $0^\circ\text{C}$  (Figure 9C).<sup>64</sup> This reaction resulted in the formation of a mixture of 5-nitro BODIPY **50** as a major product and 6-nitro BODIPY **49** as a side product. To improve the percentage yield of these mono-substituted BODIPYs **49/50**, the authors attempted the nitration reaction by treating nitro-substituted pyrrole with unsubstituted pyrrole under  $\text{POCl}_3$  acid catalyzed conditions and followed by complexation with  $\text{BF}_3 \cdot \text{OEt}_2$  (Figure 9D).<sup>64</sup>

However, the yields of mono-nitro-substituted BODIPY **49** remained the same in both synthetic strategies. The mono-sulfonyl BODIPY **51** was synthesized by drop-wise addition of 1.2 equivalents of chlorosulfonic acid to the solution of BODIPY **2** (Figure 9E) by maintaining the temperature from  $-40^\circ\text{C}$  to  $25^\circ\text{C}$  followed by quenching with  $\text{NaHCO}_3$ .<sup>65</sup>

2-Halo BODIPYs **45–47** were used to prepare various BODIPY derivatives under  $\text{Pd}(0)$  cross-coupling conditions. The reaction of 2-bromo BODIPY **46** with bis(pinacolato) diboron ( $\text{pin}_2\text{B}_2$ ) in the presence of  $\text{Cs}_2\text{CO}_3$  produces  $\beta$ – $\beta$  linked BODIPY dimer **52**.<sup>66</sup> The compounds, 2-tetraphenylethene BODIPY **53**, 2-ethynylterpyridyl BODIPY **54**, and 2-ethynylbipyridyl BODIPY **55** were also synthesized (Figure 10A) under  $\text{Pd}(0)$  conditions by the reaction of 2-halo BODIPY with boronic acid/ethynyl compound.<sup>62,67,68</sup>

Using the 2-formyl BODIPY **48**, a few BODIPY derivatives were synthesized under Schiff base and Knoevenagel reaction conditions and these derivatives were used for sensing various metal ions. For example, compound oxime BODIPY **56** was



**Figure 10** Synthesis of 2-substituted BODIPY derivatives 52–60 derived from (A) 2-halo, (B) and (C) 2-formyl functionalized BODIPYs.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/ $\text{BF}_2$ -dipyrins; h, hours; THF, tetrahydrofuran; TFA, trifluoroacetic acid; rt, room temperature.

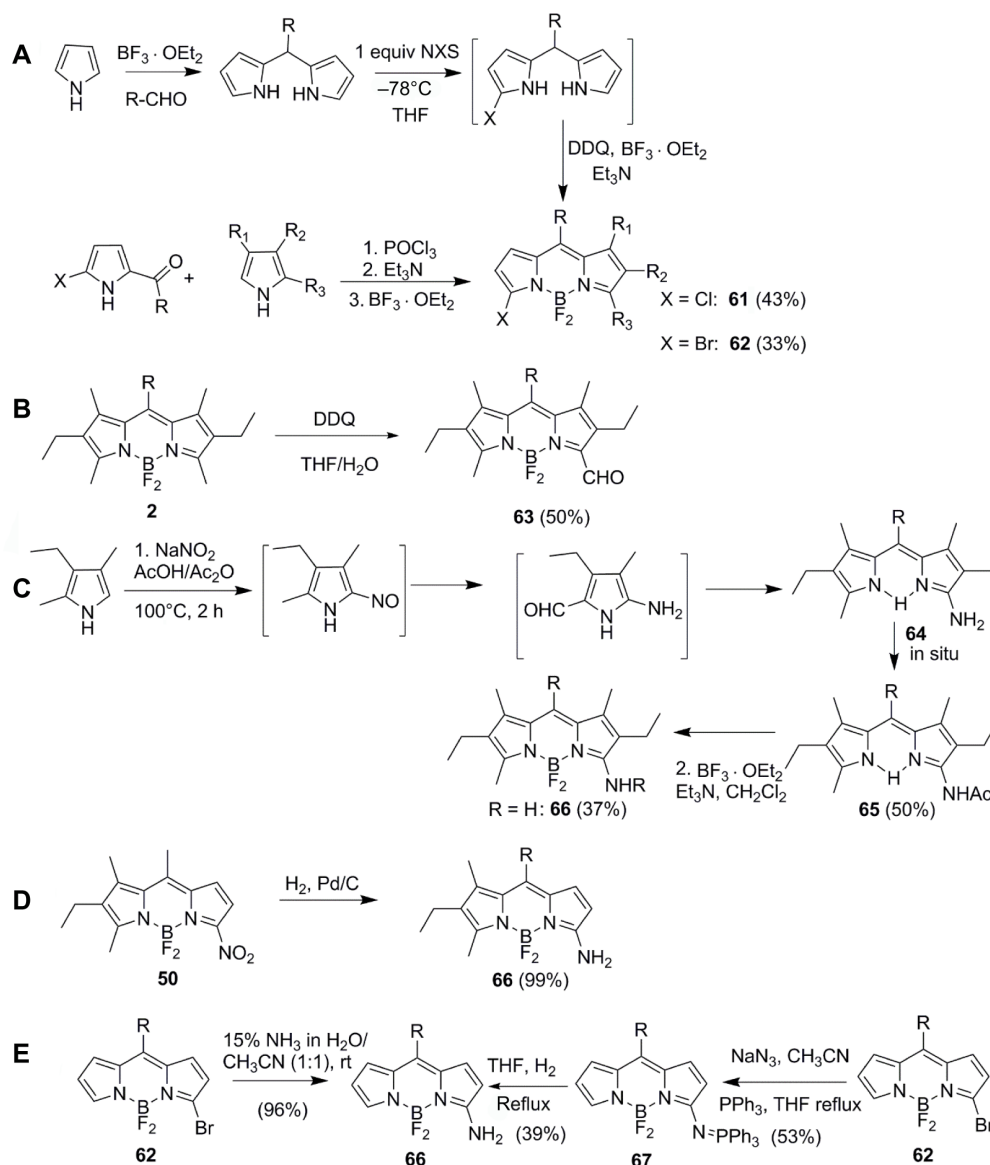
synthesized by treating 2-formyl BODIPY 48 with hydroxylamine in ethanol at room temperature (Figure 10B) and used to sense  $\text{OCl}^-$  ion whereas compound 57 was used for detection of  $\text{Hg}^{2+}$  ion.<sup>69,70</sup> BODIPY trimer 60 was synthesized from 2-formyl BODIPY 48 in a few steps which involve acid catalytic conditions followed by complexation with  $\text{BF}_3 \cdot \text{OEt}_2$  (Figure 10C) to obtain BODIPY dimer 58. The repetition of the same steps under similar conditions on BODIPY dimer 58 yielded the BODIPY trimer 60 in decent yield.<sup>71</sup>

### 3-functionalized BODIPYs

The 3-halogenated BODIPYs 61 and 62 were prepared by condensing 5-halogenated 2-acylpyrrole with substituted pyrrole in the presence of  $\text{POCl}_3$  followed by treatment with excess of  $\text{NEt}_3/\text{BF}_3 \cdot \text{OEt}_2$  (Figure 11A).<sup>58</sup> In this method, one can use any substituted pyrrole as second pyrrole to prepare a range of 3-halogenated BODIPYs 61 and 62. Alternately, treatment of meso-aryl dipyrromethane 1 with one equivalent of appropriate NXS at  $-78^\circ\text{C}$  in THF followed by oxidation with DDQ and complexation with  $\text{BF}_3 \cdot \text{OEt}_2$  in the presence of  $\text{Et}_3\text{N}$  (Figure 11A) afforded 3-halogenated

BODIPYs 61 and 62 in 43% and 33% yields, respectively.<sup>72</sup> The 3-halogenated BODIPYs 61 and 62 cannot be prepared by direct substitution of BODIPYs with halogens or any other halogenating reagents. Haefele et al reported the synthesis of 3-formylated BODIPY 63 by DDQ oxidation of 3-methyl BODIPYs 2 (Figure 11B).<sup>73</sup> The amine group was introduced on the BODIPY core in a few steps. In the first step, the tri-alkyl substituted pyrrole was treated with sodium aqueous nitrite and acetic acid/acetic anhydride (Figure 11C) to afford 3-amine substituted dipyrromethene 64.<sup>74</sup> However, during this step, some acylated dipyrin 65 was also formed. In the subsequent step, the mixture of dipyrromethenes complexed with  $\text{BF}_3 \cdot \text{OEt}_2$  in the presence of triethylamine and the resulted crude mixture of BODIPYs were purified by column chromatography to afford 3-amino substituted BODIPY 66 in decent yield. The 3-amino BODIPY 66 was also synthesized by reducing the corresponding nitro BODIPY 50 in the presence of molecular hydrogen (Figure 11D) under Pd/C catalyzed conditions.<sup>64</sup> Alternately, the 3-amino BODIPY 66 was also synthesized from 3-bromo BODIPY 62 in three steps. In the first step, the 3-bromo BODIPY 62 was treated with





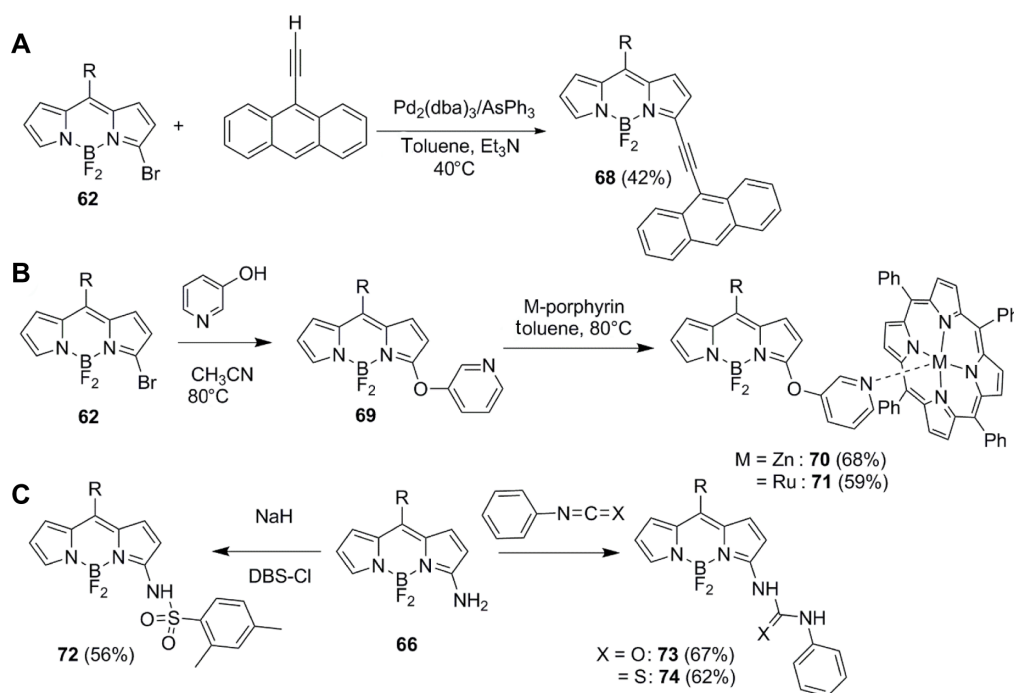
**Figure 11** Synthesis of (A) 3-halo, (B) 3-formyl, (C–E) 3-amino functionalized BODIPYs 61–66.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; h, hours; equiv, equivalent(s); NXS, N-halosuccinimide; THF, tetrahydrofuran; rt, room temperature; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

sodium azide in acetonitrile to generate 3-azido BODIPY which was then reacted with PPh<sub>3</sub> in THF (Figure 11E) and afforded 3-iminophosphorane BODIPY 67. In the subsequent step, 3-iminophosphorane BODIPY 67 was refluxed in THF/water and yielded 3-amino BODIPY 66.<sup>75</sup>

3-Halo BODIPYs 61 and 62 were subjected to Pd(0) cross-coupling conditions and synthesized a variety of BODIPY derivatives using Suzuki, Stille, and Sonogashira methods. The reaction of 3-bromo BODIPY 62 with ethynylanthracene under Sonogashira Pd(0) cross-coupling conditions (Figure 12A) produced ethyne bridged BODIPY-anthracene conjugate 68, which showed efficient energy transfer from anthracene to BODIPY unit.<sup>72</sup> The 3-mono-halogenated BODIPYs 61 and 62 were also subjected to nucleophilic substitution reactions

(Figure 12B) by treating with different types of nucleophiles in the presence of base at reflux conditions. The reaction of 3-bromo BODIPY 62 with 3-hydroxypyridine produced 3-oxypyridine BODIPY 69 which was further used to prepare non-covalent BODIPY-Zn(II) porphyrin dyad 70 and BODIPY-Ru(II) porphyrin dyad 71 (Figure 12B) assembled via Zn(II)/Ru(II)-pyridine “N” interaction.<sup>76</sup> The 3-amino BODIPY 66 was used to prepare 2,4-dinitrobenzenesulfonyl (DBS) appended BODIPY 72 by treating with DBS chloride (Figure 12C) in the presence of NaH.<sup>77</sup> The BODIPY 72 is non-fluorescent due to photo-induced electron transfer from BODIPY to DBS group. However, in the presence of thiophenols which cleave the DBS group, the fluorescence is restored and thus 72 can be used as turn-on fluorescent probe



**Figure 12** Synthesis of 3-substituted BODIPY derivatives **68–74** derived from **(A)** 3-bromo, **(B)** 3-formyl and **(C)** 3-amino functionalized BODIPYs.  
**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; DBS, 2,4-dinitrobenzenesulfonyl.

for selective detection of thiophenols.<sup>77</sup> The BODIPY urea/thiourea derivatives **73** and **74** were prepared (Figure 12C) by the reaction of 3-amino BODIPY **66** and phenylisocyanate and phenylthiocyanate respectively under CH<sub>3</sub>CN reflux conditions.<sup>75</sup> The phenyl urea BODIPY **73** acts as colorimetric and ratiometric sensor for F<sup>−</sup> ion and thiourea BODIPY **74** can act as specific chemodosimetric sensor for Hg<sup>2+</sup> ion.<sup>75</sup>

## Difunctionalized BODIPYs

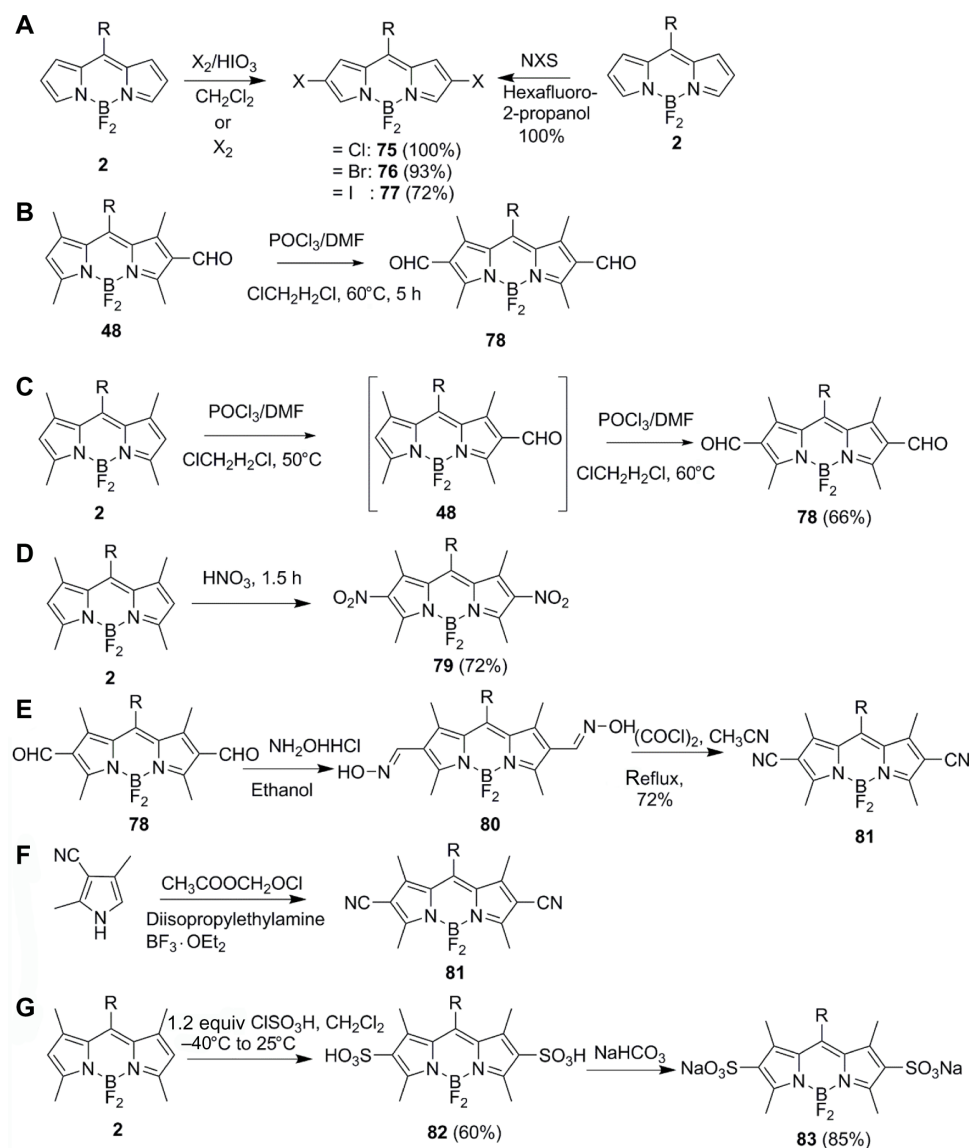
There are several reports on difunctionalized BODIPYs. Since there are six possible positions on the BODIPY core where the two functional groups can be introduced selectively to prepare difunctionalized BODIPYs, the various difunctionalized BODIPYs were prepared as described here.

### 2,6-difunctionalized BODIPYs

The 2,6-positions of BODIPY **2** bear the least positive charge and are susceptible to electrophilic attack. The 2,6-dihalogenated BODIPYs **75–77** were prepared by treating appropriate BODIPY with NXS or X<sub>2</sub> (Br<sub>2</sub>, Cl<sub>2</sub>, I<sub>2</sub>) in CH<sub>2</sub>Cl<sub>2</sub> (Figure 13A) at room temperature or other slightly varied reaction conditions.<sup>61,62</sup> Recently Wang et al showed that the regioselective dihalogenation at 2,6-positions of BODIPY **2** can be much faster when reactions were carried out in hexafluoro-2-propanol (Figure 13A) using NXS as the halogen source.<sup>78</sup> The 2,6-diformyl BODIPY **78** was prepared by treating 2-formyl BODIPY **48** under Vilsmeier–Haack

reaction conditions (Figure 13B).<sup>79</sup> However, recently it was shown that the 2,6-diformyl BODIPY **78** can be prepared in one pot by treating BODIPY **2** under Vilsmeier–Haack reaction conditions by in situ generation of 2-formyl BODIPY **48** (Figure 13C).<sup>80</sup> The 2,6-dinitro BODIPY **79** was also synthesized (Figure 13D) by treating BODIPY **2** with nitric acid at 0°C.<sup>81</sup> Similarly 2,6-dicyano BODIPY **81** was synthesized from 2,6-diformyl BODIPY **78** in two steps. In the first step, the 2,6-dioxime BODIPY **80** was prepared by treating 2,6-diformyl BODIPY **78** with NH<sub>2</sub>OH in ethanol and the resulting 2,6-dioxime BODIPY **80** was treated in a second step with (COCl)<sub>2</sub> in CH<sub>3</sub>CN (Figure 13E) to afford 2,6-dicyano BODIPY **81**.<sup>80</sup> Alternately, the 2,6-dicyano BODIPY **81** was also synthesized by reacting 3-cyano-2,4-dimethyl substituted pyrrole with acetoxyacetyl chloride followed by complexation with BF<sub>3</sub>·OEt<sub>2</sub> (Figure 13F) in the presence of diisopropylethylamine.<sup>82</sup> The 2,6-disulfonyl BODIPY **83** (Figure 13G) was prepared by using two equivalents of chlorosulfonic acid followed by quenching with NaHCO<sub>3</sub>.<sup>65</sup>

The donor-acceptor-donor system **84** was synthesized by coupling 2,6-dihalogenated BODIPY **76** with 4-borat-4,4'-dimethyl triphenylamine under transition metal catalyzed reaction conditions (Figure 14A).<sup>83</sup> The donor-acceptor-donor type triphenylamine substituted BODIPY **84** used in bulk heterojunction solar cells as electron donor exhibited photovoltaic properties with a power conversion efficiency of 0.77%. The 2,6-bis(ethynylterpyridyl) BODIPY **85** was



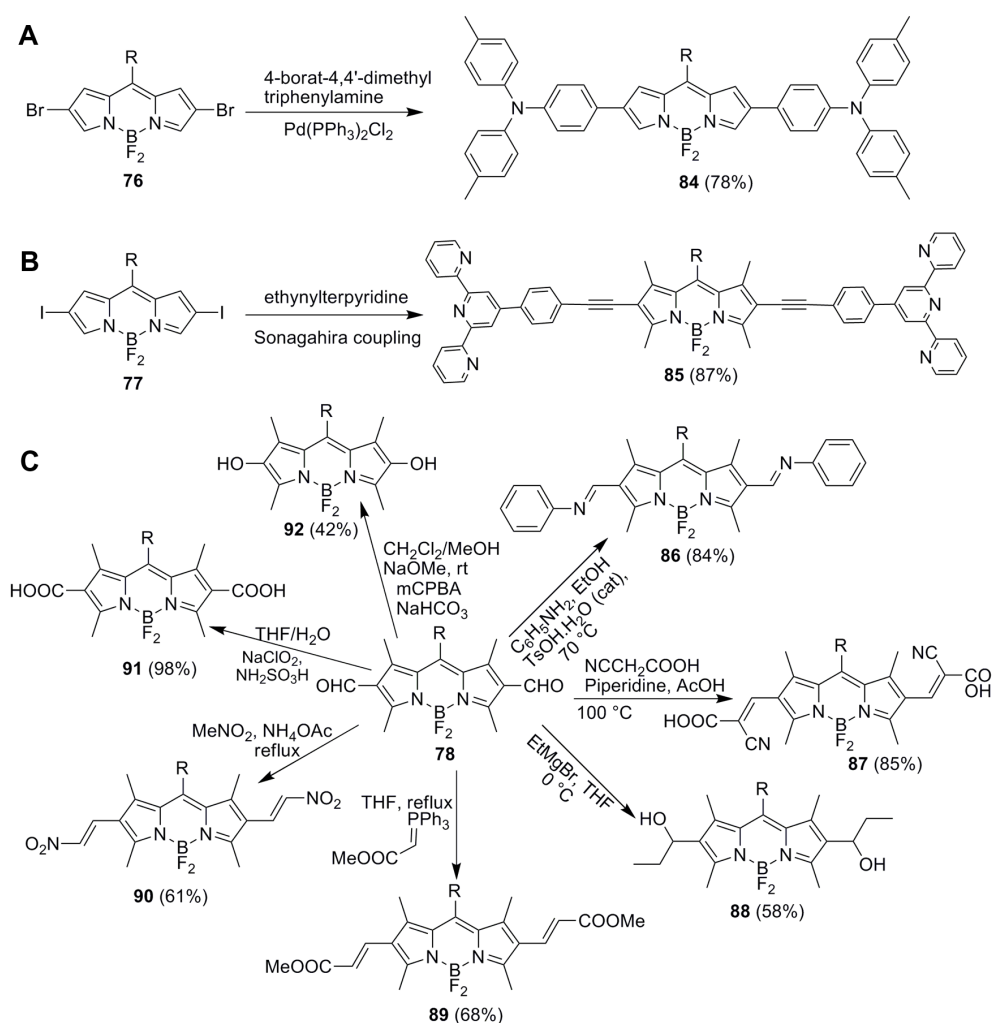
**Figure 13** Synthesis of (A) 2,6-dihalo, (B) and (C) 2,6-diformyl, (D) 2,6-dinitro, (E) and (F) 2,6-dicyano and (G) 2,6-disulfonyl functionalized BODIPYs 75–83. **Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; NXS, N-halosuccinimide; h, hours; equiv, equivalent(s).

prepared (Figure 14B) by the reaction of 2,6-dihalo BODIPY 77 with ethynylterpyridyl under Sonogashira coupling conditions.<sup>62</sup> The formyl groups present at 2,6-pyrrole carbons of BODIPY 78 were used mainly for Schiff base and Knoevenagel condensation reactions and produced new functionalized BODIPYs 86–92 as shown in Figure 14C. The 2,6-dihydroxyl BODIPY 92 was prepared by reducing the formyl groups two steps; the 2,6-dicarboxylic acid substituted BODIPY 91 was prepared by oxidation of formyl groups of 2,6-diformyl BODIPY 78 with NaClO<sub>2</sub>; the hydroxypropyl substituted BODIPY 88 was synthesized by treating 2,6-diformyl BODIPY 78 with ethylmagnesium bromide; and the dialkynyl nitro substituted BODIPY 90, divinylcyanoacetic acid substituted BODIPY 87 were synthesized under Knoevenagel conditions by treating the 2,6-diformyl BODIPY 78

with nitromethane/cyanoacetic acid.<sup>80</sup> The dialkenylester substituted BODIPY 89 was synthesized under Wittig reaction conditions by treating 2,6-diformyl BODIPY 78 with phosphorous ylide (Figure 14C).<sup>80</sup> All these  $\pi$ -extended conjugated BODIPYs exhibited a 40–50 nm bathochromic shift in their absorption and emission bands compared to 2,6-diformyl BODIPY 78 with moderate Stokes shifts and low quantum yields.

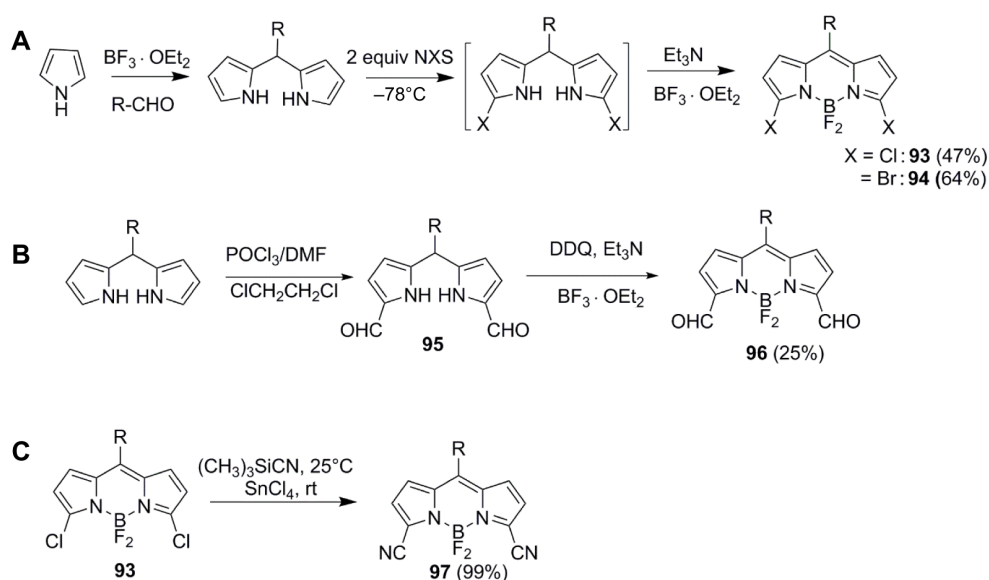
### 3,5-difunctionalized BODIPYs

The 3,5-dihalogenated BODIPYs 93 and 94 were prepared starting with meso-aryl dipyrromethane 1 as shown in Figure 15A. Treatment of meso-aryl dipyrromethane 1 with two equivalents of appropriate NXS in THF at –78°C followed by oxidation with DDQ and complexation with



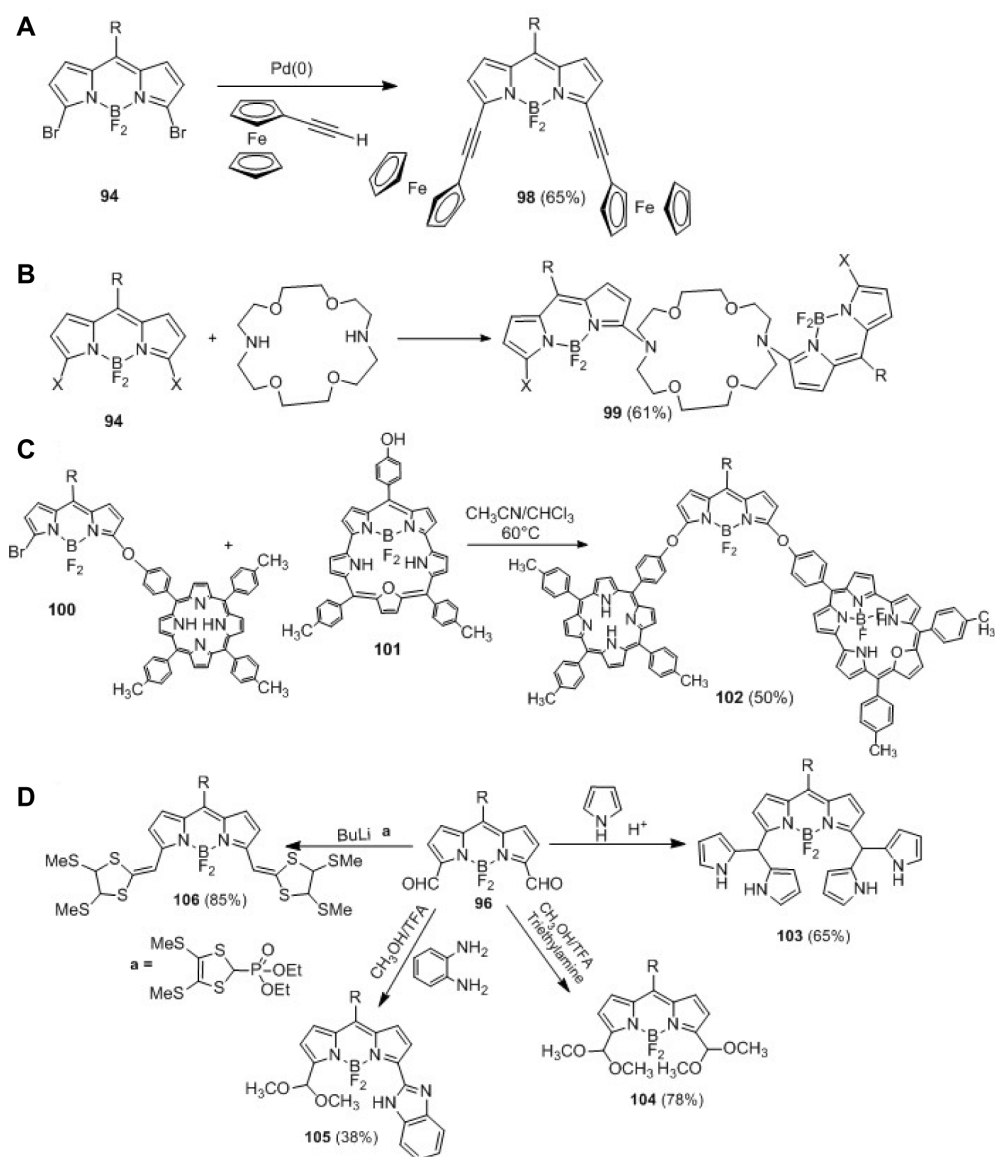
**Figure 14** Synthesis of 2,6-disubstituted BODIPYs **84–92** from **(A)** 2,6-dibromo, **(B)** 2,6-diiodo and **(C)** 2,6-diformyl functionalized BODIPYs.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; THF, tetrahydrofuran; rt, room temperature; cat, catalyst.

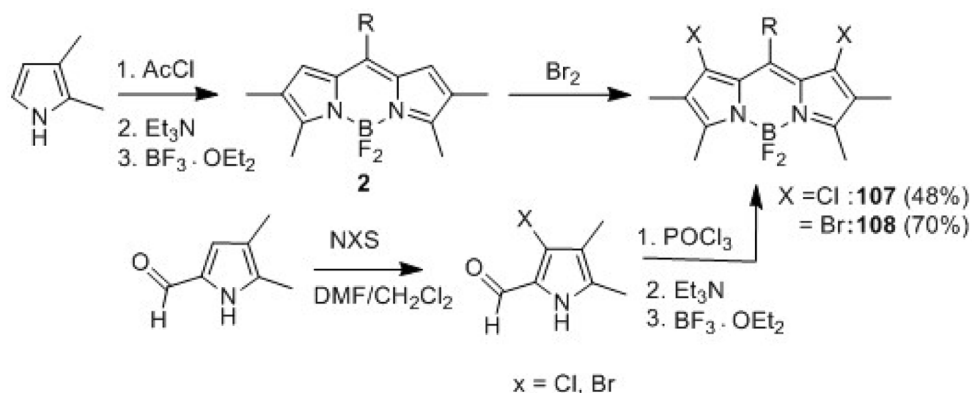


**Figure 15** Synthesis of **(A)** 3,5-dihalo, **(B)** 3,5-diformyl and **(C)** 3,5-dicyano functionalized BODIPYs **93–97**.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; equiv, equivalent(s); NXS, N-halosuccinimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; rt, room temperature.

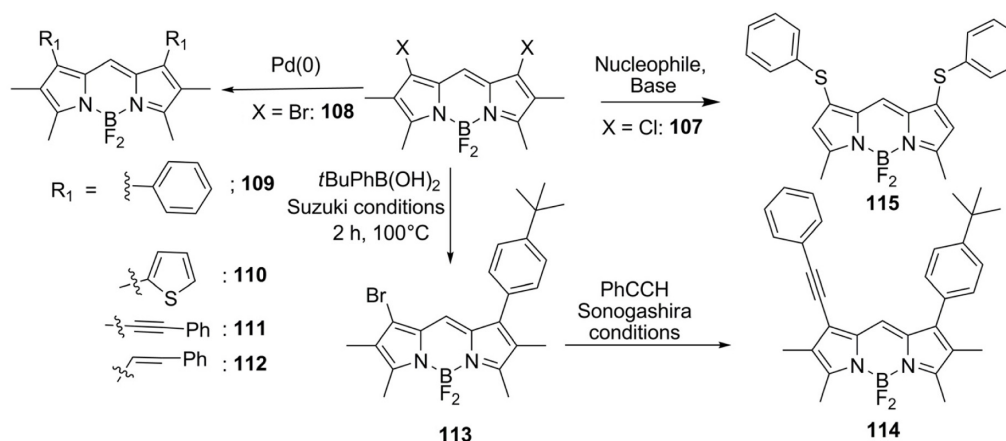


**Figure 16** Synthesis of 3,5-disubstituted BODIPY derivatives 98–106 derived from 3,5-dihalo (**A–C**), and 3,5-diformyl (**D**) functionalized BODIPYs. **Abbreviation:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrin.



**Figure 17** Synthesis of 1,7-dihalogenated BODIPYs 107 and 108. **Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; NXS, N-halosuccinimide.





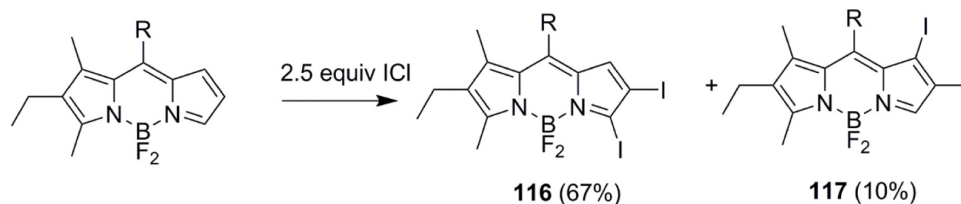
**Figure 18** Synthesis of 1,7-disubstituted BODIPY derivatives 109–115.  
**Abbreviations:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrin; h, hours.

NEt<sub>3</sub>/BF<sub>3</sub>·OEt<sub>2</sub> afforded the 3,5-dihalogenated BODIPYs 93 and 94.<sup>84–86</sup> The other halogenated BODIPYs were also formed in these reactions but column chromatography was used to separate the 3,5-dihalogenated BODIPYs 93 and 94 from the mixture of halogenated BODIPYs. This is the only reliable method available to synthesize 3,5-dihalogenated BODIPYs 93 and 94. The meso-aryl substituted 3,5-diformyl BODIPY 96 was prepared in decent yield by oxidizing the 1,9-diformyl dipyrromethane 95 with DDQ, followed by treatment with triethylamine and complexation with BF<sub>3</sub>·OEt<sub>2</sub> (Figure 15B).<sup>87</sup> Later on, Yu et al also reported the 3,5-diformyl-meso-anisyl BODIPY by following the same reaction conditions.<sup>88</sup> The 3,5-dicyano BODIPY 97 was synthesized by treating 3,5-dichloro BODIPY 93 with trimethylsilyl cyanide and SnCl<sub>4</sub> (Figure 15C) at room temperature.<sup>89</sup>

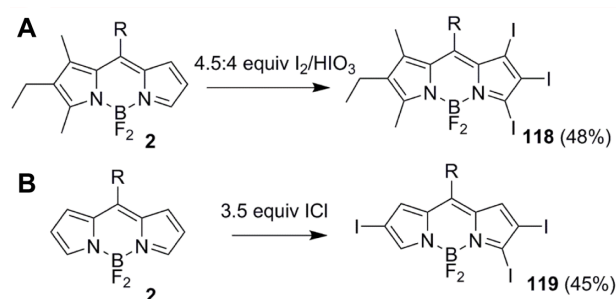
Different types of symmetrically or asymmetrically aryl/alkyl substituted BODIPY derivatives were synthesized from 3,5-dihalo BODIPYs 93/94 by the Stille, Suzuki, Heck and Sonogashira coupling reactions. The accessibility of 3,5-dihalo BODIPYs 93/94 helped in the preparation of a wide range of 3,5-diaryl substituted BODIPYs under various Pd catalyzed coupling conditions in good yields. For example, 3,5-diethynylferrocene BODIPY 98 was synthesized

(Figure 16A) from the reaction of 3,5-dibromo BODIPY 94 with ethynylferrocene under Pd(0) Sonogashira coupling conditions.<sup>85</sup> The presence of conjugated aryl groups at the 3,5-positions alters the electronic properties of the dye significantly, which was reflected in their spectral and electrochemical properties.<sup>7</sup> Furthermore, the 3,5-dihalo BODIPYs 93 and 94 were also used for various nucleophilic substitution reactions by treating with C–, O–, N–, S–, Se–, and Te– nucleophilic groups at reflux conditions (Figure 16B).<sup>86</sup> The BODIPYs containing two different types of porphyrinoids at 3,5-positions were also synthesized (Figure 16C) by treating 3-bromo-5-porphyrinyl BODIPY 100 with 4-hydroxyphenyl-BF<sub>2</sub>-oxasmaragdyrin 101 in CHCl<sub>3</sub> at 60°C.<sup>90</sup>

The 3,5-diformyl BODIPYs (96) are brightly fluorescent in solution state and exhibit good optical properties.<sup>87</sup> The 3,5-diformyl BODIPYs (96) were used as fluorescent pH sensors<sup>87</sup> and also as exclusive chemodosimetric and colorimetric sensors for CN<sup>–</sup> ion detection.<sup>91</sup> The 3,5-bis(dipyrromethanyl) BODIPY 103 was synthesized by treating the 3,5-diformyl BODIPY 96 with pyrrole under acidic conditions (Figure 16D).<sup>92</sup> The bis(dipyrromethanyl BODIPY) 103 showed a specific selectivity for fluoride ion due to the presence of four NH groups that have the ability to bind F<sup>–</sup> ion strongly.<sup>92</sup> The



**Figure 19** Synthesis of 1,2,2,3-diiodo BODIPYs 116 and 117.  
**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; equiv, equivalent(s).



**Figure 20** Synthesis of (A) 1,2,3- triiodo BODIPY 118 and (B) 2,3,6-triiodo BODIPY 119.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; equiv, equivalent(s).

BODIPY containing acetal groups at 3,5-position 104 was synthesized by treating 3,5-diformyl BODIPY 96 with a catalytic amount of TFA (trifluoroacetic acid) in methanol at room temperature and demonstrated as a fluorescent chemodosimeter for the detection of explosive picric acid in aqueous medium (Figure 16D).<sup>93</sup> The benzimidazole containing BODIPY derivative 105 was prepared by treating 3,5-diformyl BODIPY 96 with *o*-phenylenediamine in CH<sub>3</sub>OH in the presence of a catalytic amount of trifluoroacetic acid (Figure 16D) and demonstrated its use as reversible and reusable selective chemosensor for fluoride detection.<sup>94</sup> Recently Bill et al reported a “on-off-on” electrochromic system, the  $\pi$ -extended tetrathiafulvalene substituted BODIPY 106 synthesized by treating 3,5-diformyl BODIPY 96 with phosphonate ester under Horner-Wadsworth-Emmons type coupling conditions.<sup>95</sup>

### 1,7-difunctionalized BODIPYs

The 1,7-positions of BODIPY 2 are electron poor like 3,5-positions and direct halogenation on BODIPY 2 at these positions is not possible if other positions are not blocked with the substituents. Leen et al synthesized the first examples of 1,7-dihalogenated BODIPYs 107 and 108 by adopting two synthetic routes shown in Figure 17.<sup>96</sup> In the first strategy, the authors condensed the 2,3-dimethylpyrrole

with acetyl chloride in CH<sub>2</sub>Cl<sub>2</sub> followed by in situ complex formation to afford 2,3,5,6-tetrasubstituted BODIPY, which was subjected to bromination with Br<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> and afforded 1,7-dibrominated BODIPY 108 in 82% yield. In the second strategy, the 2,3-dimethylpyrrole was first formylated at 5-position under standard Vilsmeier–Haack reaction conditions, which was then halogenated at 4-position by treating with NXS and afforded 2,3-dimethyl-4-halo-5-formyl pyrrole.<sup>96</sup> The substituted pyrrole was then treated with phosphorus oxychloride to afford dipyrromethene that was then complexed with BF<sub>3</sub>·OEt<sub>2</sub> and obtained 1,7-dihalogenated BODIPYs 107 and 108 as sole product (Figure 17). Thus, the 1,7-dihalogenated BODIPYs 107 and 108 can be prepared by only blocking all other pyrrolic positions of BODIPY.<sup>96</sup>

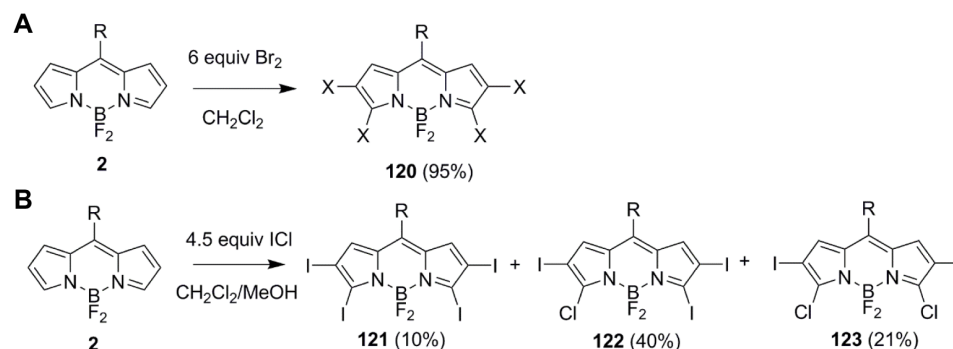
The 1,7-dihalo substituted BODIPYs 107 and 108 were subjected to Pd(0) cross-coupling reactions such as Suzuki, Heck, and Sonogashira coupling reactions 109–114 as well as nucleophilic substitution reactions (Figure 18).<sup>96</sup> Among the nucleophiles, only sulfur based nucleophiles were introduced at 1,7-positions of BODIPY 115. The extension of conjugation at 1,7-positions of BODIPY did not alter the optical properties significantly compared to 3,5-positions of BODIPY.<sup>96</sup>

### 1,2/2,3-difunctionalized BODIPYs

Ortiz et al reported synthesis of 2,3- diiodinated 116 and 1,2-diiodinated 117 BODIPYs by treating BODIPY 2 with 2.5 equivalents of ICl in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH and the resulting mixtures of diiodinated BODIPYs 116 and 117 were separated by column chromatography (Figure 19).<sup>97</sup> These kinds of dihalogenated BODIPYs 116 and 117 can be prepared only by blocking the second pyrrole ring carbons of BODIPY unit 2.

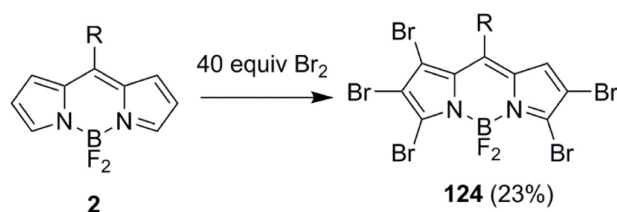
### Trifunctionalized BODIPYs

Jiao et al reported regiospecific bromination of BODIPYs by treating BODIPY 2 with liquid bromine but they failed



**Figure 21** Synthesis of (A) tetrabromo and (B) tetrahalogenated BODIPYs 120–123.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; equiv, equivalent(s).



**Figure 22** Synthesis of pentahalogenated BODIPY 124.

**Abbreviations:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrin; equiv, equivalent(s).

to isolate pure tribromo BODIPY.<sup>61</sup> Ortiz et al prepared the 1,2,3-trihalogenated BODIPY 118 by taking BODIPY 2 in which one of the pyrrole ring carbons were blocked and treated with 4.5:4 ratio of I<sub>2</sub>/HIO<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH at room temperature (Figure 20A).<sup>97</sup> The reaction resulted in the formation of a mixture of two different types of BODIPYs such as 1,2,3-trihalogenated BODIPY 118 and 2,3-dihalogenated BODIPY which were separated by column chromatography. The same research group also reported the synthesis (Figure 20B) of 2,3,6-trihalogenated BODIPY 119 by treating meso-aryl BODIPY 2 with 3.5 equivalents of ICl and the resulting mixtures of halogenated BODIPYs were separated by column chromatography to afford 2,3,6-trihalogenated BODIPY 119.<sup>97</sup>

## Tetrafunctionalized BODIPYs

Jiao et al reported the synthesis of 2,3,5,6-tetrabromo BODIPY 120 by treating BODIPY 2 with 6 equivalents of Br<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> (Figure 21A).<sup>61</sup> This method afforded the desired tetrabrominated BODIPY 120 along with other brominated BODIPYs and were separated by column chromatography. Ortiz et al prepared tetraiodinated BODIPY 121 and other tetrahalogenated BODIPYs with two different types of halogens such as iodo and chloro groups 122 and 123 by treating

BODIPY 2 with 4.5 equivalents of ICl in CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH (Figure 21B) and isolated the tetrahalogenated BODIPYs 121–123 by column chromatography.<sup>97</sup>

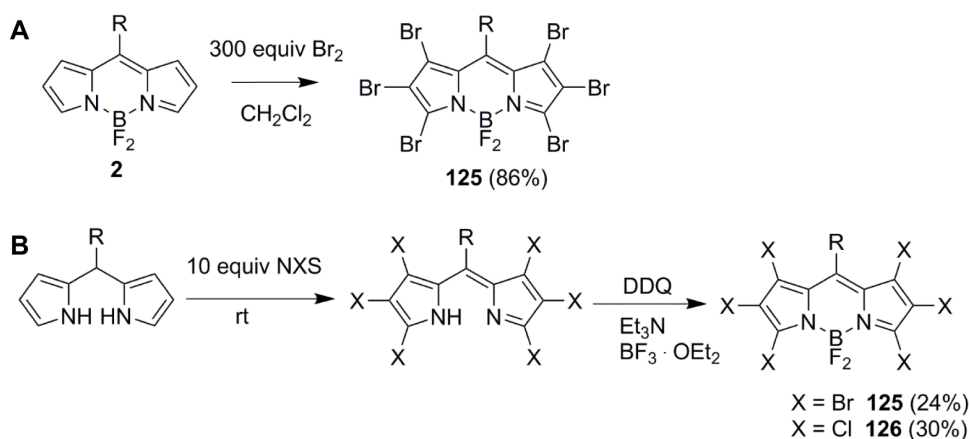
## Pentafunctionalized BODIPYs

Jiao et al prepared pentahalogenated BODIPY 124 by treating BODIPY 2 with 40 equivalents of Br<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> (Figure 22).<sup>61</sup> In this strategy, the pentahalogenated BODIPY 124 was formed as major product along with other minor brominated BODIPYs and column chromatography was used to separate and isolate the pentahalogenated BODIPY 124 from other halogenated BODIPYs.

## Hexafunctionalized BODIPYs

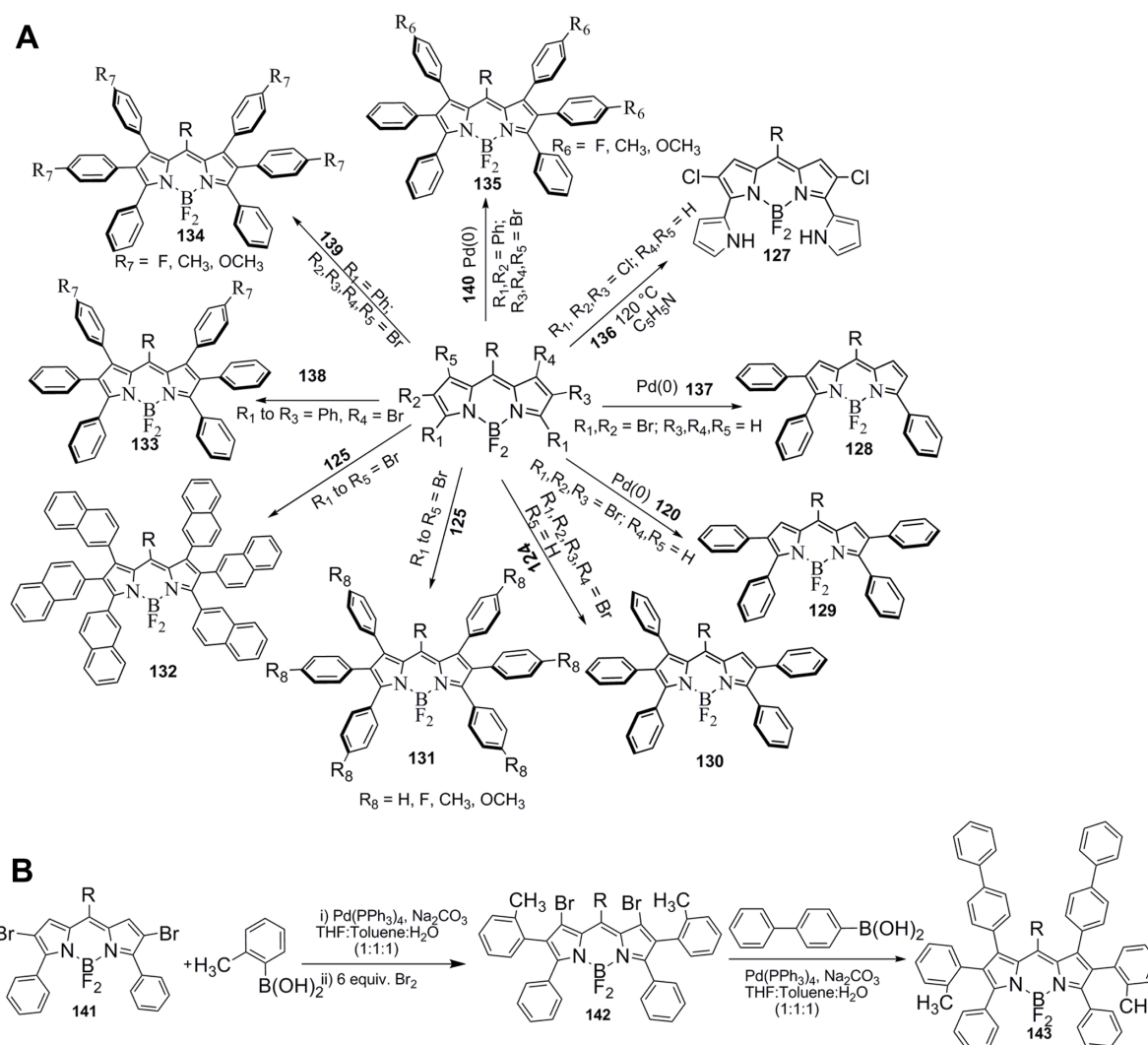
Jiao et al attempted to prepare hexabrominated meso-aryl BODIPY 125 by treating meso-aryl BODIPY 2 with 300 equivalents of Br<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub> (Figure 23A) and obtained a decent yield.<sup>61</sup> 1,2,3,5,6,7-Hexahalogenated BODIPYs 125 and 126 were also prepared by treating meso-aryl dipyrromethane 1 with excess equivalents of NXS in THF at room temperature followed by oxidation with DDQ and complexation with BF<sub>3</sub>·OEt<sub>2</sub> (Figure 23B).<sup>59,98</sup>

The tri, tetra, and pentahalogenated BODIPYs were used to synthesize corresponding aryl substituted BODIPYs 128–130 by reacting with appropriate arylboronic acids at 80°C (Figure 24A) under Suzuki coupling conditions.<sup>99</sup> The nucleophilic substitution of tetrachloro BODIPY 136 with pyrrole under reflux conditions produced 2,6-dichloro-3,5-dipyrrolyl BODIPY 127 (Figure 24A).<sup>100</sup> Furthermore, the hexahalogenated BODIPY 125 was used extensively to prepare a variety of sterically crowded hexasubstituted BODIPYs 131 and 132 such as hexaphenyl, hexatolyl, hexafluorophenyl, hexa-anisyl and hexanaphthyl.<sup>101</sup>



**Figure 23 (A and B)** Synthesis of hexahalogenated BODIPYs 125 and 126.

**Abbreviations:** BODIPYs, boron-dipyrromethenes/BF<sub>2</sub>-dipyrins; equiv, equivalent(s); NXS, N-halosuccinimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; rt, room temperature.



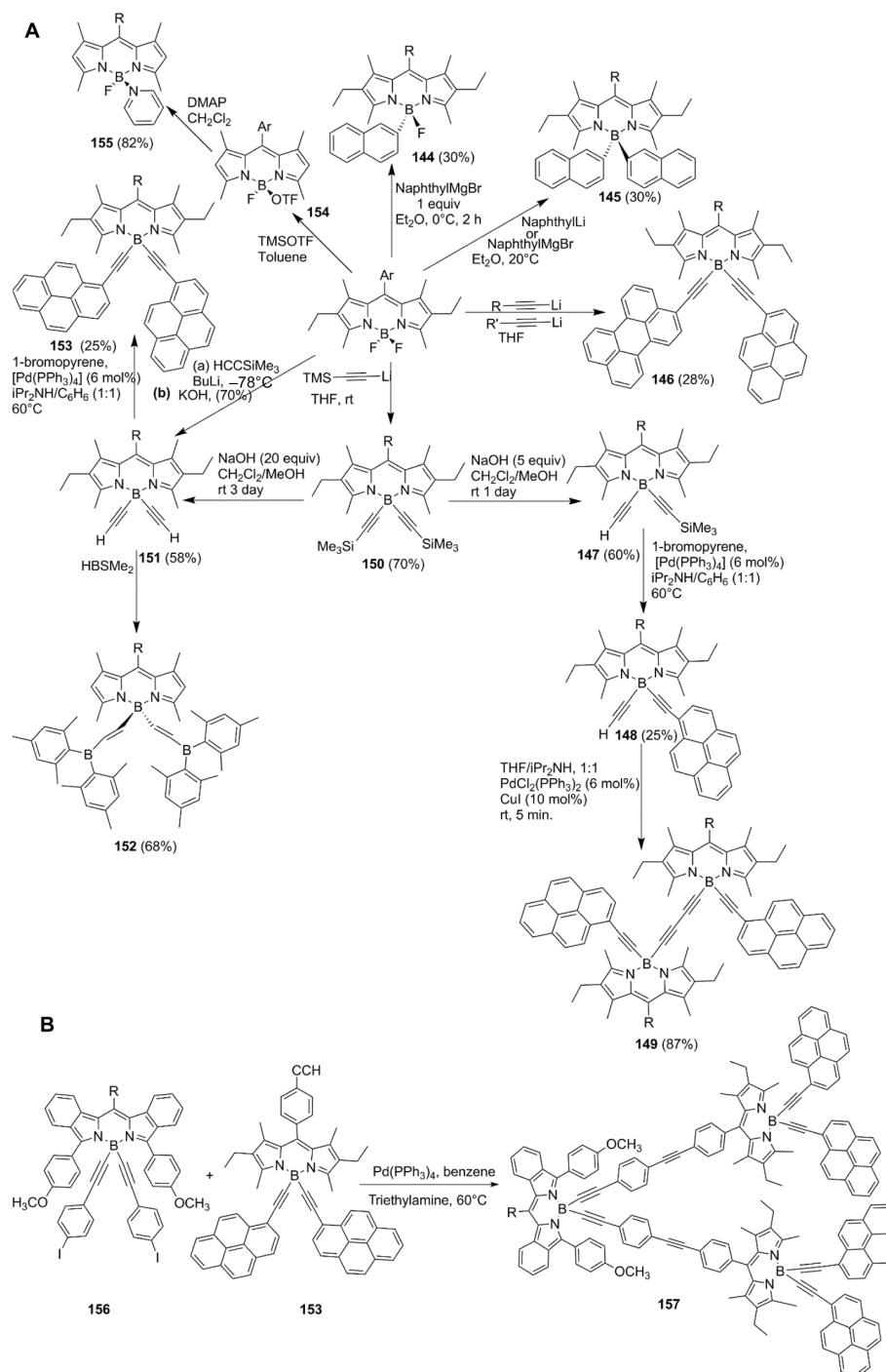
**Figure 24** Synthesis of **(A)** tri, tetra, and various types of polyarylated BODIPYs 127–135 and **(B)** hexaarylated BODIPY having three different types of substituents 143. **Abbreviations:** BODIPYs, boron-dipyrromethenes/ $\text{BF}_2$ -dipyrins; equiv, equivalent(s); THF, tetrahydrofuran.

The hexasubstituted BODIPYs with two different types of substituents (aryl/alkyl) at pyrrole carbons 133–135 were also synthesized in a step-wise manner under Pd(0) catalyzed Suzuki coupling conditions by coupling the appropriate bromo BODIPY and boronic acid at 80°C.<sup>102</sup> For example, 3,5-diphenyl-1,2,6,7-tetrabromo BODIPY 139 was coupled with different boronic acids such as fluorophenylboronic acid, tolylboronic acid, anisylboronic acid, and methylboronic acid under Suzuki coupling conditions to synthesize (Figure 24A) the corresponding hexasubstituted BODIPY with two different types (aryl/alkyl) of groups 133–135.<sup>102</sup> Hexasubstituted BODIPY with three different types of aryl groups 143 was synthesized in a sequence of steps which involve several halogenated reactions followed by Pd(0) catalyzed coupling reactions.<sup>103</sup> The 1,7-dibromo-3,5-diphenyl-2,6-di(o-tolyl) BODIPY 142 was synthesized (Figure 24B) in

two steps from 2,6-dibromo-3,5-diphenyl BODIPY 141 by coupling with o-tolylboronic acid followed by bromination with six equivalents of  $\text{Br}_2$ . In the next step, the 1,7-dibromo-3,5-diphenyl-2,6-di(o-tolyl) BODIPY 142 was treated with 4-biphenylboronic acid at 80°C to afford 1,7-bis(biphenyl)-3,5-diphenyl-2,6-di(o-tolyl) BODIPY 143.<sup>103</sup>

## Functionalization at the B(III) center of BODIPYs

In addition to functionalization of the BODIPY core at the pyrrole carbons and meso-aryl group, recently it was realized that even fluorides of  $\text{BF}_2$  moiety of BODIPY can be substituted under various conditions (Figures 25 and 26). Ulrich et al reported the first substitution of F atoms with ethynylarenes by treating BODIPY with lithiated ethynylarenes (Figure 25A) in THF under mild reaction conditions.<sup>104</sup> Using this approach,



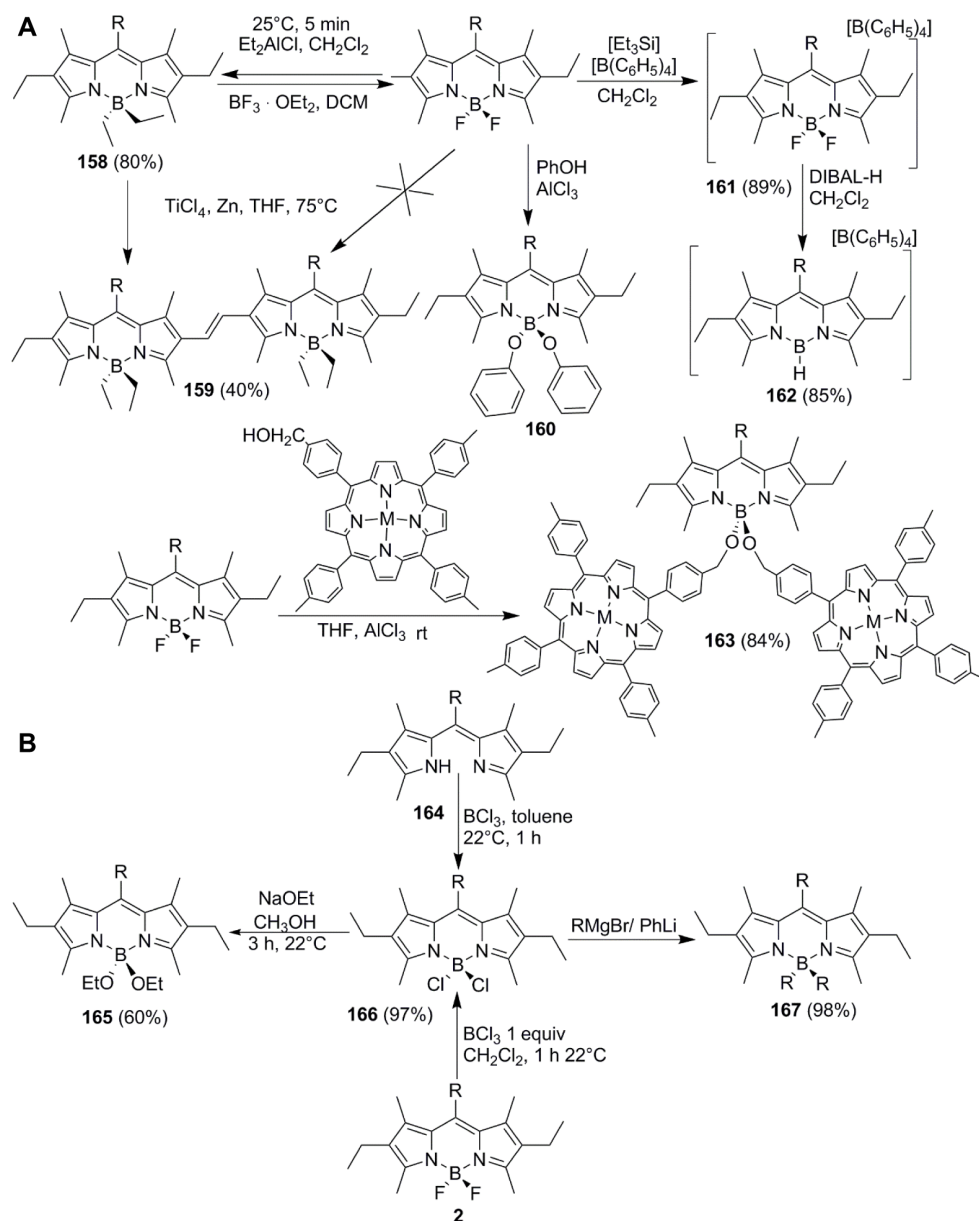
**Figure 25** Synthesis of (A) ethynyl substituted and (B) cascade type ethynyl substituted BODIPY-chromophore conjugates 144–157.

**Abbreviations:** BODIPY, boron-dipyrromethene/ $\text{BF}_2$ -dipyrin; equiv, equivalent(s); h, hours; TMSOTf, trimethylsilyl trifluoromethanesulfonate; min, minutes; THF, tetrahydrofuran; rt, room temperature.

they introduced a wide range of ethynylaryl groups at the boron center by replacing the fluoride atoms. Thus, ethynylaryl groups such as ethynylpyrene, ethynylperylene, ethynylanthracene, ethynylterpyridine along with other simple protected ethynyls were introduced (Figure 25A and B) at the boron center and produced several interesting compounds 146–153 and 156 and 157.<sup>105</sup> In some of these systems, such as ethy-

nylpyrene substituted BODIPY 153, highly efficient energy transfer was observed from pyrene to the BODIPY moiety. This synthetic approach also allowed synthesis of asymmetrical derivatives<sup>106</sup> bearing two different ethynylaryl groups at the boron center such as compound 146–148. Furthermore, Goze et al used their approach more efficiently and prepared a series of donor–spacer–acceptor triads as shown for the preparation





**Figure 26** Synthesis of F-substituted BODIPY derivatives 158–167 derived from (A) BF<sub>2</sub>-BODIPY and (B) BCl<sub>2</sub>-BODIPY.

**Abbreviations:** BODIPY, boron-dipyrromethene/BF<sub>2</sub>-dipyrin; equiv, equivalent(s); h, hours; min, minutes; THF, tetrahydrofuran.

of compound 149 and explored their intramolecular energy transfer properties.<sup>107,108</sup>

Ulrich et al also synthesized a series of various BODIPY bearing substituents such as butyl, phenyl, naphthyl, pyrenyl etc, by treating BODIPY with organometallic reagents (aryl/alkyl lithium and Grignard reagent) under mild conditions (Figure 25A).<sup>109</sup> These reactions yielded either mono-substituted 144 or disubstituted 145 products depending on reaction conditions.<sup>110</sup> These compounds were highly fluorescent and exhibited interesting redox properties. Lu et al reported the synthesis of BODIPY derivatives 152 (Figure 25A) where F atoms were substituted by BMeS<sub>2</sub>(vinyl)

groups by treating bis-acetylide BODIPY 151 with HBSMe<sub>2</sub> under hydroboration reaction conditions.<sup>111</sup>

Tahtaoui et al synthesized B(OR)<sub>2</sub>-dipyrin complexes 160, 163 by treating BODIPY with appropriate alkyl/aryl alcohol (Figure 26) in the presence of AlCl<sub>3</sub>.<sup>112,113</sup> Hudnall and Gabbai synthesized *p*-dimethylaminopyridine adduct of BODIPY by treating BODIPY with trimethylsilyltriflate followed by dimethylaminopyridine and the resulting adduct 155 was used for the detection of fluoride ions.<sup>114</sup> Recently, Bonnier et al reported the synthesis<sup>115</sup> of boreonium cations 161 (Figure 26) resulting from the abstraction of fluoride of a BODIPY, by treating it with trimethylsilyl

ion/pentafluoroarylborate ion and the borenium cation was converted to a borenium hydride 162 by treatment with DIBAL-H. Recently,  $\text{BCl}_2$ -dipyrrin 166 was prepared<sup>116,117</sup> by treating BODIPY with one equivalent of  $\text{BCl}_3$  in  $\text{CH}_2\text{Cl}_2$  or by direct reaction of dipyrrin 164 with  $\text{BCl}_3$  in toluene at room temperature (Figure 26B). The  $\text{BCl}_2$ -dipyrrin complex was also used to prepare alkyl/aryl substituted B-dipyrrin complex 167 as well as alkyloxy or aryloxy substituted B-dipyrrin complexes 165 under similar reaction conditions used for BODIPYs (Figure 26B).<sup>116,117</sup> More et al prepared  $\text{BEt}_2$ -dipyrrin 158<sup>118</sup> by treating BODIPY with  $\text{Et}_2\text{AlCl}$  and also easily converted  $\text{BEt}_2$ -dipyrrin back to BODIPY by reacting with  $\text{BF}_3\cdot\text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$ . This masking and demasking strategy was used to synthesize a BODIPY dimer 159 by McMurry coupling (Figure 26A). Thus, fluoride atoms of  $\text{BF}_2$  moiety of BODIPY are also susceptible to various reactions and allow for a wide variety of substituted boron dipyrrin complexes.

## Conclusion

Functionalized BODIPYs are highly desirable to prepare a wide variety of substituted BODIPYs that can have potential applications in research fields ranging from materials and biology to medicine. The BODIPYs are synthetically very easily accessible and have several potential sites where functionalization can be carried out to prepare the functionalized BODIPYs. Earlier, the functional group(s) were introduced at the meso-aryl group by following the standard synthetic protocol of condensing the functionalized aryl aldehydes with pyrrole under mild acid catalyzed conditions followed by oxidation and complexation with  $\text{BF}_2$  group. However, in recent times, several strategies have been developed to introduce a variety of functional groups at different sites on the BODIPY core. Thus, methods were developed to introduce the functional groups directly at the meso-position, at all pyrrole carbons of the BODIPY core, and also at the boron center. These functionalized BODIPYs were further used to prepare the desired complex BODIPYs and explore their applications in different fields, which have been discussed in other recently published reviews.<sup>12–16</sup> We anticipate that future efforts will be directed toward introducing a larger variety of functional groups on BODIPY including water-soluble groups and using dyes more effectively for various applications.

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## Disclosure

The authors have no conflicts of interest to disclose.

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