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Synthesis of novel tetrachromophoric cascade-type Bodipy dyes

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Abstract

Two series of multi-cascade scaffolds bearing a boradiazaindacene (yellow dye) or a boradibenzopyrromethene (green dye) as the final energy acceptor have been synthesized. Each scaffold contains one, two or three alkynylaryl energy donors (such as pyrene D_1, perylene D_2, and fluorene D_3) linked to the boron center. Palladium-catalyzed cross-coupling of dihalogenated Bodipy starting material enabled the step-by-step construction of the different modules. In all cases, selective irradiation in each absorbing subunit resulted in efficient energy transfer over 25 Å to the Bodipy units.

Keywords: Bodipys'; Polyaromatic; Alkyne; Fluorescence; Energy transfer

Cascade energy transfer events occur in many natural processes involving energy conversion and storage. Photosynthetic organisms contain a circular light-harvesting center which optimizes absorption of solar energy and transfers it to the reaction center where it is used to bring about reactions such as the oxidation of water to oxygen (PSI) and the fixation and transformation of carbon dioxide (PSII).[1] Both energy and electron transfer processes are involved and appear to be extremely efficient (over 90%) and very fast (sub-picosecond regime). Chemists have learned how to carefully design artificial systems mimicking some of these processes and many have found application in energy conversion devices,[2] redox switches,[3] photonic wires and gates,[4] logic systems,[5] and cassette dyes for intracellular imaging and artificial enhancement of the Stokes' shift of a given fluorescent probe.[6] Our group recently designed systems in which highly luminescent dyes were involved in ultra-fast energy cascades probably involving dipole–dipole coupling.[7] An important component of these systems was the boradiazaindacene (Bodipy) units, fluorophores which have recently attracted a lot of interest from different communities due to their outstanding properties including high extinction coefficients, large quantum yields of the singlet emitter and high stability,[8] making them attractive for diverse applications such as artificial light harvesters,[9] fluorescent sensors,[10] laser dyes,[11] or electron transfer reagents.[12]

The focus of the present work is the synthesis of two families of tetrachromophoric donor–acceptor polyads based on two Bodipy units with different absorption wavelength as the energy acceptors, these being linked via unsaturated bridges to energy donors D_1, D_2, or D_3 (Chart 1).

Recently, a new method for functionalizing the boron atom in Bodipy was developed in our laboratory. This

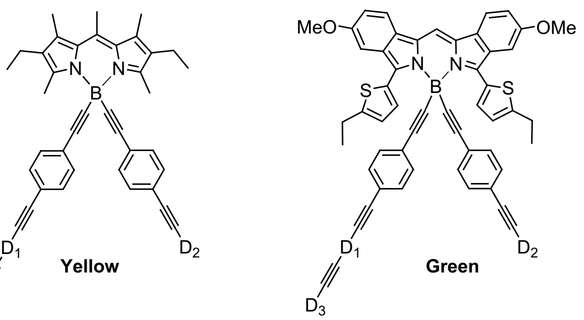

Chart 1. General structures of the target tetrachromophoric multi-cascade type of Bodipy dyes.

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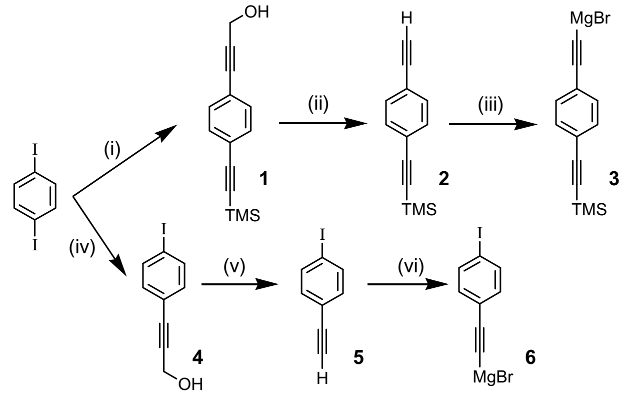
involved replacement of the fluoro substituents by carbanions, enabling the creation of one or two boron–carbon bonds,[13] each of them being useful as part of a connector to other chromophores. In particular, an asymmetrically protected 1,4-ethynylphenyl unit is an excellent connector because it is easy to generate an anion on the terminal alkyne, allowing the construction of oligomers by Pd(0) promoted reactions, and it ensures good electronic communication between the respective modules. The present work is a development of this approach.

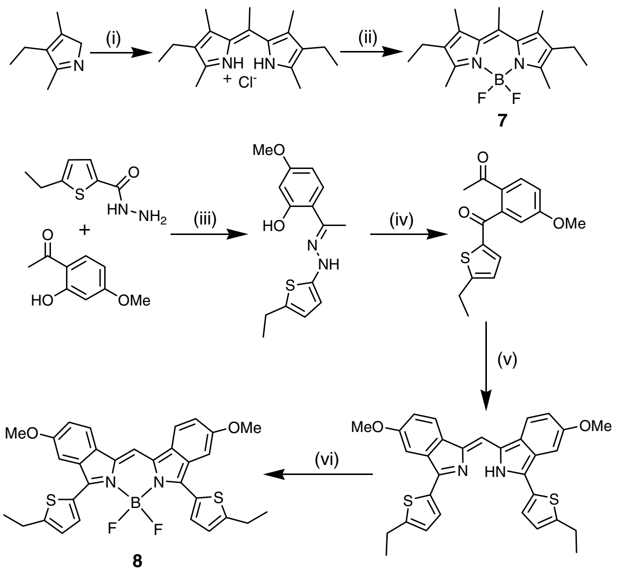
To obtain the halo-compounds **9a** and **10a**, it is necessary to prepare a 1,4-disubstituted phenyl ring carrying two different functions (Scheme 1). We chose two different strategies, the first leading to derivative **3** via a statistical cross-coupling reaction using two different alkyne sources, propargyl alcohol and trimethylsilylacetylene, and ultimately to **1** in 44% yield. The second strategy required a single equivalent of propargyl alcohol, leading to **4** in 46% yield. The propargyl substituent is useful as its polarity enables easy purification of such derivatives. Its oxidation by MnO_2,[14] followed by decarboxylation in an aprotic solvent, gave compounds **2** and **5** in 85% yield. Such removal of the CH_2OH protective group from the alkyne appeared to be more efficient than removal of $C(CH_3)_2OH$ protective group.[15] The Grignard derivatives **3** and **6** were prepared from ethylmagnesium bromide in anhydrous THF (Scheme 1).

The starting dyes **7** and **8** were prepared according to Scheme 2 using the standard preparative procedures.[11,15]

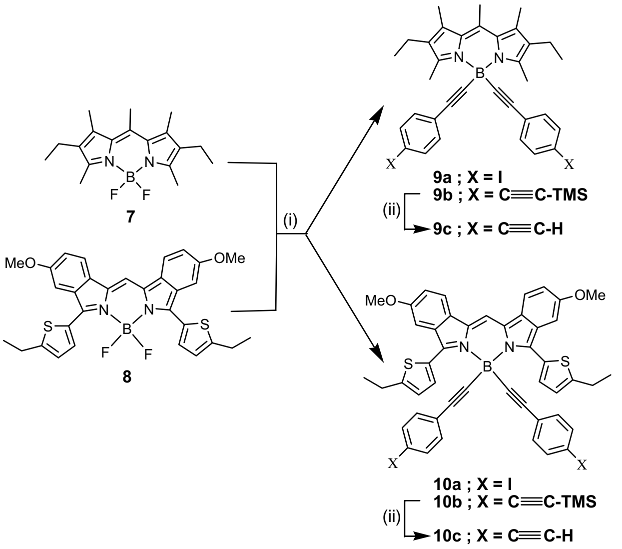
The reaction of the Grignard reagents **3** or **6** in anhydrous THF at 70 °C with chromophores **7** and **8** provided the key derivatives **9a/b** (87%) and **10a/b** (78%) (Scheme 3). In neither case was the monosubstituted compound detected by thin-layer-chromatography, despite the very slow reaction (completion over 15 h). Replacement of a single fluoro ligand was previously observed at low temperature using stoichiometric amounts of various Grignard reagents.[16] The TMS protecting groups in **9b** and **10b** were removed using K_2CO_3 under protic conditions at rt. Unfortunately, the terminal alkynes **9c** and **10c** were unstable and impossible to cross-couple with halogeno or pseudo-halogeno derivatives such as 1-bromopyrene or 4′-{[(trifluoromethyl)sulfonyl]oxy}-2,2′:6′,2″-terpyridine. Rapid polymerization of the terminal alkyne functions in **9c** and **10c** was possibly initiated by trace amounts of residual metals.



Scheme 1. Reagents and conditions: (i) trimethylsilylacetylene $[Pd(PPh_3)_2Cl_2]$, CuI, THF, *i*-Pr_2NH, then propargyl alcohol, 46%; (ii) MnO_2, KOH, Et_2O, 85%; (iii) ethylmagnesium bromide, anhydrous THF, 70 °C; (iv) propargyl alcohol, $[Pd(PPh_3)_2Cl_2]$, CuI, THF, *i*-Pr_2NH, 46%; (v) MnO_2, KOH, Et_2O, rt, 81%; (vi) ethylmagnesium bromide, anhydrous THF, 70 °C.

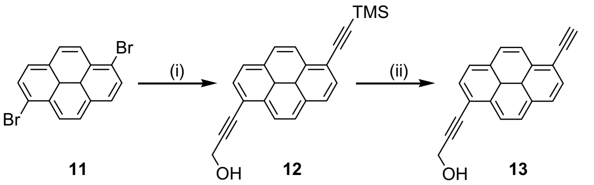


Scheme 2. Reagents and conditions: (i) aceylchloride (1 equiv), CH_2Cl_2, rt, 2 days, 65%; (ii) $BF_3·Et_2O$ (2 equiv), TEA (3 equiv), rt, 2 h, 90%; (iii) no solvent, 75 °C, 87%; (iv) $Pb(OAc)_2$, THF, 95%; (v) NH_4OAc, NH_4Cl, CH_3COOH, EtOH, reflux, 50%; (vi) (*i*Pr)$_2$EtNH, $BF_3·Et_2O$, CH_2Cl_2, 80%.



Scheme 3. Reagents and conditions: (i) compounds **3** or **6**, anhydrous THF, 70 °C; (ii) K_2CO_3, CH_2Cl_2/CH_3OH 1/1, rt.

Subsequent work focused on efficient differentiation of the two bromo positions of 1,6-dibromopyrene[17] (Scheme 4). To reach this target we used a double Sonogashira

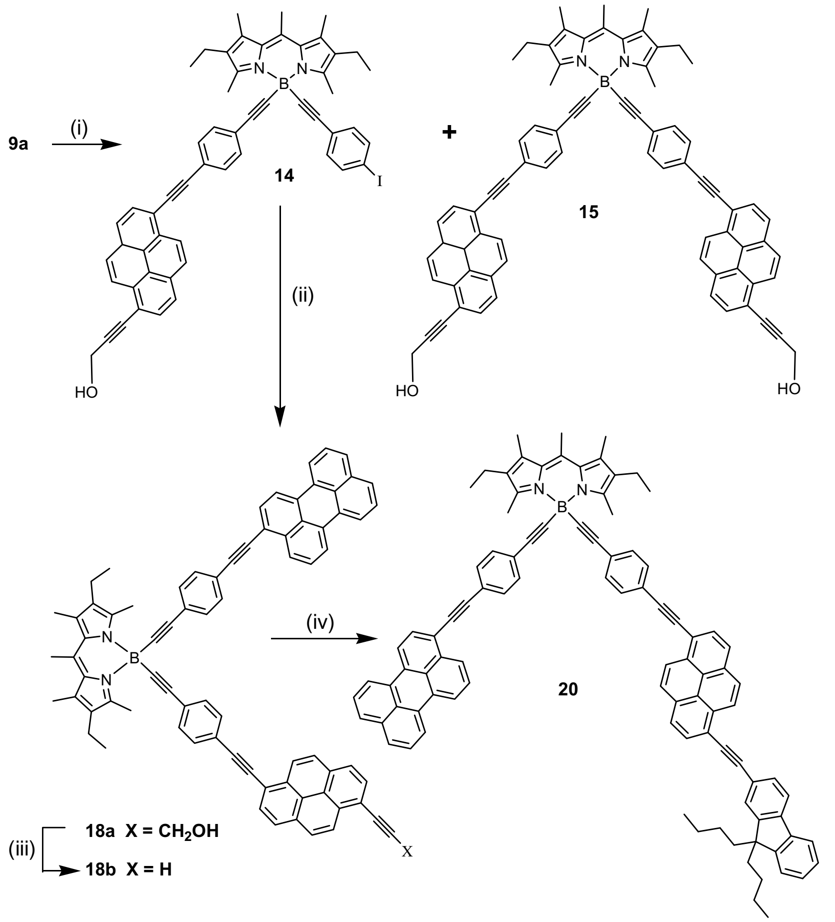


Scheme 4. Reagents and conditions: (i) $[Pd(PPh_3)_2Cl_2]$ (6 mol %), CuI (6 mol %), THF/*i*-Pr_2NH 2/1 (v/v), ethynyltrimethylsilane (1 equiv), rt, 2 h; then propargyl alcohol (5 equiv), rt, 15 h, 46%; (ii) K_2CO_3, THF, MeOH, 87%.

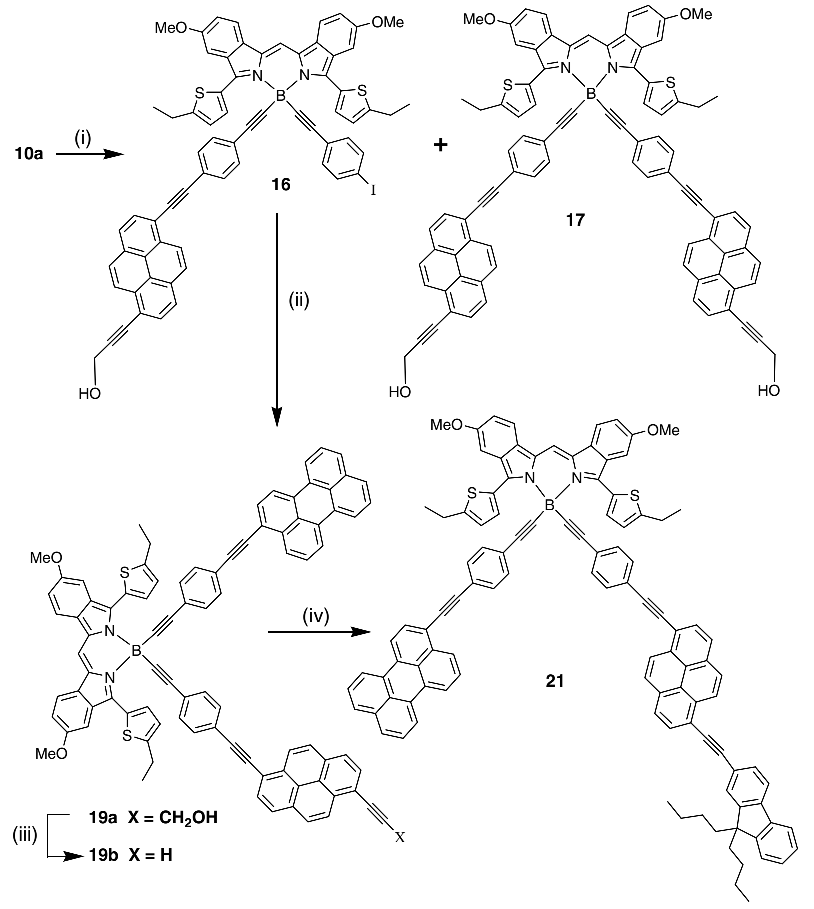
coupling reaction of **11** with ethynyltrimethylsilane as the first reagent and propargyl alcohol as the second. Derivative **12** (46%) was especially useful both because its purification was straightforward and because deprotection of the two functional groups involved completely different procedures. Thus, deprotection of the trimethylsilyl protecting group was achieved using K_2CO_3 in a protic solvent, giving **13** in 87% yield. Oxidative truncation of the propargyl group was not necessary at this stage, since it was advantageous to use the polarity engendered by the CH_2OH group in the separation of the otherwise relatively apolar Bodipy derivatives.

In the next step, we examined the coupling reaction between **13** and the preorganized dyes **9a** and **10a**. The best yields were obtained using a Pd^0 catalyst and one equivalent of the pyrene derivative **13**. To avoid any formation of the butadiyne side products, copper was excluded from these coupling reactions. Due to the facile separation of the reactant and the mono- and di-substituted products resulting from the polarity of the propargyl group, compounds **14** and **16** were isolated in respectively 72% and 46% yield. The poorly soluble bis-alcohol compounds **15** and **17** were isolated pure by filtration the crude mixture in less than 20% yield (Schemes 5 and 6).

In an effort to incorporate the donor D_2, the free iodo function present in dyads **14** and **16** was reacted with 3-ethynylperylene[18] to give **18a** (88%) and **19a** (86%). While deprotection of these compounds with a mixture of MnO_2 and KOH produced the terminal alkynes, they were too reactive to be conveniently isolated, probably for the same reasons stated above (rapid oxidative homo-polymerization induced by traces of metal). Thus, after a rapid filtration of the reaction mixture, the deprotected compounds **18b** and **19b** were allowed to react with 9,9-dibutyl-2-ethynyl-9*H*-fluorene to provide the target tetrachromophoric systems **20** (89%) and **21** (54%). As stated above, the



Scheme 5. Reagents and conditions: (i) compound **13**, $[Pd(PPh_3)_4]$, benzene, Et_3N, 60 °C, 46%; (ii) 3-ethynylperylene, $[Pd(PPh_3)_4]$, benzene, Et_3N, 60 °C, 88%; (iii) MnO_2, KOH, THF, rt, 82%; (iv) 9,9-dibutyl-2-ethynyl-9*H*-fluorene, $[Pd(PPh_3)_4]$, benzene, Et_3N, 60 °C, 89%.



Scheme 6. Reagents and conditions: (i) compound **13**, [Pd(PPh$_3$)$_4$], benzene, Et$_3$N, 60°C, compound **16**: 46%; (ii) 3-ethynylperylene, [Pd(PPh$_3$)$_4$], benzene, Et$_3$N, 60 °C, compound **19a**: 86%; (iii) MnO$_2$, KOH, THF, rt, 78%; (iv) 9,9-dibutyl-2-ethynyl-9*H*-fluorene, [Pd(PPh$_3$)$_4$], benzene, Et$_3$N, 60 °C, compound **21**: 54%.

instability of the terminal-alkyne units in **18b** and **19b** may explain the modest isolated yields.

All the present compounds were purified chromatographically using flash silica as solid phase and a mixture of dichloromethane–petroleum ether (v/v 40/60) to dichloromethane as the mobile phase. The purity of the novel dyes was assessed by NMR spectroscopy, EI-MS spectroscopy and elemental analysis. All are soluble in common organic solvents and exhibit well-defined proton NMR patterns in keeping with their molecular structures. Each Bodipy fragment presents characteristic signals in the aliphatic region of the spectra which allows easy and precise integration. In the case of the green series (bis-isoindole), a characteristic resonance signal of the thienyl H3 and H3′ protons is present at 8.1 ppm with a coupling constant of 3.5 Hz. As expected, both halogenated compounds **9a** and **10a** exhibit an AB signal around 7.20–7.30 ppm. After the first mono-coupling reaction, the presence of the pyrene unit is confirmed by the appearance of two doublets at 8.6 and 8.5 ppm as well as a characteristic singlet for the propargyl alcohol group at 4.71 ppm. For the compounds **18a** and **19a**, clear indication of the achievement of the 3-ethynylperylene coupling reaction is revealed by the presence of 11 additional protons. Finally, the target tetrachromophorics dyes are clearly characterized by the increase in the number of protons in the aromatic and aliphatic regions of the spectra. As might be expected, the sp-hybridized C atoms from the triple bonds tend to give signals lying at similar chemical shifts as the chain grows longer. The ^{13}C NMR spectra confirm the purity of the compounds. FT-IR spectra remain similar throughout the series, with the most pronounced bands occurring at $\nu = 3000$, 1650–1000, and between 850 and 650 cm^{-1}. The spectrum is dominated by vibrations associated with the aromatic rings but the acetylene stretching vibration, although rather weak, is present at about 2200 cm^{-1} in each case.

The absorption spectrum of compound **20** displays several well-resolved absorption bands in the 233–500 nm range attributed to π–π^* transitions of the different polyaromatic modules (Fig. 1). In particular the absorptions of the phenyl and fluorene rings appear at high energy (in the 220–260 nm range), whereas the pyrene absorption appears in the 260–320 nm range with a characteristic vibronic fine structure. Note that the pyrene extinction coefficient of about 80,000 M^{-1} cm^{-1} is as high as that of the phenyl/fluorene modules. The intense structured absorption in the 350–500 nm wavelength range (ε ~120,000 M^{-1} cm^{-1}) is characteristic of perylene

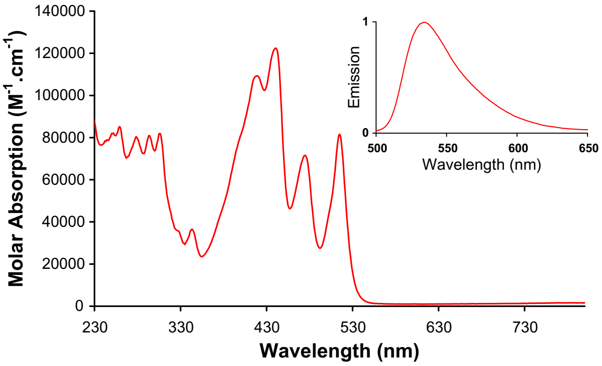


Fig. 1. Absorption spectra measured for **20** in dichloromethane at rt. Inset emission spectra measured by excitation at 475, 419, or 308 nm.

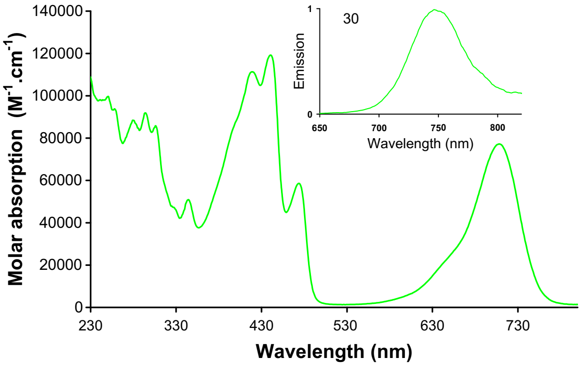


Fig. 2. Absorption spectra measured for **21** in dichloromethane at rt. Inset emission spectra measured by excitation at 708, 419, 308, and 280 nm.

absorption. The single absorption at 516 nm ($\varepsilon = 78{,}500\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$) is due to the $S_0 \rightarrow S_1$ transition of the yellow Bodipy dye.[19] The $S_0 \rightarrow S_2$ transition usually found for these dyes around 370–390 nm is hidden by the intense absorption of the perylene moiety. Compared to the respective mono-, di-, and tri-substituted dyes **9a**, **14**, and **18a**, no significant red-shift of the relative absorption of the different residues is observed. This indicates that there is little conjugation between each module which maintains its electronic individuality, as a consequence of the molecular design. Interestingly, when excited at each wavelength of the absorption spectra (Fig. 1) including the one at 516 nm, a single emission is observed at 534 nm. Only very weak residual emission of the pyrene or perylene fragments was detected, indicating that the excitonic energy is very efficiently channeled to the Bodipy dye as the final energy acceptor. The emission quantum yield of the Bodipy unit was estimated as 95% using Rhodamine 6G as the fluorescent reference.[20] The efficiency of the energy transfer processes, expressed by the ratio of the quantum yield measured by excitation of the concerned module to the quantum yield measured for excitation at 516 nm, lies in the 75–100% range.

Concerning the green series of dyes and the final compound **21**, the same trends are observed (Fig. 2). The major difference arises from the absorption of the bis-isoindole dye which has a strong absorption at 708 nm (ε about $78{,}000\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$). As previously observed for the yellow series of dyes, very efficient energy transfer to the green acceptor is effective by irradiation in each isolated residues. Little or no residual emission from the pyrene or perylene subunits attests to the ideal design. The effective emission of compound **21** is 46% using cresyl violet as the reference.[20] Also noteworthy are the excitation spectra which in both cases (excitation measured at 534 nm for **20** and at 750 nm for **21**) perfectly match the absorption spectra, showing that each module contributes to the emission of the yellow or green Bodipy acceptors.

In summary, two series of photo-sensitive Bodipy dyes bearing an increasing number of chromophoric units (pyrene, perylene, and fluorene) have been successfully synthesized using a rational protocol. The key aspect of these syntheses is the introduction of iodophenyl units via substitution at boron, enabling the stepwise construction, via Pd(0) promoted coupling reactions, of multi-chromophoric dyes. The introduction of the polar propargyl alcohol unit as a protected ethyne entity enables easy purification of the dyes. In all cases, the excitonic energy is channeled efficiently from the peripheral modules into the central Bodipy units. Work is currently in progress in order to study the kinetics of the photo-induced energy transfer in these large multi donor–acceptor systems. These series of fluorescent Bodipys' dyes nicely complement the library of exciting dyes, which has been recently reviewed.[21,22]

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