Elaborating Boron Dipyrromethene Dyes with Conjugated Polyaromatic Frameworks

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Abstract: New difluoro-bora-diaza-s-indacenes were synthesized from tetramethyl derivatives following a sequence of reactions including Knoevenagel condensation, selective cross-coupling reactions in order to extend the delocalization pathway. The introduction of flexible chains bearing a terminal ester or based on polyethylene glycol insure a good solubility and import polarity which facilitates the purification procedures. Many polyaromatic subunits (pyrene, perylene, anthracene, naphtalene, ferrocene) were fused to the main central core of the Bodipy.

Key words: Bodipy, pyrene, perylene, anthracene, palladium, vinyl, ferrocene

Contemporary research on synthetic modification of difluoro-bora-diaza-s-indacene (F-Bodipy) derivatives has been largely motivated by the need to enhance the (virtual) Stokes shift, thereby optimizing the performance in flow cytometry and fluorescence imaging technology, and to facilitate the harvesting of a larger fraction of solar energy, thereby helping to engineer improved photon collectors.[1,2] A common feature of new derivatives is that the Bodipy nucleus and the appended light harvester, usually an aryl polycycle (Figure 1), remain in weak electronic communication such that each unit retains its own identity even though intramolecular energy transfer might be extremely fast.[3,4]

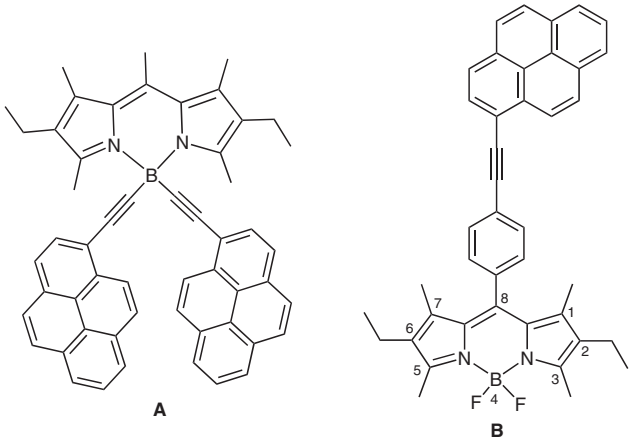

Figure 1

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Various strategies to extend the absorption properties of Bodipy dyes to the near infrared[5] have been devised based on: (i) substitution of the 3,5-positions[6] or 1,3,5,7-positions by styryl functions,[7] (ii) extension of the electronic conjugation with unsaturated linkers in the 2,6-positions[8] and 3,5-positions,[9] (iii) replacement of the *meso*-8-carbon by a nitrogen atom leading to an aza-Bodipy,[10] (iv) fusion of aromatic rings onto the Bodipy core,[11] and finally (v) the replacement of pyrrole by isoindole.[12] For these dyes, the electronic absorption and emission profiles are clearly sensitive to the delocalization over the skeleton although blue to deep-green colors are provided routinely. The substitution of the central 8-position with aryl groups has little effect on the optical properties except where these groups incorporate electron-donating substituents, like linear or cyclic tertiary amines, or electron-withdrawing substituents, like NO_2[13] or CN.[14] Otherwise, the orthogonality of the central fragment with respect to the dipyrromethene core prevents orbital contact.

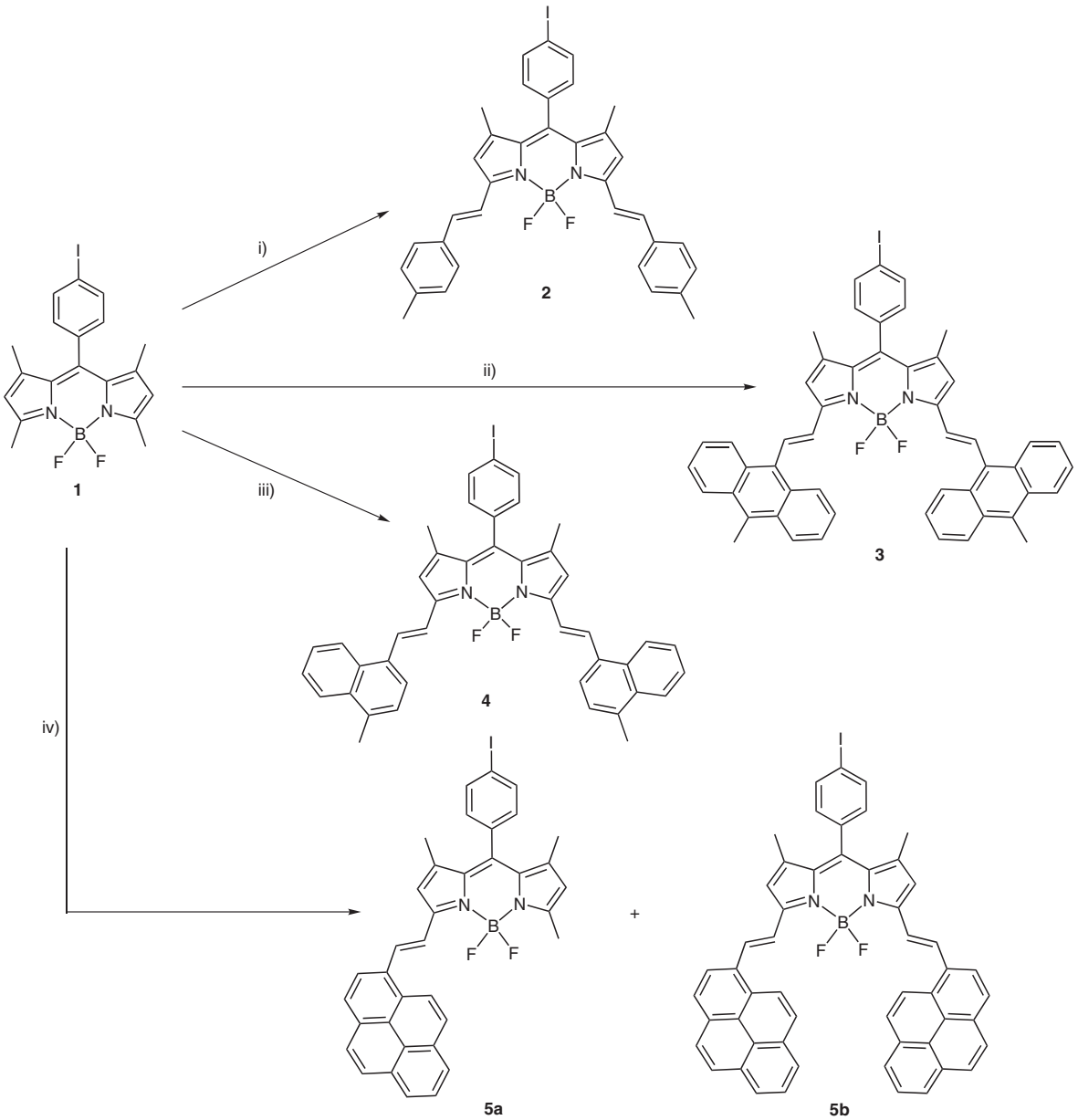
The availability of more sophisticated Bodipy dyes in which polyaromatic residues are embedded inside the delocalization pathway should allow specific problems linked to the possibility of strong absorption of photons over much of the visible spectral range and to fluorescence in the far-red region to be tackled. To this end, we have envisaged the synthesis of Bodipy dyes wherein the ancillary photon collector forms part of the overall conjugated network running throughout the dye molecule. Styryl-based connections at the 3,5-positions of the dipyrromethene core, for example, should ensure excellent conjugation across the molecule.

Despite the promise of such molecules, synthetic methodologies for their construction remain essentially unexplored, and the provision of sufficient amounts of these substances could be a bottleneck for further studies and development in materials science and optoelectronic devices.

Thus, as a response to this challenge, we describe herein an approach to the fabrication of the next-generation Bodipy dyes. This required first the development of an efficient and reliable synthesis of styryl derivatives (Scheme 1),[15] which proved to be possible using Bodipy derivatives containing acidic methyl substituents in a Knoevenagel condensation with electron-rich aldehydes.[16] Thus, reactions of 4-methylbenzaldehyde, 10-methylanthracene-9-carboxaldehyde, and 4-methyl-1-

naphthaldehyde with dye **1** produced compounds **2**–**4**, respectively. The isolated yields depended strongly on the experimental conditions (Table 1). The intermediate monosubstituted species have similar polarity to the desired disubstituted materials and thus contaminate the products unless conversion is complete. Thus, the forcing methods 6 and 7 of Table 1, involving the use of very high concentration of reactants (as the solvent evaporated) provided a reliable procedure for obtaining analytically pure disubstituted dyes. The less soluble 1-pyrenecarboxaldehyde always provided a mixture of mono- (**5a**) and disubstituted (**5b**)[17] derivatives, although these were readily separated by fractional crystallization or column chromatography in the case of **5a**. These new compounds were characterized unambiguously by NMR spectroscopy. For all styryl-based signals, the observed 16.2 Hz proton–proton coupling constant is in keeping with the *E*-configuration of the double bonds, a situation expected because of the type of condensation employed. A phenyliodo group was introduced in view of the prospect of further functionalization of the dyes by metal-promoted cross-coupling reactions (vide infra).

Encouraged by these successes, we attempted to prepare the pigments **6** and **7** using the forcing conditions of method 7 (Table 1). After multiple recrystallizations from dichloromethane–ethanol, **6** and **7** were isolated each in about 90% yield. To increase the solubility of the pigments we used two strategies of introduction of flexible chains either on the boron (position 4), or at the pseudo-*meso*-position 8. Use of a Grignard reagent for boron sub-



Scheme 1 Formation of styryl-Bodipy species via the Knoevenagel reaction using toluene, piperidine, PTSA, dryness (method 7, Table 1). *Reagents and conditions*: (i) 4-methylbenzaldehyde, 95% yield; (ii) 10-methylanthracene-9-carboxaldehyde, 75%; (iii) 4-methyl-1-naphtaldehyde, 85%; (iv) 1-pyrenecarboxaldehyde, 25% of **5a** and 30% of **5b**.

Table 1 Various Experimental Conditions for the Preparation of Blue Dyes[a]

Method	Exp. Conditions	Temp (°C)	Time	Yield (%)
1	i-PrOH, piperidine, AcOH	100	24 h	**2** (20)
2	benzene, piperidine, AcOH	100	24 h	**2** (25)
3	toluene, piperidine, AcOH	140	24 h	**2** (20)
4	toluene, piperidine, MW*	100	10 min	trace
5	toluene, piperidine, dryness[b]	140	5 min	mixture mono/bis
6	toluene, piperidine, dryness[b,c]	140	2 × 5 min	**2** (80)
7	toluene, piperidine, PTSA, dryness[b,c]	140	2 × 5 min	**2** (95)
8	toluene, piperidine, AcOH	140	2 × 5 min	**3** (35)
9	toluene, piperidine, PTSA, dryness[b,c]	140	2 × 5 min	**3** (80)
10	toluene, piperidine, AcOH	140	2 × 5 min	**4** (29)
11	toluene, piperidine, PTSA, dryness[b,c]	140	2 × 5 min	**4** (96)

[a] Reaction performed at the 200 mg scale, in 5 mL solvent and 1 mL piperidine, 200 μL AcOH or 1 crystal PTSA and using 2 equiv of the aldehyde (except for method 6 and 7 where 2 × 2 equiv were used). MW* for microwave irradiation, 1000 W 90 °C, 10 min.
[b] The solvent was distilled to dryness using a Dean–Stark setup.
[c] Conditions: 2 equiv of the aldehyde was added after the first evaporation.

stitution provided the soluble compounds **8a** and **8b**. The second strategy used palladium-promoted cross-coupling reactions with alkyne-substituted reagents (Scheme 2). In both cases the choice of the alkyne derivatives was motivated not only by the solubility increase but also by the polarity imported by the diethylene glycol residues or by the diethyl ester group. No selectivity of substitution was found with the triiodo derivative **6**, whereas a good selectivity resulted when using the mixed monoiodo/bisbromo derivative **7**. After some experimentation (Table 2), a selectivity of 78% was obtained for compound **9b**.[18] This selectivity results from the reactivity of the iodo function as well as the mild conditions used for the cross-coupling reactions (Scheme 2). Thus, a library of derivatives bearing various additional functional groups was ultimately obtained. An interesting case is provided with compound **9e**, which tolerates the subsequent use of a Grignard reagent for boron substitution with alkyne derivatives, affording the highly soluble dye **10** bearing potential reactive bromo functions.

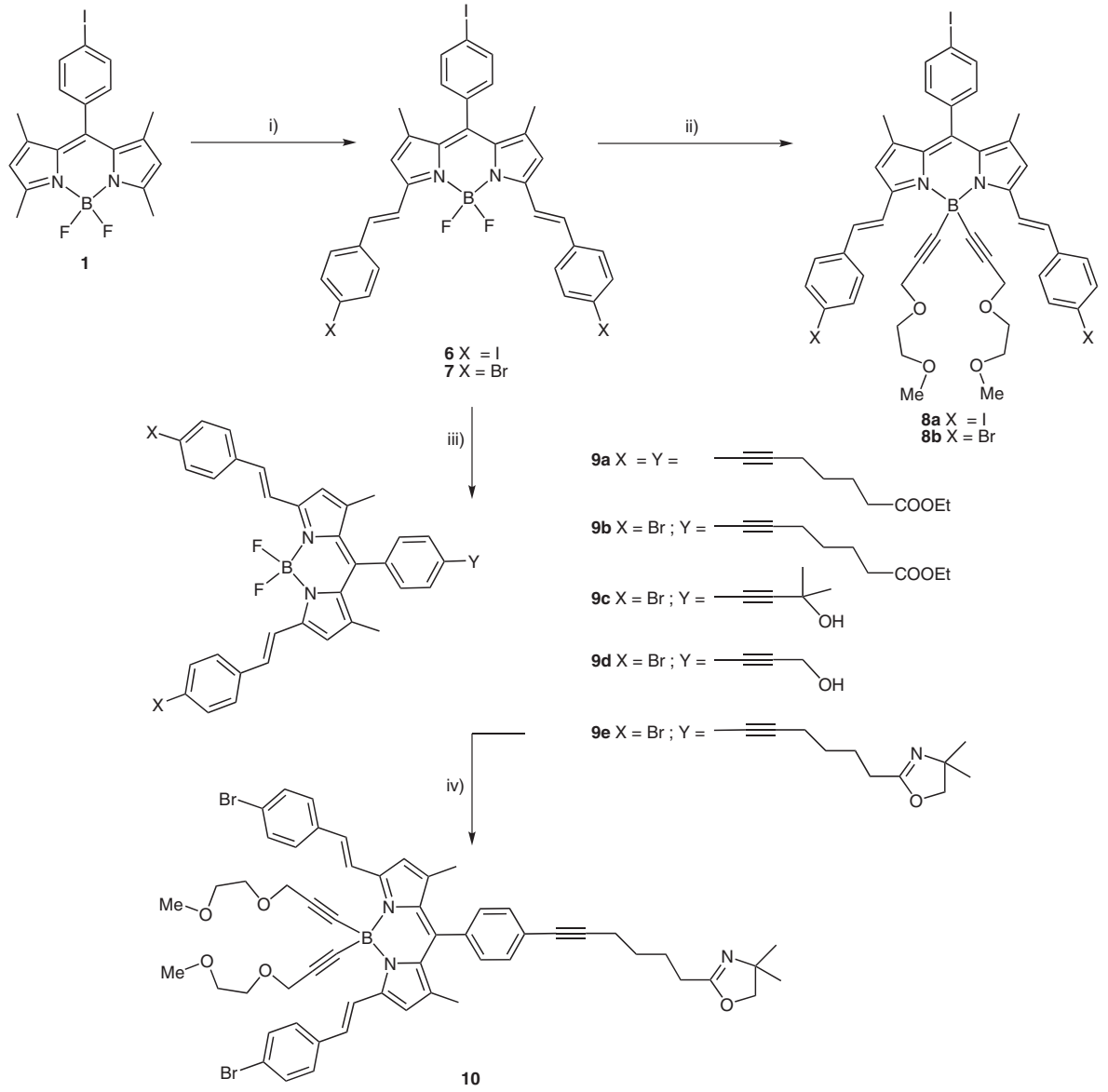
Our next target became the attachment of more elaborate polyaromatic scaffolds (Scheme 3). The cross-coupling of highly soluble **9b** with 1-ethynylpyrene[19] and 3-ethynylperylene[20] under standard conditions proved to be efficient provided an excess (2.2 equiv) of the alkyne was used to ensure that double substitution was dominant.

The next challenge was to activate a single position in the disubstituted derivative **9b** and so provide the opportunity to embed additional 'intelligent' modules designed to promote excitonic energy transfer or electron transfer, internal spin crossover, and inherent multiple redox activity.[21] Given that the bromophenyl residue is less prone to cross-

Table 2 Various Experimental Conditions for the Preparation of Dye **9b**[a]

Entry	Exp. Conditions	Nature of catalyst[b]	Yield (%)[c]
1	benzene, *i*-Pr_2NH, 80 °C, 15 h	$Pd_2(dba)_3$, Ph_3P (2 equiv)	<5
2	THF, *i*-Pr_2NH, 80 °C, 15 h	$Pd_2(dba)_3$, Ph_3P (20 equiv)	25
3	THF, *i*-Pr_2NH, 80 °C, 24 h	$Pd(OAc)_2$, Ph_3P (4 equiv)	25
4	benzene, *i*-Pr_2NH, 80 °C, 15 h	$Pd(OAc)_2$, $P(C_6H_{11})_3$ (2 equiv)	45
5	benzene, *i*-Pr_2NH, 80 °C, 15 h	$[Pd(PPh_3)_4]$	24
6	THF, Et_3N, 50 °C, 48 h	$[Pd(PPh_3)_2Cl_2]$, CuI	35
7	benzene, THF, *i*-Pr_2NH, 60 °C, 15 h	$[Pd(PPh_3)_2Cl_2]$, CuI	78

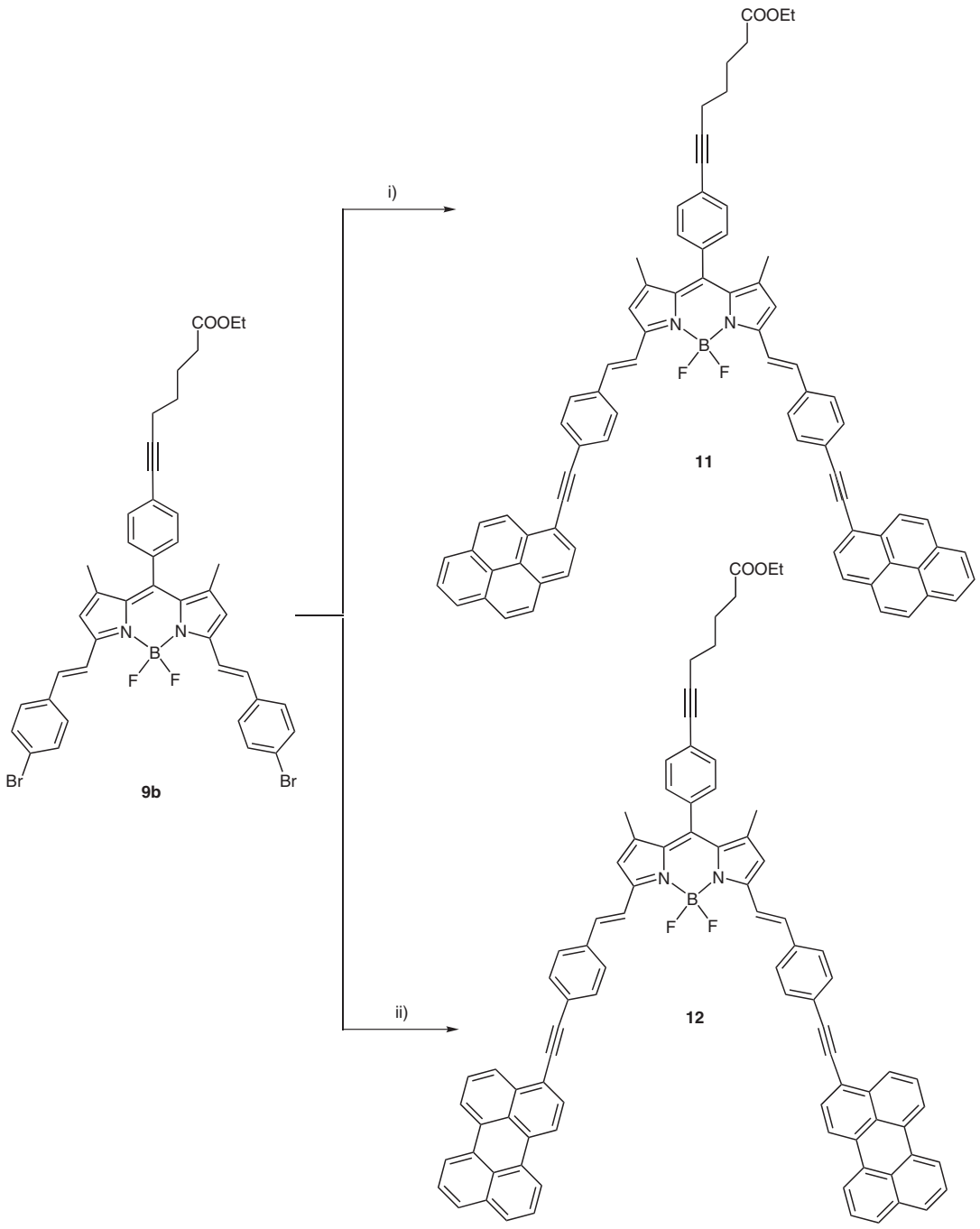
[a] Reaction performed at the 50 mg scale, in 1 mL solvent and 1 mL amine, and using 2 equiv of 6-ethylheptynoate.
[b] The dba accounts for tris(dibenzylideneacetone)diPd(0), $P(C_6H_{11})_3$ for tricyclohexylphosphine.
[c] Isolated yield obtained after column chromatography.



Scheme 2 Further functionalization of styryl-Bodipy derivatives. *Reagents and conditions*: i) 4-iodobenzaldehyde, 92% or 4-bromobenzaldehyde, 90% in toluene, piperidine, PTSA, dryness; (ii) $HC{\equiv}CCH_2OCH_2CH_2OMe$ (3 equiv), EtMgBr (2.5 equiv), THF, 60 °C, 94% for **8a** and 93% for **8b**; (iii) corresponding ethynyl derivative, $[Pd(PPh_3)_2Cl_2]$ (6 mol%), CuI (10 mol%), benzene, *i*-Pr_2NH, 80 °C, 15h, 85% for **9a**, 78% for **9b**, 82% for **9c**, 79% for **9d**, 63% for **9e**; (iv) $HC{\equiv}CCH_2OCH_2CH_2OMe$ (3 equiv), EtMgBr (2.5 equiv), THF, 60 °C, 94% for **10**.

coupling under mild conditions, we employed a lower catalyst concentration, a shorter reaction time, and substoichiometric amounts of 3-ethynylperylene. Compound **13** was obtained in 42% isolated yield from **9b** in a reproducible manner. The side product was compound **12** (20% yield), and some starting material (15%) could be recovered. With this pivotal compound in hand, the preparation of mixed derivatives such as **14**,[22] bearing both pyrene and perylene subunits linked to the Bodipy, was straightforward. Similarly, reactions with 9-ethynyl-10-methylanthracene and 1-ethynlferrocene provided dyes **15** and **16** in excellent isolated yields (Scheme 4).

Our design opens up the possibility of engineering sophisticated dyes in which the polyaromatic moieties are coupled electronically with the central dipyrromethene core via vinyl tethers. The efficiency of the substitution reactions depends on the solvent, reaction time, temperature, and concentration of reactants. Trace amounts of PTSA and a high concentration of reactants facilitated the double substitution. More soluble dyes were obtained by selectively grafting a flexible chain onto either the boron or the pseudo-*meso*-position. Cross-coupling reactions of bromo derivatives could be made relatively selective by adjusting the reaction time, catalyst concentration, and temperature. Unsymmetrically substituted dyes bearing perylene, pyrene, anthracene, and/or ferrocene groups were also prepared in variations on the Knoevenagel reactions and metal-catalyzed cross-couplings. An important factor facilitating the purification of all the present materials was the introduction of a substituent bearing a polar terminus, in particular an ester group. There is no reason why the synthesis cannot be extended to include other



Scheme 3 Synthesis of symmetrically functionalized Bodipy derivatives. *Reagents and conditions*: i) 1-ethynylpyrene (2.2 equiv), THF, diisopropylamine, $[Pd(PPh_3)_4]$ (6 mol%), 60 °C, 18 h, 89%; ii) 3-ethynylperylene (2.2 equiv) THF, diisopropylamine, $[Pd(PPh_3)_4]$ (6 mol%), 60 °C, 12 h, 80%.

polycyclic frameworks nor why cross-functionalized dyes, having additional functional groups covalently linked at the indacene backbone, cannot be prepared. Current work is focused on the study of the spectroscopic and electrochemical properties of the new dyes and results will be timely disclosed.

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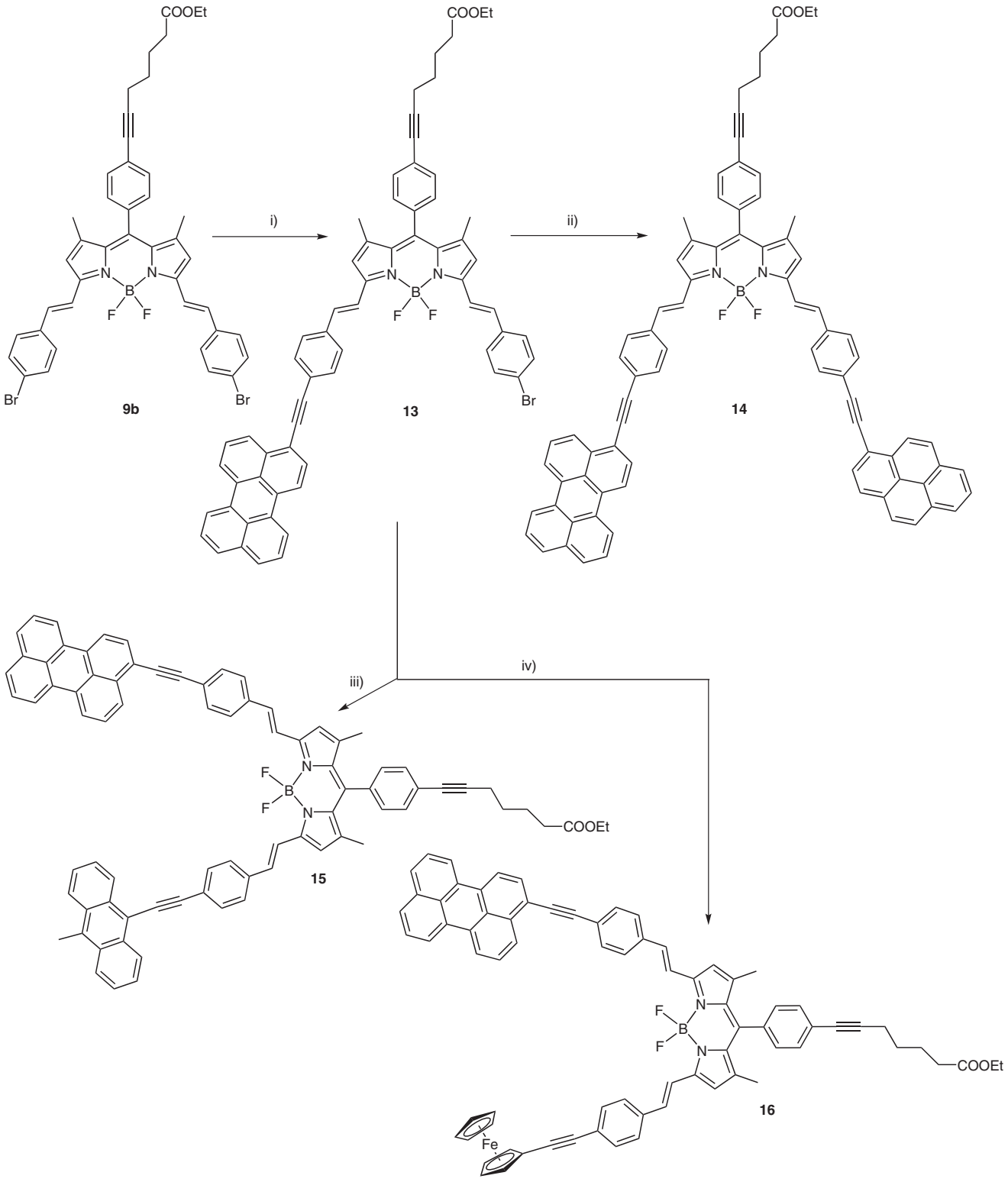

Scheme 4 Synthesis of unsymmetrically functionalized Bodipy derivatives. *Reagents and conditions*: (i) 3-ethynylperylene (0.8 equiv), THF, diisopropylamine, $[Pd(PPh_3)_4]$ (3 mol%), 50 °C, 6 h, 42%; (ii) 1-ethynylpyrene (1.2 equiv), THF, diisopropylamine, $[Pd(PPh_3)_4]$ (6 mol%), 60 °C, 12 h 79%; (iii) 9-ethynyl-10-methylanthracene (1.2 equiv), THF, diisopropylamine, $[Pd(PPh_3)_4]$ (6 mol%), 60 °C, 12 h, 84%; (iv) 1-ethynylferrocene (1.2 equiv), THF, diisopropylamine, $[Pd(PPh_3)_4]$ (6 mol%), 60 °C, 12 h, 94%.

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(17) Compound **5b**: ^{1}H (400.13 MHz, $CDCl_3$): δ = 8.61 (d, ^3J = 8.2 Hz, 2 H), 8.53 (d, ^3J = 9.3 Hz, 2 H), 8.46 (d, ^3J = 16.6 Hz, 2 H), 8.27–8.16 (m, 6 H), 8.12 (d, ^3J = 9.3 Hz, 2 H), 8.09–7.96 (M, 6 H), 7.93 (d, ^3J = 8.2 Hz, 2 H), 7.89 (d, ^3J = 8.2 Hz, 2 H), 7.37 (d, ^3J = 8.2 Hz, 2 H), 7.00 (s, 2 H), 1.26 (s, 6 H). ^{13}C{H} (100.61 MHz, $CDCl_3$): δ = 158.2, 156.6, 156.2, 154.3, 155.5, 148.2, 136.8, 139.5, 132.8, 135.7, 133.6, 135.5, 134.9, 133.6, 130.7, 129.7, 124.9, 128.9, 127.5, 128.9, 127.0, 128.6, 127.0, 125.8, 124.7, 120.4, 96.9, 15.4. MS (EI): *m/z* (%) = 874.1 (100) [M]. Anal. Calcd for $C_{53}H_{34}N_2BF_2I$ (Mr = 874.56): C, 72.79; H, 3.92; N, 3.20. Found: C, 72.44; H, 3.67; N, 3.02.
(18) Compound **9b**: ^{1}H (400 MHz, $CDCl_3$): δ = 7.70 (d, ^3J = 16.3 Hz, 2 H), 7.56–7.48 (m, 10 H), 7.27 (d, ^3J = 8.2 Hz, ca. 2 H + solvent overlap), 7.18 (d, ^3J = 16.3 Hz, 2 H), 6.64 (s, 2 H), 4.16 (q, ^3J = 7.1 Hz, 2 H), 2.50 (t, ^3J = 7.0 Hz, 2 H), 2.39 (t, ^3J = 7.3 Hz, 2 H), 1.87–1.82 (m, 2 H), 1.72–1.68 (m, 2 H), 1.49 (s, 6 H), 1.28 (t, ^3J = 7.1 Hz, 3 H). ^{13}C{^{1}H} (100 MHz, $CDCl_3$): δ = 173.9, 152.9, 142.8, 139.2, 135.9, 135.4, 134.6, 133.8, 132.7, 132.4, 1296.3, 128.8, 125.3, 123.4, 120.2, 118.4, 91.8 (C≡C), 80.7 (C≡C), 60.8, 34.3, 28.5, 24.7, 19.6, 15.3 (CH_3), 14.7 (CH_3). MS (EI): *m/z* (%) = 811.0 (50) [M], 810.0 (100) [M], 808.0 (45) [M]. Anal. Calcd for $C_{42}H_{37}N_2BF_2Br_2O_2$ (Mr = 810.37): C, 62.25; H, 4.60; N, 3.46. Found: C, 61.89; H, 4.39; N, 3.27.
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(22) Compound **14**: ^{1}H (400 MHz, $CDCl_3$): δ = 8.72 (d, ^3J = 7.8 Hz, 1 H), 8.35 (d, ^3J = 7.6 Hz, 1 H), 8.38–8.03 (m, 14 H), 7.83–7.52 (m 12 H), 7.58–7.62 (m, 4 H), 7.35–7.26 (m, 4 H), 6.74 (s, 1 H), 6.72 (s, 1 H), 4.16 (q, ^3J = 7.2 Hz, 2 H), 2.52 (t, ^3J = 7.0 Hz, 2 H), 2.39 (t, ^3J = 7.2 Hz, 2 H), 1.92–1.80 (m, 2 H), 1.73–1.67 (m, 2 H), 1.48 (s, 6 H), 1.29 (t, ^3J = 7.1 Hz, 3 H). ^{13}C{^{1}H} (100 MHz, $CDCl_3$): δ = 173.8, 153.3, 152.5, 142.9, 142.4, 139.0, 136.9, 132.7, 132.5, 132.4, 131.6, 130.1, 128.9, 128.0, 127.8, 127.7, 126.7, 126.1, 125.0, 121.4, 121.2, 121.0, 118.6, 96.5 (C≡C), 91.9 (C≡C), 91.4 (C≡C) 90.6 (C≡C), 90.2 (C≡C), 80.8 (C≡C), 60.8, 34.3, 28.5, 27.3, 24.7, 19.6, 15.30 (CH_3), 14.7 (CH_3). MS (EI): *m/z* (%) = 1151.2 (90) [M], 1150.2 (100) [M]. Anal. Calcd for $C_{82}H_{57}N_2BF_2O_2$ (Mr = 1151.15): C, 85.56; H, 4.99; N, 2.43. Found: C, 85.33; H, 4.62; N, 2.15.