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Synthesis and Functionalization of Asymmetrical Benzo-Fused BODIPY Dyes

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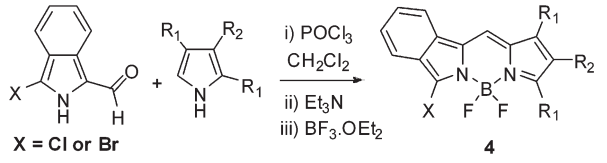

A series of asymmetrical benzo-fused BODIPY dyes were synthesized from the Sonogashira coupling and nucleophilic substitution reactions on the 3-halogenated benzo-fused BODIPY, generated from readily available 3-halogeno-1-formylisoindoles in a two-step synthetic procedure. This novel BODIPY platform provides an easy path for the linking of BODIPY fluorophore to various desired functionalities as demonstrated in this work. Most of the resulting BODIPY dyes show long-wavelength absorption and fluorescence emission, with good fluorescence quantum yields and long fluorescence lifetimes.

Boradiazaindacenes, commonly known as BODIPY dyes, are strongly UV-absorbing small molecules with high fluorescence quantum yields, sharp fluorescence emissions, large molar absorption coefficients, high photochemical stability, and low sensitivity to the environment,[1,2] and they have found wide applications in highly diverse fields,[1] such as labeling reagents,[3−5] chemosensors,[6,7] laser dyes,[8] photosensitizers,[9] and fluorescence organic devices.[10−12] The absorption and emission wavelengths for classical BODIPY chromophore center at 470−530 nm. With regard to their various applications, it is very necessary to have BODIPY dyes absorbing and emitting at longer wavelengths. Recently, we and several other groups[13−16] have achieved the red-shift of the absorption and fluorescence

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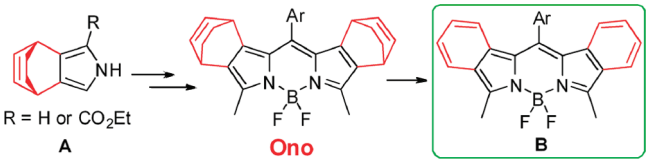


FIGURE 1. Syntheses of symmetrical benzo-fused BODIPYs **B** from norbornane-derived pyrrole **A**.[15c,d]

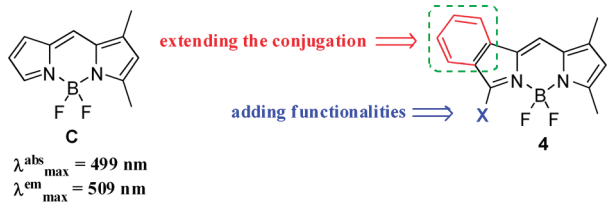
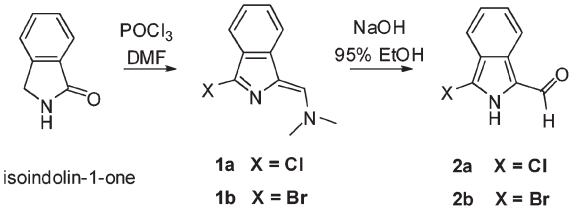


FIGURE 2. Benzo-fused BODIPY platform **4**.

SCHEME 1. Synthesis of 3-Halogeno-1-formylisoindoles 2a,b, Using Vilsmeier Haack Reactions



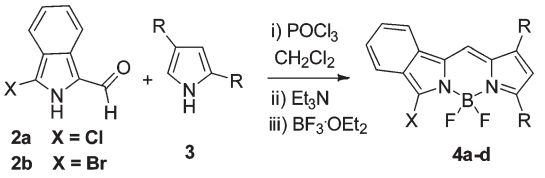
emission maxima via the chemical modification of the ready-made BODIPY core with aryl, vinyl, styryl, and arylethynyl substituents, or with a rigid ring fused to the pyrrolic position of the core. Among those, the rigid ring fused constrain molecules such as benzo-fused BODIPYs **B** shown in Figure 1 generally possess more favorable fluorescence characteristics than those of the unconstrained dyes.

Currently, the main synthetic approach for the benzo-fused BODIPYs is the retro-Diels–Alder reaction[15c,d] of norbornane-derived pyrroles **A** developed by Ono et al. as shown in Figure 1, in which high temperature is required, and less than a handful of benzo-fused BODIPYs have been reported.

Herein we report the expedious construction of a 3-halogenated benzo-fused BODIPY platform **4** as shown in Figure 2. The fusion of a benzene ring leads to the increased conjugation, while the installation of a halogenated substituent at the 3-position provides BODIPY **4** a facile way for the further functionalizations, as demonstrated in this work via Sonogashira coupling and nucleophilic substitution reactions, from which a series of asymmetrical benzo-fused BODIPY dyes have been obtained.

As the key synthetic precursors for BODIPY **4**, 3-halogeno-1-formylisoindoles **2** were synthesized from the readily available isoindolin-1-one in 40–68% yields using a modified literature procedure[18] as shown in Scheme 1, involving the Vilsmeier–Haack and the subsequent hydrolysis reactions. While we were making progress in this project, Dehaen et al.[17] reported the efficient conversion of pyrroles to 2-halogenated acylpyrroles from the in situ acylation of 2-halogenated pyrroles. These

TABLE 1. Synthesis of 3-Halogenated Benzo-Fused BODIPYs 4a–d



X	R	product	yield (%)
Cl	H	**4a**	63
Br	H	**4b**	67
Cl	CH_3	**4c**	53
Br	CH_3	**4d**	45

2-halogenated acylpyrroles were further used under acid catalyzed condition for the generation of asymmetrical BODIPYs, complementary to their previous synthetic breakthrough in the development[13a] and functionalization[13b–d] of a symmetrical 3,5-dichloro-BODIPY platform.[6d]

The resulting 3-halogeno-1-formylisoindoles **2** were used for the condensation reactions with α-unsubstituted pyrroles **3** under $POCl_3$ catalyzed condition. After subsequent treatment with triethylamine and complexation with $BF_3 \cdot OEt_2$, the desired benzo-fused BODIPYs **4a–d** were generated in 45–67% yields as shown in Table 1.

As shown in Figure S1 (Supporting Information), BODIPYs **4** showed a narrow absorption band centered between 542 and 562 nm, with a considerably weaker, broad absorption band centered at around 320 nm, similar to those previously reported BODIPY dyes. In addition, BODIPYs **4** gave high molar absorption coefficients (log ε 4.68–5.10) and favorably good fluorescence quantum yields in dichloromethane (around 0.6, Table 2). In comparison with those nonbenzo-fused BODIPY analogue **C**[19] shown in Figure 2, the fusion of a benzene ring at the pyrrolic position of BODIPYs **4c–d** leads to more than 63 nm red-shift in both the absorption and fluorescence emission maxima in dichloromethane. No significant solvatochromic shifts were observed in the absorption and emission maxima for BODIPYs **4** as shown in Table S1 (Supporting Information).

BODIPYs **4** have valuable halogenated substituents (chloro- or bromo-) at the 3-position of the BODIPY core, which provides a facile path for the efficient introduction of various functionalities to the BODIPY core via coupling or nucleophilic substitution reactions, bringing spectral changes, for example the desired red-shift of the spectra or functional materials. To demonstrate the good reactivity of the 3-halogenated substituent, BODIPY **4c** was applied in Sonogashira coupling reactions with various arylethynyl derivatives as shown in Scheme 2, from which several asymmetrical benzo-fused BODIPYs **5** were generated in 53–64% yields within 3 h at 65 °C. In comparison with BODIPY **4c**, **4d** gave a similar yield for the generation of BODIPY **5a**.

BODIPYs **5** showed typical absorption and emission features of BODIPY dyes in dichloromethane as shown in Figure 3, with strong absorption and emission maxima centered at 612–618 and 625–633 nm, respectively. In comparison with BODIPY **4c**, the newly installed arylethynyl groups in BODIPYs **5a–e** caused red-shifts of the absorption and fluorescence emission maxima up to 57 and 61 nm, respectively, as summarized in Table 2. Similar to the starting BODIPY **4c**, no

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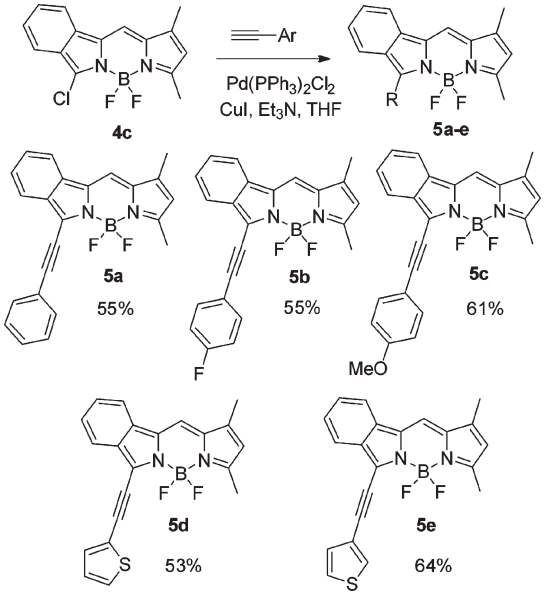
TABLE 2. Photophysical Properties of BODIPYs 4a−d, 5a−e, and 6a−f in Dichloromethane at Room Temperature

	λ_{max} (nm)	log ε_{max}	λ_{em} (nm)	Φ^a	Stokes shift (cm^{-1})	τ^b (ns)	k_r (10^7 s^{-1})	k_{nr} (10^7 s^{-1})
4a	542	4.68	562	0.62	657	8.23	7.5	4.6
4b	542	4.84	562	0.66	657	7.34	9.0	4.6
4c	562	4.70	572	0.62	311	8.83	7.0	4.3
4d	562	5.10	573	0.63	342	7.15	8.8	5.2
5a	612	4.69	629	0.89	442	7.97	11.2	1.3
5b	612	4.77	625	0.90	340	7.16	12.6	1.4
5c	616	4.53	633	0.63	436	6.91	9.1	5.4
5d	618	4.15	631	0.44	333	6.16	7.1	9.1
5e	612	4.97	628	0.80	416	7.76	10.3	2.6
6a	546	4.87	564	0.65	585	7.97	8.2	4.3
6b	574	4.86	588	0.39	415	8.20	4.8	7.4
6c	576	4.61	591	0.49	441	11.39	4.3	4.5
6d	526	4.41	583	0.61	1859	4.82	12.7	8.0
6e	548	4.20	586	0.55	1183	6.75	8.1	6.7
6f	518	4.21	559	0.20	1416	5.66	3.5	14.1

[a]Fluorescence quantum yields for BODIPYs **4a−d** (λ_{ex} = 520 nm) and **6a−e** (λ_{ex} = 520 nm) were calculated with Rhodamin B (0.49 in EtOH)[21] as the reference, while those for BODIPYs **5a−e** (λ_{ex} = 580 nm) and **6f** (λ_{ex} = 490 nm) were calculated with methylene blue[22] (0.03 in MeOH) and fluorescein (0.95 in 0.1 M NaOH)[23] as the standard, respectively. [b]τ represents the fluorescence lifetimes.

SCHEME 2. Synthesis of Asymmetrical Benzo-Fused BODIPYs 5a−e from the Derivation of 3-Chloro-Benzo-Fused BODIPY 4c, Using Sonogashira Coupling Reactions



significant solvatochromic shifts of the spectra were observed for BODIPYs **5** as summarized in Table S2 (Supporting Information). Most of BODIPYs **5** showed high fluorescence quantum yields (between 0.6 and 0.9) in dichloromethane except BODIPY **5d** (0.44) as shown in Table 2. The relatively lower fluorescence quantum yield observed in BODIPY **5d** may be attributed to a fast intramolecular charge-transfer (ICT) process from the electron-rich 2-ethynylthiophene to the BODIPY acceptor similar to those described in the literature.[16c,20] The fluorescence lifetime, which is described by a single exponential, parallels the fluorescence quantum yield value, with a lifetime of ca. 6−8 ns.

BODIPY **4c** also showed good reactivity in the nucleophilic substitution reactions at room temperature with a

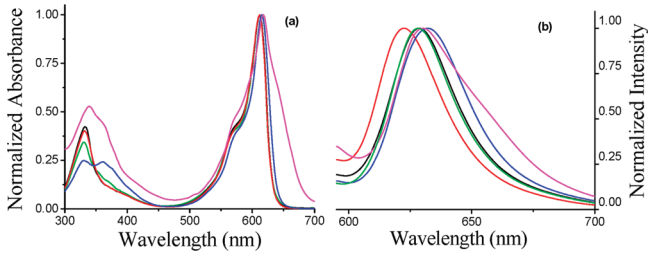
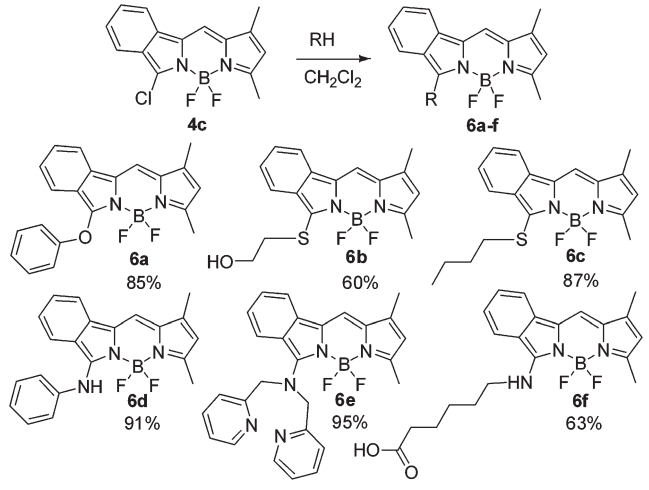


FIGURE 3. Normalized UV−vis (a) and fluorescence (b, λ_{ex} = 580 nm) spectra of BODIPYs **5a** (black), **5b** (red), **5c** (blue), **5d** (magenta), and **5e** (green) in dichloromethane at 25 °C.

SCHEME 3. The Application of 3-Chloro-Benzo-Fused BODIPY 4c in the Nucleophilic Substitution Reactions To Generate BODIPYs 6a−f



variety of nucleophiles, including oxygen-centered, sulfur-centered, and nitrogen-centered ones as shown in Scheme 3, from which BODIPYs **6** were obtained in 60−95% isolated yields. In comparison with the monosubstitution reaction on the 3,5-dichloroBODIPY,[13a] BODIPY **4c** showed comparable reactivity in reacting with various nucleophiles. The introduction of

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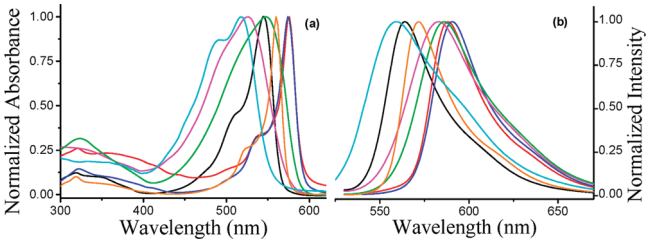

FIGURE 4. Normalized UV−vis (a) and fluorescence (b, λ_{ex} = 520 nm) spectra of BODIPYs **4c** (orange), **6a** (black), **6b** (red), **6c** (blue), **6d** (magenta), **6e** (green), and **6f** (cyan) in dichloromethane at 25 °C.

various electron donating groups without aryl-spacer to the 3-position of the BODIPY core, such as di(2-pyridylmethyl)-amine (DPA) as a good metal chelating ligand in BODIPY **6e** and the 6-aminocaproic acid as a conjugation site to biomolecules in BODIPY **6f**, provides these resulting BODIPYs with great potential as a selective fluorescent sensor or as a fluorescent labeling reagent for biomolecules.

The introduction of electron-donating substituents on the 3-position of the BODIPY core has a great effect on the photophysical properties of the BODIPY fluorophore as shown in Figure 4. In comparison with the starting BODIPY **4c**, most of BODIPYs **6** showed shifts in the absorption and emission spectra, and reduced fluorescence quantum yields in various solvents studied as summarized in Table 2 and Table S3 (Supporting Information). Among those, the installation of nitrogen-centered nucleophiles in BODIPYs **6c**−**d** gave a broader absorption band with a larger Stokes shift in dichloromethane (41−57 nm) and the other solvents investigated (up to 69 nm). The Stokes shift for most of BODIPYs **6** was greatly affected by the polarity of the solvents as summarized in Table S3 (Supporting Information): polar solvents like DMSO, MeCN, and MeOH generally gave larger Stokes shift in comparison with nonpolar solvents like toluene and hexane.

In summary, we have developed a novel 3-halogenated benzo-fused BODIPY **4** platform, easily synthesized from readily available 3-halogeno-1-formylisoindoles **2** and featured with an active reacting site at the 3-position. The application of this platform in Sonogashira coupling and nucleophilic substitution reactions generates a series of asymmetrical benzo-fused BODIPY dyes, allowing the efficient linking of the BODIPY unit to various substituents of interest as demonstrated in this work. Most of the resulting BODIPY dyes show long-wavelength absorption and fluorescence emission, with good fluorescence quantum yields and long fluorescence lifetimes.

Experimental Section

BODIPY 4c. To compound **2a** (895 mg, 5 mmol) in 10 mL of CH_2Cl_2 was added 2,4-dimethylpyrrole (620 μL, 5 mmol) in 1 mL of CH_2Cl_2 and $POCl_3$ (470 μL, 5 mmol) in 1 mL of CH_2Cl_2, respectively, at ice-cold condition under argon. The reaction mixture was stirred at ice-cold condition for 30 min, and Et_3N (7 mL) was added into the reaction mixture. The mixture was further stirred for 10 min, then $BF_3 \cdot OEt_2$ (7 mL) was added through a syringe. The reaction mixture was left stirring for 10 h, poured into 50 mL of water, and extracted with 30 mL of CH_2Cl_2. Organic layers were combined, and solvent was removed under vacuum. The crude product was purified by chromatography (silica gel, hexane/CH_2Cl_2 = 2/1, v/v) to give the desired compound **4c** as a brown powder in 53% yield (800 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.7 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.10 (s, 1H), 5.88 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 140.3, 139.8, 134.3, 132.4, 130.6, 128.5, 126.8, 126.0, 121.7, 119.1, 118.3, 117.1, 14.6, 11.3; HRMS calcd for $C_{15}H_{12}BClF_2N_2$ [M]$^+$ 304.0750, found 304.0757.

BODIPYs 5a. To a 50 mL dry Schlenk flask were added BODIPY **4c** (61 mg, 0.2 mmol), $Pd(PPh_3)_2Cl_2$ (22 mg, 3 mmol %), and CuI (13 mg, 7 mmol %) in 5 mL of freshly distilled THF. After freeze−thaw three times, Et_3N (0.4 mL) and phenylacetylene (110 μL, 1.0 mmol) in 1 mL of THF were added through a syringe into the mixture, respectively. The mixture was stirred at 65 °C for 3 h, cooled to room temperature, and filtrated through Celite, then the cake was washed with CH_2Cl_2 (3 × 20 mL). Organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$, then the solvent was removed under vacuum. The crude product was purified by chromatography (silica gel, hexane/CH_2Cl_2 = 5/2, v/v) to give the desired compound **5a** as dark blue solid in 55% yield (41 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 7.8 Hz, 1H), 8.05−8.00 (m, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.75−7.69 (m, 2H), 7.51−7.15 (m, 4H), 6.92 (s, 1H), 6.03 (s, 1H), 2.58 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.3, 136.5, 129.6, 129.5, 129.0, 128.4, 127.7, 126.3, 125.3, 124.5, 123.9, 119.6(3), 119.5(8), 119.4, 118.8, 117.8, 116.1, 115.3, 14.6, 11.3; HRMS (EI) calcd for $C_{23}H_{17}BF_2N_2$ [M]$^+$ 370.1453, found 370.1451.

BODIPYs 6a. To a 50 mL dry Schlenk flask were added BODIPY **4c** (40 mg, 0.13 mmol) and phenol (61 mg, 0.65 mmol) in 10 mL of CH_2Cl_2. Then K_2CO_3 (138 mg, 1 mmol) was added and the reaction mixture was stirred at room temperature for 10 min, poured into water, and extracted with CH_2Cl_2 (3 × 20 mL). Organic layers were combined, solvent was removed under vacuum, the crude product was purified by chromatography (silica gel, hexane/CH_2Cl_2 = 2/1, v/v), and the desired compound **6a** was obtained as a powder in 85% yield (41 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 6.6 Hz, 2H), 7.28 (d, J = 7.8 Hz, 3H), 7.19 (s, 1H), 6.94 (t, J = 7.5 Hz, 2H), 6.50 (d, J = 8.1 Hz, 1H), 5.89 (s, 1H), 2.45 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 149.1, 136.7, 134.7, 130.8, 130.2, 126.5, 125.4, 123.5, 123.2, 120.2, 120.0, 119.5, 116.2, 114.9, 14.2, 11.2; HRMS (EI) calcd for $C_{21}H_{17}BF_2N_2O$ [M]$^+$ 362.1402, found 362.1406.

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Supporting Information Available: General experimental methods, experimental procedures, compound characterization data and copies of ^{1}H NMR, ^{13}C NMR spectra and exact mass spectra for all new compounds, and UV−vis and fluorescence spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.