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ARTICLE

Highly Regioselective α-Formylation and α-Acylation of BODIPY Dyes via Tandem Cross-Dehydrogenative Coupling with *in situ* Deprotection

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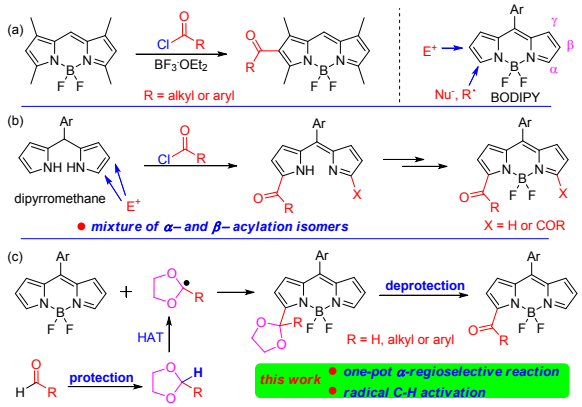
A metal-free C-H formylation and acylation of BODIPY dyes using a variety of dioxolane derivatives as aldehyde equivalent is reported, providing a postfunctionalization method for controllable synthesis of BODIPYs with carbonyl groups at 3,5-positions via a radical process. The photophysical properties of resultant dyes from this efficient one-pot, chemo- and site-selective transformation have been studied.

Introduction

Small-molecule fluorophores are critically important tools to investigate biological processes and are prevalent in many modern applications, including bioimaging, sensing and therapy.[1] Recently, boron dipyrromethene (BODIPY)[2] dyes have been widely used in highly diverse research fields,[3-6] due to their excellent spectroscopic and photophysical properties. Rapid and reliable access to functionalized BODIPY chromophores,[7,8] therefore, greatly expedites their applications in chemical biology and materials chemistry. To this end, aldehydes and ketones are versatile and high-value functional handles that can be rapidly elaborated or tethered to compounds of biological interest.[9] The synthesis of α-acylated BODIPYs from ready-made BODIPY frameworks has not yet been described. However, acylation with acid chloride through traditional Friedel-Crafts electrophilic aromatic substitution using $BF_3{\cdot}OEt_2$ as Lewis acid catalyst gave regioselectively 2-acylated BODIPYs due to the least positive charge on the 2(,6)-position(s) of the BODIPy core (Scheme 1a).[10a] A potential, as yet not reported, *de novo* synthesis route toward α-acylated BODIPYs might comprise direct (di)acylation of dipyrromethane, followed by classic oxidation, base-promoted deprotonation and complexation with $BF_3.OEt_2$ (Scheme 1b). However, mixtures of products were formed during the direct acylation of dipyrromethane using acyl chloride.[10b] In addition, limited stability of dipyrromethanes and their acylated derivatives further complicated the synthesis. Formylation of dipyrromethanes which is highly α-regioselective, followed by standard oxidation, base-promoted deprotonation and complexation with $BF_3.OEt_2$ yielded 3(,5)-(di)formylated BODIPYs.[9d,e] A fully alkylated BODIPY having a formyl group at the 3-position was created by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of the corresponding 3-methyl group.[9g]



Scheme 1. Reported β–acylation of BODIPY (a), potential α-acylated BODIPYs through *de novo* synthesis (b) and our tandem cross-dehydrogenative coupling between BODIPY and 1,3-dioxolane derivative with *in situ* deprotection (c). HAT: hydrogen atom transfer.

Due to the most positive charge of α-position of BODIPY core, various α-regioselective postfunctionalizations, such as S_NAr reaction[11] and radical reaction,[12] have been developed. Particularly, radical reactions on BODIPYs have received increasing interest due to their advantages of high reactivity, high regioselectivity and atom-economy. The highly regioselective cross-dehydrogenative coupling (CDC) has played a vital role in the construction of C–C[12a-e] and C–X (N, S)[12f-h] bonds on BODIPY core. Acetals and hemiacetals are very common protective groups of carbonyls. The weak C–H bonds

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Electronic Supplementary Information (ESI) available: Experimental details, spectroscopic/photophysical properties of selected BODIPYs, NMR and HRMS spectra for all new compounds. CCDC 1811936-1811938 and 1815587. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/x0xx00000x

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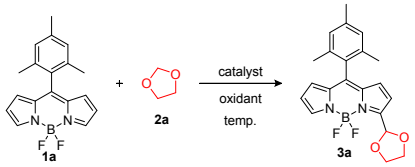
α to both O atoms in acetals and hemiacetals can undergo activation through hydrogen atom transfer in the presence of reactive radical species.[13] We envisioned a complementary approach that harnesses the direct activation of weak C–H bonds in 1,3-dioxolane derivatives and couples these intermediates with a CDC mechanism to achieve α-formylation and α-acylation of BODIPYs after *in situ* deprotection (Scheme 1c).

Results and discussion

We explored the viability of the above process with *meso*-mesityl BODIPY **2a** and 1,3-dioxolane as substrates in the presence of a radical initiator. To our delight, when the reaction was conducted using Bu_4NI (20 mol%) as catalyst and *tert*-butyl hydroperoxide (TBHP, 4 equiv) as oxidant at 90 °C for 8 h, the major product **3a** was isolated in 56% yield (Table 1, entry 1). Other catalysts, including Bu_4NBr, KI, $Pd(OAc)_2$ and $Cu(OAc)_2$, gave lower yields (entries 2-5). In the absence of catalyst, the yield of corresponding product **3a** was drastically decreased to 15% yield (entry 6). Reducing the amount of catalyst to 10 mol% also decreased the yield and, conversely, no significant improvement in product yield was observed with 30 mol% of the catalyst (entries 7-8). These results demonstrate that catalysts play an important role in this transformation. Subsequently, other oxidants were studied including DDQ, $K_2S_2O_8$ and even its analogue di-*tert*-butyl peroxide (DTBP) either failed in promoting this reaction or showed inferior results (entries 9-11).

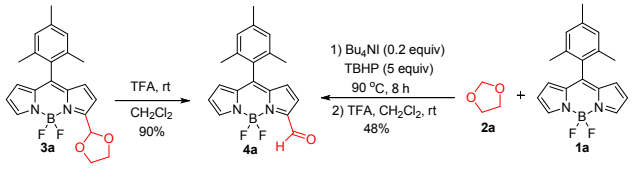
We further optimized the ratio of TBHP (entries 12-13) and found the optimal ratio of TBHP was 4 equiv. After a brief survey of reaction temperature, we found that the optimal reaction temperature was 90 °C (entries 14-15). Finally, we obtained the optimized reaction conditions to be 0.2 equiv of Bu_4NI, 4 equiv of TBHP, at 90 °C in 8 h.

Table 1. Optimization of the reaction conditions [a]

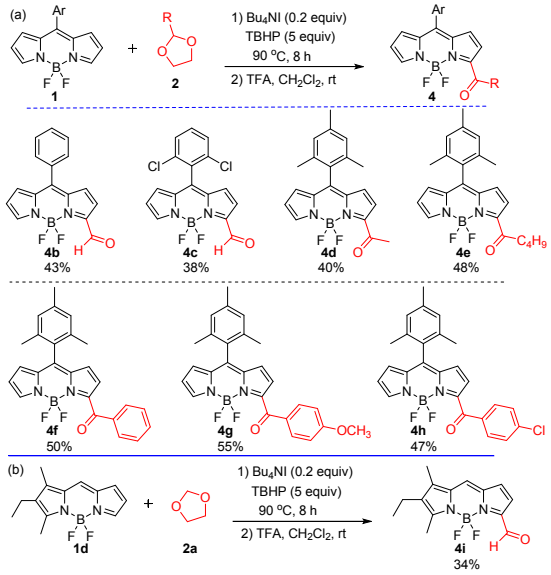


entry	catalysts	oxidants	temp. (°C)	yield [%)][b]
1	**Bu_4NI**	**TBHP**	**90**	**56**
2	Bu_4NBr	TBHP	90	36
3	KI	TBHP	90	< 5
4	$Pd(OAc)_2$	TBHP	90	25
5	$Cu(OAc)_2$	TBHP	90	32
6	------	TBHP	90	15
7	Bu_4NI	TBHP	90	33[c]
8	Bu_4NI	TBHP	90	53[d]
9	Bu_4NI	$K_2S_2O_8$	90	NR
10	Bu_4NI	DDQ	90	NR
11	Bu_4NI	DTBP	90	18
12	Bu_4NI	TBHP	90	33[e]
13	Bu_4NI	TBHP	90	52[f]
14	Bu_4NI	TBHP	80	45
15	Bu_4NI	TBHP	100	53

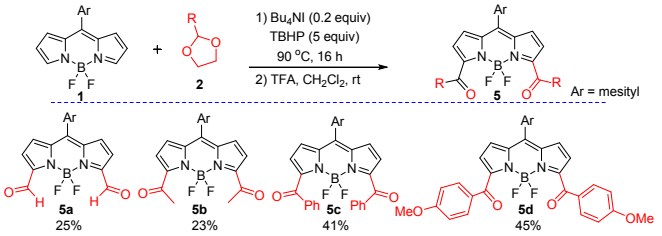
[a] Reaction conditions: **1a** (0.1 mmol), 3 mL of solvent (1,3-dioxolane serves both as reagent and solvent), catalyst (0.02 mmol), oxidant (4 equiv), 8 h. [b] Isolated yield. [c] 10 mol% catalyst. [d] 30 mol% catalyst. [e] 3 equiv TBHP. [f] 5 equiv TBHP. TBHP = *tert*-butyl hydroperoxide (70% in aqueous solution), DTBP = di-*tert*-butyl peroxide. NR = no reaction.



Scheme 2. Synthesis of α-formylBODIPY **4a**.



Scheme 3. One-pot synthesis of BODIPYs **4** from BODIPY **1** and 1,3-dioxolane **2a** and its derivatives **2b-f**.



Scheme 4. One-pot synthesis of BODIPYs **5** from BODIPY **1a** and 1,3-dioxolane **2a** and its derivatives **2b**, **2d** and **2e**.

Next, we evaluated a number of Lewis acids for hydrolysis of the dioxolane functional group on BODIPY **3a**. Trifluoroacetic acid (TFA) was found to be able to convert **3a** to α-formylBODIPY **4a** in 90% yield at room temperature (Scheme 2). Other reagents including HCl aqueous solution and $BF_3.Et_2O$ were also effective in this deprotection reaction (details in ESI). A one-pot reaction for synthesis of **4a** from BODIPY **1a** was then developed without the isolation of **3a** (Scheme 2), from which **4a** was obtained with 6 equiv of TFA in 48% yield. The regiochemistry of **4a** was confirmed by XRD structure determination (Fig. 1).

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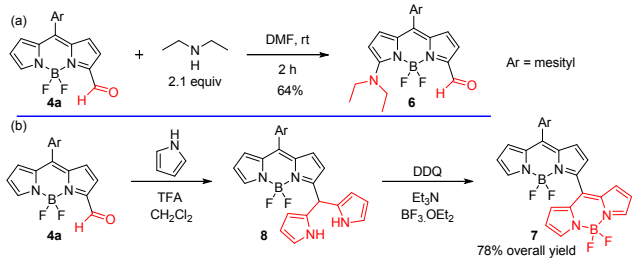
To test the versatility of this one-pot reaction, *meso*-phenylBODIPY **1b** and *meso*-2,6-dichlorophenylBODIPY **1c** reacted with 1,3-dioxolane **2a**, which, after *in situ* deprotection, provided the α-formylated products **4b** and **4c** in 43 and 38% yields, respectively (Scheme 3a). Next, 2-substituted 1,3-dioxolane derivatives **2b-f** (Fig. S1, ESI) were applied to obtain α–acylated BODIPYs, which showed higher yields than that of 1,3-dioxolane **2a**: BODIPYs **4d-h** with alkyl- or aryl-substituted carbonyl groups at the α-position were obtained in 40-55% yields (Scheme 3a). Unsymmetric BODIPY **1d** was also suitable for this reaction, giving **4i** in 34% yield using 1,3-dioxolane **2a** (Scheme 3b). By simply extending the reaction time to 16 h followed by hydrolysis in dichloromethane in the presence of TFA, the corresponding 3,5-diacylation products were major products and **5a-d** were regioselectively produced from **1a** in 23-45% yields, respectively (Scheme 4).

Finally, using **4a** as an example, further transformation of the resultant dyes was demonstrated (Scheme 5). BODIPY **4a** smoothly reacted with diethylamine in DMF at room temperature for 2 h to give BODIPY **6** in 64% yield through oxidative nucleophilic hydrogen substitution at the 5-position of the BODIPY core (Scheme 5a).[12b] A novel α-*meso* directedly linked BODIPY dimer **7** was also synthesized in 78% overall yield from the acid-catalyzed condensation of BODIPY **4a** with pyrrole (to give intermediate **8**),[15] followed by DDQ oxidation and subsequent difluoroboration (Scheme 5b, Fig. 1d).



Scheme 5. Synthesis of BODIPYs **6** and **7**.

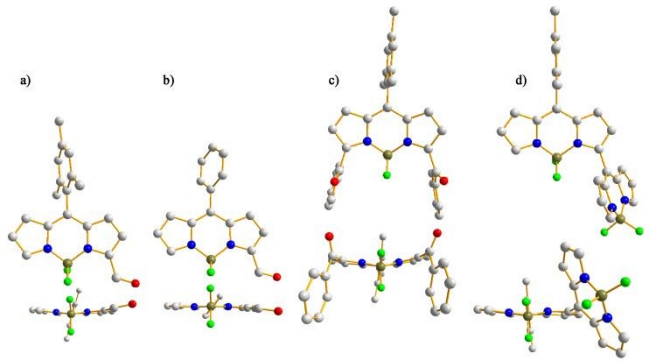


Figure 1. Top and front views of XRD structures of BODIPY **4a** (a), **4b** (b), **5c** (c) and **7** (d). C, light gray; N, blue; B, dark yellow; F, bright green, O, red. Hydrogen atoms have been removed for clarity.

Crystals of 3-formylBODIPYs **4a** and **4b**, 3,5-diacylated BODIPY **5c** and BODIPY dimer **7** (Figure 1) suitable for XRD analysis were obtained. As usual, B atoms all have slightly distorted tetrahedron geometry with the B–N distances within 1.53–1.57 Å (Table S1, ESI). The dihedral angle of two pyrrole rings in the crystal structure of **4b** is only 2.7°, indicating an almost planar BODIPY core. Slight distortions were found in **4a** and **5c** with those dihedral angles of 9.8° and 19.3°, respectively. The dihedral angles between the *meso*-aryl group and the BODIPY core are around 76°, 55°, 80° and 83° for **4a**, **4b**, **5c** and **7**, respectively. The dihedral angle of the two BODIPY core planes in dimer **7** is 61.9°, whereas each BODIPY core also has an almost planar plane with the dihedral angle of the two pyrrole rings of 6.1° and 12.1°, respectively.

Fundamental spectroscopic properties of these newly synthesized BODIPYs were investigated in dichloromethane and are summarized in Table 2. In comparison with BODIPYs **1**, BODIPYs **4** generally led to red shifts of the absorption (λ_{abs}^{max}) and fluorescence emission (λ_{em}^{max}) maxima of approximately 15-20 nm, wheras disubstituted BODIPYs **5** provided additional red shifts of about 10-30 nm. Most BODIPYs **4** and **5** showed intense fluorescence emission. However, electron-rich 4-methoxybenzoyl substituted BODIPYs **4g** and **5d** were weakly fluorescent. Diethylamine substituted BODIPY **6** displayed broad absorption bands with λ_{abs}^{max} around 470 nm (Fig. S2, ESI), which is about 50 nm blue-shifted compared with λ_{abs}^{max} of starting BODIPY **4a**. With the increase of the polarity of the solvent from cyclohexane to methanol, the λ_{em}^{max} values of **6** were significantly blue-shifted from 560 nm (in cyclohexane) to 519 nm (in methanol) and the fluorescence quantum yields were reduced from 0.18 (in cyclohexane) to 0.002 (in methanol) (Table S2, ESI). The spectroscopic features of **6** are similar to our previously reported 3-aminoBODIPY derivatives.[16]

Table 2. Photophysical properties of BODIPYs in CH_2Cl_2 at room temperature[a]

dyes	λ_{abs}^{max} [nm]	λ_{em}^{max} [nm]	ε_{abs}^{max} [M^{-1} cm^{-1}][a]	Φ[b]	Stokes shift[c] [cm^{-1}]
1a	500	522	54100	0.74	840
3a	505	522	68700	0.81	610
4a	519	536	52700	0.68	610
4b	518	538	51700	0.25	820
4c	530	551	58500	0.44	720
4d	514	533	49600	0.48	650
4e	514	532	56500	0.36	660
4f	515	534	49600	0.51	690
4g	514	535	49200	0.03	960
4h	514	532	50500	0.45	690
4i	501	549	39000	0.09	1750
5a	548	563	77800	0.40	490
5b	537	555	47700	0.37	600
5c	526	559	42200	0.14	1120
5d	525	554	50300	0.02	1000
6	470	535	42100	0.004	2580
7	514	606	75400	0.005	2950

[a] Molar absorption coefficient values rounded to the nearest 100 M^{-1} cm^{-1}. [b] Fluorescence quantum yields determined using fluorescein (Φ = 0.90 in 0.1 N NaOH aqueous solution) as reference, excited at 480 nm. Standard errors are less than 10%. [c] Stokes shift values rounded to nearest 10 cm^{-1}.

Orthogonal BODIPY dimers have been demonstrated to be good photosensitizers because of their intrinsic intramolecular

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charge transfer character through the spin-orbit charge-transfer intersystem crossing (SOCT-ISC) mechanism.[17,17-19] With dimer **7** in hand, we first measured its photophysical properties. Dimer **7** has a typical λ_{abs}^{max} at 514 nm, and a dramatically red-shifted, but very weak emission with λ_{em}^{max} at 606 nm (Fig. S18, ESI). The extremely low fluorescent quantum yield of 0.005 in dichloromethane inspired us to further study its singlet oxygen generation properties. As shown in Fig. 2, the photooxidation of 1,3-diphenylisobenzofuran (DPBF, a singlet oxygen trap molecule) was monitored at 60 s intervals in the presence of dimer **7**. The calculated singlet oxygen quantum yield for dimer **7** in toluene is 0.15 using Rose Bengal as reference.

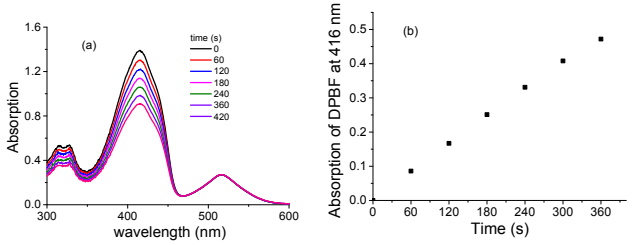

Figure 2. (a) Changes in the absorption spectrum of DPBF (5×10^{-5} M) upon irradiation in the presence of BODIPY dimer **7** (1×10^{-5} M) in toluene (recorded at 60 s intervals). (b) Plot of change in absorbance of DPBF at 416 nm vs irradiation time (λ_{irr} = 532 nm) in the presence of BODIPY dimer **7** in toluene.

Conclusions

In conclusion, we have developed an efficient protocol for the C–H formylation and acylation of BODIPY dyes using dioxolane derivatives as aldehyde equivalent. Importantly, this reaction is devoid of precious metals and regioselectively occurs at the α-positions of the BODIPY core *via* a radical pathway.

Experimental

General experimental method

Reagents and solvents were used as received from Energy Chemicals (Shanghai, China). All reactions were performed in oven-dried or flame-dried glassware and were monitored by TLC using 0.25 mm silica gel plates with UV indicator (60F-254). ^{1}H and ^{13}C NMR spectra were recorded on a 300, 400 or 500 MHz NMR spectrometer at room temperature. Chemical shifts (δ) are given in ppm relative to $CDCl_3$ (7.26 ppm for ^{1}H and 77 ppm for ^{13}C) or d6-DMSO (2.54 ppm for ^{1}H and 39.9 ppm for ^{13}C) or to internal TMS (δ = 0 ppm) as internal standard. Data are reported as follows: chemical shift, multiplicity, coupling constants and integration. High-resolution mass spectra (HRMS) were obtained using APCI-TOF in positive mode.

Photophysical Measurements

UV-visible absorption and fluorescence emission spectra were recorded on commercial spectrophotometers (Shimadzu UV-2450 and Edinburgh FS5 spectrometers). All measurements were made at 25 oC, using 5 × 10 mm cuvettes. Relative fluorescence quantum efficiencies of BODIPY derivatives were obtained by comparing the areas under the corrected emission spectrum of the test sample in various solvents with fluorescein (Φr = 0.90 in 0.1 N NaOH aqueous solution) as reference.[19] Non-degassed, spectroscopic grade solvents and 10 mm optical path length quartz cuvettes were used. Dilute solutions (0.01 < A(λex) < 0.05) were used to minimize the inner-filter effects. Quantum yields Φx were determined according to equation (1):[20]

$$\Phi_x = \Phi_r \times \frac{F_x}{F_r} \times \frac{1-10^{-A_r(\lambda_{ex})}}{1-10^{-A_x(\lambda_{ex})}} \times \frac{n_x^2}{n_r^2} \quad (1)$$

where the subscripts x and r refer respectively to the BODIPY sample x and reference (standard) fluorophore r with known quantum yield Φr in a specific solvent; F stands for the spectrally corrected, integrated fluorescence spectra; A(λex) denotes the absorbance at the used excitation wavelength λex and n represents the refractive index of the solvent (in principle at the average emission wavelength).

Crystallography

Crystals of BODIPYs **4a**, **4b**, **5c** and **7** suitable for X-ray analysis were obtained via the slow diffusion of petroleum ether into their dichloromethane solutions. The vial containing this solution was placed, loosely capped, to promote the crystallization. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were collected using a diffractometer equipped with a graphite crystal monochromator situated in the incident beam for data collection at room temperature. Cell parameters were retrieved using SMART[21] software and refined using SAINT on all observed reflections. The determination of unit cell parameters and data collections were performed with Mo Kα radiation (λ) at 0.71073 Å. Data reduction was performed using the SAINT software,[22] which corrects for Lp and decay. The structure was solved by the direct method using the SHELXS-974 program and refined by least squares method on F^2, SHELXL-97,[23] incorporated in SHELXTL V5.10.[24] CCDC-1811936 (**4a**), CCDC-1811937 (**4b**), CCDC-1811938 (**5c**) and CCDC-1815587 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis and Characterization

BODIPYs **1a-d** were synthesized according to literature procedures.[9d,11d] Compounds **2-f** were prepared from the aldol condensation reaction of aldehyde and ethylene glycol by following literature procedures.[25]

Synthesis of 3a. BODIPY **1a** (78 mg, 0.25 mmol), Bu_4NI (18 mg, 0.05 mmol) and the oxidant tert-butyl hydroperoxide (TBHP, 0.12 mL, 1.25 mmol) were dissolved in 2 mL 1,3-dioxolane **2a**, which serves both as reagent and solvent. The reaction mixture was stirred at 90 °C for 8 h. Upon completion, the reaction mixture was cooled to room temperature and was poured into dichloromethane (100 mL), washed three times with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by

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column chromatographically (silica; petroleum ether/ethyl acetate; 10:1-5:1, v/v) to provide **3a** in 55% yield (52 mg). mp 68.1-70.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 6.94 (s, 2H), 6.67 (s, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 6.57 (d, *J* = 3.6 Hz, 1H), 6.48 (s, 1H), 6.38 (s, 1H), 4.20 – 4.07 (m, 4H), 2.35 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (126 MHz, d_6-DMSO) δ 157.02, 147.89, 146.81, 139.44, 136.35, 135.54, 135.37, 131.38, 130.81, 129.94, 129.07, 120.93, 118.13, 97.11, 66.08, 21.58, 20.33. HRMS calcd. for $C_{21}H_{21}BF_2N_2O_2Na^+$ $[M+Na]^+$ 405.1556, found 405.1557.

Synthesis of 4a from 3a. To a solution of **3a** (38 mg, 0.1 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (TFA, 68 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 1 h. Upon completion, the reaction mixture was poured into dichloromethane (30 mL), washed three times with water (50 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatographically (silica; petroleum ether/ethyl acetate; 15:1-9:1 v/v) to provide **4a** in 90% yield (30 mg). mp 165.7-167.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.21 (s, 1H), 7.02 (d, *J* = 4.2 Hz, 1H), 6.98 (s, 2H), 6.92 (d, *J* = 4.4 Hz, 1H), 6.67 (d, *J* = 4.4 Hz, 1H), 6.57 (d, *J* = 4.2 Hz, 1H), 2.37 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.55, 150.86, 150.29, 148.26, 139.94, 138.20, 137.42, 136.57, 134.19, 129.43, 128.84, 127.65, 122.38, 118.76, 21.54, 20.46. HRMS calcd. for $C_{19}H_{18}BF_2N_2O$ $[M+H]^+$: 339.1475, found 339.1477.

General Procedure for the One-pot Synthesis of 4a-h. We are using **4a** (R = H, Ar = mesityl) as an example to show the general procedure for the preparation of 3-formylBODIPYs **4a-c** and 3-acylBODIPYs **4d-h**: BODIPY **1a** (78 mg, 0.25 mmol), Bu_4NI (18 mg, 0.05 mmol) and the oxidant TBHP (0.12 mL, 1.25 mmol) were dissolved in **2a** (2 mL). The reaction mixture was stirred at 90 °C for 8 h and then was cooled to room temperature. After addition of 6 equiv of TFA, the reaction mixture was stirred at room temperature for 1 h. Upon completion, the reaction mixture was poured into dichloromethane (100 mL), washed three times with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatographically (silica; petroleum ether/ethyl acetate; 15:1-9:1 v/v) to provide **4a** in 48% yield (40 mg). mp 165.7-167.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.21 (s, 1H), 7.02 (d, *J* = 4.2 Hz, 1H), 6.98 (s, 2H), 6.92 (d, *J* = 4.4 Hz, 1H), 6.67 (d, *J* = 4.4 Hz, 1H), 6.57 (d, *J* = 4.2 Hz, 1H), 2.37 (s, 3H), 2.10 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.55, 150.86, 150.29, 148.26, 139.94, 138.20, 137.42, 136.57, 134.19, 129.43, 128.84, 127.65, 122.38, 118.76, 21.54, 20.46. HRMS calcd. for $C_{19}H_{18}BF_2N_2O$ $[M+H]^+$: 339.1475, found 339.1477.

4b (R = H, Ar = Ph) was prepared in 43% yield (31 mg) from **1b** and **2a**. mp 153.4-155.2 °C. ^{1}H NMR (300 MHz, CDCl3) δ 10.39 (s, 1H), 8.23 (s, 1H), 7.67 – 7.57 (m, 5H), 7.16 (d, *J* = 4.3 Hz, 1H), 7.10 (d, *J* = 4.2 Hz, 1H), 6.86 (d, *J* = 4.1 Hz, 1H), 6.75 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.29, 150.03, 149.11, 147.62, 136.97, 136.62, 135.21, 133.12, 131.44, 130.57, 128.87, 128.69, 121.82, 118.21. HRMS calcd. for $C_{16}H_{12}BF_2N_2O$ $[M+H]^+$: 297.1005, found 297.1008.

4c (R = H, Ar = 2,6-dichlorophenyl) was prepared in 38% yield (34 mg) from **1c** and **2a**. mp 146.7-148.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.27 (s, 1H), 7.53-7.45 (m, 3H), 7.06 (d, *J* = 4.3 Hz, 1H), 6.94 (d, *J* = 4.2 Hz, 1H), 6.73 (d, *J* = 4.1 Hz, 1H), 6.60 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.85, 151.87, 148.35, 142.42, 140.72, 137.52, 134.94, 133.56, 131.73, 130.54, 128.37, 126.97, 122.59, 118.63. HRMS calcd. for $C_{16}H_{10}BCl_2F_2N_2O$ $[M+H]^+$: 365.0226, found 365.0229.

4d (R = Me, Ar = mesityl) was prepared in 40% yield (35 mg) from **1a** and **2b**. mp 91.6-93.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.97 (s, 2H), 6.92 (s, 1H), 6.85 (s, 1H), 6.63 (s, 1H), 6.55 (s, 1H), 2.70 (s, 3H), 2.37 (s, 3H), 2.09 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.78, 150.17, 149.58, 149.23, 149.13, 139.26, 137.15, 136.18, 132.75, 129.38, 128.28, 127.26, 121.84, 121.31, 28.94, 21.07, 19.95. HRMS calcd. for $C_{20}H_{20}BF_2N_2O$ $[M+H]^+$: 353.1631, found 353.1635.

4e (R = Bu, Ar = mesityl) was prepared in 48% yield (47 mg) from **1a** and **2c**. mp 148.4-150.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 6.97 (s, 2H), 6.88 (d, *J* = 4.1 Hz, 1H), 6.82 (d, *J* = 4.3 Hz, 1H), 6.61 (d, *J* = 3.6 Hz, 1H), 6.55 (d, *J* = 4.1 Hz, 1H), 3.00 (t, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 2.09 (s, 6H), 1.78-1.73 (m, 2H), 1.44-1.39 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.76, 150.56, 149.84, 149.63, 139.65, 137.73, 137.44, 136.65, 133.08, 129.88, 128.71, 127.81, 122.22, 121.04, 41.12, 26.57, 22.75, 21.55, 20.44, 14.37. HRMS calcd. for $C_{23}H_{26}BF_2N_2O$ $[M+H]^+$: 395.2101, found 395.2107.

4f (R = Ph, Ar = mesityl) was prepared in 50% yield (53 mg) from **1a** and **2d**. mp 154.8-156.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.95–7.93 (m, 2H), 7.62–7.58 (m, 1H), 7.50–7.46 (m, 2H), 6.99 (s, 2H), 6.85 (d, *J* = 4.3 Hz, 1H), 6.64 (d, *J* = 4.2 Hz, 1H), 6.62–6.59 (m, 2H), 2.38 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.45, 171.30, 149.91, 139.21, 137.78, 136.24, 133.69, 132.979, 132.76, 130.13, 129.92, 129.22, 128.43, 128.27, 128.22, 126.97, 121.94, 121.53, 21.08, 20.03. HRMS calcd. for $C_{25}H_{21}BFN_2O$ $[M-F]^+$: 395.1729, found 395.1725.

4g (R = 4-methoxyphenyl, Ar = mesityl) was prepared in 55% yield (54 mg) from **1a** and **2e**. mp 143.2-145.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.96 (d, *J* = 8.9 Hz, 2H), 6.98 (s, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 4.3 Hz, 1H), 6.63–6.60 (m, 2H), 6.57 (d, *J* = 4.1 Hz, 1H), 3.89 (s, 3H), 2.38 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.03, 164.24, 149.23, 139.58, 137.41, 136.72, 132.88, 132.71, 130.81, 129.93, 128.70, 127.97, 121.32, 114.15, 114.01, 55.92, 21.54, 20.49. HRMS calcd. for $C_{26}H_{24}BF_2N_2O_2$ $[M+H]^+$: 445.1893, found 445.1896.

4h (R = 4-chlorophenyl, Ar = mesityl) was prepared in 47% yield (52 mg) from **1a** and **2f**. mp 163.1-165.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.99 (s, 2H), 6.87 (s, 1H), 6.63-6.60 (m, 3H), 2.38 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.66, 150.73, 149.65, 148.59, 139.90, 139.75, 138.09, 137.37, 136.67, 136.62, 133.47, 131.71, 129.75, 129.25, 129.04, 128.76, 127.29, 122.24, 21.53, 20.47. HRMS calcd. for $C_{25}H_{21}BClF_2N_2O$ $[M+H]^+$: 449.1398, found 449.1397.

Synthesis of 4i. BODIPY **1d** (62 mg, 0.25 mmol), Bu_4NI (18 mg, 0.05 mmol) and the oxidant TBHP (0.12 mL, 1.25 mmol) were dissolved in **2a** (2 mL). The reaction mixture was stirred at 90 °C for 8 h and then was cooled to room temperature. After addition of 6 equiv of TFA, the reaction mixture was stirred at room temperature for 1 h. Upon completion, the

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reaction mixture was poured into dichloromethane (100 mL), washed three times with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatographically (silica; petroleum ether/ethyl acetate; 15:1-9:1 v/v) to provide **4i** in 34% yield (25 mg). mp 163.7-165.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 7.81 (s, 1H), 7.44 (s, 1H), 6.80 (s, 1H), 2.64 (s, 3H), 2.44 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 1.11 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.23, 170.19, 143.97, 140.26, 137.57, 133.72, 131.21, 130.96, 122.43, 117.83, 17.34, 13.97, 13.88, 9.72. HRMS calcd. for $C_{14}H_{15}BFN_2O$ $[M-F]^+$: 277.1318, found 277.1319.

General Procedure for the One-pot Synthesis of 5a-d. We are using **5a** (R = H, Ar = mesityl) as an example to show the general procedure for the preparation of 3,5-diformylBODIPY **5a** and 3,5-diacylBODIPYs **5b-d**: BODIPY **1a** (78 mg, 0.25 mmol), Bu_4NI (18 mg, 0.05 mmol) and the oxidant TBHP (0.12 mL, 1.25 mmol) were dissolved in **2a** (2 mL). The reaction mixture was stirred at 90 °C for 16 h and was cooled to room temperature. After the addition of 6 equiv of TFA, the reaction mixture was stirred at room temperature for 1 h. Upon completion, the reaction mixture was then poured into dichloromethane (100 mL), washed three times with water (100 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatographically (silica; petroleum ether/ethyl acetate; 10:1-5:1 v/v) to provide **5a** in 25% yield (22 mg). mp 158.7-160.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.47 (s, 2H), 7.11 (d, *J* = 4.2 Hz, 2H), 7.00 (s, 2H), 6.83 (d, *J* = 3.9 Hz, 2H), 2.38 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 184.00, 154.60, 151.55, 140.19, 138.56, 136.06, 131.47, 128.78, 128.67, 120.34, 21.17, 120.15. HRMS calcd. for $C_{20}H_{17}BF_2N_2O_2Na^+$ $[M+Na]^+$ 389.1243, found 389.1246.

5b (R = Me, Ar = mesityl) was prepared in 23% yield (20 mg) from **1a** and **2b**. mp 83.5-85.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 2H), 6.94 (d, *J* = 4.4 Hz, 2H), 6.72 (d, *J* = 4.4 Hz, 2H), 2.82 (s, 6H), 2.37 (s, 3H), 2.09 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.53, 154.02, 153.15, 139.68, 138.09, 136.00, 130.54, 129.46, 128.46, 122.85, 29.68, 21.15, 20.06. HRMS calcd. for $C_{22}H_{21}BFN_2O_2^+$ $[M-F]^+$ 375.1674, found 375.1678.

5c (R = Ph, Ar = mesityl) was prepared in 41% yield (53 mg) from **1a** and **2d**. mp 149.3-151.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.1 Hz, 4H), 7.61-7.56 (m, 2H), 7.48-7.43 (m, 4H), 7.02 (s, 2H), 6.80 (d, *J* = 3.8 Hz, 2H), 6.63 (d, *J* = 3.8 Hz, 2H), 2.39 (s, 3H), 2.20 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.99, 154.22, 151.23, 139.53, 137.31, 136.38, 136.35, 133.91, 130.30, 130.22, 129.44, 129.06, 128.46, 121.80, 21.21, 20.26. HRMS calcd. for $C_{32}H_{26}BF_2N_2O_2$ $[M+H]^+$: 519.2050, found 519.2059.

5d (R = 4-methoxyphenyl, Ar = mesityl) was prepared in 45% yield (65 mg)) from **1a** and **2e**. mp 133.7-135.9 °C. ^{1}H NMR (300 MHz, d_6-DMSO) δ 7.76 (d, *J* = 8.5 Hz, 4H), 7.11 (d, *J* = 9.7 Hz, 4H), 7.07 (s, 2H), 6.89 (d, *J* = 4.0 Hz, 2H), 6.82 (d, *J* = 3.9 Hz, 2H), 3.85 (s, 6H), 2.37 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.85, 164.29, 154.67, 139.37, 136.37, 132.71, 132.25, 130.09, 129.38, 128.39, 122.65, 121.08, 113.94, 113.74, 55.55, 21.18, 20.22. HRMS calcd. for $C_{34}H_{29}BFN_2O_4^+$ $[M-F]^+$ 559.2199, found 559.2198.

Synthesis of BODIPY 6. To a solution of 3-formylBODIPY **4a** (0.1 mmol, 33 mg) in N,N-dimethylformamide (DMF, 3 mL) was added diethylamine (0.21 mmol, 2.1 equiv). The mixture was stirred at room temperature for the 2 h under air. Upon completion, the reaction mixture was poured into dichloromethane (30 mL), washed three times with water (50 mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was purified by column chromatographically (silica; petroleum ether/dichloromethane; 2:1 v/v) to provide **6** in 64% yield (26 mg). mp 212.6-213.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 6.93 (s, 2H), 6.71 (d, *J* = 5.2 Hz, 1H), 6.36 (d, *J* = 5.3 Hz, 1H), 5.98 (d, *J* = 3.8 Hz, 1H), 3.91 (s, 4H), 2.34 (s, 3H), 2.08 (s, 6H), 1.42 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.66, 163.02, 140.51, 138.25, 138.20, 137.40, 136.22, 135.47, 130.20, 128.19, 127.36, 117.92, 117.41, 115.35, 47.32, 21.12, 20.06, 13.77. HRMS calcd. for $C_{23}H_{26}BFN_3O^+$ $[M-F]^+$ 390.2147, found 390.2149.

Synthesis of BODIPY 7. To a mixture of **4a** (33 mg, 0.1 mmol) and pyrrole (1 mL, 16 mmol) was added TFA (0.02 mL, 0.2 mmol). The reaction mixture was stirred at room temperature for 5 min and was quenched by adding 30 mL aqueous solution of NaOH (0.2 M). The reaction mixture was extracted with CH_2Cl_2 (30 mL) and the organic layer was washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified through column chromatography (silica, CH_2Cl_2) to afford dipyrromethane intermediate **8**, which was dissolved in 20 mL CH_2Cl_2 and directly used for the subsequent oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 40 mg, 0.2 mmol) at room temperature for 1 h. The resultant mixture was further treated with triethylamine (1 mL, 7.2 mmol) for 20 min, and was complexed with boron trifluoride etherate (3 mL, 23.9 mmol) for 2 h at room temperature. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:5, v/v) to give **7** as a red solid in 78% yield (40 mg). mp 233.4-235.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 2H), 7.93 (s, 1H), 7.01 (s, 4H), 6.82 (d, *J* = 3.8 Hz, 1H), 6.74 (d, *J* = 3.6 Hz, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 6.52 (d, *J* = 3.6 Hz, 3H), 2.39 (s, 3H), 2.17 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.46, 147.59, 146.66, 145.34, 139.33, 136.54, 136.41, 136.29, 136.21, 135.15, 132.15, 131.82, 129.35, 128.45, 128.39, 121.83, 120.53, 118.51, 21.18, 20.07. HRMS calcd. For $C_{27}H_{22}B_2F_3N_4^+$ $[M-F]^+$ 481.1977, found 481.1979.

Conflicts of interest

There are no conflicts to declare.

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