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Synthesis of 2,6-Disubstituted BODIPY Dyes Using Palladium-Catalyzed Cross-Coupling Reaction with Indium Organometallics and Indium-Catalyzed Alkyne Hydroarylation Reactions †

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Abstract: The synthesis of functionalized BODIPY dyes at C2 and C6 positions by palladium-catalyzed cross-coupling reactions with triorganioindum reagents (R_3In) and indium-catalyzed alkyne hydroarylation reactions is reported. The two-fold palladium-catalyzed cross-coupling reaction of R_3In (150 mol%) with 2,6-dihalogenated BODIPYs allowing disubstituted π-conjugated BODIPYs in moderate yiels. In addition, the indium(III)-catalyzed intermolecular double hydroarylation reaction of alkynes with *meso*-substituted BODIPYs also provide a straightforward method for the regioselective synthesis of 2,6-dialkenyl-BODIPY dyes. Both synthetic procedures represent economical strategies for the synthesis of 2,6-disubstituted BODIPY derivatives. Futhermore, the photophysical properties of the novel compounds prepared were studied by UV-Vis and fluorescence. The experimental values showed bathochromically shifted absorption and emission according with the electron-richness of the substituents and high quatum yields.

Keywords: indium(III)-catalysis; indium organometallics; BODIPYs; cross-coupling; alkyne hydroarylation; optical properties

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1. Introduction

During the last three decades the synthetic utility of indium(III) organometallics and halides have been continuously increased. Indium organometallics (R_3In) have been shown as useful reagents in metal-catalyzed cross-coupling reactions [1], and indium(III) halides as efficient π-acids for the electrophilic activation of alkynes [2]. Furthermore, the application of these methodologies has allowed the synthesis of different natural products and novel organic materials.

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) and derivatives belong to a class of structurally fascinating compounds with interesting fluorescent properties, that have found widespread applications in a broad range of scientific fields [3], as a result of their photophysical properties [4]. In particular, polyfluorinated BODIPYs have been used for the preparation of fluorescent perfluorocarbon nanoemulsions with application for simultaneous fluorescent and ^{19}F NMR imaging [5].

Hitherto, different strategies for the introduction of suitable substituents (e.g., aryl, alkenyl) at C2 and C6 positions of the BODIPY scaffold have been reported like metal-catalyzed cross-coupling reactions [6], or C–H functionalization using palladiummediated oxidative olefination [7], respectively. However, the development of economical and sustainable strategies to functionalized BODIPYs still of current interest.

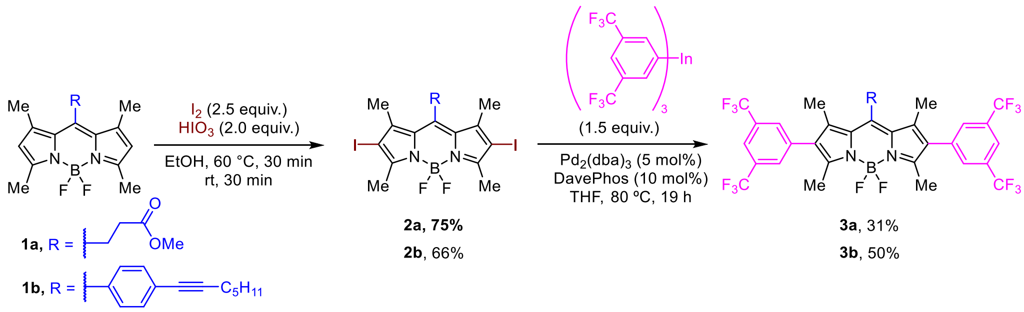
Following our ongoing interest in the synthesis of functional BODIPY dyes, herein we report the synthesis of 2,6-disubstituted BODIPY dyes by palladium-catalyzed cross-coupling using R_3In and indium(III)-catalyzed alkyne hydroarylation reactions.

2. Results and Discussion

2.1. Functionalization of BODIPY by Pd-Catalyzed Cross-Coupling Reactions with R_3In

Our investigation started studying the palladium-catalyzed cross-coupling reaction of halogenated BODIPY **2a** with tris[3,5-bis(trifluoromethyl)phenyl]indium. BODIPY **2a** was prepared through iodination of **1a** and compound **1a** was obtained applying our recently developed microwave-assisted one-pot strategy (Scheme 1) [8].

Considering the prior expertise of our group in cross-coupling reactions [1], $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd_2(dba)_3$ in the presence of DavePhos as ligand were selected as palladium sources. During the optimization process, we found that treatment of **2a** with tris[3,5-bis(trifluoromethyl)phenyl]indium (150 mol%) in the presence of $Pd_2(dba)_3$ (5 mol%) and DavePhos (10 mol%) in TFF at 80 °C led to the formation of 2,6-disubstituted BODIPY **3a** in 31% yield, whereas the use of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ did not improve the yield.



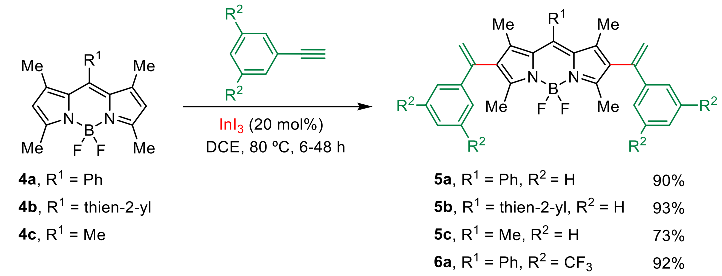
Scheme 1. Synthesis of BODIPYs **3a–3b** by two-fold Pd-catalyzed cross-coupling reaction with R_3In.

We next investigated the applicability of the cross-coupling reaction to dihalogenated BODIPY **2b** bearing an aryl substituent at *meso* position. Similarly, the two-fold Pd-catalyzed cross-coupling reaction of **2b** with tris[3,5-bis(trifluoromethyl)phenyl]indium under the optimal conditions afforded the BODIPY **3b** in higher 50% yield.

This synthetic transformation using R_3In provides an atom economical alternative to other organometallics as all three organic groups attached to the metal can transfer.

2.2. Functionalization of BODIPY by Indium(III)-Catalyzed Intermolecular Alkyne Hydroarylation

Having developed the Pd-catalyzed cross-coupling reactions on dihalogenated BODIPYs, we turned our interest to explore indium(III)-catalyzed alkyne hydroarylation reactions to the synthesis of 2,6-dialkenyl-BODIPY dyes. In this case, we studied the reactivity of the intermolecular arylalkyne hydroarylation with BODIPYs bearing different substituents at *meso* position (**4a–4c**, Scheme 2) [8]. The corresponding 2,6-dialkenyl-BODIPY derivatives **5a–5c** and **6a** were efficiently synthetized in good yields (73–93%), according to our recent methodology using available InI_3, outline in Scheme 2 [9]. The reaction proceeds in good yields with Markovnikow regioselectivity through electrophilic π-activation mode.



Scheme 2. Synthesis of 2,6-dialkenyl BODIPY dyes through π-acid catalysis.

This indium(III)-catalyzed intermolecular double alkyne hydroarylation reaction, offers an effective and economically viable approach to synthesizing these valuable compounds.

2.3. Photophysical Properties

After successful synthesis we studied the optical properties of BODIPY dyes by UV-Vis absorption and fluorescence emission in $CHCl_3$ at room temperature. All synthetized compounds showed a narrow absorption band assigned to the $S_1 \leftarrow S_0$ transition, and also a narrow emission bandwidth ranging from 538 to 565 nm (Figure 1a and 1b, respectively). Interestingly, BODIPY **6a** presents the highest extinction coefficient (Ɛ = 79,174 $M^{-1}cm^{-1}$) related to the electron-richness of the substituent on the alkenyl moiety when compared with **5a** (Ɛ = 64,944 $M^{-1}cm^{-1}$). On the other hand, BODIPY **5b** carrying thien-2-yl group at *meso* position displayed bathochomic shift when compared with both compounds **5a** and **5c** bearing 1-(phenyl)ethynyl moiety at C2 and C6 positions. As expected, BODIPY dyes showed high quantum yields (Φ_F = 0.72–0.94) that lies to their rigid π-conjugated structures, meanwhile the low Φ_F for **5b** (Φ_F = 0.14) could be attributed to the freedom of rotation of thien-2-yl moiety at *meso* position, increasing the energy lost to non-radiative [10].

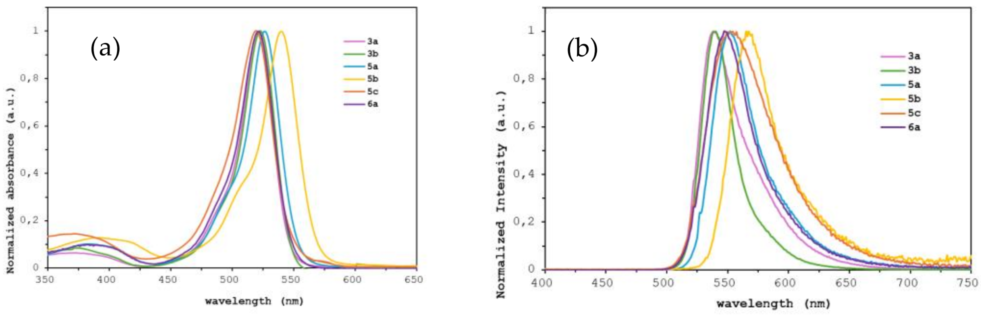


Figure 1. (**a**) UV-Vis absorption and (**b**) fluorescence spectra of compounds **3a–3a, 5a–5c** and **6a**.

3. Materials and Methods

3.1. General Information

Indium(III) halides were used as received under argon in a glovebox system. BODIPYs (**1a–1b** and **4a–4c**) were prepared according to the literature [8]. BODIPYs **2a** and **2b** were synthetized by iodination procedure [11]. The solution of $InCl_3$ (0.45 M in THF) was prepared from commercial indium trichloride. Triorganoindium compounds were obtained according to previously published method [12]. Flash column chromatography was performed using silica gel. ^{1}H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on a 300 MHz Bruker NMR spectrometer and calibrated to the solvent peak. DEPT data were used to assign carbon types. Mass spectra were recorded on a Magnetic Sector EI or a QSTAR ESI mass spectrometer, operating in the positive ionization mode.

3.2. Chemistry

3.2.1. General Procedure for the Pd-Catalyzed Cross-Coupling Reaction

A Schlenk tube, equipped with a stirring bar and filled with argon, was charged with halogenated BODIPY (0.16 mmol), $Pd_2(dba)_3$ (0.006 mmol), DavePhos (0.025 mmol) and THF (0.16 M). A solution of tris[3,5-bis(trifluoromethyl)phenyl]indium (0.19 mmol) was added dropwise. The resulting mixture was heated at 80 °C for 20 h, cooled to rt and quenched by a few drops of MeOH. The solvent was evaporated and the residue was diluted with Et_2O (25 mL). The organic phase was washed with saturated aqueous NH_4Cl (2 × 10 mL), dried and the solvent concentrated in vacuo. The resulting crude was purified by column chromatography (3-5% EtOAc/hexanes) to afford, after concentration and high vacuum drying, the corresponding BODIPYs **3a–3b**.

*Methyl 3-(2,8-bis(3,5-bis(trifluoromethyl)phenyl)-5,5-difluoro-1,3,7,9-tetramethyl-5H-4l⁴,5l⁴-dipyrrolo [1,2-c:2′,1′-f][1,3,2]diazaborinin-10-yl)propanoate (**3a**).*

Red solid (31% yield), mp 203–204 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (s, 2H), 7.63 (s, 4H), 3.67 (s, 3H), 3.43 (t, J = 8.3 Hz, 2H), 2.63 (t, J = 8.5 Hz, 2H), 2.42 (s, 6H), 2.32 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7 (C), 153.5 (2 x C), 145.5 (2 x C), 137.4 (2 x C), 135.8 (2 x C), 132.1 (q, $^2J_{CF}$ = 34.5 Hz, 4C), 131.6 (2 x C), 131.5 (C), 130.5 (4 x CH), 123.0 (q, $^1J_{CF}$ = 274.5 Hz, 4 x C), 121.4 (2 x CH), 52.3 (CH_3), 35.2 (CH_2), 24.1 (CH_2), 14.5 (3 x CH_3), 13.2 (CH_3); HRMS (EI): calc for $C_{33}H_{25}BF_{14}N_2O_2$ [M]$^+$ 758.1780, found 758.1778.

*2,8-Bis(3,5-bis(trifluoromethyl)phenyl)-5,5-difluoro-10-(4-(hept-1-yn-1-yl)phenyl)-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo [1,2-c:2′,1′-f][1,3,2]diazaborinine (**3b**).*

Orange solid (50% yield), mp 227–229 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.64 (s, 4H), 7.58 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.56 (s, 6H), 2.43 (t, J = 7.3 Hz, 2H), 1.63 (q, J = 7.3 Hz, 2H), 1.34-1.49 (m, 10H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (C), 143.1 (C), 140.1 (2 x C), 135.8 (2 x C), 133.6 (C), 132.7 (2 x CH), 131.9 (q, $^2J_{CF}$ = 32.9 Hz, 4C), 131.4 (2 x C), 131.2 (2 x C), 130.2 (4 x CH), 127.7 (2 x CH), 125.8 (2 x C), 123.2 (q, $^1J_{CF}$ = 272.9 Hz, 4 x C), 121.2 (2 x CH), 92.8 (C), 79.7 (C), 31.1 (CH_2), 28.3 (CH_2), 22.2 (CH_2), 19.4 (CH_2), 14.0 (CH_3), 13.3 (CH_3), 13.0 (3 x CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.86 (s, 4 x CF_3), –145.80 (q, $J_{B\text{-}F}$ = 33.1 Hz, 2 x F); HRMS (EI) calcd for $C_{42}H_{33}N_2BF_{14}$ [M]$^+$ 842.2508; found 842.2508.

3.2.2. General Procedure for the Indium(III)-Catalyzed Double Intermolecular Alkyne Hydroarylation Reaction of BODIPYs

A flame dried Schlenk flask was charged with InI_3 (20 mol%), BODIPYs **4a–4c** (0.2 mmol) in DCE (~0.1 M) and arylalkyne (14 equiv.). The resulting solution was heated in an oil bath at 80 °C and monitored by TLC. The reaction was cooled to rt and the solvent was removed. The resulting crude was purified by flash chromatography on silica gel (EtOAc/hexanes) to afford the corresponding 2,6-dialkenylated BODIPYs (**5a–5c** and **6a**) which were characterized by ^{1}H NMR, ^{13}C NMR and HRMS [9].

3.3. Physical Measurements

UV-Vis absorption and fluorescence spectra were recorded using a spectrofluorometer equipped with a pulsed xenon flash-lamp as a light source. Compounds were excited at their excitation maxima to record the emission spectra. The concentration of the compound solutions ($CHCl_3$) were adjusted to $7.5 \cdot 10^{-7}$ M. Fluorescence quantum yields (Φ_F) values for compounds **5a–5c** and **6a** were determined by comparison with rhodamine 6G in ethanol and form compounds **3a** and **3b** fluorescein in NaOH 0.1 M as reference (Φ_F = 0.94) [13] and (Φ_F = 0.92) [14], respectively.

4. Conclusions

In summary, we report the first examples of the palladium-catalyzed cross-coupling reactions using indium organometallics (R_3In) with 2,6-dihalogenated BODIPYs. The di-coupling products were obtained with atom economy in moderate yields. Likewise, the indium(III)-catalyzed intermolecular double hydroarylation reactions of arylalkynes with *meso*-substituted BODIPYs is reported. The reaction takes place through electrophilic π-activation mode using indium triiodide as catalyst, to provide branched 2,6-dialkenyl BODIPYs with Markovnikov regioselectivity in excellent yields. The optical properties of the resulting BODIPY dyes were studied displaying fluorescence emissions from 538 to 565 nm and high quantum yields (up to $\Phi_F = 0.96$).

Author Contributions:

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