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Spectral Dispersion and Water Solubilization of BODIPY Dyes via Palladium-Catalyzed C–H Functionalization

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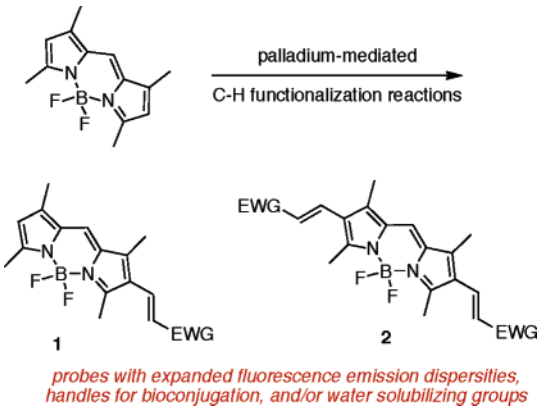
ABSTRACT



Fluorescent probes 1 and 2 were prepared directly from tetramethyl-BODIPY via palladium-mediated C–H functionalization reactions.

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes are valuable for biomedical applications because they have sharp fluorescence emissions and high quantum yields.[1] One of the challenges in design and syntheses of these probes is preparing derivatives with extended conjugation that fluoresce at longer wavelengths while maintaining high quantum yields. Typical approaches to this problem include: (i) halogenating BODIPY followed by organometallic couplings to introduce alkene-, alkyne-, or arene-substituted systems;[2−4] (ii) Knoevenagel-type condensations of some methyl-substituted BODIPYs (because methyl groups in appropriate positions are somewhat acidic);[5,6] or (iii) de novo syntheses of the BODIPY core from modified pyrroles.[7,8]

Recently, there has been a renaissance in palladium-catalyzed activation of aromatic compounds,[9,10] particularly as a means to functionalize pyrroles[11−13] and indoles.[14−16]

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We wondered if the same strategies could be used for the particular case of BODIPY dyes, to give substituted derivatives with well-resolved fluorescence emissions (Figure 1); this paper explores that concept.

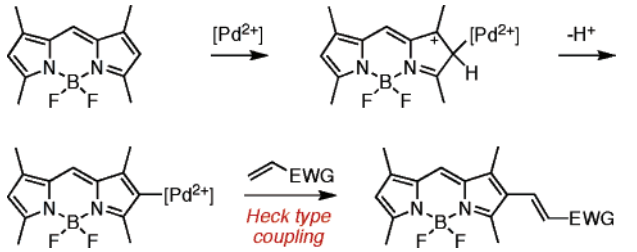


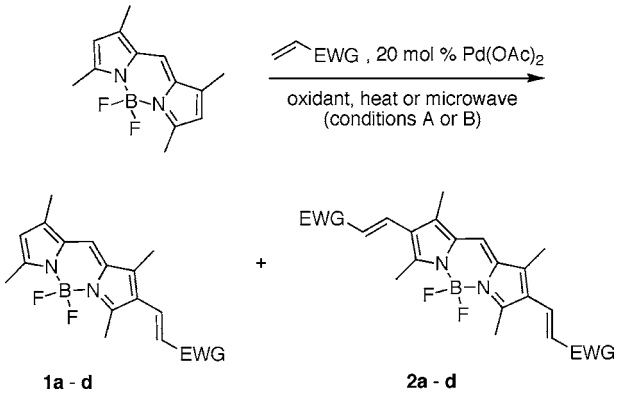
Figure 1. Guiding hypothesis for producing BODIPY dyes with extended conjugation in a single reaction.

The Heck-type coupling shown in Figure 1 liberates HPdX(2+) species that disproportionate to Pd(0) and HX; consequently, reoxidants are required to make the reaction catalytic in palladium. Two sets of conditions were explored to bring this about. Method A in Table 1 features *tert*-butyl benzoyl peroxide as a reoxidant in a mixed solvent system. These conditions were devised by Gaunt[13,16] on the basis of Larock's discovery that solvent systems containing DMSO ligate palladium zero preventing formation of insoluble aggregates.[17−19] Method B is a minor modification by us, based on other conditions originating from Larock and Gaunt, but with microwave irradiation.

Table 1 indicates method A gave good overall yields when the EWG group was an ester and that products from mono- (**1**) and di- (**2**) substitution were formed. These were easily separable via flash chromatography (entries 1 and 2). Entry 3 shows that the predominant product **1c** arose from monosubstitution when an α,β-unsaturated acid was the electrophile. A very low yield of the monosulfonated product **1d** was isolated in entry 4. The diminished yield in this reaction reflects difficulties encountered in the isolation procedure for the sulfonic acid and perhaps some attenuation of alkene electrophilicity associated with the negatively charged sulfonate form.

The fact that both mono- and disubstituted products were formed in some cases gave a good dispersion of UV

Table 1. Oxidative Functionalization of Tetramethyl-BODIPY[a]



entry	compound type	EWG	isolated yield (%) method	1	2
1	a	CO_2Me	A	61	30
2	b	CO_2Bu	A	56	28
3	c	CO_2H	A	29	trace
4	d	SO_3H	B	2	0

[a] Method A: 20 mol % of $Pd(OAc)_2$, ^tBuOOBz, AcOH/dioxane/DMSO, 35 °C, 5 days. Method B: 20 mol % of $Pd(OAc)_2$, $Cu(OAc)_2$, DMF:DMSO, microwave (200 W, cooling, 80 °C, 30 min).

absorbance and fluorescence emissions for the series as a whole (Figure 2). Further, the molar absorbtivities of the dyes are comparable to the starting material,[20] and their quantum yields tend to be excellent. Brightness of dyes is a function of absorbance and quantum yields, thus it is unsurprising that compounds **1** and **2** are colorful to the eye and brilliant when irradiated (Figure 2c). Spectral data for all the dyes in EtOH are collected in Table 2. The sharpness of the

Table 2. Spectral Properties Measured in Ethanol

	λ_{max} (nm)	$\log(\epsilon_{max})$	λ_f (nm)	fwhm (nm)[a]	Φ_f
1a	527	4.80 ± 0.01	549	40	0.73 ± 0.01
2a	559[b]	4.13 ± 0.01	580	45	0.51 ± 0.02
1b	528	4.79 ± 0.01	551	39	0.73 ± 0.01
2b	560	4.48 ± 0.01	580	37	0.52 ± 0.01
1c	531	4.43 ± 0.02	570	58	0.42 ± 0.02
1d	529	–[c]	560	50	0.25 ± 0.01
3e	518	4.37 ± 0.02	525	24	0.72 ± 0.01
4e	530	4.86 ± 0.01	539	25	0.92 ± 0.05
3f	517	4.80 ± 0.01	527	25	0.78 ± 0.01
4f	529	4.74 ± 0.01	540	24	0.89 ± 0.01

[a] Full width at half-maximum height: a measure of the sharpness of the fluorescence peaks. [b] Measured in ethyl acetate. [c] Quantity isolated was too small for accurate measurement.

fluorescence emissions (characterized by full width at half-maximum (fwhm)) was comparable to the parent 1,3,5,7-tetramethyl-BODIPY (22 nm) but tended to become slightly broader with increased conjugation.

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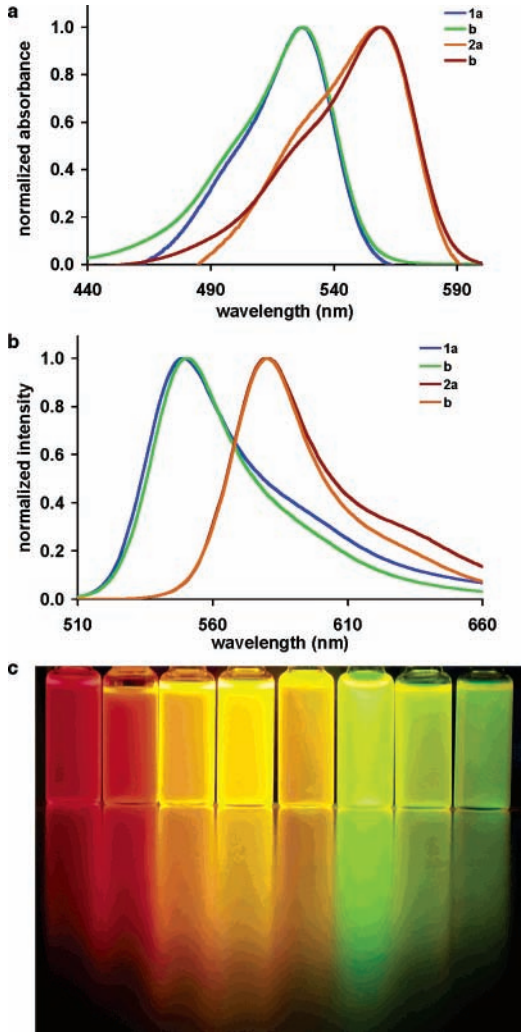


Figure 2. Normalized (a) absorbance and (b) emission spectra of dyes **1a**,**b** and **2a**,**b** in EtOH (1.23×10^{-5} M, excited at the respective λ_{max}) with the exception of **2a** which was measured in EtOAc due to poor solubility in EtOH. (c) Photograph of the dyes **2a**, **2b**, **1b**, **1a**, **4f**, **4e**, **3f**, and **3e** (in that order) under UV irradiation.

There are relatively few BODIPY dyes that are water soluble and even fewer well-documented synthetic procedures to make them.[21,22] Dye **1c** is slightly water soluble and has a carboxylic acid that could be activated with water solubilizing groups, e.g., a sulfonated *N*-hydroxysuccinimide. Consequently, it has some potential for covalent linking to biomolecules. BODIPY **1d** is water soluble and could find other applications where fluorescence in aqueous media is required. For these reasons, we chose to study these two dyes in aqueous buffers at different pH values (Figure 3). Over a pH range of 6.05−8.04, the fluroescence emissions vary by only 3 nm. This is a marked contrast to fluorescein dyes for which equilibria between xanthane and ring-closed lactone

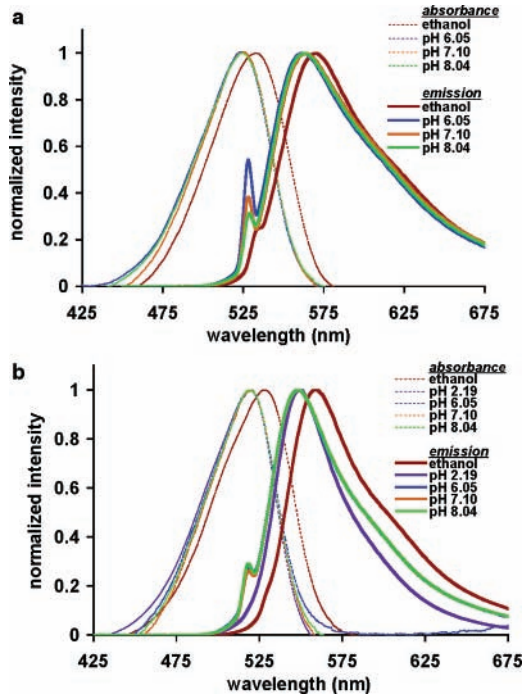
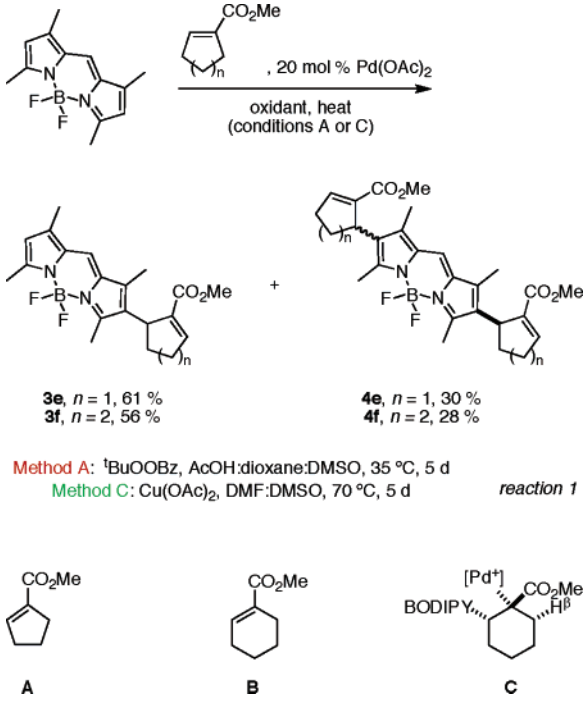


Figure 3. Normalized absorbance and emission spectra of (a) **1c** and (b) **1d** in various solvents (1.23×10^{-5} M in ethanol and 1.00×10^{-5} M in buffer). Buffers used were: pH = 2.19, citric acid; pH = 6.05, MES/LiOH; pH = 7.10, bisTris/H_3PO_4; pH = 8.04, HEPES/LiOH.

forms cause the emission wavelengths and intensities to vary greatly over a similar pH range.

Reaction 1 shows the C−H functionalization process applied to two α,β-unsaturated esters, **A** and **B**. As before, mono- and disubstituted products were isolated (**3** and **4**,



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respectively), but the alkene double bond was shifted out of conjugation with the BODIPY core. Presumably, the migratory insertion intermediates like **C** cannot undergo β-elimination to form an alkene in conjugation with the BODIPY part; the only hydrogen available on the same face of the carbocyclic ring is the one marked H^{β} above, which takes the alkene out of conjugation. The products **4** are probably mixtures of diastereomers, but the two chiral centers are so far apart that the NMR data are as if this were essentially one compound.

In summary, palladium-mediated C−H functionalization reactions provide a direct way to extend the conjugation of the tetramethyl-BODIPY system. The strategy does not require that halogenated or metalated intermediates be isolated prior to the coupling reaction. Mono- and disubstituted products can be obtained; these have brilliant fluorescence with emissions that span 525−570 nm. Further, the methodology has potential for syntheses of systems with handles for bioconjugation and inclusion of water-solubilizing groups.

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Supporting Information Available: Experimental procedures and characterization data for the new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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