

3- and 5-Functionalized BODIPYs via the Liebeskind-Srogl reaction†

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Chemoselective cross-coupling reactions were demonstrated for C–S bonds in the BODIPY dyes **1** and **4**, and similar reactions were applied to make the two-dye cassette system **11**.

Organometallic cross coupling reactions are useful for extending the conjugation of 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene, or BODIPY® (here abbreviated BODIPY) dyes to give probes that fluoresce at longer wavelengths. Usually this is achieved *via* inherently basic processes (Suzuki¹ and Sonogashira²) that tend to cause partial decomposition of BODIPY dyes. Furthermore, chemoselective reactions involving different halides in the same molecule are sometimes desirable, but hard to achieve *via* these transformations. For instance, the C–Cl sites of systems like **A**³ are reactive for Sonogashira and Suzuki reactions,⁴ but competitive reactions of the aryl bromide site would be expected. This paper describes how Liebeskind-Srogl reactions^{5–7} can be used to achieve chemoselective couplings to BODIPY dyes under neutral conditions; further, this transformation was used to give a water-soluble two dye cassette system.

It has been demonstrated that Liebeskind-Srogl couplings can be used to substitute thioalkyl groups at the C⁸ position of the BODIPY core.⁸ Chemoselective Liebeskind-Srogl couplings at thioalkyl groups over aryl bromides have also been demonstrated.⁹ Consequently we felt that selective substitution at the 3,5-positions as in compound **1** would be possible. In actuality, phenyltin (**a**) and electron-rich aryl-tin (**c**) reagents cleanly gave the disubstituted products **3**, some monosubstituted intermediate was isolated for the electron-deficient aryl group tested (**b**), but in no case was the aryl-bromide affected (Scheme 1).

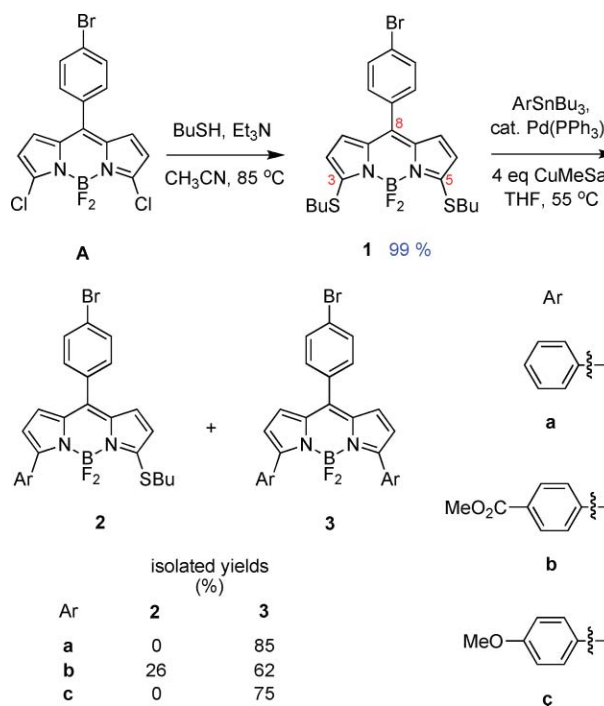
Fig. 1 shows normalized absorbance (a) and fluorescence (b) spectra for compounds **1–3**. The newly installed aryl groups shift both maxima to the red, as previously described for 3,5-diaryl-BODIPY dyes.¹⁰ More extensive spectroscopic data for these products is shown in Table 1. Both *para*-electron withdrawing (CO₂Me) and donating (OMe) groups shifted the maximum fluorescence wavelength to red (8 nm and 33 nm respectively, compare **3a**, **3b** and **3c**).

meso-(4-Bromoaryl)BODIPY substituents like those in compounds **2** and **3** can be further elaborated *via* Sonogashira reactions. However, recent unpublished data from our laboratories have shown that there are advantages to using copper-mediated alkyne-azide coupling reactions^{12,13} to join two BODIPY

Table 1 Photophysical properties of compounds **1–3** in EtOAc

compd	$\lambda_{\text{abs max}}$ (nm)	ϵ_{max} (L mol ⁻¹ cm ⁻¹)	$\lambda_{\text{fl max}}$ (nm)	fwhm (nm) ^a	Φ_f ^b
1	577	46700	595	47	0.40 ± 0.04
2b	571	50600	597	59	0.58 ± 0.01
3a	555	52400	588	49	0.14 ± 0.01
3b	559	44000	596	48	0.36 ± 0.03
3c	581	51900	621	41	0.38 ± 0.01

^a Full width at half maximum height of fluorescence (fwhm). ^b Rhodamine 101 ($\Phi = 1.0$ in ethanol) as standard.¹¹



Scheme 1 Synthesis of 3- and 5-functionalized BODIPY via Liebeskind-Srogl reaction. CuMeSal = copper(i) 3-methylsalicylate.

fragments together to form two-dye cassette systems. Azido-functionalized dyes are required to achieve this. Thus the sequence outlined in Scheme 2a was performed to generate the azidodicarboxylic acid system **9**. Coupling of the dithioether **4**, which is synthesized from **B**,³ to the appropriate 4 eq stannane gave 17% of the corresponding monosubstituted material **5**, and 66% the desired disubstituted product **6** (see supporting information). However, using 4 eq 4-methoxycarbonylphenylboronic acid afforded **6** in quantitative yield. We think the boronic acid is much more stable than the tin compound under the reaction conditions. A mild ester hydrolysis¹⁴ of this material, and reduction of the azide gave the amine **8** which was then converted to the azide **9**.

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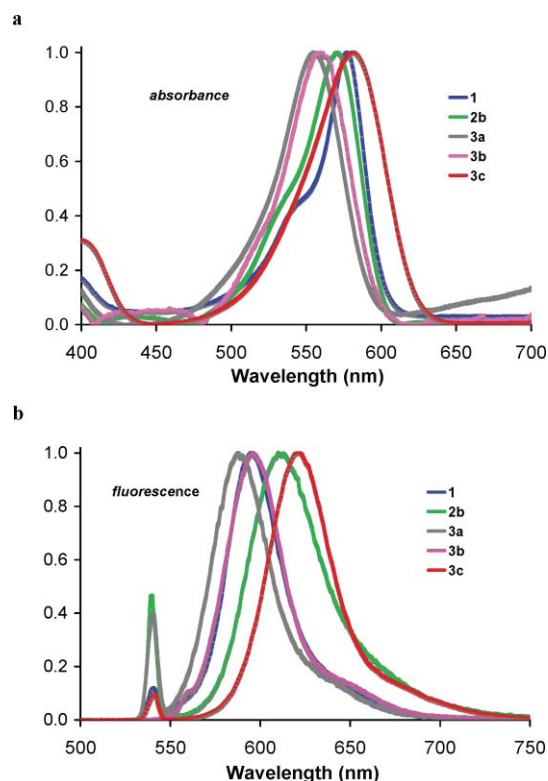
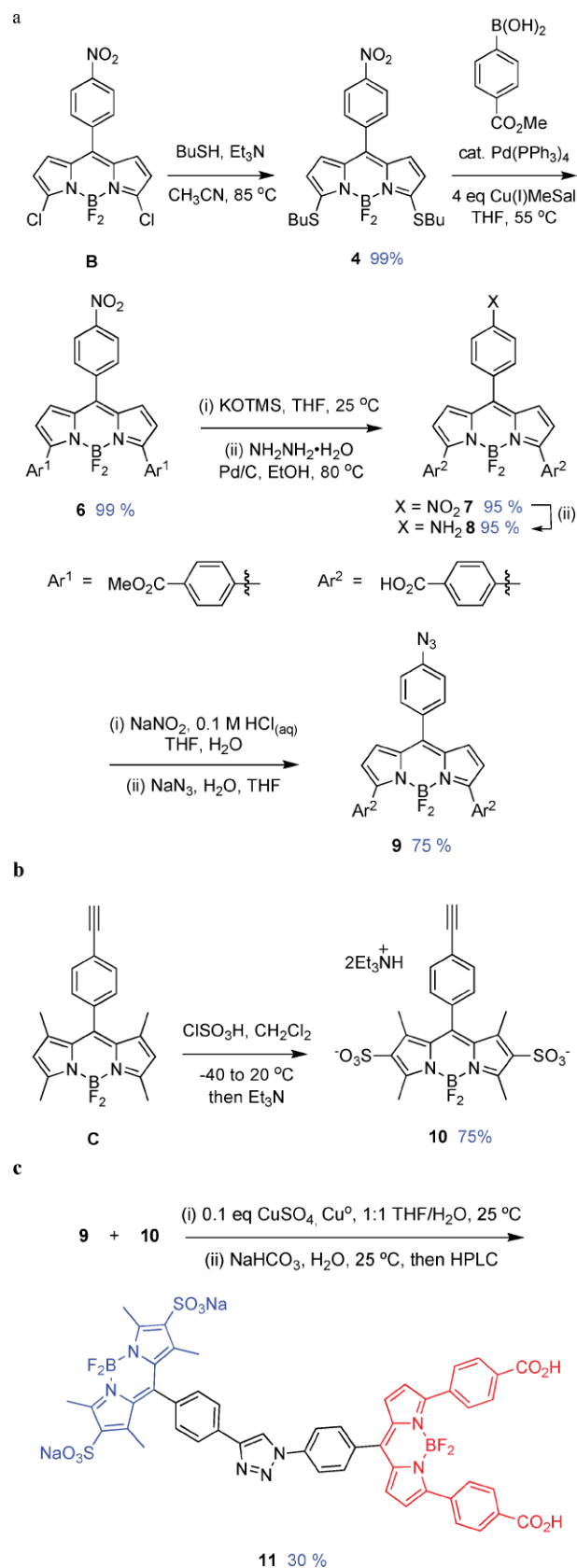


Fig. 1 (a) Normalized absorbance spectra of compounds **1–3** (1×10^{-6} M) in EtOAc. (b) Normalized fluorescence spectra of compounds **1–3** (1×10^{-7} M) in EtOAc with excitation at 540 nm.

The sulfonated BODIPY alkyne **10** was formed from the known starting material **C**¹⁵ *via* sulfonation conditions recently reported by us (Scheme 2b).³ Finally, the appropriately functionalized BODIPYs, azide **9** and alkyne **10**, were joined *via* the click reaction shown in Scheme 2c. The final product **11** is highly water soluble. It was isolated *via* preparative reverse phase HPLC.

Cassette **11** is designed to function as a “through bond energy transfer” (TBET) system. These feature two dye components that are prevented from becoming completely planar because of steric issues. Thus the UV-visible absorption spectrum of **11** and **BSA-11** has two maxima corresponding to the donor fragment and the acceptor part (Fig. 2a).

Motivation for making TBET cassettes is derived from the fact that they can be excited at a much shorter wavelength (donor absorbance) than their fluorescence emission (from acceptor part). This leads to enhanced spectral resolution of emission peaks if several dyes are used together. However, three major obstacles have emerged from our research efforts: (i) making the cassettes in water soluble form; (ii) obtaining good energy transfer from the donor to the acceptor in an aqueous medium (cassettes that work well in less polar solvents can be poor in water); and, (iii) maintaining good energy transfer when the cassette is conjugated to a protein. Cassette **11** is quite water soluble, so that parameter is satisfied. To quantitate the function of the cassettes we measure their overall quantum yields for the acceptor fluorescence emission when excited at the donor. We also use a parameter called the energy transfer efficiency (ETE%) which is defined as $\text{ETE}\% = (\text{quantum yield of the acceptor fragment in the cassette excited at the donor}) / (\text{quantum yield of the acceptor fragment in the cassette excited at the acceptor}) \times 100$.



Scheme 2 Synthesis of energy transfer cassette **11**.

the cassette excited at the donor)/(quantum yield of the acceptor fragment in the cassette excited at the acceptor) \times 100.

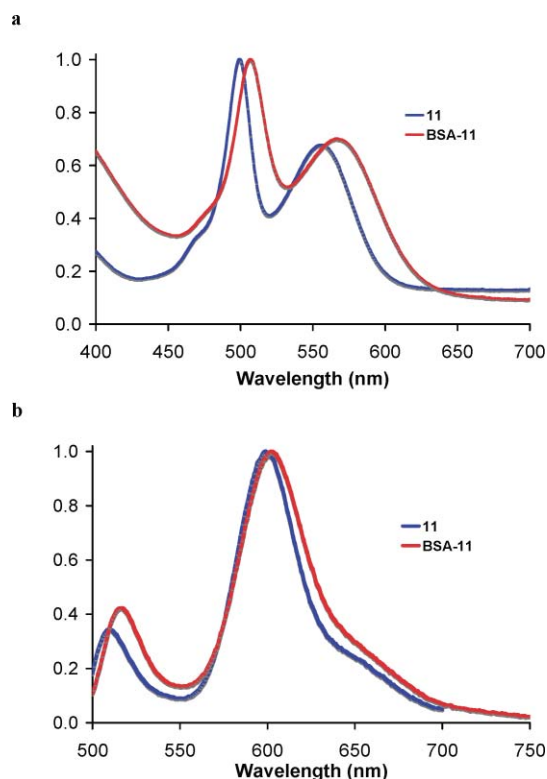


Fig. 2 (a) Normalized absorption of **11** and **BSA-11** in pH = 7.4 PBS buffer. (b) Normalized fluorescence spectra of **11** and **BSA-11** in pH = 7.4 PBS buffer.

The overall quantum yield of **11**, and its ETE% for **11** in pH 7.4 phosphate buffer were determined as 0.23 and 85%. Qualitatively, the undesirable “leakage” of fluorescence from the donor is seen at about 520 nm in Fig. 2b.

Cassette **11** was activated by forming an ester of *N*-hydroxysuccinimide (see supporting information) and conjugated to bovine serum albumin (BSA). This caused the absorbance maxima to be red-shifted by about 8 nm, but had little impact on the fluorescence maxima (Fig. 2). The overall quantum yield of the **BSA-11** conjugate, and its ETE% for pH 7.4 phosphate buffer were determined as 0.10 and 75%.

In summary, the work described here indicates that Liebeskind-Srogl couplings provide another dimension for chemoselectivity in construction of BODIPY dye derivatives.

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