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COMMUNICATION

Diversity-oriented derivatization of BODIPY based on regioselective bromination†

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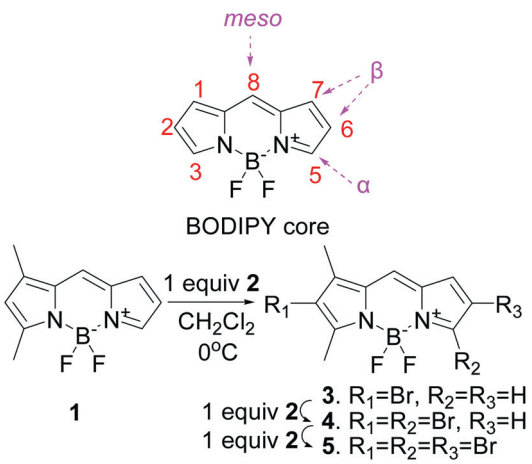
Regioselectively brominated BODIPYs were shown to undergo nucleophilic substitution and Sonogashira coupling reactions with a one-pot procedure, yielding diversely substituted fluorophores.

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes represent a class of extremely popular fluorophores with various valuable properties, such as excellent thermal and photochemical stability, high and environment-independent fluorescence quantum yields, narrow emission bandwidth, good solubility and chemical robustness.[1,2] They have been widely applied as labeling reagents for biomolecules,[3] fluorescent switches,[4] chemosensors,[5] and laser dyes.[6] This remarkable versatility has sparked intense research on new modification strategies to enable linking to biological substrates and also to tune their optical properties. Several new tactics for BODIPY functionalization have been developed,[7–9] among which, halogenation of the BODIPY core is of primary importance because the introduction of a halogen atom onto the BODIPY core facilitates further diverse derivatization through (i) aromatic nucleophilic substitution[8] or (ii) palladium-catalyzed coupling reactions.[9] These two types of reactions exhibit different regioselectivities in that the former is confined exclusively to α-halogenated BODIPYs, while the latter is applicable to both α- and β-BODIPY halides (Scheme 1). Hence, the application of these reactions in tandem to a single multi-halogenated BODIPY would provide an access to more sophisticated structures. However, no such methodology has been established. The objective of the present work was therefore to develop a facile method for diversity-oriented derivatization of regioselectively brominated BODIPYs through a cascade of nucleophilic substitutions and Sonogashira couplings.

Our study started with 1,3-dimethyl-BODIPY (**1**) since it represents the simplest stable structure free of substituents at the α- and β-positions.[1] Compound **1** was synthesized by a classical route through condensation of 2,4-dimethylpyrrole and pyrrole-2-carboxyaldehyde, followed by treatment with boron trifluoride etherate.[10]

Initially, **1** was treated with bromine (Br_2). Unlike the recent report that 8-phenyl-BODIPY undergoes efficient stepwise bromination with bromine,[11] our reaction resulted in a mixture of products hard to purify chromatographically, maybe due to the more electron-rich nature of **1**.[11] Fortunately, ^{1}H-NMR spectra analysis of the mixture showed the inclusion of mono-, di- and tri-brominated products, implying that stepwise dipyrrin bromination might be possible using a more mild brominating agent. The reaction was then attempted with *N*-bromosuccinimide, but this was also unsuccessful. Next, benzyl triethyl ammonium perbromide (**2**) was explored. Much to our delight, treating compound **1** in dichloromethane with one equiv of **2** at 0 °C yielded the mono-brominated product **3** almost quantitatively. Under similar conditions, **3** could be transformed into the di-brominated derivative **4** efficiently, and **4** could be further brominated to yield the tri-brominated BODIPY **5** (Scheme 1). Compounds **4** and **5** can also be obtained in a straightforward way by direct bromination of **1** with the proper amount of **2** with high yields (98% and 96%, respectively) (ESI†).

The exact structures of the products were identified by 2D NMR spectra analysis. The strong correlations of 1- and 3-methyl protons (δ 2.24, 2.61) to a quaternary carbon atom



Scheme 1 IUPAC numbering system for BODIPY core and stepwise bromination of **1** with $PhCH_2N^+Et_3Br_3^-$ (**2**).

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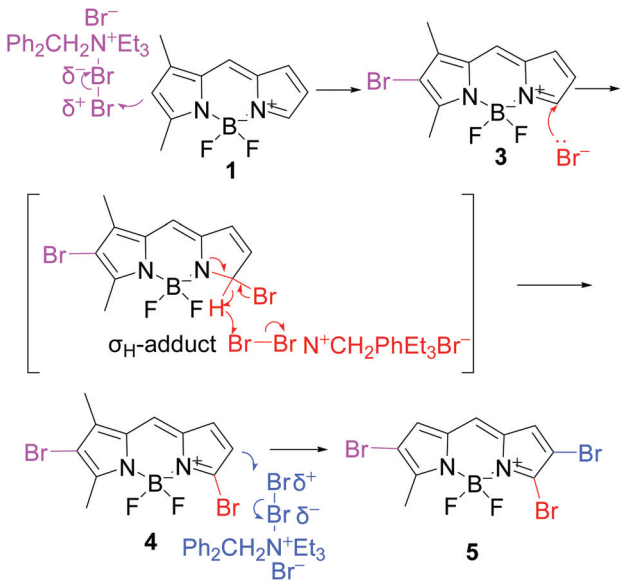


Scheme 2 Proposed mechanism for the stepwise bromination of **1**. The reaction is supposed to be an electrophilic bromination–oxidative nucleophilic substitution–electrophilic bromination process. The first bromination step is the basis for the second step because the electron withdrawing effect of 2-bromine makes the σ_H-adduct exist long enough to be oxidized and transformed to **4**.

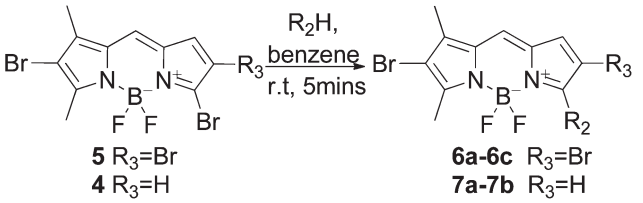
(δ 111.12, C-2) in the HMBC spectrum of **3** indicated the structure to be 2-bromo-1,3-dimethyl-BODIPY. The cross-peak between H-6 (δ 7.56) and a quaternary carbon atom at δ 111.12 (C-5) in the HMBC spectrum of **4** indicated that the second bromine atom was attached to the 5-position. Accordingly, the correlation of H-7 (δ 6.94) to a quaternary carbon atom (δ 127.91, C-6) in the HMBC spectrum of **5** showed that the 6-position was the site for the third bromination (ESI†).

This regioselectivity in the stepwise brominations may be explained by an electrophilic bromination–oxidative nucleophilic substitution–electrophilic bromination process (Scheme 2). Compound **1** is intrinsically electron rich and so will readily undergo electrophilic substitution reactions.[1] Its 2-position, which is the most nucleophilic owing to the electron-donating effect of the neighboring methyl groups, is therefore the most susceptible to electrophilic attack by the polarized $PhCH_2N^+Et_3Br_3^-$ complex to produce the mono-brominated product **3**. The unsubstituted α-position of **3** is so positively-charged due to the electron-withdrawing inductive effect of N, 4-F, and 2-Br that it is nucleophilically attacked by Br^-, forming a σ_H-adduct.[12] Affected by the electron withdrawing effect of 2-bromine, this adduct exists long enough to be oxidized by **2** and transformed instantly to **4**. Further electrophilic bromination at the least positive charged 6-position of **4** gives **5**. This mechanism is supported by Mulliken-charge analysis performed using Gaussian 09.

After successful synthesis of the desired multi-brominated dyes, we next set out to explore a strategy for diversity-orientated derivatization of **4** and **5** first through aromatic nucleophilic substitution at the 5-position and then *via* Sonogashira cross-coupling at the 6- (or 2-) position.

Piperidine was tried first as a nitrogen-centered nucleophile to attack tri-brominated BODIPY **5**. Under the reported conditions

Table 1 Nucleophilic substitutions of **4–5** in benzene at room temperature



Product	Nucleophile[a] (R_2H)	R_2	Yield (%)
6a	Piperidine		98
6b	Diethylamine		95
6c	Benzenethiol		97
7a	Piperidine		93
7b	Diethylamine		90

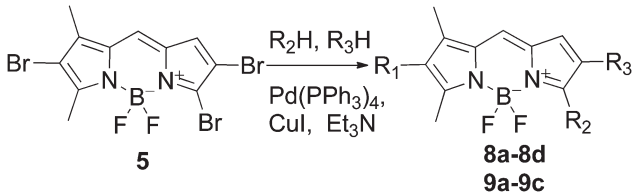
[a] At least two equiv N centred nucleophile were needed for the reaction to proceed fast. While for "sulfur" centred nucleophile, one equiv Et_3N was required to work as a basic catalyst.

for the nucleophilic substitution of α-chlorinated BODIPY,[8] treatment of compound **5** in acetonitrile with 2 equiv piperidine at room temperature failed to yield the expected product **6a**. A variety of experimental conditions were tried. It was finally revealed that the solvent was of crucial importance. Nonpolar solvents, such as benzene or toluene, were favored, in which the reaction was rapid at room temperature to furnish **6a** approximately quantitatively. However, polar solvents, *e.g.* DMF, acetone or methanol, led to decomposition of compound **5** slowly in the presence of the nucleophile. Other nucleophiles, such as diethylamine or the S-based nucleophile, benzenethiol, were next tried under the optimized reaction conditions and all gave good results. Likewise, nucleophilic substitutions of compound **4** were also carried out smoothly in benzene to furnish the corresponding products in good yields (Table 1).

The above nucleophilic substitutions of **4–5** proceeded so rapidly and efficiently that it inspired us to carry out the nucleophilic substitution and Sonogashira coupling in the same way. The regioselectivity of the two reactions may be ensured by their greatly different rates.

To this end, compound **5**, together with one equiv of a nucleophile (R_2H), was subjected to standard Sonogashira conditions. As expected, compound **5** was reactive in benzene (containing 10% Et_3N) at 60 °C, resulting in products which were nucleophilically substituted at the 5-position as well as coupled with the alkynyl (R_3H) at the 6-position (compounds **8a–8d**, Table 2). This regiochemistry for Sonogashira coupling with priority for the 6-position over the 2-position may be attributed to the steric hindrance of the 2-position due to the neighboring methyl groups. More forcing conditions, namely increasing the amount of alkyne, elevating the reaction temperature and prolonging the reaction time, allowed Sonogashira coupling to take place at both the 6- and 2-positions, producing multi-derivatized compounds **9a–9c** with fair yields (Table 2). Benzenethiol as a typical

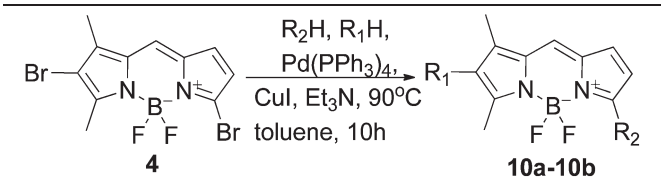
Table 2 One-pot synthesis of diversely substituted BODIPYs starting from compound **5**



Product[a]	R_1	R_2[b]	R_3	Yield (%)
8a	Br	N		72
8b	Br	N		70
8c	Br	N		68
8d	Br	N		69
9a		N		55
9b		N		50
9c		O		53

[a] To obtain compounds **8a–8d**, one equiv nucleophile (R_2H) plus two equiv alkyne (R_3H) were needed, and the reactions proceeded in benzene (containing 10% Et_3N) at 60 °C for 6 h. While for **9a–9c**, one equiv nucleophile (R_2H) plus four equiv alkyne (R_3H) were needed, and the reactions took place in toluene (containing 10% Et_3N) at 90 °C for 10 h. [b] For compound **9c**, one equiv EtONa was used as the nucleophile.

Table 3 Multi-derivatization of compound **4** in a one-pot way

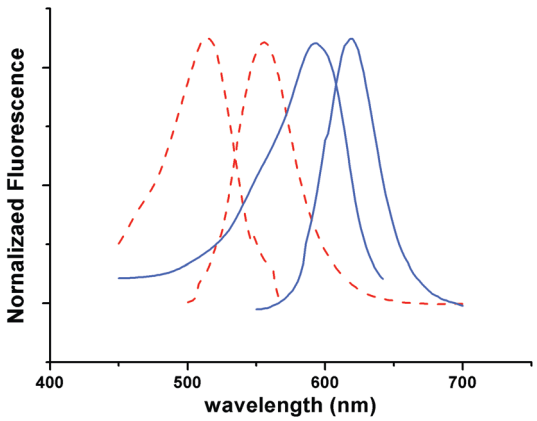


Product	R_1	R_2	Yield (%)
10a		N	68
10b		N	66

'sulfur' centred nucleophile was also tried in this method. Although compound **6c** was formed efficiently, as shown by TLC analysis, it failed to couple with the alkyne. This may be due to the inactivation effect of the sulfur atom on the Pd(0) catalyst. Similarly, compound **4** also showed good reactivity under this one-pot condition, giving **10a–10b** in moderate yields (Table 3).

Photophysical data of the diversely substituted BODIPYs in dichloromethane are summarized in Table 4. All the compounds show long wavelength emissions and the profiles are clearly sensitive to the extent of electron delocalization over the skeleton. Compounds **3–5** exhibit low quantum yields imparted by the heavy atom effect[13] and redshifted emission features that grow with increasing dipyrrin bromination. Incorporation of a hetero

Table 4 Absorption and emission profiles of **7b** (red dash) and **9a** (blue solid), and optical properties of compounds **3–10** in CH_2Cl_2 at rt[a]



Compd	λ_{abs} (nm)	ε (M^{-1} cm^{-1})	λ_{em} (nm)	Φ[b] (%)
3	517	76 500	528	0.13
4	525	63 700	544	0.08
5	535	76 500	552	0.10
6a	563	83 200	586	0.36
6b	567	82 100	590	0.33
6c	546	86 200	578	0.30
7a	510	80 500	558	0.31
7b	510	81 400	556	0.28
8a	562	82 400	592	0.40
8b	578	86 900	606	0.36
8c	552	82 600	596	0.32
8d	570	84 600	606	0.32
9a	589	85 700	620	0.56
9b	585	86 000	620	0.54
9c	570	86 300	608	0.53
10a	527	85 400	574	0.50
10b	526	84 800	568	0.49

[a] Determined in CH_2Cl_2 (not degassed) solution, *ca.* 1×10^{-6} M. [b] Quantum yields were accomplished by comparison with fluorescein (Φ 0.95, in 0.1 M NaOH) with the following equation where $\sum[F]$ is the integrated fluorescence intensity, Abs is absorbance at λ_{ex} 496 nm, and n represents the refractive index. For CH_2Cl_2 and 0.1 M NaOH, we used refractive indices of 1.424 and 1.335 respectively. $\Phi^{sample} = \Phi^{standard}Abs^{standard}\Sigma[F^{sample}](n^{sample})^2/Abs^{sample}/\Sigma[F^{standard}]/(n^{standard})^2$.

atom (*N*, *O*, or *S*) at the 5-position results in a remarkable red-shift (~30 nm), due to the p–π conjugation effect. Extension of the π-electron conjugation by the attachment of alkynyl groups at the 6- (7-) position also induces a bathochromic-shift.

In short, we have established a facile one-pot method for the fast construction of diversely substituted BODIPYs based on the efficient regioselective bromination of 1,3-dimethyl-BODIPY. This strategy will not only facilitate the modification of the dyes' solubility and spectroscopic properties, but enable their easy linkage to biomolecules or other groups of interest.

Acknowledgements

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