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Synthesis of *Meso*-Halogenated BODIPYs and Access to *Meso*-Substituted Analogues

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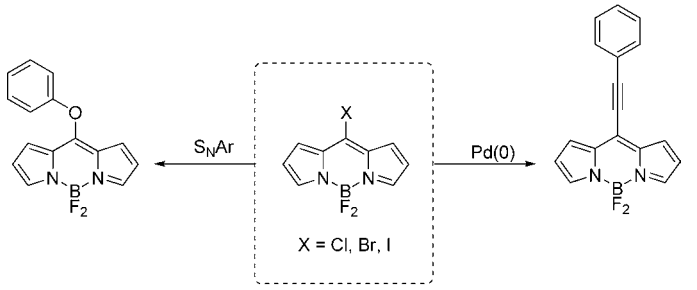
ABSTRACT



8-Halogenated boradiaza-*s*-indacenes can be efficiently prepared from dipyrrylketones. The new dyes react smoothly with nucleophiles to yield N-, O-, and S-substituted chromophores, as well as transition-metal-catalyzed cross-coupling reactions. The nature of the new substitutent has a strong influence on the spectral properties of the dyes.

Boradiaza-*s*-indacene (*bo*ron *dipy*rrin or *bo*ron *dipy*rromethene, BODIPY) dyes have earned a prominent place as outstanding fluorophores for use in fluorescent materials, labels, and probes.[1] A rich chemistry has been developed for the decoration of the BODIPY scaffold with reactive functionalities.[2] Derivatization at the 8-position, or *meso*-position, is a preferred method for the construction of complex BODIPY fluorophores because of the straightforward synthesis starting from aromatic aldehydes or acylium equivalents.[2,3]

An elegant alternative to the introduction of functionality at the 8-position by linear synthesis is the use of 8-methylthioBODIPYs. Such thioethers, introduced by Bielmann and co-workers, undergo nucleophilic aromatic substitution (S_NAr via addition−elimination) with amines to form dyes with blue-shifted UV−vis absorption and fluorescence spectra in comparison to common boradiaza-*s*-indacenes.[4] This work was followed by reports on the palladium-catalyzed derivatization of the BODIPY scaffold using the Liebeskind−Srogl cross-coupling starting from 8-methylthioBODIPYs and boronic acids.[5] Bielmann's methodology[4] has found application in the preparation of blue-emitting boron dipyrrin dyes.[6]

However, the scope of thioether substitutions remains limited when compared to the plethora of reactions described for aromatic halogens.[7] To fill this void, we report the synthesis of 8-halogenated (Cl, Br, I) boron

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dipyrromethenes and their substitution via S_NAr yielding heteroatom (N, O, S) *meso*-substituted derivatives and by palladium-catalyzed Suzuki, Stille, and Sonogashira cross-coupling.

Our proposed synthesis, outlined in Scheme 1, introduces the halogen through deoxygenative substitution on a dipyrrylketone. An early mention of this reaction dates back to the work of Fisher and Ort, where a chlorinated dipyrrin was obtained by the action of phosgene.[8] Because we wanted to avoid this highly toxic gas, other synthetic routes toward halogenated dipyrrins were investigated.

Following literature procedures,[9] the oxidative conversion of dipyrrylthioketone to symmetric ketone **1** using hydrogen peroxide is efficient and fast, and product **1** is isolated as a crystalline solid. Initial attempts to bring about halogenation of ketone **1** used phosphorus oxychloride and showed rapid conversion to the dipyrrinium salt. In situ deprotonation and complexation subsequently resulted in a single fluorescent compound, which was identified as the target *meso*-chlorinated compound **2a**. Similarly, phosphorus oxybromide converted di(pyrrol-2-yl)methanone **1** to a *meso*-brominated dipyrrinium salt, which was deprotonated and complexed in situ to yield **2b**. Additional efforts to screen for other halogenating agents, such as $SOCl_2$, PCl_3, and PCl_5, all resulted in lowered yields and significant side product formation. The use of PI_3 as iodinating agent was unsuccessful. The resulting mixture was contaminated with several byproducts, and a good yield of the desired borondiaza-*s*-indacene could not be attained. All attempts at fluorination led to a complex reaction mixture.

However, halogen exchange could be achieved by stirring chlorinated **2a** in acetone in the presence of sodium iodide. In this modified Finkelstein procedure, insoluble sodium chloride precipitates and drives the reaction to the *meso*-iodinated dye **2c**, which is isolated in good yield.

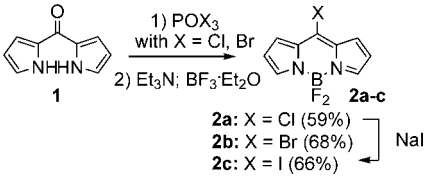
In the direct conversion of the ketone to sulfonates, by reaction with trifluoromethyl or nonaflyl sulfonyl anhydride, the yellow color of a dipyrrin intermediate is observed, but complexation with boron trifluoride did not result in the formation of the boron heterocycle.

Despite early worries about the stability of such halogenated compounds, compounds **2** proved to be stable at room temperature as highly crystalline solids.

8-HaloBODIPYs are interesting compounds because they are very promising starting materials for the preparation of more complex *meso*-substituted BODIPY analogues via elaboration on the reactive halogen through, e.g., S_NAr or transition-metal-catalyzed transformations (Suzuki, Stille, Heck, Negishi, Sonogashira, etc.).

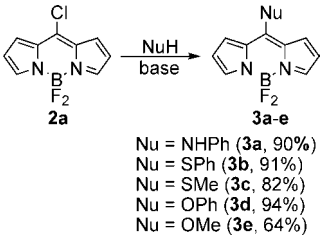
The chloride substituent is an efficient leaving group in S_NAr reactions. 8-ChloroBODIPY **2a** can be used to prepare the previously reported amine **3a**[4] and thioether fluorophores **3b** and **3c**,[4] which are isolated in high yield after stirring with the suitable nucleophile and a base.

Scheme 1. Synthesis of 8-Halogenated BODIPY Dyes



Similarly, 8-substituted ethers can be obtained by nucleophilic displacement of the halogen substituent. As such, aryl (**3d**) and alkyl (**3e**) ethers were obtained by reaction of **2a** and phenol or methanol under basic conditions (Scheme 2).

Scheme 2. Nucleophilic Displacement of Chlorine on Dye **2a**



Transition-metal-catalyzed cross-coupling of 8-haloBODIPYs with arylboronic acids is an alternate strategy to the classic condensation−oxidation sequence of pyrroles and aromatic aldehydes.[2] Thus, standard Suzuki (Table 1, entries 1−4) and Stille (Table 1, entry 5 and 6) cross-coupling procedures efficiently led to the substituted dyes **4a** and **4b** (Table 1). Heteroaromatic groups can also be introduced, as exemplified by the formation of 8-(2-thienyl)BODIPY **4c** (Table 1, entry 6), which is a potential building block for the preparation of novel luminescent materials.[5a] Beneficially, our method eliminates the need for Cu^+ reagents, which are required in the Liebeskind−Srogl cross-coupling of 8-methylthioBODIPYs with boronic acids.[5] All halogenated (Cl, Br, I) compounds **2** undergo the Suzuki and Stille reactions with varying yields.

Sonogashira cross-coupling with phenylacetylene with the iodinated dye **2c** led to complex reaction mixtures in which the desired product could only be observed in trace amounts. The side reactions and decomposition could be circumvented by shifting to the chlorinated dye **2a**, which reacted very rapidly at low temperatures (30 min at 0 °C) to provide alkyne **4d** in good yield (Table 1, entry 7). Such alkynes with bathochromically shifted spectra are interesting for the development of new sensors and fluorescent materials, but their synthesis has previously only been reported from unstable propynoyl chloride.[10]

Expansion of the methodology to substituted pyrroles and the corresponding dipyrrylketones, such as **5**, led to the synthesis of both symmetrically and asymmetrically

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(8) Fisher, H.; Ort, H. *Liebigs Ann. Chem.* **1933**, *502*, 237.
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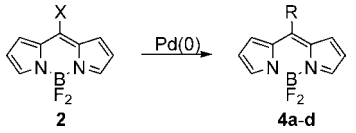
Table 1. Palladium-Catalyzed Cross-Coupling Reactions (Suzuki, Stille, Sonagashira) of 8-HaloBODIPY

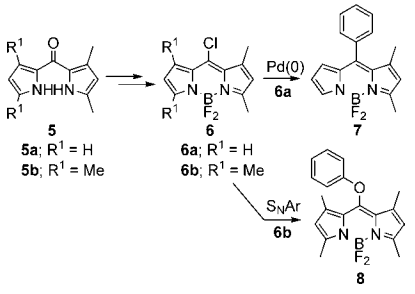


entry	X	reaction type	R	yield	product 4
1	Cl	Suzuki	Ph	36	**4a**
2	Br	Suzuki	Ph	53	**4a**
3	I	Suzuki	Ph	75	**4a**
4	I	Suzuki	4-MeOPh	58	**4b**
5	Br	Stille	Ph	73	**4a**
6	Br	Stille	2-thienyl	61	**4c**
7	Cl	Sonogashira	C≡CPh	76	**4d**

core-substituted 8-chloroBODIPY dyes (Scheme 3). In proof-of-concept reactions, compounds such as **6a**,**b** displayed the same reactivity as the unsubstituted systems **2** in both S_NAr and Pd-catalyzed cross-coupling. For instance, Suzuki cross-coupling of **6a** with phenylboronic acid yields dye **7**, while the nucleophilic displacement of chlorine by phenolate yields ether **8**.

The substituted dipyrryl ketones **5** were not readily availlable, as the oxidation of thioketones failed and no general synthetic route has yet been described. Eventually, dipyrryl ketones **5** were prepared in moderate yield through pyrrolic Vilsmeier reagents (Supporting Information),[11] and the full scope of this reaction is currently under investigation. It is also noteworthy that for asymmetric dipyrryl ketone **5a** an equilibrium between two tautomeric forms could be observed in the ^{1}H NMR spectrum (Supporting Information).

Scheme 3. Synthesis of the Substituted 8-ChloroBODIPYs **6** and Their Subsequent Functionalization



The rich variety of the groups introducible at the 8-position of BODIPY derivatives with this method leads to a set of dyes with UV−vis absorption and fluorescence emission spectra covering a broad range of the visible spectrum (Figure 1, extended figure in the Supporting Information). Table 2 summarizes some key spectroscopic and photophysical data of selected derivatives in tetrahydrofuran (THF) solution. Full details will be described elsewhere.

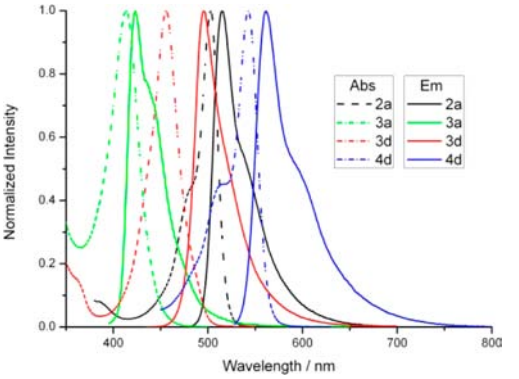


Figure 1. Normalized, visible absorption spectra and corresponding fluorescence emission spectra of a selection of 8-substituted BODIPY dyes in THF.

The spectra display the typical narrow absorption and fluorescence emission bands of classic difluoroboron dipyrrins. The broadest spectral bands are found for the 8-*N*-aniline derivative **3a** and to a lesser degree for the *meso*-O-substituted dyes **3d** and **3e**. The Stokes shifts are generally quite small with exceptions for **3d** and **3e**. The dyes with 8-N (**3a**) or 8-O (**3d**, **3e**) substituents have blue-shifted absorption and fluorescence emission spectra with respect to unsubstituted BODIPY.[12] This hypsochromic shift is related to the electron-donating character of the heteroatom and is markedly larger for N than for O. In contrast, 8-halogens (Cl in **2a**, Br in **2b**, I in **2c**) have a negligible effect on the spectral maxima. Conversely, the 8-ethynylphenyl group in **4d** leads to red-shifted absorption and fluorescence emission spectra compared to those of unsubstituted and classic boron dipyrrin dyes. This indicates that this 8-substituent extends the π-conjugation. The *meso*-O derivatives **3d** and **3e** have very high fluorescence quantum yields Φ, whereas the 8-aniline (**3a**) and 8-thiophenol (**3b**) analogues are nearly nonfluorescent. The heavy atom effect on Φ is clearly seen in the series of 8-halo dyes **2a**−**c**.

To conclude, an efficient synthesis of 8-halogenated boradiaza-*s*-indacenes **2** has been described starting from dipyrrylketones. N-, O-, and S-centered nucleophiles reacted smoothly with **2** via S_NAr, yielding a range of new fluorophores with hypsochromically shifted spectra compared to classic boron dipyrrin dyes. Compounds **2** are also useful scaffolds for the preparation of 8-aryl-, 8-heteroaryl-, and 8-alkynyl-substituted BODIPYs via palladium-catalyzed Suzuki, Stille, and Sonogashira cross-coupling reactions. Current synthetic efforts are focused on the

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Table 2. Spectroscopic and Photophysical Data of BODIPY Dyes in THF

product	$\lambda_{abs}(max)^a$ (nm)	$\lambda_{em}(max)^b$ (nm)	$\Delta\nu^c$ (cm^{-1})	$fwhm_{abs}{}^d$ (cm^{-1})	$fwhm_{em}{}^e$ (cm^{-1})	Φ^f
2a	503	515	463	921	1388	0.72 ± 0.01
2b	504	517	499	880	1424	0.496 ± 0.008
2c	507	519	456	860	1530	0.159 ± 0.006
3a	413	420	404	2233	2059	0.002 ± 0.001
3d	456	495	1728	1685	1504	0.96 ± 0.04
3e	443	486	1997	1670	1575	0.90 ± 0.05
4d	543	561	591	961	1426	0.66 ± 0.03
6a	495	510	594	1155	1416	0.737 ± 0.005
6b	502	513	427	774	1386	0.416 ± 0.008

[a] Absorption maximum. [b] Fluorescence emission maximum. [c] Stokes shift [$= 1/\lambda_{abs}(max) - 1/\lambda_{em}(max)$]. [d] Full width at half height of the maximum of the absorption band. [e] Full width at half height of the maximum of the fluorescence emission band. [f] Fluorescence quantum yield ± one standard uncertainty.

optimized synthesis of symmetric and asymmetric 8-haloBODIPYs.

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Supporting Information Available. Detailed experimental procedures and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.