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Cl-BODIPYs: a BODIPY class enabling facile *B*-substitution†

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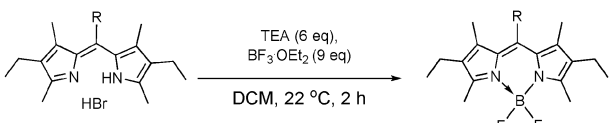
***Cl*-BODIPYs, synthesized in high yields from dipyrrins under air- and moisture-free conditions, are extremely facile to substitution at boron compared to their corresponding *F*-BODIPYs, opening up a new route to BODIPYs functionalized at boron.**

Compounds containing the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY) framework have wide application as dyes, fluorescent probes in biological systems, and materials for incorporation into electroluminescent devices.[1,2] Their wide utility is due to their high thermal and photochemical stability, chemical robustness and tunable fluorescence properties.[1,2]

Substitution of the fluorine atoms at the boron centre to give *B*-aryl, *B*-alkenyl, *B*-alkoxy and *B*-aryloxy derivatives, often under harsh conditions, generates a wide variety of *C*-BODIPY[3–6] and *O*-BODIPY[7–10] compounds. Recently, more exotic BODIPY derivatives have been synthesized,[11,12] including an *H*-BODIPY.[13] However, to our knowledge, dihalogen BODIPY analogues of the heavier halogens have not been reported. This is unsurprising as boron-halogen bond strengths decrease in the order F $\gg$ Cl > Br > I. Consequently, B–Cl, B–Br and B–I bonds are much more labile than B–F bonds.[14] The majority of *B*-substitution reactions starting from *F*-BODIPYs either require high temperatures or occur at room temperature in low yields (<60%). Due to the increased lability of the boron halogen bonds in *X*-BODIPYs, *B*-substitution in these derivatives would likely occur under milder conditions in higher yields, when compared to their corresponding *F*-BODIPYs. Changing the substitution at the BODIPY boron centre from fluorine to the heavier halogens will presumably have a significant effect on the fluorescence properties of the resulting *X*-BODIPYs: the presence of the heavier halogens will likely facilitate fluorescence quenching and enhance non-radiative decay pathways by increasing spin–orbit coupling.

There is only one reported BODIPY analogue that contains a B–X bond (X $\neq$ F). In this example, a *meso*-methyl substituted dipyrrinato sodium complex was treated with $PhBCl_2$ to produce the BODIPY analogue bearing one chloride and one phenyl substituent at the boron centre.[15] There are two literature examples of the reaction of a dipyrrin or dipyrrinato complex with a boron trihalide other than a BF_3 adduct. In the first example, a dipyrrin bearing a catechol-functionalized *meso*-position was treated with BCl_3 to give a mixture of three cyclic oligomers where the boron centre linked one dipyrrin to another by binding to the dipyrrin moiety of one molecule and the catechol moiety of the second molecule.[16] In the second example, a series of three dipyrrins, featuring protected phenols in the α-positions, were exposed to BBr_3. These reactions resulted in the isolation of phenoxy *O*-BODIPYs, presumably *via* (unisolated) *Br*-BODIPY intermediates.[17] Although BODIPY analogues of the heavier halogens have not been isolated, BCl_2, BBr_2 and BI_2 β-diketiminato complexes, which are structurally related to dipyrrins, can be generated *via* treatment of a silyl protected β-diketiminate with BCl_3, BBr_3 and BI_3.[18,19] All of these complexes were prepared and manipulated in a dry and oxygen-free atmosphere and were characterized using single-crystal X-ray diffraction studies.[18,19] Similarly, structurally related di-boryl BF_2, BCl_2 and BBr_2 complexes of porphyrins are known.[20]

F-BODIPYs are routinely synthesized from dipyrrins or dipyrrin salts *via* reaction with excess triethylamine and $BF_3{\cdot}OEt_2$. We have shown previously that the symmetrical BODIPYs **2a** and **2b** may be generated in high yields from the corresponding dipyrrin HBr salts as shown in Scheme 1.[21]



1aHBr R = H
1bHBr R = Ph

2a R = H; 89 %
2b R = Ph; 83 %

Scheme 1 Synthesis of *F*-BODIPYs **2**.

We postulated that reacting dipyrrins with BCl_3, BBr_3 or BI_3 would provide access to *X*-BODIPYs. Under air- and moisture-free conditions, and using BCl_3 as shown in Scheme 2, the first *Cl*-BODIPYs, **3a** and **3b**, were successfully synthesized in yields of 98% and 97%, respectively. Indeed, to solutions of **1a** and **1b** in toluene one equivalent of BCl_3 was added drop-wise, with immediate visual effects: for **1a**, the solution changed from yellow to red-orange with a green fluorescent tinge; the orange solution of **1b** became dark red with a pink fluorescent tinge. In each case the reaction mixture was stirred for 1 h at room temperature, then filtered over Celite, and the filtrate concentrated *in vacuo* to give a red powder. Both products are stable under an inert atmosphere, but succumb to decomposition in air and/or moisture.

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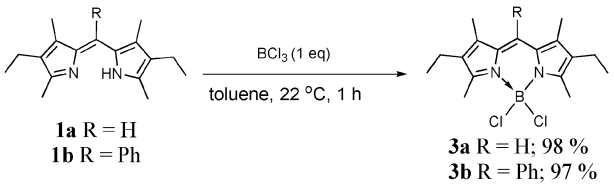


1a R = H
1b R = Ph

3a R = H; 98 %
3b R = Ph; 97 %

Scheme 2 Synthesis of *Cl*-BODIPYs.

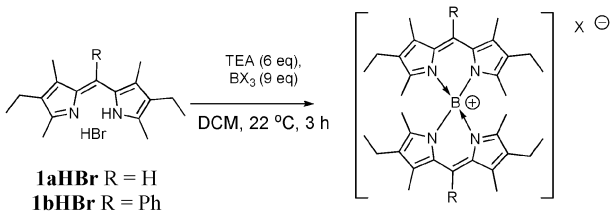
The *Cl*-BODIPYs exhibit significant fluorescence in solution although, unsurprisingly, less than the corresponding *F*-BODIPYs. The quantum yields for complexes **3a** and **3b** were measured in dichloromethane and were found to be ϕ_F = 0.45 and 0.40, respectively: emission at 546 nm for both. Although these quantum yields are significantly lower than those of the corresponding *F*-BODIPY analogues (ϕ_F = 1.00 for **2a** and ϕ_F = 0.82 for **2b**) these *Cl*-BODIPYs still exhibit considerable fluorescence. This decrease in fluorescence quantum yield for the *Cl*-BODIPYs is unsurprising, as the heavier halogens facilitate fluorescence quenching.

The methodology used to produce *Cl*-BODIPYs **3a** and **3b** was evaluated utilizing BBr_3 and BI_3. In both cases a single, common product was isolated in impure form, and we were unable to purify it satisfactorily. The product was deep red in solution but still exhibited slight fluorescence. The reaction was conducted in a variety of solvents, with toluene producing the best results. The crude material was washed with hexanes and filtered over Celite. Further attempts at purification included filtering the reaction mixture through both a silica and alumina plug. However, the instability of the product resulted in decomposition during these procedures.

We postulated that *X*-BODIPYs might be generated *in situ*, by way of similar methodology classically used for the synthesis of *F*-BODIPYs (shown in Scheme 1), and then trapped *via* the addition of an alcoholic solvent to give the corresponding well-known *O*-BODIPYs. To test this theory we added six equivalents of triethylamine to a dichloromethane solution of the dipyrrin hydrobromide salts (**1aHBr**, **1bHBr**), followed by nine equivalents of the boron trihalide as a 1.0 M solution in dichloromethane (in the case of BCl_3 and BBr_3) or as a solid (in the case of BI_3). After 24 h, the solution was treated with methanol resulting in an immediate colour change. The consequent deep red solutions were subjected to an aqueous work-up and the resulting mixtures were purified over neutral alumina.

As expected, the heavier halogen *X*-BODIPY analogues were not isolated from the reaction mixtures and, interestingly, neither were the corresponding *O*-BODIPYs. The resulting products were deep red in colour and not fluorescent. Characterization revealed the first dipyrrinato boronium cations, **4a** and **4b**, isolated with a counter-anion corresponding to the boron trihalide used, as shown in Scheme 3. In all cases, isolated starting material made up the mass balance.

X-ray diffraction-quality crystals of **4aI**, containing an iodide counterion, were grown and analyzed. The X-ray crystal structure‡ is shown in Fig. 1. The environment around the boron is tetrahedral with N-B-N angles ranging from 106.67(16)° to 112.07(16)° and the B–N bond lengths range from 1.547(2) Å to 1.550(2) Å, which is within the sum of covalent radii for the B and N atoms (1.55 Å).[22] The two dipyrrinato units are nearly orthogonal to each other, with 95° and 85° angles



1aHBr R = H
1bHBr R = Ph

4aCl R = H, X = Cl; 8 %
4aBr R = H, X = Br; 12 %
4aI R = H, X = I; 56 %
4bI R = Ph, X = I; 60 %

Scheme 3 Synthesis of boronium salts **4** using boron trihalides.

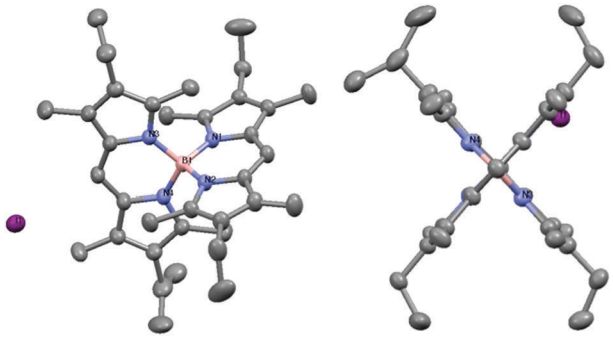
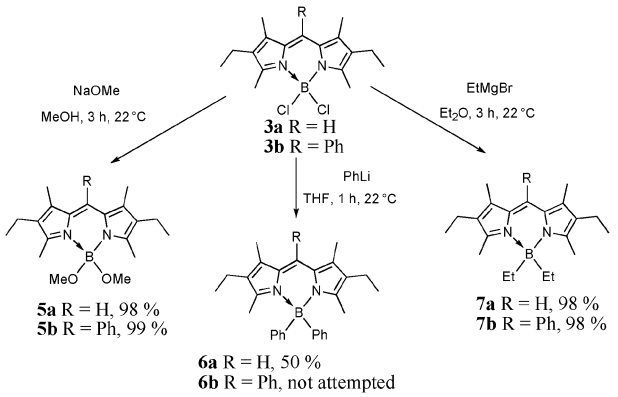


Fig. 1 Thermal Ellipsoid Diagram (50%) of **4aI**. Hydrogen atoms have been removed for clarity.

between the planes made up by the dipyrrinato units. This orthogonality of dipyrrinato ligands is a common feature of homoleptic dipyrrinato complexes and is enforced by the steric crowding of the methyl groups in the 1- and 9-positions of the dipyrrinato ligand.[23] There is some observable disorder in an ethyl group attached to one of the dipyrrinato ligands.

Having explored the reactions of BCl_3, BBr_3, and BI_3 with dipyrrins, we turned our attention to the reactivity of the new *Cl*-BODIPYs. Due to the difference in boron-halogen bond strengths between the B–F and B–Cl bond, we expected that substitution at the boron atom in the *Cl*-BODIPYs would be much more facile than in the corresponding *F*-BODIPYs. To investigate the differences in reactivity, we synthesized dialkyl, diaryl and dialkoxy BODIPYs from the new *Cl*-BODIPYs (Scheme 4) and applied the same conditions to *F*-BODIPYs.

Dialkyl *C*-BODIPYs (**7a** and **7b**) and *O*-BODIPYs (**5a** and **5b**) were synthesized in quantitative yields at room temperature from *Cl*-BODIPYs **3**, while the diaryl *C*-BODIPY **6a** was synthesized with a 50% yield (Table 1). As EtMgBr was added to solutions of **3a** and **3b** in anhydrous diethyl ether, in each case an orange precipitate formed immediately as the solutions became red-orange. Synthesis of the *O*-BODIPYs was achieved by adding NaOMe to a solution of each *Cl*-BODIPY in anhydrous methanol, resulting in orange solutions with a bright green fluorescent tinge. Upon completion, the reaction mixture was washed with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the *O*-BODIPY products **5a** and **5b** as orange and red crystalline solids, respectively. The diaryl *C*-BODIPY **6a** was synthesized by addition of PhLi to a solution of **3a** in anhydrous THF resulting in an immediate colour change to dark red with a red fluorescent tinge. After



Scheme 4 Synthesis of *C*- and *O*-BODIPYs from *Cl*-BODIPYs **3**.

Table 1 Summary of *F*-BODIPY **2a** and *Cl*-BODIPY **3a** reactivity[a]

	Starting material	
B-Substitution conditions	*Cl*-BODIPY **3a**	*F*-BODIPY **2a**
NaOMe, MeOH, 3 h, 22 °C	**5a**, 98%	No Reaction
PhLi, THF, 1 h, 22 °C	**6a**, 50%	**6a** and **6b** (1.0 : 0.2) after 24 h, 36%
EtMgBr, Et_2O, 3 h, 22 °C	**7a**, 98%	**7a**, 67%

[a] Percentage yields correspond to isolated yields.

1 h the reaction mixture was filtered over Celite and the resulting filtrate was concentrated *in vacuo* to give a crude red-brown powder containing the desired product **6a** (50% isolated yield) as well as several other compounds in minor amounts, including the trisubstituted *meso*-phenyl derivative **6b**: we have shown previously that when *B*-arylation reactions are carried out on *meso*-H *F*-BODIPYs, unwanted *meso*-substituted byproducts are also produced.[21,24]

When the corresponding *F*-BODIPY **2a** was treated under the same conditions, only trace product was observed. This is unsurprising as reported procedures for *O*-BODIPY synthesis starting from *F*-BODIPYs require treatment with sodium methoxide at elevated temperature[7] or treatment with methanol following pre-activation with $AlCl_3$:[10] using *Cl*-BODIPYs, rather than *F*-BODIPYs, is clearly more fruitful. *O*-BODIPY syntheses from phenols *via* an intramolecular process are the exception and proceed at room temperature.[9,17] When *F*-BODIPY **2a** was treated with PhLi under the same conditions used to generate **6a** from *Cl*-BODIPY **3a**, a mixture of **6a** and the corresponding *meso*-phenyl substituted derivative (**6b**) was generated in a 36% overall yield after an extended reaction time. Procedures for diaryl *C*-BODIPY synthesis are routinely carried out at room temperature with yields $<50\%$.[3,25] When *F*-BODIPY **2a** was treated under the same conditions used to generate **7**, *C*-BODIPY **7a** was produced in 67% yield. This yield was much lower than that obtained when starting from *Cl*-BODIPY **3a**. This is in agreement with the reported procedures for dialkyl *C*-BODIPY formation which are either conducted at room temperature with yields under 60%[25,26] or elevated temperature with high yields.[21]

In short, the first BODIPYs featuring chloro substituents at the boron centre are reported. *Cl*-BODIPYs are easily synthesized under inert conditions, using dipyrrin free bases and BCl_3. *Cl*-BODIPYs are stable under inert conditions and exhibit significant fluorescence in solution, although they emit less intensely than the corresponding *F*-BODIPYs. *Cl*-BODIPYs are facile to substitute at boron, using mild conditions and short reaction times, to give high yields of BODIPY analogues that have previously been somewhat challenging to prepare from the corresponding *F*-BODIPYs. Given the increased reactivity of *Cl*-BODIPYs over *F*-BODIPYs, we anticipate that this new class of compound will see significant application as a synthetic intermediate. Attempts to utilize classical conditions (BX_3 and NEt_3) for the synthesis of *X*-BODIPYs ($X \neq F$), met with the isolation of the first boronium salts featuring dipyrrinato ligands.

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Notes and references

‡ Crystallographic data, compound **4aI** (CCDC 842813): $C_{34}H_{46}N_4BI$, F.W. 648.48. Primitive monoclinic, $P2_1/c$, $Z = 4$, $a = 10.9061(4)$ Å, $b = 14.5040(5)$ Å, $c = 21.1718(7)$ Å, $\beta = 100.216(2)^\circ$, $V = 3295.91(20)$ Å^3, $T = 173(1)$K, 25 370 reflections (9298 unique, $R_{int} = 0.042$), $R = 0.0361(3\sigma)$, Rw = 0.0414(3σ, 6538 reflections).

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