ChemComm

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Activation and deprotection of *F*-BODIPYs using boron trihalides†

Cite this: *Chem. Commun.*, 2014, **50**, 7028

Received 11th April 2014,
Accepted 6th May 2014

DOI: 10.1039/c4cc02706j

www.rsc.org/chemcomm

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The activation of *F*-BODIPYs with boron trihalides, followed by treatment with a nucleophile, effects facile substitution at boron; using water as the nucleophile promotes deprotective removal of the $-BF_2$ moiety and thereby production of the corresponding parent dipyrrin salt in quantitative yield under extremely mild conditions.

Compounds containing the 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene (*F*-BODIPY) framework are used as dyes, as fluorescent probes in biological systems, and as materials in electroluminescent devices.[1–3] The wide utility of these compounds derives from their high thermal and photochemical stabilities, as well as their chemical robustness and tunable fluorescence properties.[4–6] Recent research has focused on the synthesis of BODIPYs with substituents other than fluorine at the boron centre, with the goal of creating BODIPYs with unique spectroscopic properties. A wide range of *B*-alkynyl (*E*-BODIPY) and *B*-alkyl (*C*-BODIPY) derivatives have thus been synthesized, alongside other variants[7–21] including *Cl*-BODIPYs, compounds that allow for facile substitutions at the boron center courtesy of the weaker B–Cl bond *cf.* B–F bond.[22,23] For many years the removal of the $-BF_2$ moiety from *F*-BODIPYs, to generate the dipyrrin, lay unconquered but recently we published an effective deprotection route involving rather harsh treatment with alkoxides to exploit the Lewis acidic nature of boron.[24,25] Herein we report the deprotection of *F*-BODIPYs to generate their dipyrrin salts under extremely mild conditions involving BX_3 Lewis acids and water. The strategy relies upon a prior activation of the BODIPY B–X bond, and as such is also an effective route by which to substitute at boron. The same strategy promotes facile nucleophilic substitution at boron.

Earlier work with *Cl*-BODIPYs revealed their sensitivity to air and moisture.[22,23] Therefore, we formally investigated the course of the reaction when water is introduced as the nucleophile to substitute at the boron centre of the *Cl*-BODIPY, with the hope of generating the dihydroxy *O*-BODIPY, which we knew to be unstable.[25] Reaction of *F*-BODIPY **1a** with BCl_3 (1 eq.), under an inert atmosphere, achieved complete conversion to the *Cl*-BODIPY.[23] We were then delighted to discover that removal of the solvent and subsequent dissolution of the *Cl*-BODIPY in excess acetone : water (10 : 1), afforded a quantitative yield of the dipyrrin as its HCl salt (Table 1, entry 1). The HCl salt was isolated as an orange solid after extraction from the acetone–water solution with CH_2Cl_2.

The scope of this mild *F*-BODIPY deprotection extends to various functionalities around the dipyrrinato core (Table 1): alkyl and keto substituents (entries 1–5) were tolerated, and *F*-BODIPYs featuring a *meso*-phenyl group (entries 5 and 6), were also converted to their HCl salts in quantitative yields. The *F*-BODIPY **1g**, featuring an ester substituent, was successfully converted to the *Cl*-BODIPY. However, the addition of water was followed by complete decomposition of the material, rather than isolation of the dipyrrin as its HCl salt.

Cognisant that HBr salts of dipyrrins are more crystalline than other HX salts,[26] *F*-BODIPYs **1a** and **1g** were reacted with BBr_3. The reactions were carried out in the same manner as described above but with the initial addition of BBr_3, instead of BCl_3. Pleasingly, the revised protocol quantitatively converted the *F*-BODIPYs **1a** and **1g** into the dipyrrin HBr salts **2a** and **2g**, respectively (Table 1, entries 1 and 7, parentheses). Given this success, we hypothesised that the reaction of *F*-BODIPYs with BBr_3 gives the corresponding *Br*-BODIPYs,[23] an interesting proposition given that we had previously been unable to isolate *Br*-BODIPYs after the reaction of lithium dipyrrinato salts with BBr_3.[22] The *F*-BODIPY **1a** was thus dissolved in anhydrous CCl_4, and BBr_3 was then added. The reaction mixture was subsequently concentrated *in vacuo* to quantitatively return the *Br*-BODIPY **3a**, the first *Br*-BODIPY to be isolated (Scheme 1). ^{11}B NMR characterisation clearly revealed a singlet at −5.89 ppm, *cf.* the triplet at 0.76 ppm for the starting material *F*-BODIPY. The isolation of this material supports the notion that the deprotection protocol, as described for **1a** and **1g** above, occurs through

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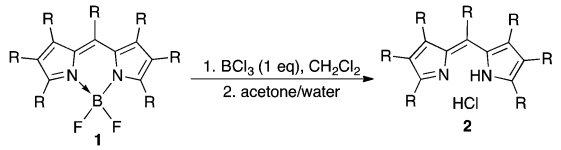
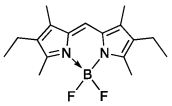
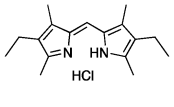
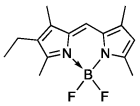
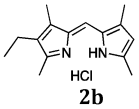
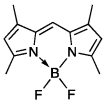
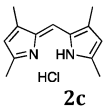
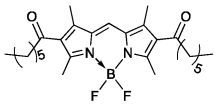
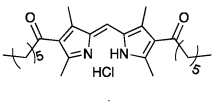
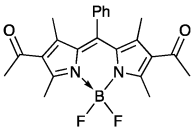
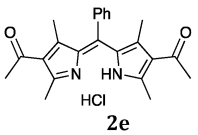
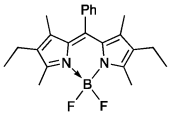
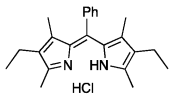
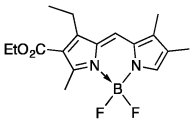
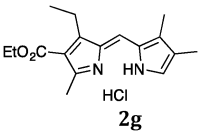
† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra. CCDC 996669. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02706j

Table 1 Conversion of *F*-BODIPYs to dipyrrin HCl salts



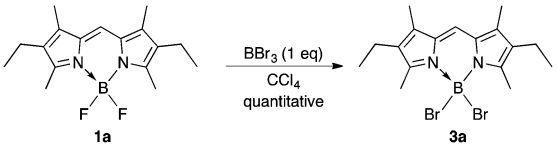
1 2

Entry	*F*-BODIPY	Product	Isolated yield (%)
1	 **1a**	 **2a**	>99 (>99%)[a]
2	 **1b**	 **2b**	>99
3	 **1c**	 **2c**	>99
4	 **1d**	 **2d**	>99
5	 **1e**	 **2e**	>99
6	 **1f**	 **2f**	>99
7	 **1g**	 **2g**	N/A (>99%)[a]

[a] Yields for the synthesis of the HBr salt using BBr_3.

the *Br*-BODIPY: reaction with water would then produce the unstable dihydroxy *O*-BODIPY, followed by decomposition to liberate the dipyrrin.

To continue exploring the reactions of *F*-BODIPYs with boron trihalides, we turned our attention to the fluoro analogue. The *F*-BODIPY **1a** was dissolved in anhydrous CH_2Cl_2 and treated with $BF_3{\cdot}OEt_2$ (1 eq.). The reaction mixture immediately changed from a fluorescent bright orange to a fluorescent red/purple colour, indicative of an interaction/activation between the *F*-BODIPY and the added BF_3. The reaction mixture was stirred for 10 minutes, and then 3 eq. water was added; 2 eq. to give the dihydroxy *O*-BODIPY, plus one 1 eq. to result in hydrolysis of the covalent N–B bond thus liberating boric acid. At this point



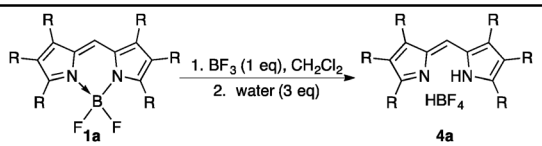
1a **3a**

Scheme 1 Synthesis of a *Br*-BODIPY.

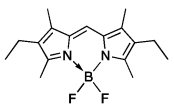
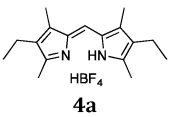
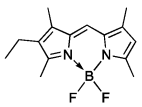
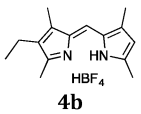
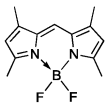
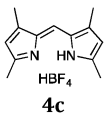
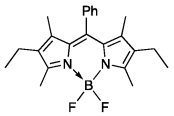
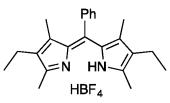
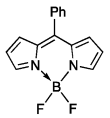
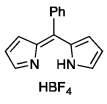
the solution turned a dull yellow, characteristic of a dipyrrin salt. After an aqueous work-up, an orange powder was recovered. Complete characterisation of this compound revealed it to be the first HBF_4 salt of a dipyrrin, isolated in quantitative yield (Table 2, entry 1). ^{11}B NMR spectroscopy revealed a boron singlet at −0.65 ppm, indicating the BF_4 counter-ion.[27] Curiously, if a large excess of water was added to the reaction mixture (rather than the addition of just 3 eq. water), the original fluorescent bright orange of the *F*-BODIPY would be returned and starting material was quantitatively recovered. Clearly the stoichiometry of the added water dramatically alters the outcome of the protocol: excess water quenches the BF_3, yet controlled amounts of water react at the boron centre of the *F*-BODIPY, courtesy of Lewis acid pre-activation by BF_3.

The scope of the deprotective method, *i.e.* *F*-BODIPY activation by BF_3 followed by the controlled addition of water, was briefly explored by varying the alkyl substituents around the dipyrrinato core (Table 2, entries 1–3). Decreasing extents of

Table 2 Conversion of *F*-BODIPYs to dipyrrin HBF_4 salts



1a **4a**

Entry	*F*-BODIPY	Product	Isolated yield (%)
1	 **1a**	 **4a**	>99
2	 **1b**	 **4b**	91
3	 **1c**	 **4c**	80
4	 **1e**	 **4e**	45
5	 **1h**	 **4h**	5

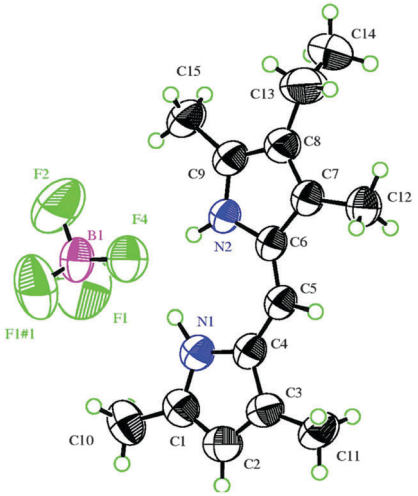


Fig. 1 Ellipsoid diagram (50%, H atoms omitted) of HBF_4 salt **4b**.

substitution around the pyrrolic scaffold resulted in reduced yields of the dipyrrin HBF_4 salts. Furthermore, moving from *meso*-H to *meso*-phenyl substitution resulted in a drastic decrease in yield (entries 4 and 5 *cf.* 1). In each case, the remaining starting material could always be recovered. These results suggest that the electron-donating ability of the substituents alter the degree of activation induced by the addition of BF_3, and thereby affect the degree of subsequent substitution at boron by water: formation of the dihydroxy *O*-BODIPY is critical to the deprotective removal of the BF_2 moiety and consequent liberation of the dipyrrin.

It has been documented that the HBr salts of dipyrrins are crystalline and are thus more commonly synthesized and used than other HX salts.[26] However, we herein report that dipyrrin HBF_4 salts easily surpass the HBr variants in terms of crystallinity. Indeed, our dipyrrin HBF_4 salts were easily crystallised *via* the slow evaporation of solvent from a CH_2Cl_2 solution. A single crystal of **4b-HBF$_4$** was characterised using X-ray crystallography (Fig. 1), clearly indicating the BF_4 counter-ion.‡ It should be noted that the when the microcrystalline material was left on the bench top, after several months we occasionally witnessed loss of the BF_4 counter ion. However, when the salt was left in crystalline form the material remained unchanged. To investigate exchange of the BF_4 counterion, we treated a solution of **4a-HBF$_4$** in CH_2Cl_2 with aqueous HBr, followed by an aqueous work-up, and we achieved complete conversion of the **4a-HBF$_4$** salt to the **4a-HBr** salt.

Deprotection *via* reaction of *F*-BODIPYs with $BF_3{\cdot}OEt_2$ and the controlled addition of water must clearly proceed through an alternative pathway to those involving BCl_3 and BBr_3 whereby the corresponding *Cl*/*Br*-BODIPYs are unequivocally formed as intermediates. We propose that the addition of $BF_3{\cdot}OEt_2$ to *F*-BODIPYs results in activation of a B–F bond of the *F*-BODIPY (Fig. 2).[16] In the absence of a nucleophile, the activation is terminated when the Lewis acid is quenched during work-up, and thus quantitative recovery of the *F*-BODIPY ensues. In the presence of a nucleophile, such as water, the activated BODIPY is susceptible to attack at boron to result in cleavage of the BODIPY B–F bonds en route

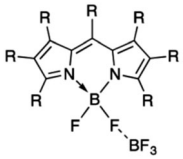
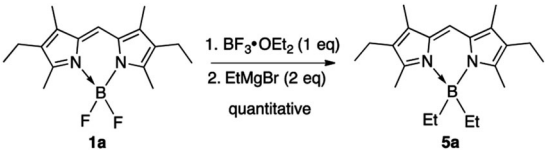


Fig. 2 Proposed activation of *F*-BODIPYs by BF_3.



Scheme 2 Synthesis of a *C*-BODIPY.

to overall loss of the BF_2 moiety and accompanying formation of boric acid, alongside formation of the BF_4 anion (boron from $BF_3{\cdot}OEt_2$).

The formation of the activated intermediate is further supported by its reaction with a nucleophile other than water. Indeed, reaction of **1a** with $BF_3{\cdot}OEt_2$, followed by treatment with 2 eq. of EtMgBr resulted in complete conversion to the corresponding *C*-BODIPY (**5a**) as shown in Scheme 2. Clearly the B–F bond is more susceptible to nucleophilic attack in the presence of $BF_3{\cdot}OEt_2$, as it has been shown previously that the reaction of **1a** with 2 eq. of EtMgBr does not reach completion at room temp.[23]

In an attempt to characterise the activated intermediate (Fig. 2), we treated **1a** with 1 eq. of $BF_3{\cdot}OEt_2$, and analysed the corresponding ^{11}B and ^{19}F NMR spectra. The spectra clearly indicated activation of the *F*-BODIPY boron centre. In the ^{11}B spectrum, the triplet of the starting material (**1a**) presented as a rather sharp singlet alongside a singlet corresponding to the BF_3 boron center: in neither case was coupling was observed between boron and fluorine. Meanwhile, in the ^{19}F NMR spectrum, the typical quartet of **1a** was absent and instead a severely depressed (low intensity) broad singlet signal was observed. Since the anticipated coupling between boron and fluorine was not observed, we used variable temperature ^{11}B and ^{19}F NMR to look for exchange processes. At -60 °C the coupling between boron and fluorine was revealed. However, as the temperature was increased (Fig. 3), the signals coalesced. These results suggest facile room-temperature exchange of the fluorine atoms on the *F*-BODIPY with those of the BF_3 present in solution.

The formation of dipyrrin HBF_4 salts using $BF_3{\cdot}OEt_2$ and controlled amounts of water provides potential insight into the traditional route used for the synthesis of *F*-BODIPYs. *F*-BODIPYs are typically synthesised by reacting the dipyrrin HBr salt, or free-base, with excess NEt_3 (6 eq.) and $BF_3{\cdot}OEt_2$ (9 eq.).[28] Despite these excesses, the reaction is surprisingly moisture-sensitive. With the knowledge that $BF_3{\cdot}OEt_2$ activates *F*-BODIPYs, we can now appreciate that the formation of *F*-BODIPYs under non-anhydrous conditions is reversible, and that even the anhydrous process is susceptible to non-productive interference by nucleophiles.

To summarize, we have developed an extremely high yielding and mild methodology for the deprotection of *F*-BODIPYs using

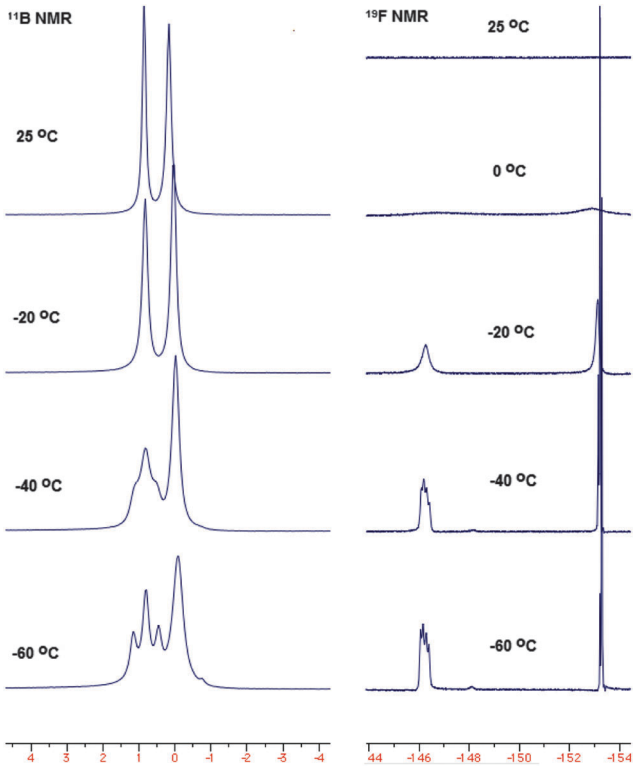


Fig. 3 VT NMR spectra of **1a** and $BF_3{\cdot}OEt_2$.

Cl- and *Br*-BODIPYs as *in situ* intermediates. Furthermore, we have isolated the first *Br*-BODIPY. We have highlighted the benefit of using either the chloro- or bromo-intermediate over the other, based on the characteristic stability of the resulting HX salt and the virtue of the substituents about the dipyrrolic framework. We also demonstrate the use of $BF_3{\cdot}OEt_2$ to deprotect *F*-BODIPYs, *via* the activation of the boron centre of the BODIPY. These reactions provide the first HBF_4 salts of dipyrrins, which are extremely crystalline. This same strategy can be used to achieve extremely mild nucleophilic substitution at boron. Furthermore, we suggest caution should Lewis acid-induced activation of a peripheral substituent of a BODIPY be required: activation of the BX_2 moiety is likely to ensue, followed by nucleophilic substitution at boron that may result in undesired overall loss of boron from the BODIPY framework.

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Killam Trusts for financial support of this work.

Notes and references

‡ Crystallographic data, compound **4b** (CCDC 996669): $C_{15}H_{21}N_2BF_4$, F.W. 316.15. Primitive orthorhombic, *Pnma* (#62), $Z = 4$, $a = 17.4172(8)$ Å, $b = 7.0912(4)$ Å, $c = 13.2491(8)$ Å, $\beta = 100.216(2)^\circ$, $V = 1636.38(15)$ Å^3, $T = 173(1)$ K, 10 434 reflections (2620 unique, $R_{int} = 0.052$), $R = 0.0595$ (2.5σ), $R_w = 0.0654$ (2.5σ, 1130 reflections).

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