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Conversion of 4,4-Difluoro-4-bora-3a, 4a-diaza-*s*-indacenes (*F*-BODIPYs) to Dipyrrins with a Microwave-Promoted Deprotection Strategy

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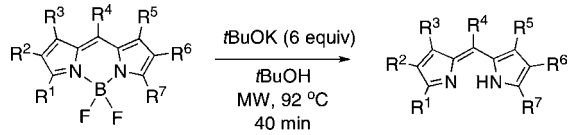
ABSTRACT



4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacenes (*F*-BODIPYs) have been deprotected to give the corresponding free-base dipyrrins by heating a solution of the *F*-BODIPY in *tert*-butanol under 600 W of microwave irradiation in the presence of 6 equiv of potassium *tert*-butoxide for 40 min at 92 °C. Investigations of BODIPY modification at the *meso* position have also been undertaken and a *meso*-butyl product has been isolated.

Compounds containing the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY) framework have wide applications as dyes, as fluorescent probes in biological systems, and as materials for incorporation into electroluminescent devices.[1] Such wide utility bespeaks their high thermal and photochemical stability, as well as their chemical robustness and tunable fluorescence properties.[2−4] Use of substituents other than fluorine at the boron center of the BODIPY core is currently under wide investigation with the goal of identifying BODIPYs with exotic spectroscopic properties. Indeed, a variety of *B*-aryl (*C*-BODIPY) and *B*-alkynyl (*E*-BODIPY) derivatives have been synthesized with organolithium or Grignard reagents.[5−9] Furthermore, *B*-alkoxy and *B*-aryloxy derivatives (both termed *O*-BODIPYs) have been synthesized via fluorine displacement with sodium alkoxides or alcohols in the presence of Lewis acids.[10−13] More recently, BODIPY borenium cations have been synthesized by way of fluoride abstraction,[14] and three examples of BODIPY boronium cations with a DMAP ligand coordinating to the boron center have also been reported.[14,15]

F-BODIPYs are routinely synthesized in high yields by trapping the parent dipyrrin as its BF_2 complex. According to a recently reported procedure *F*-BODIPYs can be generated from α-formyl pyrroles in one pot, without isolation (or even work-up) of the parent dipyrrin.[16] *F*-BODIPYs are chemically robust and, as they are highly stable and fluorescent, are easily purified at each consecutive synthetic step in a derivitization strategy. In contrast, the

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parent dipyrrins are historically difficult to chemically manipulate and purify, presumably by virtue of the inherent azafulenium and pyrrolic nitrogen moieties.[17] Strategies have been developed to protect the dipyrrin as a zinc[18] or tin[19] complex prior to functionalization, to thus facilitate purification, although these strategies are limited by the lability of such dipyrrinato complexes under acidic conditions.

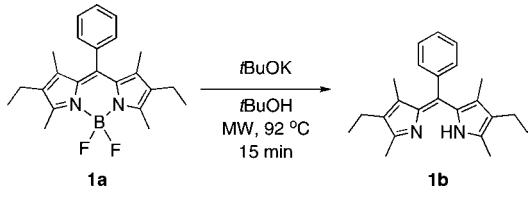
Ideally, dipyrrins could be protected as stable BODIPY compounds, chemically modified, purified, and then deprotected to give functionalized dipyrrins. However, to our knowledge, the boron center has not been removed from BODIPYs to generate the parent dipyrrin. Here we disclose the first reported method by which to generate dipyrrins from their corresponding *F*-BODIPY analogues.[20]

Several strategies might be applied to deprotect *F*-BODIPYs and return the parent dipyrrin: (i) protonation of the dipyrrinato nitrogen atoms and release of the $-BF_2$ moiety; (ii) nucleophilic attack at the boron center and cleavage of the B−N bonds to give the dipyrrinato anion; (iii) nucleophilic attack at the *meso*-position and cleavage of the N−B bonds, with subsequent protonation and elimination of the nucleophile to return the dipyrrin; or (iv) attack at the (planar) nitrogen atoms.

As *F*-BODIPYs are stable to strong acid, and cognizant that boron−oxygen bonds are stronger than boron−nitrogen bonds,[21] we investigated the use of oxygen-based reagents to effect cleavage of the B−N bonds in *F*-BODIPYs. Small oxygen-based nucleophilies are known to react with BODIPYs to give *O*-BODIPYs, and so the less nucleophilic potassium *tert*-butoxide was selected as a potential deprotection agent.

meso-Aryl dipyrrins are more stable than *meso*-unsubstituted dipyrrins,[17] and so *F*-BODIPY **1a** was chosen for deprotection studies, with the free-base dipyrrin **1b** as the target product (Scheme 1). The reaction was attempted at

Scheme 1. Deprotection of BODIPY **1a** with *t*BuOK under Microwave Irradiation



atmospheric pressure with conventional heating at 85 °C for 24 h, and the corresponding dipyrrin was isolated in an irreproducible crude yield of around 23%. This extremely encouraging result prompted further investigations. When the reaction was carried out under microwave irradiation, we were delighted to observe that the desired free-base **1b** was generated in high yield: heating a sealed mixture of **1a** and 6 equiv of potassium *tert*-butoxide in *tert*-butanol to 92 °C under 600 W microwave irradiation (see the Supporting Information for technical details), followed by an aqueous basic work-up, gave the parent dipyrrin **1b** in 92% isolated yield (Table 1, entry 1).

Table 1. Optimization of Microwave-Assisted Deprotection of BODIPY **1a**

	reagent	solvent	time/min	temp/°C	yield/%
1	*t*BuOK (6 equiv)	*t*BuOH	15	92	92
2	*t*BuOK (3 equiv)	*t*BuOH	15	92	0[a]
3	NaH (6 equiv)	DMF	15	92	0[b]
4	NaH (6 equiv)	DMF	15	165	0[b]
5	LiHMDS (6 equiv)	DMF	15	165	0[b]
6	KI (6 equiv)	DMF	120	165	0[a]

[a] Starting material recovered quantitatively. [b] Decomposition.

Heating the reaction mixture under 600 W of microwave irradiation at 82 and 72 °C resulted in the complete consumption of starting material, but as the temperature was decreased the degree of decomposition increased (Figure S1, Supporting Information). The use of other stoichiometries of **1a**:*tert*-butoxide was investigated (Table 1, entry 2), as were other non-nucleophilic bases (lithium hexamethyldisilazane and sodium hydride), but NMR spectroscopic analysis indicated the formation of only trace amounts of **1b**, alongside many decomposition products (Table 1, entries 3−5). The use of iodide was also investigated (as a nucleophile), but only starting material was recovered (Table 1, entry 6). Interestingly when sodium isopropoxide was used with **1a**, in place of potassium *tert*-butoxide, the *O*-BODIPY with two *B*-isopropoxide groups was isolated in 47% yield along with trace amounts of deprotected product. These results indicate that the non-nucleophilic nature and steric bulk of the *tert*-butoxide are important to the observed deprotection reactivity.

The optimized method was applied to deprotect a series of *F*-BODIPYs (Table 2), with a 40-min reaction time proving to be optimal. *meso*-Aryl *F*-BODIPYs **1a** and **2a** were deprotected successfully in high isolated yield as was the *meso*-unsubstituted analogue **3a**. The β- and *meso*-unsubstitued dipyrrins **4a** and **5a**[16] were also deprotected (CAUTION **4b** is a sternutator). This method was applied to the unsymmetrical *F*-BODIPY **6a**[22] to give **6b** in excellent isolated yield.

A series of BODIPYs with substituents on the boron center were investigated to explore the scope of the deprotection reaction. The *O*-BODIPYs **7a** and **8a**, both bearing two *B*-alkoxy substituents, could not be deprotected under the optimized conditions, and starting material was quantitatively

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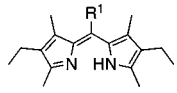
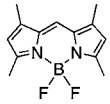
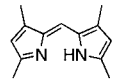
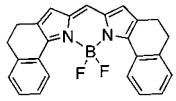
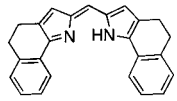
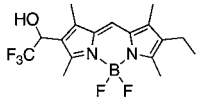
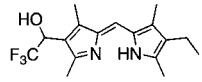
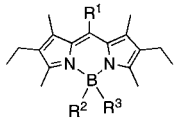
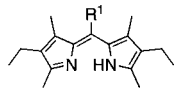
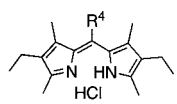
Table 2. Microwave-Assisted Deprotection of *F*-BODIPY Derivatives (6 equiv *t*BuOK, *t*BuOH, 92 °C, 600 W, 40 min)

starting material	product	yield/ %[a]
		
1a, R^1 = Ph	**1b**, R^1 = Ph	91
2a, R^1 = 4-CF_3-C_6H_4	**2b**, R^1 = 4-CF_3-C_6H_4	90
3a, R^1 = H	**3b**, R^1 = H	90
		
4a	**4b**[b]	86[b]
		
5a	**5b**	51
		
6a	**6b**	93
		
7a, R^1 = Ph, R^2 = R^3 = OMe	**1b**, R^1 = Ph	0[c]
8a, R^1 = H, R^2 = R^3 = OMe	**3b**, R^1 = H	0[c]
9a, R^1 = H, R^2 = F, R^3 = OMe	**3b**, R^1 = H	75
10a, R^1 = H, R^2 = R^3 = Me	**3b**, R^1 = H	0[c]
		
11a, R^4 = Bn	**11b**, R^4 = Bn	88
12a, R^4 = Me	**12b**, R^4 = Me	85

[a] All yields are isolated yields. [b] Isolated as its zinc complex. [c] Starting material recovered.

recovered even after an extended reaction time. Interestingly, with one *B*-alkoxy substituent, as in **9a**, the deprotection was successful and dipyrrin **3b** was obtained in an isolated yield of 75%. This result again infers the importance of a steric component to the success of the deprotection. With two *B*-methyl groups (*C*-BODIPY **10a**), the deprotection was also unsuccessful. The *meso*-benzyl and *meso*-methyl BODIPYs **12a** and **11a**, respectively, were deprotected successfully in high yield to generate the corresponding unstable *meso*-substituted dipyrrins,[23] which were isolated as their HCl salts (to prevent tautomerization to the vinylic dipyrroles) through a modification of the work-up procedure. Attempts to remove trace amounts of *tert*-butanol from compound **11b** resulted in conversion to the vinylic dipyrrole, which was, unsurprisingly, unstable in solution.

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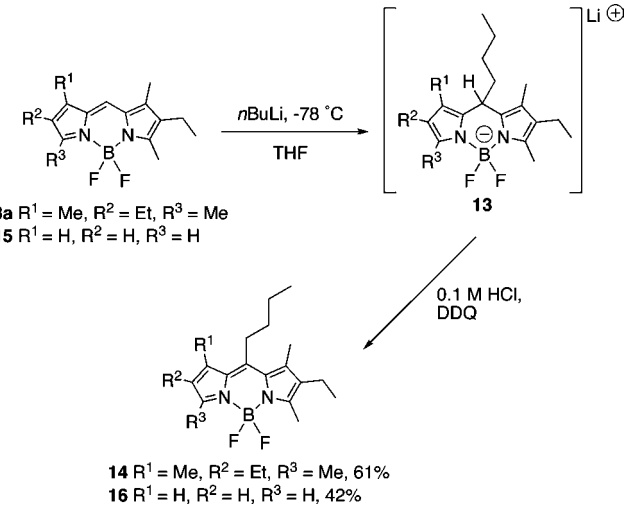
Although BODIPY **3a** has been synthesized on large scale in high yields (see the Supporting Information for a 5 g scale procedure giving a 91% isolated yield) the scale of the microwave-promoted reaction is limited by the size of the sealed microwave vessels available. Isolated yields of **3b** on scales larger that 500 mg are also limited by purification methods, as this material is only of moderate stability and decomposes during column chromatography. Similar problems are encountered in the large-scale purification of **1b**; fortunately, the majority of the crude dipyrrin products are pure enough to be used in subsequent reactions without purification.

Once a successful deprotection strategy had been found, the possibilities for synthetic modification of *F*-BODIPY derivatives were investigated. Our goal was to modify the *meso*-position of the *F*-BOIDPY and compound **3a** was selected for modification studies. The double bond at the *meso*-position in the *F*-BODIPY could be subject to nucleophilic attack similar to that observed in analogous porphyrin and metallo-porphyrin examples.[24,25] However, some organolithium reagents are known to attack the boron center to give *C*-BODIPYs,[26] so the reactions were conducted at low temperature in attempts to limit undersirable reactivity.

Treatment of **3a** with *n*-butyllithium resulted in loss of the typical dipyrrin color. The addition of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) resulted in the return of the characteristic dipyrrin hue, and subsequent isolation of *meso*-butyl *F*-BODIPY **14** in 61% yield (Scheme 2). On the basis of the

Scheme 2. Alkylation of BODIPYs **3a** and **16** with *n*BuLi



3a R^1 = Me, R^2 = Et, R^3 = Me
15 R^1 = H, R^2 = H, R^3 = H

14 R^1 = Me, R^2 = Et, R^3 = Me, 61%
16 R^1 = H, R^2 = H, R^3 = H, 42%

color changes that occurred during the reaction, we propose that the reaction proceeds through an addition−elimination mechanism. After the initial nucleophilic attack of the butyl anion at the *meso*-position an intermediate (**13**) is formed, and loss of hydride gives *F*-BODIPY **14** as the final product.[14,15]

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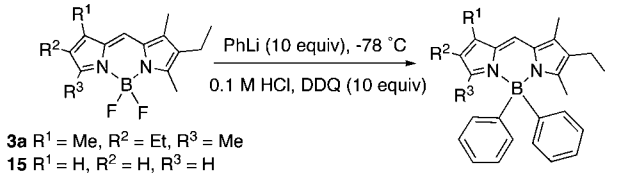
As expected, *F*-BOIDPY **15** also underwent alkylation with *n*BuLi to give **16** (Scheme 2). Given our demonstrated success with removal of the BF_2 moiety from *meso*-alkylated *F*-BODIPYs **11a** and **12a**, these two reactions constitute a new route to *meso*-substituted free-base dipyrrins.

When **3a** was treated with phenyllithium at −78 °C, only starting material was observed. No products were observed until the temperature reached above −30 °C, and the starting material was not consumed until the reaction reached room temperature. Treatment of **3a** with phenyllithium at −45 °C followed by warming to room temperature resulted in the isolation of *C*-BODIPY **17** with two *B*-phenyl groups (Scheme 3) in low yield, with no production of the *meso*-substituted product. The *meso*-position of *F*-BODIPY **3a** is presumably too sterically hindered to allow the approach of the phenyl group. Treatment of *F*-BODIPY **15** with phenyl lithium results in a mixture of products in which *C*-BODIPY **18** was the major product.

Scheme 3. Alkylation of BODIPYs **3a** and **15** with PhLi



3a R^1 = Me, R^2 = Et, R^3 = Me
15 R^1 = H, R^2 = H, R^3 = H

17 R^1 = Me, R^2 = Et, R^3 = Me
18 R^1 = H, R^2 = H, R^3 = H

In summary, a one-step method for generating dipyrrins in high isolated yields from their *F*-BODIPY analogues under microwave irradiation has been developed. The operationally facile method is general for *meso*-substituted, *meso*-unsubstituted, symmetrical, and unsymmetrical *F*-BODIPYs. The mechanisms of the transformation and the deprotection of electron-poor BODIPYs are currently under investigation, as is the application of this method in the widespread synthesis and purification of dipyrrins. Furthermore, *F*-BODIPY molecules can also be treated with *n*-butyllithium to generate the corresponding *meso*-butyl-substituted *F*-BODIPYs in moderate to low yields.

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Supporting Information Available: Experimental procedures and NMR characterization data for all previously unpublished compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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