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An Improved Method for the Synthesis of *F*-BODIPYs from Dipyrrins and Bis(dipyrrin)s

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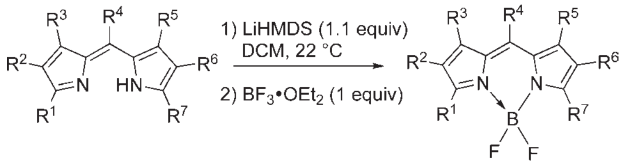
ABSTRACT



An improved methodology for the synthesis of *F*-BODIPYs from dipyrrins and bis(dipyrrin)s is reported. This strategy employs lithium salts of dipyrrins as intermediates that are then treated with only 1 equiv of boron trifluoride diethyletherate to obtain the corresponding *F*-BODIPYs. This scalable route to *F*-BODIPYs renders high yields with a facile purification process involving merely filtration of the reaction mixture through Celite in many cases.

Compounds containing the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY)[1–3] framework are known for their high thermal and photochemical stability, chemical robustness, and chemically tunable fluorescence properties, making them a highly desirable synthetic target. *F*-BODIPYs are generally synthesized by trapping a dipyrrin[4,5] as its BF$_2$ complex through a reaction with BF$_3$•OEt$_2$ and NEt$_3$.[2] To the best of our knowledge, all *F*-BODIPY formation reactions reported in the literature use an excess of both the amine base and BF$_3$•OEt$_2$.

Bis(dipyrrin)s consist of two dipyrrins attached through a linker.[4,5] Given the large number of reported *F*-BODIPYs, it is surprising that there are few examples of bis(*F*-BODIPY)s. There are two examples of *meso*-H, α-linked bis(*F*-BODIPY)s with varying alkyl substituents about the BODIPY core.[6] In addition, there is a closely related example containing a *meso*-phenyl substituent. Two examples of bis(*F*-BODIPY)s attached *via* long fatty acid/phospholipid chains through their α-positions are commercially available.[7] A bis(*F*-BODIPY) attached *via* a long glycoside chain through the α-position[8] has also been reported.

We first attempted to synthesize bis(*F*-BODIPY)s using traditional methods (excess NEt$_3$ and BF$_3$•OEt$_2$ in dichloromethane solution).[2] However, these reactions resulted in complex mixtures that could not be successfully purified. Similar difficulties have been reported previously in the synthesis of bis(*F*-BODIPY)s.[9]

To investigate the formation of *F*-BODIPYs in more detail, and to optimize the reaction conditions for eventual application toward the synthesis of bis(*F*-BODIPY)s, we

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(7) Bis-BODIPY® FL C11-PC <http://products.invitrogen.com/ivgn/product/B7701> last accessed March 14th, 2012; Red/Green BODIPY® PC-A2 <http://products.invitrogen.com/ivgn/product/A10072> last accessed March 14th, 2012.

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worked with a simple alkyl substituted dipyrrin hydrobromide salt (**1HBr**, Scheme 1). Our goal was to find the ratio of $NEt_3/BF_3/$**1HBr** at which the greatest conversion of dipyrrin to its corresponding *F*-BODIPY was achieved: we postulated that these conditions could be applied to the synthesis of bis(*F*-BODIPY)s. The amine base is essential for the observed reactivity: when the dipyrrin HBr salt was treated with $BF_3{\bullet}OEt_2$ alone, no reaction occurred. To analyze the outcome of the reactions, the ratio of free-base (**1**) to *F*-BODIPY (**1BF$_2$**) was determined *via* integration of the *meso*-H peaks in the ^1H NMR spectra of the crude reaction mixtures recorded after workup.

Scheme 1. Synthesis of **1** and **1BF$_2$** from Dipyrrin Hydrobromide Salt **1HBr**

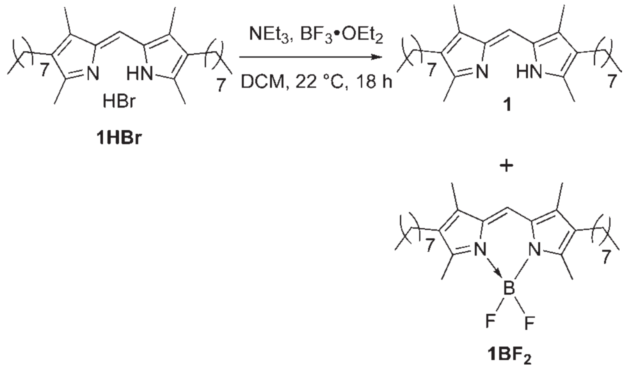


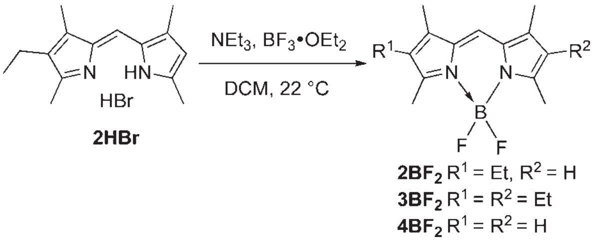
Table 1. Proportions of **1** and **1BF$_2$** from the Dipyrrin Hydrobromide Salt **1HBr** upon Varying the Equivalents of $BF_3{\bullet}OEt_2$

entry	equiv of $BF_3{\bullet}OEt_2$	equiv of NEt_3	ratio of products (**1**:**1BF$_2$**)
1	1	6	1:0
2	2	6	33:1
3	3	6	7.7:1
4	4	6	4.7:1
5	5	6	2.4:1
6	6	6	1.2:1
7	7	6	1:5
8	9	6	0:1

When equal equivalents of $BF_3{\bullet}OEt_2$ and NEt_3 were used (Table 1, entry 6), we saw almost equal amounts of **1** and **1BF$_2$** in the product mixture. It was only when the equivalents of $BF_3{\bullet}OEt_2$ exceeded the equivalents of NEt_3 that we began to see the desired product **1BF$_2$** forming in large proportions (Table 1, entries 7 and 8). In fact, using 9 equiv of $BF_3{\bullet}OEt_2$ and 6 equiv of NEt_3 ensured that **1HBr** was converted solely to **1BF$_2$** (Table 1, entry 8), and these are indeed the conditions routinely used for the formation of *F*-BODIPYs from dipyrrin HBr salts.[10]

Interestingly, we found that this general procedure for the synthesis of *F*-BODIPYs often suffers from irreproducible results when the dipyrrin hydrobromide salt is unsymmetrical. Indeed, when attempting to synthesize *F*-BODIPY **2BF$_2$** from the unsymmetrical hydrobromide salt **2HBr** we were surprised to isolate a mixture of three products, as shown in Scheme 2.

Scheme 2. Synthesis of Scrambled *F*-BODIPYs from an Unsymmetrical Dipyrrin



Using X-ray crystallographic analysis, we unambiguously confirmed the presence of the desired unsymmetrical *F*-BODIPY (**2BF$_2$**) along with two (scrambled) symmetrical *F*-BODIPY products (**3BF$_2$** and **4BF$_2$**) (see Supporting Information). Attempts were made to optimize the reaction by modifying the choice of solvent and adjusting the temperature and the equivalents of $BF_3{\bullet}OEt_2$ and NEt_3. In all cases, a mixture of **2BF$_2$**, **3BF$_2$**, and **4BF$_2$**, separable only via recrystallization, was isolated with **2BF$_2$** as the major product.

Finally, the general conditions for the synthesis of *F*-BODIPYs often cause problems in larger scale reactions (>1 g). Indeed, during *F*-BODIPY formation reactions, a $BF_3{\bullet}NEt_3$ adduct[11] byproduct is formed. Purification *via* column chromatography is usually required to remove this adduct, which generally has a higher R_f value than the desired *F*-BODIPY product. In our experience on larger scales, the presence of this adduct makes product isolation challenging at both the extraction and purification stages.

The problems that arise when synthesizing bis(*F*-BODIPY)s, *F*-BODIPYs of unsymmetrical dipyrrins, and simple *F*-BODIPYs on a large scale highlight the need for the development of a targeted synthetic approach to *F*-BODIPYs. To address this challenge, we sought an amine-free procedure for the synthesis of *F*-BODIPYs. This strategy necessitates the need for formation of the dipyrrinato anion prior to the addition of $BF_3{\bullet}OEt_2$. We have previously developed methodology for the synthesis and isolation of dipyrrinato lithium salts using either *n*-BuLi[12] or, more successfully, LiHMDS.[13] Dipyrrinato lithium salts have been successfully employed as precursors to

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[10] Crawford, S. M.; Thompson, A. *Org. Lett.* **2010**, *12*, 1424–1427.

[11] Fox, A.; Hartman, J. S.; Humphries, R. E. *J. Chem. Soc., Dalton Trans.* **1982**, 1275–1283.

[12] Cipot-Wechsler, J.; Al-Sheikh Ali, A.; Chapman, E. E.; Cameron, T. S.; Thompson, A. *Inorg. Chem.* **2007**, *46*, 10947–10949.

[13] Al-Sheikh Ali, A.; Cipot-Wechsler, J.; Crawford, S. M.; Selim, O.; Stoddard, R. L.; Cameron, T. S.; Thompson, A. *Can. J. Chem.* **2010**, *88*, 725–735.

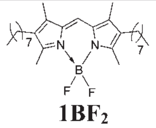
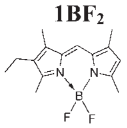
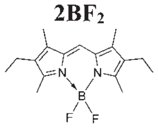
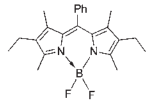
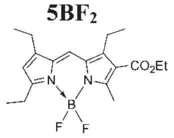
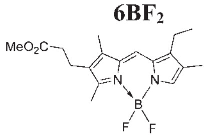
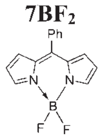
dipyrrinato metal complexes,[12−14] and we envisioned that they could also be suitable precursors to *F*-BODIPYs.

We started by using a series of isolated dipyrrinato lithium salts, prepared using LiHMDS and the corresponding dipyrrin HBr salt.[13] We were delighted to find that when these dipyrrinato lithium salts were treated with just 1 equiv of $BF_3\bullet OEt_2$ the resulting *F*-BODIPYs could be isolated in high yields. Furthermore, we found that isolation of the intermediate dipyrrinato lithium salt was unnecessary: generation of the lithium salt from the corresponding dipyrrin and/or dipyrrin hydrobromide salt *in situ* (using 1.1 or 2.2 equiv of LiHMDS, respectively), followed by the addition of 1 equiv of $BF_3\bullet OEt_2$, gave comparable yields of the resulting *F*-BODIPYs, with purification requiring merely a filtration through Celite to remove the LiF byproduct.

To demonstrate the utility of this newly developed methodology, we synthesized a variety of *F*-BODIPYs (Scheme 3, Table 2) including those with *meso*-H and *meso*-Ph substituents. Substituted and unsubstituted pyrrolic skeletons were well-tolerated by the new methodology, as were conjugated and alkanoate esters. In all cases, isolation of the desired product was facile: the reaction mixtures were filtered over a pad of Celite (or Celite and silica) to produce yields typically $>80\%$. Notably, the unsymmetrical *F*-BODIPY **2BF$_2$** was synthesized in high yield using this method, without the observation of scrambled products (Table 2, entry 2).

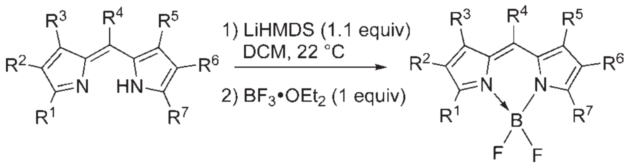
Furthermore, this new procedure is scalable (Table 2, entry 3). As the reaction only requires 1 equiv of $BF_3\bullet OEt_2$, and no NEt_3, the previously observed $BF_3\bullet NEt_3$ byproduct is not produced and therefore isolation of the *F*-BODIPY products is significantly easier. Furthermore, the reaction was scaled to 1 g, outside of the glovebox, under an inert atmosphere using anhydrous conditions to result in a 94% isolated yield of **3BF$_2$** (Table 2, entry 3c). It should be noted that the *F*-BODIPY **3BF$_2$** could also be prepared by reacting the free-base dipyrrin **3** with 1 equiv of $BF_3\bullet OEt_2$ (without formation of the intermediate lithium dipyrrinato complex), such as with the formation of *Cl*-BODIPYs.[15] However, this reaction produced lower yields (50%) compared to the method involving *in situ* formation of the lithium salt (94%).

Table 2. Synthesis of *F*-BODIPYs from Dipyrrinato Lithium Salts Using 1 equiv of $BF_3\bullet OEt_2$

entry	*F*-BODIPY product	yield (%)
1	 **1BF$_2$**	98^a
2	 **2BF$_2$**	91^a
3	 **3BF$_2$**	94^a, 93^b, 94^c
4	 **5BF$_2$**	88^a
5	 **6BF$_2$**	85^a
6	 **7BF$_2$**	81^a
7	 **8BF$_2$**	60^a

^{a} Glovebox, 50 mg scale. ^{b} Glovebox, 250 mg scale. ^{c} Inert atmosphere conditions outside of glovebox, 1 g scale.

Scheme 3. Synthesis of *F*-BODIPYs from Dipyrrinato Lithium Salts Using 1 equiv of $BF_3\bullet OEt_2$



A common approach for synthesizing *F*-BODIPYs involves oxidation of the corresponding dipyrromethane with DDQ to form the free-base dipyrrin which is trapped *in situ* as the *F*-BODIPY upon the addition of 6 equiv of TEA and 9 equiv of $BF_3\bullet OEt_2$:[2] using this approach, we obtained **5BF$_2$** in 50% yield from the corresponding dipyrromethane, after column chromatography (Scheme 4). We compared this approach to our new strategy, again starting from the dipyrromethane. Thus, 3.3 equiv of LiHMDS and then just 1 equiv of $BF_3\bullet OEt_2$ were added to the reaction mixture directly after the oxidation reaction involving DDQ. The reaction was performed under nitrogen, and the workup required an acid/base wash followed by a simple filtration through a pad of silica, rather than chromatography *per se*, to afford pure **5BF$_2$** in 52% yield on an 800 mg scale, outside the glovebox, again demonstrating scalability and practicality. Thus, our new methodology is easily melded with the much-trusted route from dipyrromethanes that bypasses the need to isolate/purify dipyrrins or their HX salts.

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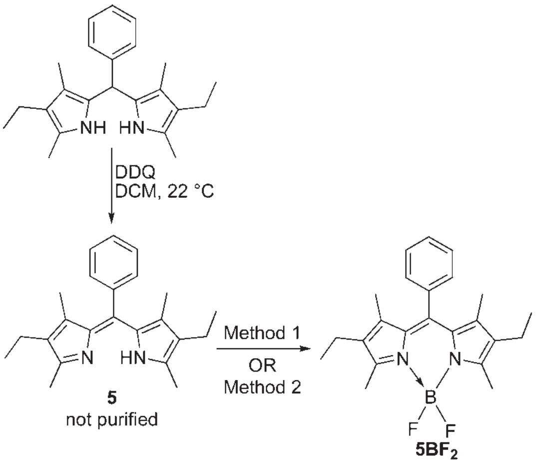
Scheme 4. Synthesis of *F*-BODIPYs via in Situ Trapping of Dipyrrins

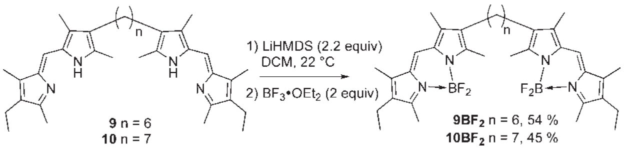


Method 1: 6 equiv NEt_3, 9 equiv $BF_3•OEt_2$, 50% after column chromatography

Method 2: (a) 3.3 equiv LiHMDS; (b) 1 equiv $BF_3•OEt_2$, 52% after filtration through silica

Given the success of this improved methodology for *F*-BODIPY formation, the same conditions were applied to bis(dipyrrin)s in an attempt to synthesize bis(*F*-BODIPY)s in appreciable yields (Scheme 5). To solutions of the free-base bis(dipyrrin)s **9** and **10** in dichloromethane, LiHMDS in tetrahydrofuran was added dropwise. The reaction mixtures were stirred for 2 h to allow formation of the dilithium salts to occur. Solutions of $BF_3•OEt_2$ in dichloromethane were then added dropwise, and the reaction mixtures were stirred for another 3 h. Upon completion, the reaction mixtures were filtered through Celite. The crude materials were purified over silica to give the desired bis(*F*-BODIPY)s **9BF$_2$** and **10BF$_2$** in isolated yields of 54% and 45%, respectively, significantly higher than those previously obtained for bis(*F*-BODIPY)s.

Scheme 5. Synthesis of bis(*F*-BODIPY)s



In conclusion, we have developed an improved methodology for *F*-BODIPY formation utilizing the lithium salt of the free-base dipyrrin and only 1 equiv of $BF_3•OEt_2$. This strategy has significant benefits over traditional conditions for synthesizing *F*-BODIPYs (excess $BF_3•OEt_2$ and NEt_3), and we anticipate widespread application toward the synthesis of these fluorescent compounds. In our new methodology, NEt_3 is not required and therefore a $BF_3•NEt_3$ adduct byproduct is not formed: filtration through Celite suffices for most purifications. The strategy may be applied to the isolated free-base dipyrrin, or to the approach involving trapping the dipyrrin *in situ* once it has formed *via* oxidation of the corresponding dipyrromethane. Indeed, using our new strategy for the synthesis of *F*-BODIPYs *via in situ* trapping of dipyrrins, themselves formed after oxidation of dipyrromethanes, gives comparable yields and simpler purifications than the usual approach. Our methodology avoids the synthesis of scrambled byproducts in the formation of *F*-BODIPYs. Furthermore, using this new methodology bis(*F*-BODIPY)s were synthesized in yields appreciably higher than have previously been attained.

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Supporting Information Available. Experimental procedures, characterization data for new compounds, and selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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