

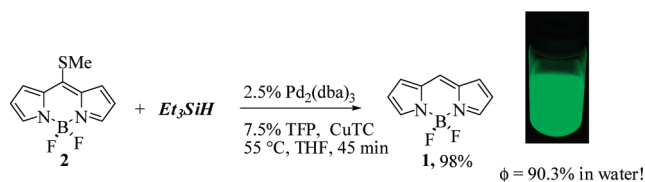
## The Smallest and One of the Brightest. Efficient Preparation and Optical Description of the Parent Borondipyromethene System

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Fully unsubstituted 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) **1** was prepared. Reaction of 8-thiomethylbodipy **2** with triethylsilane in the presence of a catalytic amount of Pd and a stoichiometric amount of copper(I) thienyl-2-carboxylate (CuTC) in THF at 55 °C gave compound **1** in nearly quantitative yield. This compound displays high quantum yields (up to 93%) in polar solvents including water. Its optical properties and crystal structure are discussed.

Since the discovery of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene derivatives (also called borondipyromethenes or BODIPYs)<sup>1</sup> in 1968 by Treibs and Kreuzer,<sup>2</sup> scientists worldwide have realized the unique and exciting properties of such compounds.<sup>3</sup> These properties render them very

useful for numerous applications, among which are fluorescent switches,<sup>4</sup> electroluminescent films,<sup>5</sup> laser dyes,<sup>6</sup> and chemosensors<sup>7</sup> just to name a few. To tailor the properties of these analogues, particularly aimed at obtaining high quantum yields, chemists have varied the core structure in several ways involving a large number of synthetic steps (Chart 1).<sup>8–15</sup>

There are literally hundreds of different BODIPY dyes described in the literature with impressive structural variations. However, as Burgess mentions,<sup>3a</sup> there are still “synthetic limitations for even some simple BODIPY systems”. Among them is the unsubstituted parent system **1** (Figure 1).

The parent system remained elusive until very recently, mentioned in the literature only as a theoretical reference for calculations.<sup>16</sup>

The attempts to prepare **1** had hitherto failed because the dipyrromethene precursor, albeit reported in the literature,<sup>17</sup> is very unstable and decomposes even at –40 °C.<sup>3a</sup>

In this context, Peña-Cabrera and co-workers reported in 2007<sup>18</sup> a mild and general method to prepare 8-substituted BODIPY dyes via Liebeskind–Srogl cross-coupling (LSCC)<sup>19</sup> (Scheme 1).

The success of this process and other similar reactions reported in the literature<sup>20</sup> is based upon the fact that the thiomethyl group is bonded to an electron-withdrawing group.

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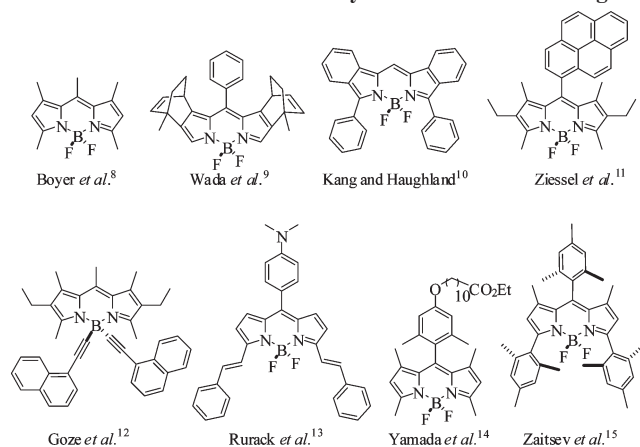
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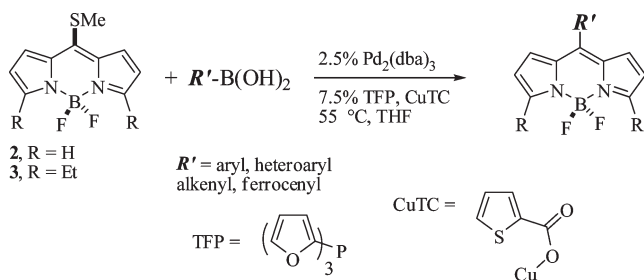
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CHART 1. Selected BODIPY Dyes with  $\Phi$  of 90% or Higher

## SCHEME 1. Application of the LSCC in the Synthesis of meso-Substituted BODIPY Dyes



A related reaction that involves thioorganics is the so-called Fukuyama reaction<sup>21</sup> (Scheme 2).

One of the features of the Fukuyama reaction that stands out is that the thioalkyl group on the thiol ester serves as a proton surrogate in the aldehyde synthesis. Inspired by these observations, it seemed feasible to replace the thiomethyl group in **2** with a proton under the Fukuyama conditions in order to furnish the parent compound **1**; the results are reported herein.

After subjecting **2** to the standard Fukuyama reductive conditions ( $\text{Et}_3\text{SiH}$ , Pd/C, acetone, rt) as well as to some variations thereof (using acetonitrile as a higher boiling solvent), we observed either no reaction or decomposition after 24 h. We then decided to explore the LSCC conditions shown in Scheme 1, using  $\text{Et}_3\text{SiH}$  instead of a boronic acid. The results are illustrated in Table 1.

After just a few attempts, we were delighted to see that **1** was obtained under these remarkably mild conditions (entry 5) in nearly quantitative yield after only 45 min.

Although no mechanistic study has been carried out for this particular system, the observations of Table 1 suggest that the reduction of **2** follows a different path from the normal Fukuyama thiol ester reduction<sup>22</sup> (Scheme 3).

In sharp contrast with the reaction mechanism outlined in Scheme 3, reduction of **2** requires a stoichiometric amount of thiophilic CuTC to remove the MeS fragment from the

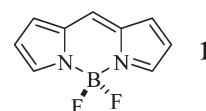
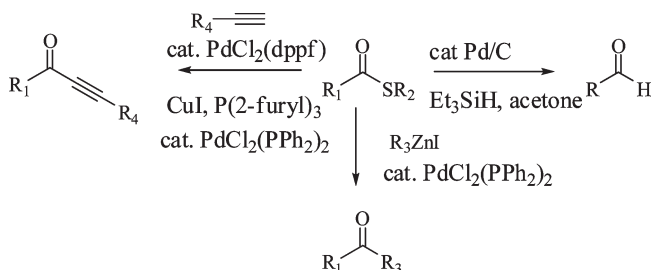


FIGURE 1. Structure of the parent BODIPY system.

## SCHEME 2. The Fukuyama Coupling Reaction

TABLE 1. Survey of Reaction Conditions for the Synthesis of **1**

entry	Pd <sub>2</sub> (dba) <sub>3</sub>	TFP	CuTC (equiv)	Et <sub>3</sub> SiH (equiv)	results <sup>a</sup>
1	✓	✓	×	3	NR <sup>b</sup>
2	×	×	3	1	NR
3	✓	✓	1	1	1:2 = 1.7 <sup>c</sup> after 2 days
4	✓	✓	3	1	1:2 = 1.7 after 2 days
5	✓	✓	3	3	1, 98% after 45 min

<sup>a</sup>All the reactions were carried out in THF at 55 °C. <sup>b</sup>NR: no reaction after 2 days. <sup>c</sup>Calculated from the <sup>1</sup>H NMR spectrum of the crude reaction mixture.

oxidative addition intermediate in direct analogy with the normal LSCC<sup>23</sup> (entry 5, Table 1). Once removal of the MeS moiety occurs, 2-thienylcarboxylate may coordinate to oxophilic Si to form a transient pentacoordinated species<sup>24</sup> from which hydride would transfer to Pd. Reductive elimination of this species would form the observed product (Figure 2).

Attempting the reaction in the absence of CuTC results in no reaction (entry 1, Table 1). It is well-known that CuTC promotes C–C bond formation by itself;<sup>25</sup> however, no reaction was observed in the absence of Pd (entry 2, Table 1).

Spectral data showed no unexpected features. Both <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1** indicated that its symmetric nature and combustion analysis results matched those of the expected structure. The parent BODIPY is a crystalline red solid with excellent bench-life. It can be handled in air with no decomposition. It is highly recommended to handle it in a

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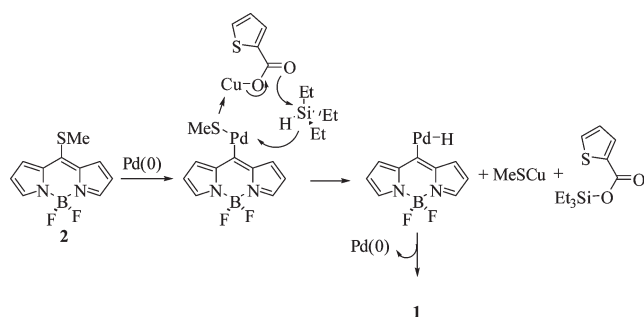


FIGURE 2. Working hypothesis for the formation of **1**.

SCHEME 3. Reported Mechanism for the Fukuyama Thiol Ester Reduction

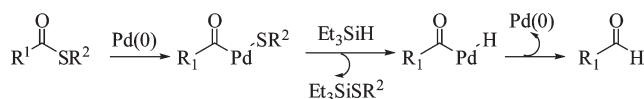
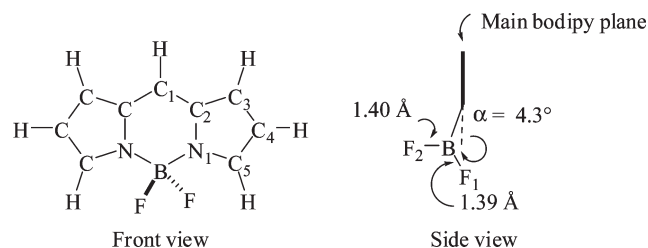


TABLE 2. Selected Bond Distances of **1**



bond	bond length (Å)	
	X-ray	theoretical
C <sub>1</sub> –C <sub>2</sub>	1.3833(16)	1.390
C <sub>2</sub> –C <sub>3</sub>	1.4100(15)	1.418
C <sub>3</sub> –C <sub>4</sub>	1.3700(17)	1.387
C <sub>4</sub> –C <sub>5</sub>	1.4001(16)	1.411
C <sub>5</sub> –N <sub>1</sub>	1.3386(15)	1.339
C <sub>2</sub> –N <sub>1</sub>	1.3913(12)	1.393
N <sub>1</sub> –B	1.5450(14)	1.569
B–F <sub>1</sub>	1.3875(12)	1.392
B–F <sub>2</sub>	1.3958(13)	1.392

well-ventilated fume hood since as a powder, it causes rather strong nose, skin, and throat irritation.

The crystal structure of **1** shows interesting features (Table 2). The B atom is not coplanar with the rest of the molecule, rather, it deviates a 4.3° angle from the main plane. It also displays two slightly different B–F bond distances. The molecule as a whole features a very slight bending to give a “saddled” geometry in the opposite direction from the B atom.

The unit cell contains four molecules of **1** stacked in a head-to-tail fashion to optimize the  $\pi$ – $\pi$  interactions as well as a response to the dipole moment caused by the F atoms.

To understand the structural properties of **1**, we carried out a series of DFT calculations, which were performed in Gaussian 03 with use of the B3LYP/6-311++G(d,p) level. The optimized structure adopts a planar C<sub>2v</sub> symmetry. This

TABLE 3. Optical Properties of Compound **1** in Different Solvents<sup>a</sup>

solvent	$\lambda_{ab}$ (nm)	$\lambda_{em}$ (nm)	$\Phi_F$ (%)
cyclohexane	504	515	68.8
toluene	505	535	68.8
chloroform	505	526	76.2
THF	500	516	76.8
ethyl acetate	499	511	80.8
ethanol	499	535	93.0

<sup>a</sup> $\lambda_{ab}$  = absorption maximum,  $\lambda_{em}$  = emission maximum,  $\Phi_F$  = fluorescence quantum yield estimated by using fluorescein as the standard ( $\Phi_F$  = 79% in 0.1 M NaOH solution).



FIGURE 3. Photograph of a water solution of **1** under UV light.

small discrepancy with the X-ray structure can be assigned to the packing forces in the crystalline state of **1**. Indeed, theoretical calculations are obtained in the gas phase without any intermolecular interactions, whereas the packing forces could disrupt the planarity of the aromatic  $\pi$ -system of **1** in the solid state (nonsymmetric crystalline cell). Interestingly, the smallest vibrational frequency for **1** is only 16 cm<sup>-1</sup> and it is associated with boron movement out-of-plane. The calculated dipole moment of **1** is 4.5 D (see the SI), supporting the presence of dipole–dipole interactions in the crystal structure.

BODIPY **1** is quite emissive and has a high quantum yield in both nonpolar and polar solvents (Table 3). The UV absorption spectra are basically the same in all the solvents with a slight blue-shift in polar solvents. The absorption spectra of **1** do not show major variations with solvent polarity; however, its emission behavior does. In cyclohexane, ethyl acetate, and THF, the emission maximum  $\lambda_{em}$  is around 515 nm with a relatively small Stokes shift. In chloroform and acetonitrile, the  $\lambda_{em}$  red-shifts by ~10 nm, whereas in toluene and ethanol, the  $\lambda_{em}$  moves to 535 nm. However, there is no apparent correlation between the solvent polarity and the  $\lambda_{em}$ , at least in the set of solvents studied. Measurements on the quantum yields of **1** in different solvents show that as the solvent polarity increases, the quantum yield increases as well.

Surprisingly, **1** is sparingly soluble in water. It absorbs at 498 nm and fluoresces at 516 nm with a  $\Phi_F$  of 90.3% (at 10<sup>-5</sup> M, fluorescence quantum yield estimated by using fluorescein as the standard,  $\Phi_F$  = 79% in 0.1 M NaOH solution). Its high  $\Phi_F$ , water-solubility, and nearly flat conjugated structure may open an important window of opportunity for biological applications. Figure 3 shows a picture of a water solution of **1** under UV light.

In conclusion, we have achieved the synthesis of the parent BODIPY **1** in excellent chemical yield under mild conditions. The title compound displays high quantum yields in polar solvents including water. We envisage a number of applications both practical and theoretical for this simple derivative.

The crystal structure of **1**, along with the optical data, may be used as an experimental starting point to rationally design

similar dyes for specific purposes. A further observation that could be drawn only after **1** was experimentally studied was that in the majority of the cases reported in the literature, substituents in the different positions of **1**, far from increasing the  $\Phi$  of the BODIPY core, lower it. Finally, an aspect of this chemistry that warrants a more detailed study is the possibility to use a thioalkyl group as a proton surrogate in other systems, since it could be removed under mild reaction conditions in high yield.<sup>26</sup> A systematic study of the influence of functional groups in different positions of **1** is underway in our laboratory and the results will be disclosed in due course.<sup>27</sup>

### Experimental Section

The X-ray diffraction intensity data were collected at 173 K on a diffractometer with graphite-monochromated Mo K $\alpha$  radiation. The intensity data were processed by using the SAINT and SADABS routines, and the structure solution and refinement were carried out by the SHELXTL suite of X-ray programs (version 6.10).

(26) Lindsey et al. have been able to remove a thioalkyl group from the pyrrole  $\alpha$  position using either Raney nickel in boiling EtOH (yield 38–66%) (Thamyongkit, P.; Bhise, A. D.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 903) or a 25-fold excess of NaBH<sub>4</sub> with the concomitant reduction of other functional groups (Dogutan, D. K.; Zaidi, S. H. H.; Thamyongkit, P.; Lindsey, J. S. *J. Org. Chem.* **2007**, *72*, 7701).

(27) **Note Added in Proof:** During the submission process, the authors became aware of a report where **1** was prepared by using the traditional process described in ref 17. The parent BODIPY system was prepared in 5–10% yield, reflecting, as pointed out in this work, the high instability of the dipyrromethene precursor: Tram, K.; Yan, H.; Jenkins, H. A.; Vassiliev, S.; Bruce, D. *Dyes Pigm.* **2009**, *82*, 392.

**Synthesis of 1.** An oven-dried, 50 mL Schlenk tube containing a magnetic stir bar was charged with thiomethylbodipy **2**<sup>28</sup> (120 mg, 0.5 mmol), triethylsilane (176 mg, 1.5 mmol), and dry tetrahydrofuran (3 mL) under N<sub>2</sub>. The solution was sparged with N<sub>2</sub> for 10 min, whereupon copper(I) thiophene-2-carboxylate (288 mg, 1.5 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (12 mg, 0.013 mmol), and tri-2-furylphosphine (9 mg, 0.038 mmol) were added under N<sub>2</sub>. The reaction mixture was immersed into a preheated oil bath at 55 °C. The mixture was stirred for 45 min and then was allowed to reach rt. The crude material was adsorbed on silica gel and the product was purified by flash chromatography (SiO<sub>2</sub> gel, EtOAc/hexanes gradient) to give 96 mg (98%) of a dark-red crystalline solid. For X-ray analysis, **1** was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/petroleum ether. TLC (20% AcOEt/hexanes) *R<sub>f</sub>* 0.3; mp 157.8–158.6 °C; IR (KBr, cm<sup>-1</sup>) 969 (s), 1063 (s), 1112 (s), 1166 (s), 1292 (s), 1397 (s), 1605 (s), 691 (m), 758 (m), 1410 (m); <sup>1</sup>H RMN (200 MHz, CDCl<sub>3</sub>)  $\delta$  6.6 (br s, 2H), 7.2 (br d, *J* = 4.0 Hz, 2H), 7.4 (s, 1H), 7.9 (br s, 2H); <sup>13</sup>C RMN (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  119.0, 131.5, 135.4, 145.3. Anal. Calcd for C<sub>9</sub>H<sub>7</sub>BF<sub>2</sub>N<sub>2</sub>: C, 56.31; H, 3.68; B, 5.63; F, 19.79; N, 14.59. Found: C, 56.49; H, 3.74; N, 14.41.

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**Supporting Information Available:** CIF, ORTEP diagram, <sup>1</sup>H, <sup>13</sup>C NMR spectra, and dipole moment diagram of **1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(28) Prepared according to: Goud, T. V.; Tutar, A.; Biellmann, J.-F. *Tetrahedron* **2006**, *62*, 5084.