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Simple, General, and Efficient Synthesis of Meso-Substituted Borondipyrromethenes from a Single Platform

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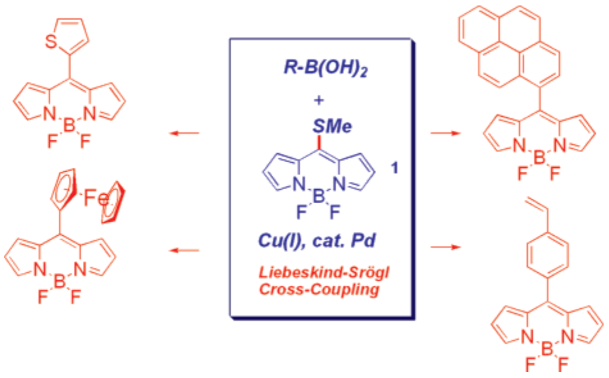
ABSTRACT



An unprecedented synthesis of 8-substituted-borondipyrromethenes is described starting from 8-thiomethylbodipy 1. Aryl, heteroaryl, alkenyl, and organometallic boronic acids smoothly reacted with 1 in the presence of a catalytic amount of Pd(0) and a stoichiometric amount of Cu(I)-2-thienylcarboxylate *under neutral conditions* to give the corresponding Bodipy analogues in good to quantitative yields (20 examples). A remarkable reactivity was observed in some cases, e.g., ferrocenylboronic acid gave the product in 98% isolated yield after *only 10 min* at 55 °C.

Subsequent to the report by Treibs and Kreuzer[1] concerning the synthesis of monomeric borondipyrromethenes or Bodipy dyes[2] (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) in 1968, scientists have found numerous applications for this family of compounds. Highlights of their applications include the synthesis of light-harvesting arrays,[3] biological probes,[4] supramolecular fluorescent gels,[5] ion sensors,[6] and fluorescent stains,[7] among others.

Despite the significance of their applications, further research has been hampered due to the fact that their synthesis and functionalization are not straightforward and because the examples that are commercially available are

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[1] Treibs, A.; Kreuzer, F.-H. *Liebigs. Ann. Chem.* **1968**, *718*, 208.

[2] Haugland, R. P. *The Handbook. A Guide to Fluorescent Probes and Labeling Technology*, 10th ed.; Molecular Probes Inc.: Eugene, OR, 2005.

[3] (a) Wagner, R. W.; Lindsey, J. S. *Pure Appl. Chem.* **1996**, *68* (7), 1373. (b) Yilmaz, M. D.; Bozdemir, O. A.; Akkaya, E. U. *Org. Lett.* **2006**, *8* (13), 2871. (c) Li, F.; Yang, S. I.; Ciringh, Y.; Seth, J.; Martin, C. H.; Singh, D. L.; Birge, R. R.; Bocian, D. F.; Holten, D.; Lindsey, J. L. *J. Am. Chem. Soc.* **1998**, *120*, 10001.

[4] (a) Ueno, T.; Urano, Y.; Kojima, H.; Nagano, T. *J. Am. Chem. Soc.* **2006**, *128* (33), 10640. (b) Yogo, T.; Urano, Y.; Ishitzuka, Y.; Maniwa, F.; Nagano, T. *J. Am. Chem. Soc.* **2005**, *127* (35), 12162.

[5] Camere, F.; Bonardi, L.; Schmutz, M.; Ziessel, R. *J. Am. Chem. Soc.* **2006**, *128* (14), 4548.

[6] Zeng, L.; Miller, E. W.; Pralle, A.; Isacoff, E. Y.; Chang, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 10.

[7] Dahim, D.; Mizuno, N. K.; Li, X.-M.; Momsen, W. E.; Momsen, M. M.; Brockman, H. L. *Biophys. J.* **2002**, *83*, 1511.

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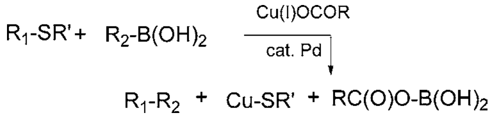
exceedingly expensive. The classic Lindsey method,[3a] used so far in most syntheses of 8-aryl-substituted (meso-derivatives) Bodipy's, requires the treatment of an aryl aldehyde with a large excess of pyrrole under acid catalysis to produce the corresponding dipyrroarylmethane. Oxidation with DDQ, followed by exposure to triethylamine and BF_3-etherate, yields the Bodipy dyes in modest overall yields (ca. 10%).[3c] More recently, however, Lindsey introduced a protocol whereby a just over stoichiometric amount of pyrrole is needed to prepare meso-substituted dipyrromethanes in acceptable yields in the presence of a catalytic amount of $InCl_3$. The disadvantages of this modification include the need for a two-step sequence to incorporate a thioalkyl protecting group of the α-position of pyrrole, and an additional deprotection step after the condensation with the aldehyde.[3d]

The drawbacks of the classic Lindsey methodology include laborious purifications,[8] a separate synthesis of the starting aldehyde if it is not commercially available, and incompatibility of the functional groups on the aryl ring of the aldehyde to (a) acid, (b) DDQ oxidation, and (c) strong Lewis acid exposure. The oxidation step may be avoided if, instead of an aldehyde, an acid chloride is used in the condensation step with pyrrole.[9] However, the necessity to prepare a highly reactive acid chloride arises.

In recent years, major contributions have appeared in the literature to surmount the challenging functionalization of the Bodipy core system.[10] Despite these efforts, however, an efficient synthesis of the core system and, particularly, that of the *meso*-aryl-substituted Bodipy derivatives remained elusive.

In direct connection with the present work, the Liebeskind group reported a novel and efficient Pd-catalyzed, Cu(I)-mediated cross-coupling reaction of thioethers (or thiol esters) with organostannanes and boronic acids *under neutral conditions* (Scheme 1).[11]

Scheme 1. The Liebeskind−Srögl Cross-Coupling



$$R_1\text{-}SR' + R_2\text{-}B(OH)_2 \xrightarrow[\text{cat. Pd}]{\text{Cu(I)OCOR}} R_1\text{-}R_2 + Cu\text{-}SR' + RC(O)O\text{-}B(OH)_2$$

Later in a seminal paper, Biellmann and collaborators reported a straightforward synthesis of 8-thiomethylbodipy **1**.[12]

1

Analyzing the structure of **1**, we reasoned that the thiomethyl group, being attached to an electron-withdrawing moiety, might participate in the Liebeskind−Srögl cross-coupling reaction with boronic acids just like thiolesters do in the cases reported in the literature.[11] We now present the results of such chemistry.

Initial testing of the reactivity was carried out under the different reaction conditions for the reaction of **1** and phenylboronic acid. Using different Pd sources ($Pd_2(dba)_3$/trifurylphosphine (TFP), $Pd(dppf)Cl_2$, $Pd(PPh_3)_4$), Cu(I)-2-thienylcarboxylate (CuTC), and 1.5 equiv of $PhB(OH)_2$ resulted in the formation of the product after 8 h. However, the reactions never went to completion and a significant amount of biphenyl[13] was produced. The use of bulky phosphines (P^tBu_3, S-Phos) resulted in either formation of trace amounts of 8-phenylbodipy **2** or in no reaction at all, with the concomitant formation of biphenyl. An increase in the effective concentration of the boronic acid (3 equiv) to have enough of this starting material to participate in the Liebeskind−Srögl (L-S) cross-coupling thus driving the reaction to completion was attempted. This resulted in virtually 100% conversion and significant reduction of the reaction time. Comparable isolated yields of **2** were obtained with either $Pd_2(dba)_3$/TFP or $Pd(PPh_3)_4$ (91% and 89%, respectively). Thus, it was decided to use the $Pd_2(dba)_3$/TFP system not only because it gave slightly better yield, but also due to the fact that $Pd(PPh_3)_4$ is somewhat air-sensitive.

A library of 20 derivatives was synthesized (Table 1), the photophysical properties of which will be reported elsewhere. The reactions displayed 100% conversion in all cases. Electron-rich arylboronic acids smoothly reacted with **1** to give the desired compounds (**5**, **6**, **8**, **9**, **11**, **18**, **2**) in good to almost quantitative yields (71−96%). Styryl-substituted Bodipy **8** is of special significance not only because it was obtained in 96% after only 25 min, but also because it is itself a very promising starting material for the preparation of more complex Bodipy analogues via elaboration on the double bond, e.g., the Heck reaction, homo- and cross-metathesis, etc. Electron-poor arylboronic acids showed similar reactivity, the corresponding Bodipy analogues (**10**, **12**−**14**) were prepared in good to excellent yields. Compound **13** was prepared in 62% isolated yield only after ***10 min***. It is important to highlight the synthesis of bromoaryl derivatives **12**−**14**. Since the L-S reaction works in the absence of base, **12**−**14** cannot participate further in Suzuki-type reactions, which might lead to polymerization. One can easily envision the use of these Br-analogues as reaction partners in the rich plethora of transition metal-catalyzed transformations.

To evaluate the possibility of synthesizing rotationally rigid 8-substituted Bodipy's,[4] we studied the reactivity of **1** with

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[8] Boyle, R. W.; Bruckner, C.; Posakony, J.; James, B. R.; Dolphin, D. *Organic Syntheses*; Wiley: New York, 2004; Collect. Vol. X, p 370.

[9] Thorensen, L. H.; Kim, H.; Welch, M. B.; Burghart, A.; Burgess, K. *Synlett* **1998**, 1276.

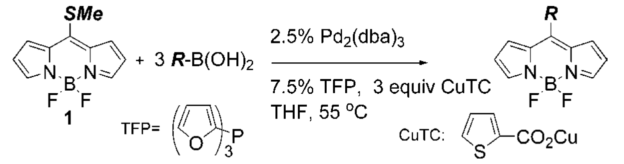
[10] Ziessel, R.; Ulrich, G.; Harriman, A. *New J. Chem*. **2007**, *31*, 496.

[11] (a) Yang, H.; Hao, L.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. *J. Am. Chem. Soc*. **2007**, *129* (5), 1132 and references cited therein. (b) Wittenberg, R.; Srögl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett*. **2003**, *5* (17), 3033. (c) Liebeskind, L. S.; Srögl, J. *J. Am. Chem. Soc*. **2000**, *122* (45), 11260.

[12] Goud, T. V.; Tutar, A.; Biellmann, J.-F. *Tetrahedron* **2006**, *62*, 5084.

[13] This result was observed despite the rigorous deoxygenation of the reaction mixture (N_2 purge for 20 min) prior to the addition of both Cu(I) and Pd. Addition of the boronic acid in small portions did not improve the percent of conversion.

Table 1. Scope of the Reaction of **1** with Boronic Acids



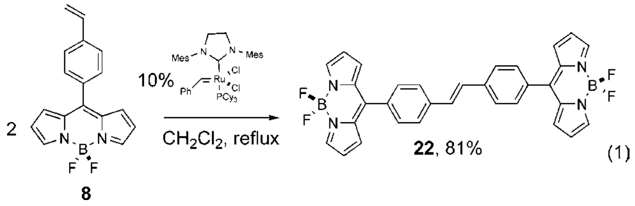
entry	R-	reaction time	compd, yield[a]
1	(E)-$MeOC_6H_4CH{=}CH$-	1 h	**3**, 91
2	*trans*-$CH_3CH{=}CH$-	1 h	**4**, 66
3	3,4-dimethoxyphenyl-	50 min	**5**, 71
4	4-biphenyl-	5 h	**6**, 79
5	2-biphenyl-	2 h	**7**, 81
6	p-$CH_2{=}CH{-}C_6H_4$-	25 min	**8**, 96
7	p-$MeSC_6H_4$-	2 h	**9**, 83
8	p-$CHOC_6H_4$-	30 min	**10**, 76
9	p-$Me_2NC_6H_4$-	1 h	**11**, 78
10	p-BrC_6H_4-	1 h	**12**,[b] 78
11	m-BrC_6H_4-	*10 min*	**13**, 62
12	o-BrC_6H_4-	70 min	**14**, 83
13	1-pyrenyl-	*15 min*	**15**, 67
14	*ferrocenyl-*	*10 min*	**16**, 98
15	4-dibenzofuranyl-	2 h	**17**, *93*
16	p-$MeOC_6H_4$-	3 h	**18**, 81
17	2-thienyl-	3 h	**19**, 78
18	2-(5-methyl)thienyl-	40 min	**20**, 84
19	2-furyl-	*10 min*	***21***, 87
20	phenyl-	1 h	**2**, 91

[a] Isolated yields. [b] The reaction was run at room temperature.

ortho-substituted, sterically demanding boronic acids. It was, once again, greatly gratifying to observe that *o*-bromophenyl- (**14**), *o*-biphenyl- (**7**) and pyrenylbodipy's (**15**) were prepared in 83% (70 min), 81% (2 h), and 67% (15 min), respectively, illustrating that the steric bulk of the starting boronic acids did not compromise either the reaction times or the efficiency of the process.

Heteroarylboronic acids also showed excellent reactivity (**17**, **19**, **20**, **21**), and good to almost quantitative yields were observed. Thienyl-susbtituted Bodipy **19** could potentially be used as a building block for the preparation of novel luminescent materials.[14] A substrate with remarkable reactivity was observed in this series; 2-furylboronic acid reacted with **1** and after only 10 min and **21** was isolated in 87%. Alkenylboronic acids followed the same pattern as the other boronic acid studied, i.e., upon reaction with **1**, alkenyl-containing Bodipy's **3** and **4** were prepared in 91% and 66% yield, respectively, after 1 h. To the best of our knowledge, there is only one additional precedent in the literature for the preparation of 8-alkenyl-substituted Bodipy's.[12] Presumably the vinyl group, being directly attached to a strongly electron-withdrawing Bodipy core, will participate in a range of transformations typical of activated double bonds. The reaction of ferrocenylboronic acid with **1** deserves a special comment. *Ferrocenylbodipy **16** was obtained quantitatively in only 10 min* representing the best example of the L-S cross-coupling hitherto documented.

Further elaboration of the products obtained was carried out. Homometathesis[15] of **8** was achieved in 81% (eq 1).[16]



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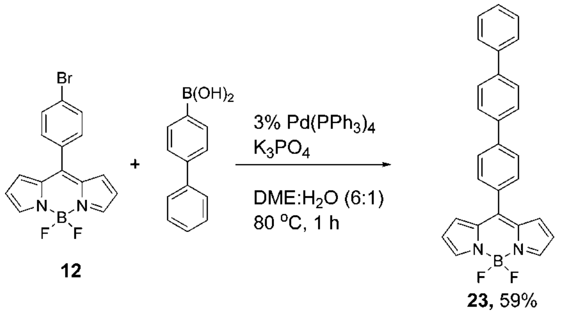
(1)

Likewise, Bodipy **12** smoothly participated in the Suzuki coupling to give **23** in 59% (eq 2).



(2)

In conclusion, we have devised a novel and highly efficient method to prepare 8-substituted Bodipy's that features the following characteristics: (1) it is highly convergent, (2) it does not involve the tedious preparation of the dipyrromethane derivatives, (3) no separate aldehyde synthesis is needed for each analogue, (4) the substituents at the meso-position are not exposed to acid, an oxidation step, or a strong Lewis acid as in the Lindsey method, (5) the method allows for the preparation of a rich variety of highly substituted 8-aryl groups *under neutral conditions* from readily available starting materials and catalysts, (6) the reactions are operationally simple since both starting material and product are brightly colored and in most cases we observed spot-to-spot reactions, (7) it uses nontoxic boronic acids,[17] and (8) the structures of the final products lend themselves to additional elaboration to build more complex derivatives.

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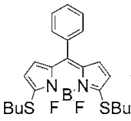
[14] (a) Turbiez, M.; Freré, P.; Allain, M.; Videlot, C.; Ackermann, J.; Roncali, J. *Chem. Eur. J.* **2005**, *11*, 3741. (b) Schwab, P. F. H.; Smith, J. R.; Michl, J. *Chem. Rev.* **2005**, *105*, 1197.

[15] Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

[16] The Bodipy fragments appear in **22** connected to a motif that is present in many relevant nanoarquitectures, see: Tour, J. M. *Chem. Rev.* **1996**, *96*, 537.

[17] For another precedent for the functionalization of the Bodipy core using boronic acids, see: Rohland, T.; Qin, W.; Boens, N.; Dehaen, W. *Eur. J. Org. Chem.* **2006**, 4658. However, it is used to introduce aryl groups at the 3 and 5 positions, uses basic conditions, and takes place *only* upon μ-wave radiation at a high temperature (150 °C) albeit for short periods of time.

[18] We are currently exploring the L-S cross-coupling of 3,5-bis-(butylthio)bodipy **24**,



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prepared by using the method reported in the literature for similar compounds (see ref 16). The results will be reported in due course.

Further functionalization of **2**−**21**, and exploration of the reactivity of **1** with organostannannes, alkylboronic acids, organocuprates, and organozinc derivatives are underway in our laboratory[18] and the results will be reported in due course.

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Supporting Information Available: A complete description of all of the experimental procedures as well as the characterization of all of the compounds in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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