Inorganic Chemistry
Cite This: Inorg. Chem. 2018, 57, 14493−14496
Communication
pubs.acs.org/IC

Lewis-Acid-Catalyzed BODIPY Boron Functionalization Using Trimethylsilyl Nucleophiles

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Supporting Information

ABSTRACT: A novel and straightforward strategy for boron functionalization in boron dipyrromethenes (BODIPYs) is developed. In particular, this synthetic strategy provides new possibilities for the synthesis of sp^2 N-substituted (B-NCS and -NCO), benzotriazole- and trifluoroacetamide-substituted BODIPYs that were hitherto unknown. These new BODIPYs display an array of highly desirable photophysical properties ($0.04 < \Phi_f < 0.86$), paving the road for further investigations in material applications.

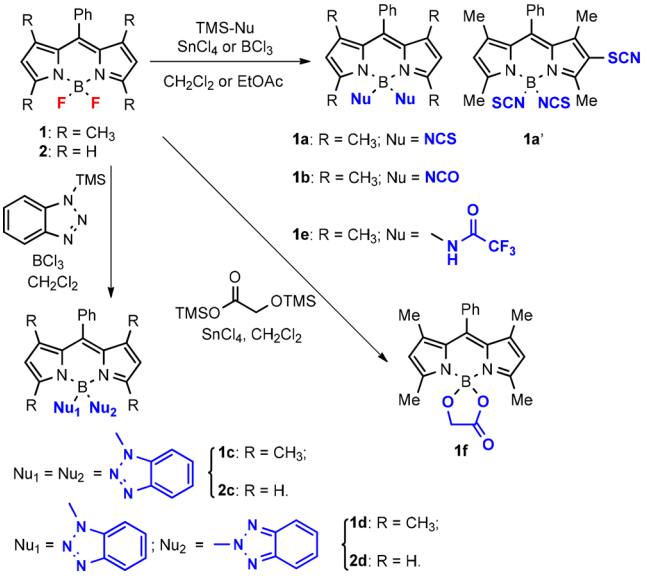
Boron dipyrromethene (BODIPY) dyes have several attractive properties, including high photochemical stability, strong absorption in the visible region, and sharp fluorescence emission with high quantum yields. These make them highly desirable for applications in molecular imaging and therapy, such as in biological labeling[1−3] and photodynamic therapy,[4] and also as fluorescent switches[5] and energy-transfer cassettes.[6] Although a multitude of functionalization reactions at the BODIPY periphery have been reported,[5,7,8] boron functionalization has lagged behind and still remains a challenge. To date, a limited number of BODIPYs substituted with O,[9,10] C (aryl, ethynyl, and ethynylaryl),[11−13] Cl,[14−17] and sp^3 N[18] have been reported. Although these BODIPYs display only slight changes in their absorption and/or emission wavelengths, their aqueous solubility, stability,[19] Stokes shifts, fluorescence quantum yields, and redox properties can be tuned by introducing different substituents on the B atom.

Trimethylsilyl nucleophiles (Me_3Si-Nu or TMS-Nu) possess several advantages, including high chemical stability and low toxicity; they are also easier to handle and have increased solubility in organic solvents compared with proton nucleophiles (HNu). Therefore, the use of TMS-Nu for boron functionalization is a very attractive methodology that allows the preparation, under mild conditions, of functionalized BODIPY derivatives that otherwise could not be synthesized.

In 2008, Burgess and co-workers reported the formation of 4,4′-dicyano-BODIPYs when TMS-CN was used as the nucleophile in S_NAr reactions of C-halogenated BODIPYs, under the catalysis of boron trifluoride or tin(IV) chloride ($SnCl_4$).[20] More recently, our studies revealed that 4,4′-dicyano-BODIPYs showed significantly enhanced stability, particularly toward acidic conditions (excess trifluoroacetic acid),[21] and enhanced fluorescent quantum yields and/or Stokes shifts compared with difluoroboron (BF_2)-substituted BODIPYs.[21,22] On the basis of these published results, we set out to investigate the reactivity of BODIPYs in the presence of other TMS-Nu. It should be noted that the axial functionalization reactions of subphthalocyanines (SubPc-Cl) with O-, C-, S-, and N-based nucleophiles have been investigated. In 2015, Torres et al. demonstrated the reactivity of TMS-Nu toward SubPc-Cl to afford the corresponding O-, N-, and CN-functionalized SubPc compounds.[23] In addition, Nielsen et al. further optimized a milder reaction using trimethylsilyl-capped acetylenes in high yields.[24]

Herein, boron substitution reactions with several commercially available TMS-Nu are investigated for the synthesis of novel BODIPYs bearing a variety of substituents on the B atom (Scheme 1). Lewis acid catalysts ($SnCl_4$ or BCl_3) are employed

Scheme 1. Boron Functionalization Using TMS-Nu



for the simultaneous activation of BF_2 and TMS-Nu, with the formation of volatile TMS-F as the driving force for the reactions.

On the basis of our previous research, we chose to use 4,4′-difluoro-1,3,5,7-tetramethyl-8-phenyl-BODIPY (**1**) as the starting material for the boron functionalization reactions.[21,25] Targeting pseudohalogenated BODIPYs at the B position, we started by using trimethylsilyl isothiocyanate (TMS-NCS) as the nucleophile in the presence of $SnCl_4$ as the Lewis acid

Received: September 28, 2018
Published: November 19, 2018

DOI: 10.1021/acs.inorgchem.8b02775
Inorg. Chem. 2018, 57, 14493−14496

catalyst. Because of its two main resonance structures, the isothiocyanate anion could react to potentially afford the B-NCS or B-SCN-functionalized BODIPYs upon the nucleophilic substitution of F atoms. However, only B-NCS BODIPY (**1a**) was obtained in 95% yield after 20 min of reaction in ethyl acetate, as determined using X-ray diffraction (XRD) analysis (see Figure 1, **1a**). The B atom in **1a** has N_4 coordination with

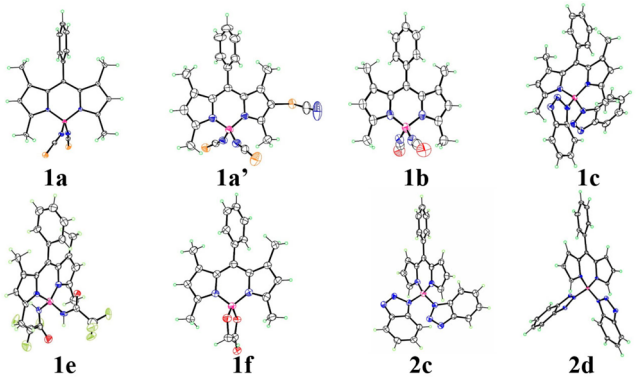
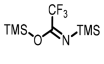
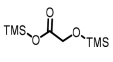


Figure 1. X-ray structures of BODIPYs **1a**, **1a′**, **1b**, **1c**, **1e**, **1f**, **2c**, and **2d** with 50% ellipsoids.

mean B−N distances of 1.524 Å to NCS and 1.532 Å to pyrrole. The central C_3N_2B ring of BODIPY is nearly planar, with a mean deviation of 0.021 Å. The singlet peak at −9.99 ppm in the ^{11}B NMR spectrum of **1a** unambiguously implies disubstitution on the B atom. To the best of our knowledge, this is the first report of a sp^2-N-substituted BODIPY at the B position. Interestingly, when the reaction was performed in a dichloromethane solvent, using 10 equiv of TMS-NCS overnight at room temperature (entry 2, Table 1), the major product obtained was 4,4′-diisothiocyanato-2-thiocyanato-BODIPY (**1a′**) in 41% overall yield. In the structure of **1a′** (Figure 1), the B atom has N_4 coordination with mean B−N distances of 1.517 Å to NCS and 1.531 Å to pyrrole. The central C_3N_2B ring of the BODIPY is nearly planar, with mean deviation of 0.009 Å. Presumably, in the formation of **1a′** using a large excess of TMS-NCS, the nucleophilic substitution reaction takes place first at the B atom, followed by an electrophilic aromatic substitution reaction at the 2 position. Such reactivity at the 2 position has been previously observed by da Silva Emery et al. upon the reaction of BODIPY with oxone and NH_4-SCN.[26] To provide further insight into the reactivity with pseudohalogens, TMS-NCO was selected for a comparison with the TMS-NCS reaction. However, under the catalysis of $SnCl_4$, only a trace amount of the B-NCO product **1b** was formed. However, when the milder Lewis acid catalyst BCl_3 was used instead, the disubstituted BODIPY **1b** was obtained in 43% yield (entry 3, Table 1). Presumably, in this case, **1** was converted into the highly reactive 4,4′-dichloro-BODIPY, which then reacted with TMS-NCO to produce the targeted boron-functionalized BODIPY. For **1b**, in N_4 coordination of the B atom, the mean B−N distances are 1.468 Å to NCO (smaller than in the case of NCS) and 1.546 Å to pyrrole (larger than in the cases of **1a** and **1a′**). The latter larger B−N bond length might be indicative of a lower stability of **1b** relative to **1a**.[25] The central C_3N_2B ring of the BODIPY is nearly planar, with a mean deviation of 0.015 Å.

Table 1. Isolated Yields of B-Substituted BODIPYs after Purification by Chromatography and ^{11}B NMR Chemical Shifts

Entry	BODIPY	TMS-Nu	Lewis Acid	Product (%yield)	^{11}B (ppm)
1	**1**	TMS-NCS	$SnCl_4$	**1a** (95)	-9.99
2	**1**	TMS-NCS (excess)	$SnCl_4$	**1a'** (41)	-10.05
3	**1**	TMS-NCO	BCl_3	**1b** (43)	-7.78
4	**1**		BCl_3	**1c** (25) **1d** (11)	0.42 0.63
5	**2**		BCl_3	**2c** (34) **2d** (14)	0.22 0.16
6	**1**		$SnCl_4$	**1e** (23)	-3.43
7	**1**		$SnCl_4$	**1f** (93)	5.67

Different from the classical "click" reaction using azides and alkynes to achieve the cycloaddition products, the 1-(trimethylsilyl)-1*H*-benzotriazole reagent provides a one-step facile and efficient method for benzotriazole incorporation into molecules. The reaction of **1** with this reagent using BCl_3 as the catalyst resulted in a 25% yield of disubstituted product **1c** and 11% of rearranged product **1d** in which the benzotriazoles are linked via the N1 atom alone or via the N1 and N2 atoms, respectively (entry 4, Table 1). In the case of the less hindered BODIPY **2**, 34% of the product **2c** was obtained along with 14% of the rearranged byproduct **2d**. The structures of boron-functionalized products **1c**, **2c**, and **2d** were unambigously confirmed by XRD (see Figure 1). In the structures of **1c**, **2c**, and **2d**, the B−N (pyrrole) distances have a mean (of 8) value of 1.538 Å, similar to those in **1a** and **1a′**, and a mean B−N (benzotriazole) distance of 1.545 Å. However, unlike the previous structures, the central C_3N_2B ring of BODIPY deviates from planarity, with the B atom lying 0.227 Å (mean of 4) out of the best plane of the other five atoms. In the ^1H NMR spectra of **1c**, the protons on the 3,5-methyl groups are dramatically shifted from 2.56 to 1.63 ppm compared with those of **1**, possibly because of the anisotropic effect of the benzotriazole substituents. The ^{11}B NMR spectra of **1c**, **1d**, **2c**, and **2d** show a singlet between 0.2 and 0.6 ppm, significantly downfiled-shifted from those observed for **1a** and **1b**.

Taking advantage of bis(trimethylsilyl) reagents, cyclic BODIPY compounds can also be readily synthesized. Upon the reaction of **1** with bis(trimethylsilyl)acetamide in the presence of $SnCl_4$ (entry 7, Table 1), the cyclic BODIPY **1f** was synthesized in 93% yield. In comparison with a previous report using dicarboxylic acids under microwave irradiation at 120 °C, our reaction conditions are milder and more efficient.[27] In the structure of **1f**, the mean (of 4 over two molecules) B−N distance is 1.545 Å and the mean B−O distance is 1.475 Å. The central ring of the BODIPY is fairly planar, with a mean deviation of 0.024 Å. In the ^{11}B NMR spectrum of **1f**, a significantly downfield-shifted singlet at 5.7 ppm was observed.

Utilizing *N*,*O*-bis(trimethylsilyl)trifluoroacetamide, the sp^3 N-substituted BODIPY **1e** was also synthesized in moderate yield (entry 6, Table 1). Similar to a previously published N-BODIPY bearing *N*,*N′*-ditosylethylenediamine on the B atom,[18] the strong electron-withdrawing character of the trifluoroacetate

DOI: 10.1021/acs.inorgchem.8b02775
Inorg. Chem. 2018, 57, 14493−14496

substituents on the amine reduces the electron-donating ability of the N atoms, thus stabilizing N-BODIPY. In the eight independent molecules of **1e**, the mean B−N (pyrrole) distance is 1.556 Å and the mean B−N (amide) distance is 1.526 Å. The conformation of the central C_3N_2B ring of BODIPY is intermediate between the fairly planar ones found in **1a**, **1a′**, **1b**, and **1f** and those in the benzotriazole compounds, with the B atom significantly out of the plane. The out-of-plane deviation of the B atom is smaller here, with a mean value (of 8) of 0.103 Å. In each molecule, one of the trifluoroacetamide ligands has its NH pointing inward, while the other presents its O atom inward, forming an intramolecular N−H···O hydrogen bond. The mean N···O distance over the eight molecules is 2.783 Å.

The spectroscopic properties of all BODIPYs in tetrahydrofuran (THF) were evaluated, and the results are shown in Table 2. Similar to **1**, strong absorptions at around 505 nm were observed for the boron-functionalized BODIPYs, and fluorescence emission maxima were in the range 510−522 nm. On the other hand, the relative fluorescence quantum yields varied dramatically, with **1a′** displaying the highest quantum yield (0.86) and **2c** the lowest (0.04). The significantly decreased fluorescence quantum yield observed for BODIPYs **1c**/**2c** and **1d**/**2d** is likely due to the nonradiative decay of the free-rotating benzotriazole substituents on the B atom. Furthermore, enhancement in the fluorescence quantum yield was observed for the B-NCS and B-NCO BODIPYs **1a** and **1b** compared with the BF_2-BODIPY **1**, suggesting that these compounds could be further used in fluorescence-labeling applications. As shown in Figure S31, the calculated highest occupied molecular orbital (HOMO)−lowest unoccupied molecular orbital (LUMO) gaps for the boron-functionalized BODIPY derivatives decrease in the order **1a′** > **1b** > **1a** ≈ **1c** ≈ **1e** ≈ **1f**. This trend is in agreement with the experimental spectroscopic results. The presence of an electron-withdrawing −SCN group on the 2 position of **1a′** results in the lowest HOMO and LUMO energies of this series of compounds.

Table 2. Spectroscopic Properties of BODIPYs in THF at Room Temperature

BODIPY	λ_{abs}^{max} (nm)	ε (L mol^{-1}cm^{-1})	λ_{emi}^{max} (nm)	Φ_f	Stokes shift (nm)
1	501	47100	512	0.37	11
1a'	497	38000	510	0.86	13
1a	505	69200	516	0.48	11
1b	502	74100	513	0.48	11
1c	506	25700	517	0.08	11
1d	506	25100	517	0.11	11
1e	505	51300	515	0.48	10
1f	505	77600	515	0.23	10
2c	506	14100	522	0.04	16
2d	506	14800	520	0.13	14

In summary, a one-step synthesis of novel B-substituted BODIPYs is described using commercially available TMS reagents. The novel B-substituted BODIPYs have desirable structural and photophysical characteristics that warrant their further investigation for potential applications in bioconjugation, fluorescence labeling, and metal sensing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.8b02775.

Synthetic procedures, ^{1}H, ^{13}C, and ^{11}B NMR spectra, and crystallographic and density functional theory data (PDF)

Accession Codes

CCDC 1856888−1856890, 1856892−1856894, 1864131, and 1865862 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (Grant CHE 1800126).

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DOI: 10.1021/acs.inorgchem.8b02775
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