

Conjugate-like addition of soft nucleophiles to 8-alkenylBODIPYs

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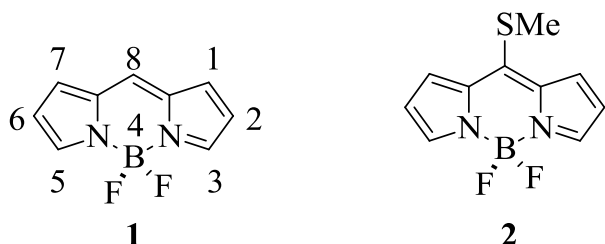
Abstract

Meso-phenylethenylBODIPY **8** was prepared using the Liebeskind-Srogl cross-coupling reaction. The reactivity of **8** was evaluated in the addition of soft nucleophiles observing that, in all the cases studied, the addition took place exclusively at the β -alkene position with good chemical yields under mild conditions. While the starting BODIPY **8** was non-emissive, all of the adducts were highly fluorescent in MeOH, except for *meso*-coumarinBODIPY **11**. However, when the fluorescence of **11** was measured in EtOAc, a 41-fold increase was observed. This behaviour was explained in terms of a photoinduced electron-transfer phenomenon. Copyright © 2018 VBRI Press.

Keywords: BODIPY, *meso*-alkenylBODIPY, conjugate addition, fluorescence

Introduction

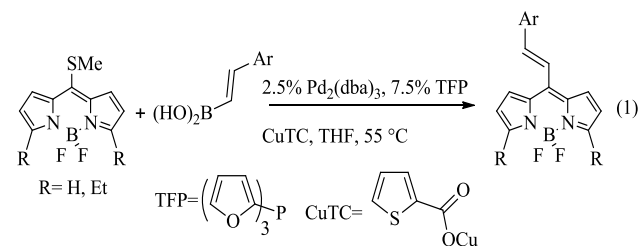
Borondipyrromethenes (BODIPYs) **1**, [1] are a type of fascinating small molecules.



They possess several chemical and photophysical [2] properties that render them amenable for numerous applications. [3][4] In addition to having narrow absorption and emission bands, some have high quantum yields (Φ), and excellent solubility in most organic solvents. Moreover, there are many chemical transformations that can be carried out at the different BODIPY positions thereby controlling not only the emission properties, but also their solubility, even in water. The typical preparation involved and acid-catalyzed condensation of pyrrole with an aromatic aldehyde, followed by DDQ oxidation of the intermediate dipyrromethane, and finally, treatment of the resulting dipyrin with $\text{BF}_3\text{-OEt}_2$ in the presence of triethylamine. [5] In 2006, Biellmann et al. [6] reported the synthesis, photophysical properties, and preliminary reactivity of 8-methylthioBODIPY **2**. Over the last ten years, our group has demonstrated that such compound is a privileged building block. We have shown that **2** engages in completely new modes of reaction through which novel derivatives, with previously unknown

properties, have been prepared. Thus, BODIPY **2** can react with: boronic acids, organostannanes, organozinc derivatives, alcohols, phenols, 1,3-dicarbonyl compounds, amines, phosphines, carbohydrates, polyarylamines [7].

Using the so-called Liebeskind-Srogl cross-coupling reaction, [8] we reported the preparation of a family of 8-alkenylBODIPYs (eq. 1). [9]



These compounds have interesting optical properties. When there is a Csp^2 directly connected to the 8-position, the chromophore is non-emissive, however, when there is a Csp^3 at the same position, the product displays very highly intense fluorescence (Fig. 1).

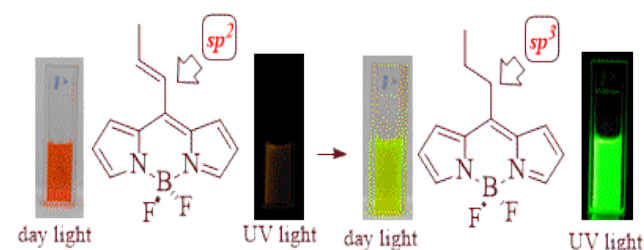


Fig. 1. Changes in the optical properties of the BODIPY core with the substituent at the 8-position.

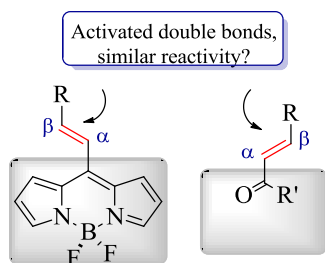


Fig. 2. Similarity in the reactivity of activated double bonds.

We reasoned that the double bond at the 8-position of the BODIPY core would behave as an activated double bond, just like that of an α,β -unsaturated ketone (Fig. 2).

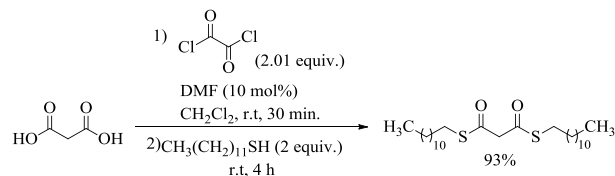
Knowing that there are many biologically important nucleophiles, we set out to investigate the addition of soft nucleophiles to the β -position of 8-alkenylBODIPYs. It was also anticipated that, upon addition, the initially non-emissive chromophores, would display high fluorescence.

Experimental

General Methods. ^1H and ^{13}C NMR spectra were recorded on a 200 or 500 MHz spectrometers in deuteriochloroform (CDCl_3) or $(\text{CD}_3)_2\text{CO}$ with either tetramethylsilane (TMS) (0.00 ppm ^1H , 0.00 ppm ^{13}C), chloroform (7.26 ppm ^1H , 77.160 ppm ^{13}C)¹ or acetone (2.17 ppm ^1H , 29.840 ppm or 206.260 ppm)¹ as internal reference. Data are reported in the following order: chemical shift in ppm, multiplicities (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), exch (exchangeable), app (apparent)), coupling constants, J (Hz), and integration. IR peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium 40-67%), and w (weak 20-40%).

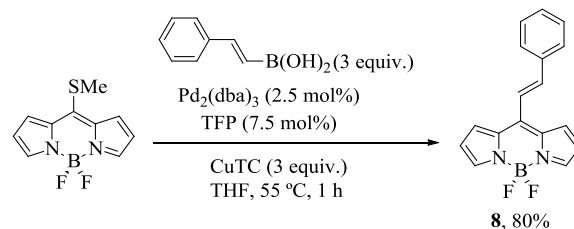
8-Methylthiobodipy, [6] and CuTC,[10] were prepared according to the literature procedures. The other reactants, ligands, and catalysts were commercially available.

Synthesis of *S, S*-didodecyl propanebis(thioate)



By adaption of a procedure by Fukuyama *et al.*, [11] to a solution of malonic acid (120.7 mg, 1.1600 mmol, 1.00 equiv.) in CH_2Cl_2 (3.0 mL) was added oxalyl chloride (200 μL , 2.3319 mmol; 2.01 equiv.) and DMF (9 μL , 0.1160 mmol, 10 mol%). The solution was stirred for 30 min at r.t., and to this solution was added 1-dodecanethiol (556 μL , 2.3200 mmol, 2 equiv.). After stirring for 4 h at r.t., the reaction mixture was adsorbed on SiO_2 -gel. After flash-chromatography (SiO_2 -gel, 3:97 EtOAc/hexanes) purification, gave the thiol ester as a colorless oil (1.0786 mmol, 510 mg); yield = 93%; TLC (3:97 EtOAc/Hexanes

$R_f = 0.4$); IR (KBr, cm^{-1}): 2924 (s), 2853 (s), 1702 (s), 1678 (s), 1465 (m), 1409 (w), 1378 (w), 1282 (m), 1190 (w), 1062 (m), 1043 (m), 989 (m), 920 (w), 722 (w), 675 (w), 642 (m), 569 (w); ^1H NMR (500 MHz, CDCl_3) δ 3.75 (s, 2H), 2.90 (t, $J = 7.4$ Hz, 4H), 1.60 – 1.54 (m, 4H), 1.35 – 1.24 (m, 36H), 0.86 (t, $J = 6.9$ Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 190.74, 57.90, 32.02, 29.74, 29.67, 29.57, 29.46, 29.28, 29.18, 28.88, 22.79, 14.21; HRMS (ESI⁺): m/z calcd. for $\text{C}_{27}\text{H}_{53}\text{O}_2\text{S}_2$ $[\text{M}+\text{H}]^+$, 473.3481; found 473.3472.

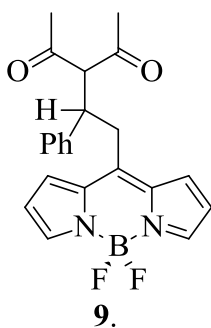


BODIPY 8. According to procedure reported in the literature.[9] An oven-dry Schlenk tube, equipped with a stir bar, was charged with *trans*-2-Phenylvinylboronic acid (1.2600 mmol, 186.5 mg, 3 equiv.), 8-Methylthiobodipy (0.4200 mmol, 100 mg, 1 equiv.) and dry THF (4.2 mL) under N_2 . The stirred solution was sparged with N_2 for 10 min, whereupon Copper(I) thiophene-2-carboxylate (1.2600 mmol, 240.3 mg, 3 equiv), $\text{Pd}_2(\text{dba})_3$ (0.0105 mmol, 9.6 mg, 2.5 mol%), and Tri(2-furyl)phosphine (0.0315 mmol, 7.3 mg, 7.5 mol%) were added under N_2 . The reaction mixture was immersed into a pre-heated oil bath at 55 $^\circ\text{C}$. After 1 hour, the reaction mixture was allowed to reach room temperature and was adsorbed on SiO_2 -gel. After flash-chromatography (SiO_2 -gel, 1:4 EtOAc/hexanes) purification, compound **1** was obtained as a cherry solid (0.3400 mmol, 100 mg); yield = 80%; ^1H NMR (300 MHz, CDCl_3): δ 7.85 (s, 2H), 7.61-7.58 (m, 2H), 7.44-7.41 (m, 5H), 7.32 (d, $J = 4\text{Hz}$, 2H), 6.52 (d, $J = 3\text{Hz}$, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.80, 143.84, 143.07, 135.66, 133.95, 130.63, 129.26, 128.39, 128.09, 121.24, 117.97.

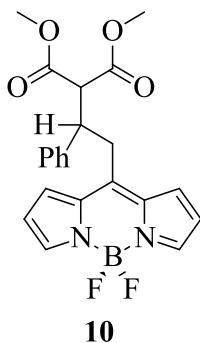
General Procedure for Synthesis of Michael-adducts.

In a bottom flask, equipped with a stir bar, was charged with **1** (0.0680 mmol, 20 mg, 1 equiv.), the corresponding Michael donor (5 equiv.) and 2.3 mL of CH_3CN . Next, Triethylamine (5 equiv., except for KCN) was added to the solution and the mixture was stirring to room temperature. After TLC showed that the reaction went to completion, 5 mL of H_2O were added, the organic layer was extracted with EtOAc (3 x 10 mL), the organic phases were combined and washed with brine (2x10 mL). After, the organic phase was dried over MgSO_4 anhydrous to be filtered and concentrated in vacuo. The residue was re-dissolved in EtOAc and was adsorbed on SiO_2 -gel. After flash-chromatography (SiO_2 -gel, EtOAc/hexanes gradient) purification, Michael adducts were obtained as colored solids. For purposes of characterization, the solid product was crystallized from CH_2Cl_2 /petroleum ether.

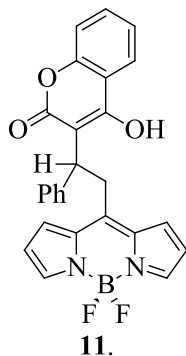
Adduct 9. According to (GP): **1** (0.0680 mmol, 20 mg, 1 equiv.), Acetylacetone (0.3400 mmol, 35 μ L, 5 equiv.) and 2.3 mL of CH_3CN . Next, Triethylamine (0.3400 mmol, 47 μ L, 5 equiv.). The product was isolated as an orange solid (0.0406 mmol, 16.0 mg); yield = 60%; TLC (1:1 EtOAc/Hexanes R_f = 0.4); mp = 203 - 205 $^\circ\text{C}$; IR (KBr, cm^{-1}): 1699 (m), 1572 (m), 1413 (w), 1393 (m), 1359 (w), 1263 (m), 1193 (w), 1116 (m), 1083 (m), 950 (w); ^1H NMR (200 MHz, CDCl_3) δ 7.75 (s, 2H), 7.20 - 7.05 (m, 5H), 6.98 - 6.93 (m, 2H), 6.39 (dd, J = 4.1 Hz, J = 1.4 Hz, 2H), 4.44 (d, J = 11.6 Hz, 1H), 3.96 (td, J = 11.2 Hz, J = 3.5 Hz, 1H), 3.24 (dd, J = 12.0 Hz, J = 3.5 Hz, 1H), 2.72 (dd, J = 11.9 Hz, J = 11.0 Hz, 1H), 2.37 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 203.20, 201.96, 146.27, 143.95, 138.53, 135.90, 129.29, 128.98, 128.19, 128.15, 118.31, 75.56, 48.42, 37.31, 31.34, 28.15; HRMS (ESI+): m/z calcd. for $\text{C}_{22}\text{H}_{21}\text{B}_1\text{F}_2\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$, 417.1560; found 417.1567.



Adduct 10. According to (GP): **1** (0.0680 mmol, 20 mg, 1 equiv.), Dimethyl malonate (0.3400 mmol, 47 μ L, 5 equiv.) and 2.3 mL of CH_3CN . Next, Triethylamine (0.3400 mmol, 48 μ L, 5 equiv.). The product was isolated as an orange solid (0.0340 mmol, 14.5 mg); yield = 50%; TLC (1:2 EtOAc/Hexanes R_f = 0.3); mp = 195 - 196 $^\circ\text{C}$; IR (KBr, cm^{-1}): 1752 (w), 1731 (m), 1566 (m), 1413 (w), 1413 (w), 1392 (m), 1262 (m), 1232 (m), 1114 (m), 1083 (m), 953 (w); ^1H NMR (300 MHz, CDCl_3) δ 7.74 (s, 2H), 7.19 - 7.10 (m, 5H), 7.03 - 7.00 (m, 2H), 6.39 (dd, J = 4.2 Hz, J = 1.6 Hz, 2H), 3.99 (d, J = 10.7 Hz, 1H), 3.91 - 3.81 (m, 4H), 3.52 (dd, J = 12.3 Hz, J = 3.7 Hz, 1H), 3.43 (s, 3H) 2.93 (dd, J = 12.2 Hz, J = 10.8 Hz, 1H). ^{13}C NMR (50 MHz, CDCl_3) δ 168.96, 167.59, 146.55, 143.71, 138.47, 135.72, 128.96, 128.75, 127.89, 127.83, 118.10, 118.07, 57.14, 53.22, 52.74, 48.95, 36.40; HRMS (ESI+): m/z calcd. for $\text{C}_{22}\text{H}_{21}\text{B}_1\text{F}_2\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$, 449.1459; found 449.1471.

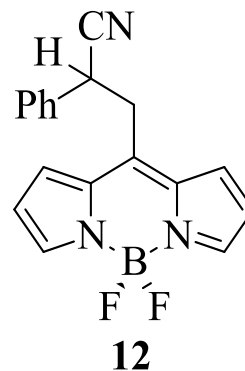


Adduct 11. According to (GP): **1** (0.0680 mmol, 20 mg, 1 equiv.), 4-Hydroxycoumarin (0.1700 mmol, 27.6 mg, 2.5 equiv.) and 2.3 mL of CH_3CN . Next, Triethylamine (0.1700 mmol, 24 μ L, 2.5 equiv.). The product was isolated as an orange solid (0.0548 mmol, 25 mg); yield = 81%; TLC (2:1 EtOAc/Hexanes R_f = 0.7); mp = 213 - 215 $^\circ\text{C}$; IR (KBr, cm^{-1}): 3306 (m), 2924 (m), 1681 (w), 1611 (w), 1471 (w), 1413 (w), 1393 (m), 1359 (w), 1263 (m), 1193 (w), 1116 (m), 1083 (m), 950 (w); ^1H NMR (200 MHz, CDCl_3) δ 7.75 (s, 2H), 7.20 - 7.05 (m, 5H), 6.98 - 6.93 (m, 2H), 6.39 (dd, J = 4.1 Hz, J = 1.4 Hz, 2H), 4.44 (d, J = 11.6 Hz, 1H), 3.96 (td, J = 11.2 Hz, J = 3.5 Hz, 1H), 3.24 (dd, J = 12.0 Hz, J = 3.5 Hz, 1H), 2.72 (dd, J = 11.9 Hz, J = 11.0 Hz, 1H), 2.37 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3) δ 203.20, 201.96, 146.27, 143.95, 138.53, 135.90, 129.29, 128.98, 128.19, 128.15, 118.31, 75.56, 48.42, 37.31, 31.34, 28.15; HRMS (ESI+): m/z calcd. for $\text{C}_{22}\text{H}_{21}\text{B}_1\text{F}_2\text{N}_2\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$, 417.1560; found 417.1567.

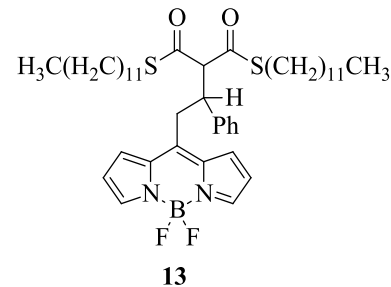


1622 (i), 1568 (i), 1411 (m), 1394 (i), 1263 (i), 1215 (m), 1200 (m), 1116 (i), 1082 (i), 1069 (i), 955 (m), 754 (m); ^1H NMR (500 MHz, Acetone) δ 7.94 (d, J = 8.0 Hz, 1H), 7.81 (s, 2H), 7.62 - 7.54 (m, 3H), 7.47 (d, J = 3.8 Hz, 2H), 7.34 - 7.18 (m, 5H), 6.52 (d, J = 4.1 Hz, 2H), 5.09 - 5.01 (m, 1H), 4.24 - 3.89 (m, 2H); ^{13}C NMR (126 MHz, Acetone) δ 162.53, 161.60, 153.74, 150.82, 150.79, 144.37, 143.18, 136.71, 136.69, 132.94, 129.71, 129.01, 128.93, 127.47, 124.73, 123.80, 118.73, 118.71, 117.23, 116.66, 108.42, 108.40, 45.00, 33.40; HRMS (ESI+): m/z calcd. for $\text{C}_{26}\text{H}_{19}\text{B}_1\text{F}_2\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, 479.1354; found 479.1353.

Adduct 12. According to (GP): **1** (0.0680 mmol, 20 mg, 1 equiv.), Potassium cyanide (0.1020 mmol, 6.7 mg, 1.5 equiv.). The product was isolated as an orange solid (0.0591 mmol, 19.0 mg); yield = 87% ^1H -NMR (200 MHz, CDCl_3) δ 7.88 (s, 2H), 7.42-7.27 (m, 5H), 7.09 (d, J = 4Hz, 2H), 6.51 (d, J = 4Hz, 2H), 4.18-4.11 (m, 1H), 3.60-3.50 (m, 1H), 3.37-3.27 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3) δ 145.39, 142.17, 135.51, 134.38, 129.80, 129.38, 128.60, 127.58, 119.57, 119.15, 40.30, 37.28.[12]



Adduct 13. According to (GP): **1** (0.0680 mmol, 20 mg, 1 equiv.), *S,S*-didodecyl propanebis(thioate) (0.1700 mmol, 80.4 mg, 2.5 equiv.) and 2.3 mL of CH_3CN . Next, Triethylamine



(0.1700 mmol, 24 μ L, 5 equiv.). The product was isolated as a red solid (0.0340 mmol, 14.5 mg); yield = 88%; TLC (1:2 EtOAc/Hexanes R_f = 0.3); mp 190 - 191 $^\circ\text{C}$; IR (KBr, cm^{-1}): 2922 (s), 2852 (s), 1684 (s), 1572 (s), 1485 (w), 1468 (w), 1455 (w), 1412 (m), 1398 (m), 1358 (w), 1266 (m), 1232 (w), 1197 (m), 1124 (s), 1090 (s), 1037 (m), 953 (m), 774 (w), 765 (w), 755 (w) 699 (w); ^1H NMR (500 MHz, CDCl_3) δ 7.72 (s, 2H), 7.14 - 6.98 (m, 7H), 6.37 (dd, J = 4.2 Hz, J = 1.6 Hz, 2H), 4.44 (d, J = 11.3 Hz, 1H), 4.05 (td, J = 11.5 Hz, J = 3.1 Hz, 1H), 3.31 (dd, J = 12.4, J = 3.2 Hz, 1H), 3.07 (t, J = 7.4 Hz, 2H), 2.87 (t, J = 12.0 Hz, 1H), 2.72 - 2.61 (m, 2H), 1.69 - 1.61 (m, 2H), 1.43 - 1.37 (m, 2H), 1.31 - 1.05 (m, 38H), 0.88 (t, J = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 193.42, 191.38, 146.29, 143.67, 137.61, 135.67, 128.89, 128.65, 128.13, 127.82, 118.10, 118.09, 73.63, 50.10, 36.10, 32.05, 30.25, 29.77, 29.72, 29.69, 29.62, 29.52, 29.48, 29.35, 29.22, 29.09, 28.99, 28.93, 28.45, 22.83, 14.26; HRMS (ESI+): m/z calcd. for $\text{C}_{44}\text{H}_{65}\text{B}_1\text{F}_2\text{N}_2\text{O}_2\text{S}_2\text{Na}$ $[\text{M}+\text{Na}]^+$, 789.4448; found 789.4421.

Results and discussion

The set of soft pro-nucleophiles chosen for this work are shown in **Fig. 3**.

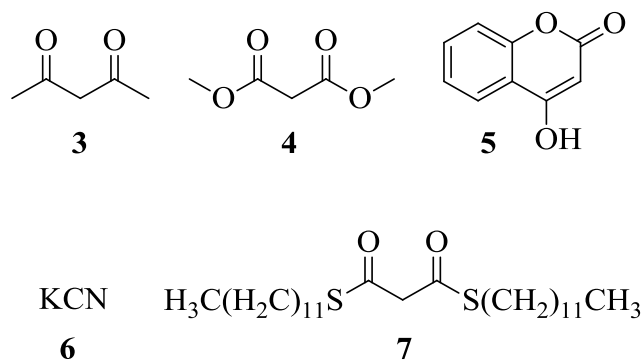
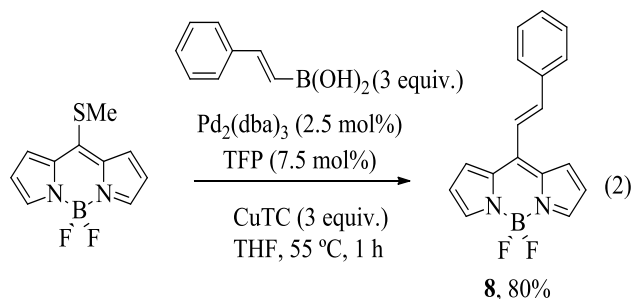


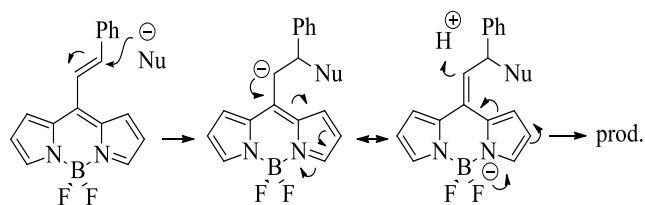
Fig. 3. Pro-nucleophiles studied

BODIPY **8** was prepared according to the literature procedure (eq. 2).[9]



With BODIPY **8** available, we proceeded to carry out the addition of nucleophiles **3-7**. The results are illustrated in **Table 1**.

The conjugate-like nucleophilic addition took place smoothly at rt to yield the expected adducts **9-13**. Our hypothesis borne out, in all the cases studied, the nucleophile added exclusively to the β -position of BODIPY **8**. The chemical yields ranged from medium to good, with excellent reaction times. The regiochemistry of the addition can be explained in terms of the resonance stabilization by the BODIPY core, of the negative charge that develops on the α -C atom, after the addition takes place (Scheme 1).



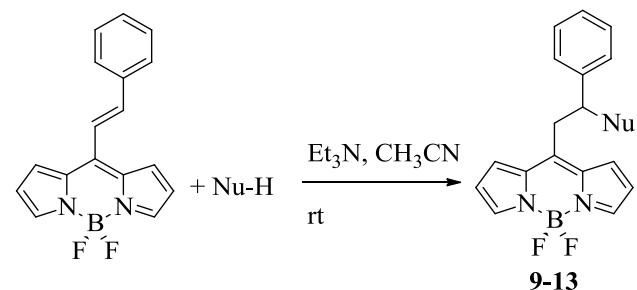
Scheme 1. Resonance stabilization of the negative charge on the α -C atom upon nucleophilic addition.

Table 1. Conjugate-like addition of soft nucleophiles on 8-phenylethynylBODIPY **8**.

Entry	Nu-H	Product/ % yield ^a	Reaction time
1	3	 9 , 60%	1 h
2	4	 10 , 50%	1.5 h
3	5	 11 , 81%	15 min
4	6	 12 , 87%	1 h ^b
5	7	 13 , 88%	30 min

^aReaction conditions: BODIPY **8** (1 equiv.), Nu-H (5 equiv.), Et₃N (5 equiv.).

^bIn the case of the addition of KCN (1.5 equiv.), no Et₃N was added.



The photophysical properties of the products are shown in **Table 2**.

Table 2. Photophysical Properties for all the Michael-adducts.^a

Comp	λ_{ab} (nm)	λ_{em} (nm)	Φ_F (%)	Stokes shift/ (cm^{-1})	$\log \epsilon_{max}$ / ($\text{M}^{-1}\text{cm}^{-1}$)
9	497	508	80.9	436	4.95
10	497	508	80.7	436	4.94
11	494 494 ^b	503 509	1.6 65.6	362 596	4.93 5.47
12	502	514	74.9	465	4.99
13	498	509	82.9	434	5.22
1	498	507	80.8 ¹³	356	5.02
8	410, 513	524	-----	5306, 409	-----

^aMeasured in MeOH at a concentration of 1×10^{-6} M. λ_{ab} = absorption maximum, λ_{em} = emission maximum, Φ_F = fluorescence quantum yield estimated by using parent borondipyrromethene **1** system (Φ_F = 80.8% in EtOAc) as the standard.[13]

^bMeasured in EtOAc

Both the absorption and emission spectra of **8**, show significant differences from those of the adducts **9-13**. The UV-Vis spectrum of **8** shows two absorption bands at 410 and 513 nm, whereas that of the adducts show a main band at around 500 nm. However, the absorption spectra of products **9-13** do not display major differences among them (Figure S1). For example, adducts **9,10** and **13**, having a 1,3-dicarbonyl substituent (diketone, diester, and dithioester, respectively) at the BODIPY 8-position, present optical properties practically identical (**Table 2**). This seems to indicate that none of the 1,3-dicarbonyl substituents affect the optical properties of the BODIPY core. The quantum yield (Φ) of adducts **9, 10**, and **13** is high and comparable to that of the parent BODIPY **1** (80.8%).

To determine the influence of the different meso-substituents, the absorption and emission spectra of **10, 11** and **12** were compared to those of the parent BODIPY [13] (Figure S2). The absorption bands of adducts **10** and **11** present a hypsochromic shift of 1 and 3 nm, respectively, with respect to the parent BODIPY **1**, whereas **12** presents a bathochromic shift of 4 nm.

The emission band of **10** presents a bathochromic shift of 1 nm. On the other hand, **11** presents a hypsochromic shift of 4 nm when measured in MeOH, but, when measured in EtOAc, a bathochromic shift of 2 nm is observed. Finally, **12** shows a bathochromic shift of 7 nm with respect to the emission band of **1**.

Noteworthy is the observation that the quantum yield of **11** in EtOAc is 41-fold larger than when measured in MeOH. The reduction in the fluorescence may occur via a photoinduced electron-transfer (PET) process. It is reported that in PET three-component systems

(fluorophore-spacer-receptor), the receptor interaction with H^+ inhibits the PET phenomenon (Figure S3).[14] In analogy, it is proposed that the diminished fluorescent emission of **11** may occur via the mechanism shown in **Fig. 4**. In the present case, the PET may arise when the coumarin hydroxyl group forms a hydrogen bond with MeOH thereby developing a partial positive charge.

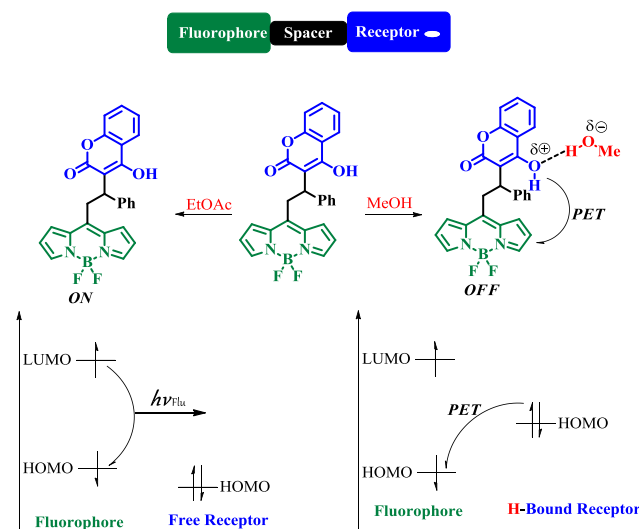


Fig. 4. Possible mechanism for the ON-OFF fluorescence mechanism of **11**.

Conclusion

Nucleophilic addition of five soft nucleophiles was carried out on 8-phenylethenylBODIPY **8**. This reaction took place smoothly at rt with medium to high chemical yields, and with complete regioselectivity for the β -alkenyl position. We have demonstrated that indeed, such position is electrophilic, similar to that of an α,β -unsaturated carbonyl compound. As expected, all the adducts, except for **11**, were highly fluorescent in MeOH. However, when measured in EtOAc, the quantum yield of **11** increased 41-fold.

Finally, it was concluded that neither 1,3-dicarbonyl nor CN^- moieties perturb the optical properties of the BODIPY core.

Acknowledgements

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Author's contributions

Conceived the plan: E. P.-C.; Performed the experiments: E. A.-M.; Data analysis: E. P.-C., E. A.-M; Wrote the paper: E. P.-C., E. A.-M. Authors have no competing financial interests.

Supporting information

Supporting informations are available from VBRI Press.

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