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Synthesis and Substitution of 8-(4,6-Dichloropyrimidin-5-yl)-BODIPY

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meso-Dichloropyrimidyl-BODIPY dyes are readily substituted by nucleophiles or through palladium-catalysed coupling reactions, while retaining excellent quantum yields of fluorescence.

Introduction

Although the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (better known under its commercial name "BODIPY") fluorophore has been known since 1968, there has been tremendous growth in research into this interesting dye in recent years.[1] Dyes of this class currently enjoy great popularity because of their photostabilities, relatively high fluorescence quantum yields Φ_f and molar absorption coefficients $\varepsilon(\lambda)$.

This recent rise in popularity of the BODIPY fluorophore has sparked research directed towards reactive dyes for convenient labelling and modification of the dye. Of the several approaches used, here we mention only those based on the reactivity of acidic 3,5-methyl groups,[2] sulphide-substituted dyes[3] and a range of halogenated structures.[4]

In the course of our research we have reported on the reactivities of 3,5-dihalogenated BODIPY dyes. These products can be elaborated both by nucleophilic aromatic substitution,[5] with a wide range of nucleophiles, and by palladium-catalysed coupling reactions.[6] The introduction of these new substituents directly on the fluorescent system profoundly changes the spectral properties of the fluorophore.[7] Although this can be beneficial for several photophysical applications, as well as for the introduction of large bathochromic shifts in the UV/Vis absorption and fluorescence spectra of the compounds, some drawbacks must also be acknowledged. The introduction of nucleophiles on the dye often leads, for example, to decreased fluorescence quantum yields (Φ_f) or lowered stabilities.[7a] It can therefore be desirable to introduce a functionality that exhibits similar reactivity, but at the *meso*-position, where substitution should have no direct influence on the spectroscopic properties.

Here we report the synthesis of BODIPY dyes substituted at their *meso*-positions with a 4,6-dichloropyrimidine subunit. This moiety has previously been used by us in several research projects and has proved its reactivity towards nucleophiles and transition-metal-catalysed coupling reactions.[8]

Results and Discussion

Synthesis

meso-(4,6-Dichloropyrimidin-5-yl)-BODIPY compounds were conveniently prepared by established procedures[1] (Figure 1). Starting from commercially available 4,6-dihydroxypyrimidine (**1**) we were able to obtain the dichlorinated pyrimidinealdehyde **2** in good yield by a previously published procedure.[9] Acid-catalysed condensations of this aldehyde with the selected pyrroles **3a**–**d** yielded the dipyrromethanes **4a**–**d**. The unsubstituted dipyrromethane **4a** can also be prepared by a previously reported method.[10] This method employs only 3 equiv. of pyrrole and water as the solvent, in contrast to the standard procedure, in which pyrrole is the solvent. In the case of an α-substituted-pyrrole, polycondensation is not an issue, and the commercially available 2,4-dimethylpyrrole (**3b**) can undergo the condensation under trifluoroacetic acid (TFA) catalysis conditions in dichloromethane. The other α-substituted pyrroles, **3c** and **3d**, can be obtained through Trofimov reactions, which furnish the pyrroles in single-step fashion with moderate yields and potential for large-scale reactions.[11]

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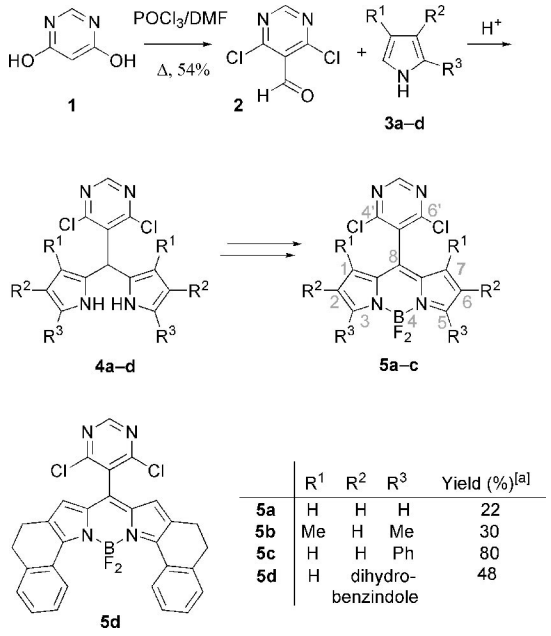


	R1	R2	R3	Yield (%)[a]
5a	H	H	H	22
5b	Me	H	Me	30
5c	H	H	Ph	80
5d	H	dihydro-benzindole		48

Figure 1. Synthesis of **8**-(4,6-dichloropyrimidin-5-yl)-BODIPY. [a] Overall yields from **2**.

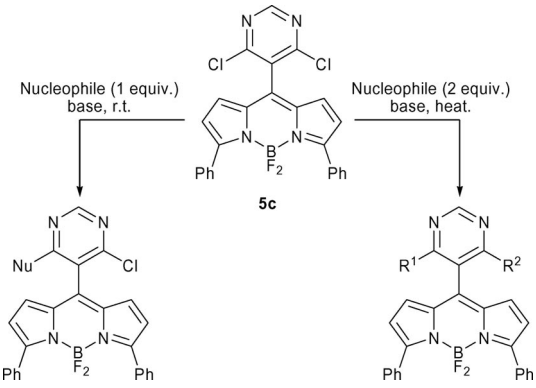
These dipyrromethanes **4a**–**d** were then oxidized to the corresponding dipyrromethenes with DDQ. In a final step, the dipyrromethenes were complexed with boron trifluoride by treatment with triethylamine in dichloromethane. These entire sequences could also be performed in one-pot procedures with fair to good yields. The desired BODIPY dyes **5a**–**d** can then be purified by flash column chromatography and crystallization.

Nucleophilic Substitution

We initially applied this protocol to 2,4-dimethylpyrrole (**3b**), which resulted in the 1,3,5,7-tetramethyl-substituted BODIPY **5b**. We then treated this compound with several nucleophiles under a wide range of conditions to test its reactivity in nucleophilic aromatic substitution. Almost no reaction could be observed, however, and it was only after several hours in DMF at elevated temperatures that we were able to observe substitution by thiophenol. After disappearance of the starting material, only a 15% yield of the monosubstituted product **6** could be recovered. This might be caused by steric hindrance by the 1- and 7-methyl groups, which might disfavour the transition state of the nucleophilic attack. To test this hypothesis, we decided to continue work with the 1,7-unsubstituted compounds **5c** and **5d**.

With the 3,5-diphenyl dye **5c** as a model system, substitution with several nucleophiles was examined, and immediate incorporation of these nucleophiles with excellent yields could be observed (Table 1). Most reactions proceeded with superb yields, and spectroscopically pure samples could be obtained after flash column chromatography or recrystallization. Substitutions with phenol were carried out in DMF with 18-crown-6 as a catalyst, to yield both the monosubstituted **7** and the disubstituted product **8**. Similar yields were obtained for substitution with 2-naphthol to afford dye **9**. The crown ether catalyst was not necessary with the sulfur nucleophile thiophenol **10**. Again, use of longer reaction times and more nucleophile led to the disubstituted product **11**. Nitrogen-centred nucleophiles such as aniline and piperidine did not react under the conditions described here.

Table 1. Nucleophilic substitutions on 3,5-diphenyl-BODIPY **5c**.



Product	R1	R2	Conditions[a]	Time [h]	Yield[b]
7	OPh	Cl	A	16	98
8	OPh	OPh	A	60	85
8	OPh	OPh	B	4	96
9	ONaphth	ONaphth	B	4	75
10	SPh	Cl	A	4	93
11	SPh	SPh	A	40	91
11	SPh	SPh	B	1	93
12	OPh	SPh	B	1	80
13	OPh	SMe	A	20	94

[a] Conditions: A) room temp., DMF; B) 100 °C, DMF. [b] Isolated yields for a 0.2 mmol reaction.

Aliphatic oxygen nucleophiles (methoxide and ethoxide) showed only limited reactivity resulting in sluggish reactions, and no product could be isolated.

We were also able to perform nonsymmetric substitutions by adding a second nucleophile after the completion of the first substitution, which could be followed by thin-layer chromatography. Thus, after complete substitution with phenol, addition of an equivalent of thiophenol or sodium thiomethoxide resulted in the nonsymmetrically substituted dyes **12** and **13**.

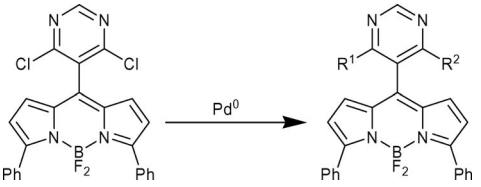
At room temperature the developed method is very mild, but takes 16 to 60 hours. Gentle heating of the reaction mixtures speeded up the reactions and all were complete in a few hours. Heating to 100 °C also allowed the disubstituted products to be obtained within acceptable reaction times. It is noteworthy that the first substitution lowers the reactivity of the remaining chlorine significantly. In the presence of 1 equiv. of nucleophile only monosubstituted product was observed.

Palladium-Catalysed Reactions

We next turned our attention to palladium-catalysed coupling reactions (Table 2). On trying to apply the Suzuki protocol under standard conditions we saw very slow reac-

tions, and it was only after several hours at elevated temperatures that coupling began to be observed. To get the reactions to acceptable speeds, rather large amounts of catalyst had to be used.

Table 2. Palladium-catalysed substitutions on 3,5-diphenyl-BODIPY **5c**.[a]



Product	R^1	R^2	Conditions	Time	Yield (%)
14	Ph	Cl	A	72 h	22
14	Ph	Cl	B	15 min	63
15	Ph	Ph	B	15 min	89
14	Ph	Cl	C	16 h	72
15	Ph	Ph	C	24 h	64
16	C≡CPh	Cl	D	16 h	69
17	C≡CPh	C≡CPh	D	24 h	56
18	*N*-piperidine	Cl	E	1 h	51

[a] A) Conventional Suzuki reaction: $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux. B) Microwave Suzuki reaction, toluene, 150 W. C) Stille reaction: Ph_4Sn, $Pd(PPh_3)_4$, Na_2CO_3, toluene, reflux. D) Sonogashira reaction: phenylacetylene, $Pd(PPh_3)_4$, CuI, THF/*i*Pr_2EtN, reflux. E) Hartwig–Buchwald reaction: piperidine, Pd_2dba_3, KHMDS, toluene.

Because microwave irradiation is known to speed up these reactions, we attempted microwave-enhanced Suzuki reactions.[7b] Fortunately, we were able to isolate the desired product **14** (Table 2) in excellent yields after only fifteen minutes of microwave irradiation at 130 °C. To obtain the doubly arylated dye **15** it was sufficient to use two equivalents of the boronic acid.

Unlike the Suzuki reactions, the Stille reaction of our model system with tetraphenyltin proceeded at an acceptable rate under conventional heating conditions, and either the monosubstituted **14** or the disubstituted dye **15** were obtained after reflux in toluene.

The Sonogashira reaction was tested with phenylacetylene with an amine base in THF at reflux. After a few hours reaction time at 50 °C, we were able to isolate either the monosubstituted **16** or the disubstituted product **17** in good yields. Again, there was good selectivity of the substrate for monosubstitution over disubstitution. Only small amounts of the disubstituted product could be observed as the synthesis of monosubstituted dye approached completion.

All attempts to apply the substrate in Heck reactions led to total decomposition of the chromophore.

Finally, we sought an alternative route to the much sought-after amine-substituted dyes, which have been impossible to prepare by nucleophilic substitution. Hartwig–Buchwald-type palladium-catalysed aminations have rapidly become an established route to substituted amines.[12] Although initial experiments with bases such as tertiary butoxide or phosphate were unsuccessful, a switch to a strong base with sterically demanding ligands allowed us to obtain the aminated dye. Running the reaction under the same conditions but with omission of the palladium catalyst did not yield the product, so we can rule out an anionic mechanism of nucleophilic substitution by an amide nucleophile. Unfortunately, but not to our surprise, the bis-aminated dye remained elusive, due to the very strong deactivation caused by the first substituent. Long reaction times under the active conditions only led to monosubstitution and subsequent decomposition.

Spectroscopic Properties

Both the unsubstituted and the substituted BODIPY dyes show spectroscopic properties similar to those of previously described boron dipyrromethene dyes (i.e., narrow bands of absorption and emission with small Stokes shifts; Table 3). There is no significant influence of the substituents on the spectroscopic characteristics. A small hypsochromic shift of about 10 nm is visible with oxygen-substituted dyes **8** and **9**. With the amine-substituted dye **18**, no strong influence of the amine could be observed. The quantum yields of fluorescence (Φ_f) remain relatively high, indicating that no photoinduced electron transfer takes place.

Table 3. Spectroscopic data for selected BODIPY dyes in cyclohexane, THF and acetonitrile.

Product	Solvent	λ_{abs}(max)[a] [nm]	λ_{em}(max)[b] [nm]	$\Delta\tilde{\nu}$[c] [cm^{-1}]	Φ_f
5a	cyclohexane	518	537	683	0.98
	THF	517	537	720	0.66
	CH_3CN	514	532	658	0.68
5c	cyclohexane	579	608	824	0.58
	THF	575	607	917	0.57
	CH_3CN	568	602	994	0.71
5d	cyclohexane	649	660	257	0.77
	THF	648	662	326	0.47
	CH_3CN	645	657	283	0.31
11	cyclohexane	580	607	767	0.89
	THF	579	610	878	0.52
	CH_3CN	575	603	808	0.67
8	cyclohexane	570	600	877	0.79
	THF	570	602	933	0.74
	CH_3CN	560	593	994	0.91
10	cyclohexane	580	606	740	0.82
	THF	579	607	797	0.57
	CH_3CN	570	603	960	0.68
17	cyclohexane	574	602	810	0.75
	THF	573	604	896	0.63
	CH_3CN	565	603	1115	0.75
14	cyclohexane	578	605	772	0.60
	THF	578	607	827	0.62
	CH_3CN	568	601	967	0.75
15	cyclohexane	578	606	799	0.60
	THF	578	608	854	0.54
	CH_3CN	570	599	849	0.89
18	cyclohexane	575	603	808	0.51
	THF	576	605	832	0.43
	CH_3CN	568	600	939	0.50

[a] Absorption maximum. [b] Fluorescence emission maximum. [c] Stokes shift.

The choice of the pyrrole moiety determines the properties of the resulting dye. Through variation of the substituents on the pyrrole ring, dyes with absorption and emission from green up to the near infrared can be obtained (Figure 2 and Table 3).

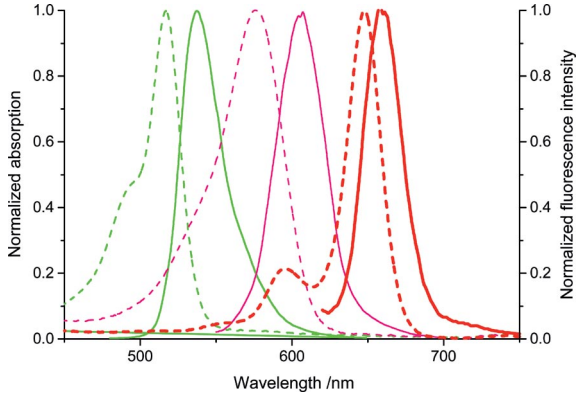


Figure 2. Normalized absorption (dash line) and fluorescence emission (solid line) spectra of **5a** (green), **5c** (pink) and **5d** (red) in THF.

Of particular interest is the fact that the fluorescence quantum yields (Φ_f) are high and remain high in solvents of increasing polarity. This is presumably because of hindered rotation of the *meso*-pyrimidyl ring as a consequence of the 4′,6′-substituents.[13] Rotation of an aryl ring at the 8-position has been identified as one of the major pathways of nonradiative decay of the excited state, and this has been used to increase Φ_f through the introduction of bulky aryl groups or simply by replacing the aryl substituent by hydrogen or a small alkyl chain.[5b,14]

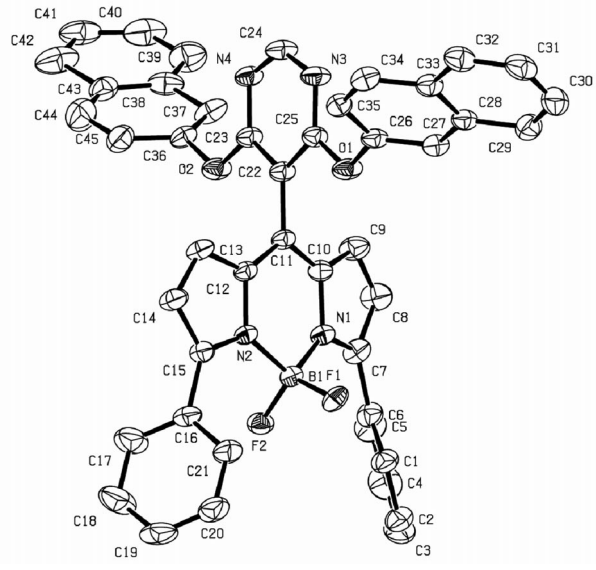


Figure 3. ORTEP representation of compound **9** with displacement ellipsoids at the 20% probability level. A solvent molecule (CH_2Cl_2) and H atoms are omitted for clarity. Unit cell parameters: *a* 13.2343(7), *b* 9.6985(5), *c* 30.3228(17), *β* 90.321(3), space group $P2_1/c$.

Further evidence for this restricted rotation could be found in an X-ray analysis. As shown in Figure 3, the crystal structure of dye **9** is in line with most previously reported BODIPY dyes, with the two planar pyrrole subunits and the boron atom forming a plane in the BODIPY ring system. The two fluorine atoms are equidistant above and below the plane of the pyrrole moieties, and the F–B–F plane is almost perpendicular (89.91°) to the plane of the BODIPY core. Moreover, the pyrimidine residues and the BODIPY core are linked to form an approximate orthogonal arrangement, with an angle of 79.69° between the planes made up by the BODIPY core atoms (B1, N1, C10, C11, C12, N2) and by the pyrimidine ring (N3, C25, C22, C23, N4, C24). Steric interactions between the 4′-/6′-substituents and the 1- and 7-hydrogen atoms make the rotation energetically strongly disfavoured.

Conclusions

We have developed a new and easily accessible BODIPY scaffold that can be substituted by nucleophilic aromatic substitution or through transition-metal-catalysed cross-coupling reactions. The spectral properties of the dyes do not depend on the introduced substituents, but can be related directly to the starting 8-(4,6-dichloropyrimidin-5-yl)-BODIPYs. By this approach, reactive dyes with absorption and emission spectra throughout the visible spectrum are available as fluorescent probes and for labelling purposes.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded at room temperature with a Bruker Avance 300 instrument operating at a frequency of 300 MHz for ^1H and 75 MHz for ^{13}C. In cases of ambiguous assignments, spectra were recorded with a Bruker Avance 400 or a Bruker 600. ^1H NMR spectra were recorded in $CDCl_3$ and referenced to tetramethylsilane (δ = 0.00 ppm) as an internal standard. ^{13}C NMR spectra were referenced to the $CDCl_3$ (δ = 77.67 ppm) signal. Mass spectra were recorded with a Hewlett–Packard 5989A mass spectrometer (EI mode and CI mode). High-resolution mass data were obtained with a Kratos MS50TC instrument. Melting points were taken with a Reichert Thermovar and are uncorrected. Microwave irradiation experiments were carried out with a dedicated CEM-Discover mono-mode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W. Absorption spectra were determined with a Varian UV-Cary 100 spectrophotometer. Fluorescence spectra measurements were performed with a Hitachi F-4500 spectrofluorimeter. For the determination of the relative fluorescence quantum yields (Φ_f), only dilute solutions with absorbance below 0.1 at the excitation wavelength (λ_{ex}) were used. Rhodamine 6G in H_2O (λ_{ex} = 488 nm, Φ_f = 0.76), rhodamine B in H_2O (λ_{ex} = 540 nm, Φ_f = 0.41) and cresyl violet (λ_{ex} = 560 nm, Φ_f = 0.55) in methanol were used as fluorescence standards. The Φ_f values reported in this work are the averages of multiple (generally three or four) fully independent measurements. The Φ_f values were determined with non-degassed samples.

CCDC-742655 (for **9**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for BODIPY Synthesis. 8-(4,6-Dichloropyrimidin-5-yl)-3,5-diphenyl-BODIPY (5c): 4,6-Dichloropyrimidine-5-carbaldehyde (**2**, 1.77 g, 10 mmol) and 2-phenylpyrrole (**3c**, 2.86 g, 20 mmol, 2 equiv.) were dissolved in CH_2Cl_2 (100 mL) under nitrogen. A few drops of trifluoroacetic acid were added, and the reaction was followed by TLC. After the disappearance of the starting material, DDQ (2.27 g, 10 mmol) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was cooled to 0 °C with an ice bath, triethylamine (14 mL, 100 mmol, 10 equiv.) was added, and the solution was stirred for 10 min, after which boron trifluoride etherate (14 mL, 110 mmol, 11 equiv.) was added dropwise. The ice bath was removed and the reaction mixture was stirred for 5 d at room temperature. The solution was taken up in diethyl ether (300 mL), washed with water (3 × 200 mL), dried with $MgSO_4$ and filtered, and the solvents were evaporated to dryness. The crude residue was purified by column chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield the BODIPY **5c** (3.910 g, 80% total yield) as a purple crystalline solid; m.p. 102 °C. ^{1}H NMR (300 MHz): δ = 8.98 (s, 1 H, 1′-H), 7.91 (m, 4 H), 7.44 (m, 6 H), 6.67 (s, 4 H) ppm. ^{13}C NMR (75 MHz): δ = 162.2, 161.1, 158.8, 135.2, 132.1, 131.7, 130.3, 139.7, 128.5, 127.5, 122.4 ppm. MS (EI): *m*/*z* = 490. HRMS: calcd. for $C_{25}H_{15}BCl_2F_2N_4$ 490.07349; found 490.07346.

8-(4,6-Dichloropyrimidin-5-yl)-BODIPY (5a): HCl (37%, 1 mL) was added to distilled water (250 mL) and the solution was stirred under nitrogen for 10 min. Pyrrole (2.1 mL, 30 mmol) was added to the solution, which was stirred until a clear solution was obtained. 4,6-Dichloropyrimidine-5-carbaldehyde (1.77 g, 10 mmol) was then added in portions over 10 min. After a few min, the clear solution had become opaque, and a precipitate had begun to form. The mixture was stirred at room temperature for 6 h, filtered through a glass filter and thoroughly washed with water. The solid could be dried under vacuum to yield sufficiently pure dipyrromethane. Further purification could be effected by dissolving the crude solid in dichloromethane, drying over $MgSO_4$, filtering and concentrating to dryness. This solid was then stirred in petroleum ether for 6 h to remove trace impurities. From here on the general procedure was followed, starting with the oxidation with DDQ. After oxidation and complexation, the product (745 mg, 22% from the starting aldehyde) was obtained as a red solid; m.p. 108 °C. ^{1}H NMR (300 MHz): δ = 8.98 (s, 1 H, 1′-H), 8.01 (s, 2 H), 6.72 (s, 2 H), 6.58 (s, 2 H) ppm. ^{13}C NMR (MHz, 75): δ = 159.3, 147.2, 139.9, 120.4 ppm. MS (EI): *m*/*z* = 338. HRMS: calcd. for $C_{13}H_7BCl_2F_2N_4$: 338.01089; found 338.01076.

8-(4,6-Dichloropyrimidin-5-yl)-1,3,5,7-tetramethyl-BODIPY (5b): BODIPY **5b** (1.18 g, 30% total yield) was obtained by the General Procedure as a red solid; m.p. 142 °C. ^{1}H NMR (300 MHz): δ = 8.93 (s, 1 H, 1′-H), 6.07 (s, 2 H), 2.59 (s, 6 H), 1.54 (s, 6 H) ppm. ^{13}C NMR (75 MHz): δ = 161.6, 158.5, 158.1, 141.1, 129.8, 128.7, 122.3, 15.0, 14.1 ppm. MS (EI): *m*/*z* = 394. HRMS: calcd. for $C_{17}H_{15}BCl_2F_2N_4$ 394.0735 found 394.07362.

Dihydrobenzindole-8-(4,6-dichloropyrimidin-5-yl)-BODIPY (4d): BODIPY **4d** (1.303 g, 48% total yield for a 5 mmol reaction) was obtained by the General Procedure as a blue solid; m.p. >300 °C. ^{1}H NMR (300 MHz): δ = 8.95 (s, 1 H, 1′-H), 8.80 (d, *J* = 7.8 Hz, 2 H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.29 (s, 2 H), 6.31 (s, 2 H), 2.94 (t, *J* = 6.6 Hz, 4 H), 2.70 (t, *J* = 6.6 Hz, 4 H) ppm. MS (EI): *m*/*z* = 542. HRMS: calcd. for $C_{29}H_{19}N_4BF_2Cl_2$ 542.1048; found 542.10487.

8-(4-Chloro-6-phenylsulfanylpyrimidin-5-yl)-1,3,5,7-tetramethyl-BODIPY (6): BODIPY **5b** (79 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of thiophenol (103 μL, 0.5 mmol, 2.5 equiv.) and K_2CO_3 (69 mg, 0.5 mmol). The mixture was stirred at 100 °C under nitrogen for 4 h. After disappearance of the starting material, the mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by column chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **6** (15 mg, 16%) as a red solid; m.p. 235 °C. ^{1}H NMR (300 MHz): δ = 8.68 (s, 1 H, 1′-H), 7.46 (m, 5 H), 6.09 (s, 2 H), 2.61 (s, 6 H), 1.68 (s, 6 H) ppm. ^{13}C NMR (75 MHz): δ = 172, 158.5, 157.9, 141.4, 135.8, 130.4, 130.3, 129.9, 129.7, 126.6, 124.7, 122.1, 15.1, 14.2 ppm. MS (EI): *m*/*z* = 468. HRMS: calcd. for $C_{23}H_{20}BClF_2N_4S$ 468.1158; found 468.11591.

8-(4-Chloro-6-phenoxypyrimidin-5-yl)-3,5-diphenyl-BODIPY (7): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of phenol (18.8 mg, 0.2 mmol, 1 equiv.), K_2CO_3 (28 mg, 0.2 mmol) and a catalytic amount of 18-crown-6 (2.64 mg, 0.01 mmol, 5%). The mixture was stirred at room temperature until the starting material had disappeared. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **7** (107.4 mg, 98%) as a purple solid; m.p. 130 °C. ^{1}H NMR (300 MHz): δ = 8.70 (s, 1 H, 1′-H) 7.91 (d, *J* = 4.5 Hz, 4 H), 7.43 (m, 8 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.08 (d, *J* = 7.2 Hz, 2 H), 7.85 (d, *J* = 3.6 Hz, 2 H), 6.68 (d, *J* = 3.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 168.5, 161.6, 160.5, 158.7, 152.0, 135.9, 132.3, 131.8, 130.1, 129.9, 129.6, 128.6, 128.5, 126.6, 122.0, 121.6, 114.8 ppm. MS (EI): *m*/*z* = 548. HRMS: calcd. for $C_{31}H_{20}BClF_2N_4O$ 548.1387; found 548.13968.

8-[4,6-Bis(phenoxy)pyrimidin-5-yl]-3,5-diphenyl-BODIPY (8): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of phenol (37.6 mg, 0.4 mmol, 2 equiv.), K_2CO_3 (56 mg, 0.4 mmol) and a catalytic amount of 18-crown-6 (5.2 mg, 0.02 mmol, 5%). The mixture was stirred at 100 °C until the starting material had disappeared. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **8** (103 mg, 85%) as a purple solid; m.p. 218 °C. ^{1}H NMR (300 MHz): δ = 8.51 (s, 1 H, 1′-H), 7.90 (d, *J* = 5.7 Hz, 4 H), 7.41 (m, 10 H), 7.24 (m, 2 H), 7.11 (d, *J* = 7.8 Hz, 4 H), 7.04 (d, *J* = 3.3 Hz, 2 H), 6.69 (d, *J* = 3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 168.9, 159.8, 158.6, 152.5, 136.7, 132.5, 132.2, 129.8, 129.6, 128.9, 128.4, 126.2, 121.7, 121.6, 100.7 ppm. MS (EI): *m*/*z* = 606. HRMS: calcd. for $C_{37}H_{25}BF_2N_4O_2$ 606.2089; found 606.20569.

8-(4,6-Bis-2-naphthoxypyrimidin-5-yl)-3,5-diphenyl-BODIPY (9): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of 2-naphthol (57.6 mg, 0.4 mmol, 2 equiv.), K_2CO_3 (56 mg, 0.4 mmol) and a catalytic amount of 18-crown-6-ether (5.2 mg, 0.02 mmol, 5%). The mixture was stirred at 100 °C until the starting material had disappeared. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **9** (106 mg, 75%) as a purple solid; m.p. 134 °C. ^{1}H NMR (600 MHz): δ = 8.55 (s, 1 H, 1′-H), 7.98 (d, *J* = 6.6 Hz, 4 H), 7.93 (d, *J* = 9.0 Hz, 2 H), 7.89 (d, *J* = 8.4 Hz, 2 H), 7.84 (d, *J* = 7.8 Hz, 2 H), 7.63 (s, 2 H), 7.49–7.55 (m, 4 H), 7.43–7.49 (m, 6 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 7.21 (d, *J* = 4.2 Hz, 2 H), 6.79 (d, *J* = 4.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 169.0, 159.9, 158.5, 150.0, 136.7, 133.9, 132.5, 132.1, 131.6,

129.9, 129.8, 129.6, 128.9, 128.4, 128.0, 127.7, 126.9, 126.0, 121.6, 121.1, 117.5, 100.8 ppm. MS (ESI): *m/z* = 707.

8-(4-Chloro-6-phenylsulfanylpyrimidin-5-yl)-3,5-diphenyl-BODIPY (10): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of thiophenol (20.5 μL, 0.2 mmol, 1 equiv.) and K_2CO_3 (28 mg, 0.2 mmol). The mixture was stirred at room temperature until the starting material had disappeared. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **10** (101 mg, 90%) as a purple solid; m.p. 230 °C. ^{1}H NMR (300 MHz): δ = 8.73 (s, 1 H, 1′-H), 7.93 (d, J = 3.9 Hz, 4 H), 7.43–7.50 (m, 11 H), 6.80 (s, 2 H), 6.69 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 173.1, 160.8, 159.3, 158.1, 135.7, 135.3, 132.7, 132.2, 130.3, 130.2, 129.7, 129.6, 128.7, 128.5, 127.1, 123.8, 122.2 ppm. MS (EI): *m/z* = 564. HRMS: calcd. for $C_{31}H_{20}BClF_2N_4S$ 564.1158; found 564.11681.

8-[4,6-Bis(phenylsulfanyl)pyrimidin-5-yl]-3,5-diphenyl-BODIPY (11): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of thiophenol (41 μL, 0.4 mmol, 2 equiv.) and K_2CO_3 (56 mg, 0.4 mmol). The mixture was stirred at 100 °C until the starting material had disappeared. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **11** (115 mg, 90%) as a purple solid; m.p. 192 °C. ^{1}H NMR (600 MHz): δ = 8.59 (s, 1 H, 1′-H), 7.95 (d, J = 7.2 Hz, 4 H), 7.49 (d, J = 6.6 Hz, 4 H), 7.45 (m, 6 H), 7.40 (m, 2 H), 6.93 (d, J = 3.6 Hz, 2 H), 6.71 (d, J = 3.6 Hz, 2 H) ppm. ^{13}C NMR (150 MHz): δ = 168.9, 160.5, 157.7, 135.6, 135.5, 132.4, 130.0, 129.8, 129.7, 129.4, 128.9, 128.4, 128.0, 122.0, 121.8 ppm. MS (EI): *m/z* = 638. HRMS: calcd. for $C_{37}H_{25}BF_2N_4S_2$ 638.1582; found 638.15739.

8-(4-Phenoxy-6-phenylsulfanylpyrimidin-5-yl)-3,5-diphenyl-BODIPY (12): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of phenol (18.8 mg, 0.2 mmol, 1 equiv.), K_2CO_3 (56 mg, 0.4 mmol) and a catalytic amount of 18-crown-6 (2.64 mg, 0.01 mmol, 5%). The mixture was stirred at 100 °C until TLC analysis indicated complete disappearance of the starting material. Thiophenol (20.5 μL, 0.2 mmol, 1 equiv.) was then added and stirring at 100 °C was continued until the reaction was complete. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **12** (99.5 mg, 80%) **12** as a purple solid; m.p. 112 °C. ^{1}H NMR (600 MHz): δ = 8.37 (s, 1 H, 1′-H), 7.97 (d, J = 7.2 Hz, 4 H), 7.46 (d, J = 7.2 Hz, 2 H), 7.09 (t, J = 7.2 Hz, 4 H), 7.05 (m, 2 H), 7.04 (t, J = 3.0 Hz, 2 H), 7.02 (t, J = 7.2 Hz, 3 H), 6.95 (d, J = 7.8 Hz, 2 H), 6.88 (t, J = 7.2 Hz, 1 H), 6.67 (d, J = 4.8 Hz, 2 H), 6.38 (d, J = 4.2 Hz, 2 H) ppm. ^{13}C NMR (150 MHz): δ = 171.7, 166.4, 160.2, 128.3, 152.3, 136.1, 135.6, 133.2, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.4, 128.0, 126.1, 121.8, 121.7, 111.7 ppm. MS (EI): *m/z* = 622. HRMS: calcd. for $C_{37}H_{25}BF_2N_4SO$ 622.1810; found 622.17992.

8-(4-Methylsulfanyl-6-phenoxypyrimidin-5-yl)-3,5-diphenyl-BODIPY (13): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (5 mL), followed by the addition of phenol (18.8 mg, 0.2 mmol, 1 equiv.), K_2CO_3 (28 mg, 0.2 mmol) and a catalytic amount of 18-crown-6 (2.64 mg, 0.01 mmol, 5%). The mixture was stirred at 100 °C until TLC analysis indicated complete disappearance of the starting material. Sodium thiomethoxide (15 mg, 0.2 mmol, 1 equiv.) was then added and stirring at 100 °C was continued until the reaction was complete. The mixture was poured into diethyl ether and washed with water (3 × 100 mL), dried, filtered and concentrated to dryness. The crude product was purified by flash chromatography (silica, dichloromethane/petroleum ether 1:1 v/v) to yield BODIPY **13** (99.5 mg, 80%) as a purple solid; m.p. 106 °C. ^{1}H NMR (400 MHz): δ = 8.69 (s, 1 H, 1′-H), 7.91 (d, J = 7.2 Hz, 4 H), 7.46–7.38 (m, 8 H), 7.24 (t, J = 7.2 Hz, 1 H), 7.07 (d, 2 H), 6.90 (d, J = 7.8 Hz, 2 H), 6.64 (d, J = 4.8 Hz, 2 H), 2.57 (s, 3 H, –SMe) ppm. ^{13}C NMR (200 MHz): δ = 172.2, 165.9, 160.1, 157.9, 152.4, 135.9, 132.4, 129.9, 129.7, 129.69, 129.65, 129.7, 128.4, 126.0, 121.7, 121.6, 111.8, 13.6 ppm. MS (EI): *m/z* = 560. HRMS: calcd. for $C_{32}H_{23}BF_2N_4OS$ 560.16537; found 560.16554.

8-(6-Chloro-4-phenylpyrimidin-5-yl)-3,5-diphenyl-BODIPY (14)

Microwave Procedure: BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in toluene (1 mL) and the resulting solution was purged with nitrogen. Phenylboronic acid (29 μL, 0.26 mmol, 1.3 equiv.) was added, followed by tetrakis(triphenylphosphane)palladium (11 mg, 0.02 mmol, 10 mol-%). The mixture was irradiated at 130 °C and 150 W for 15 min, allowed to cool to room temperature and poured into diethyl ether (150 mL). The organic layer was washed with water (3 × 200 mL), dried and filtered, and the solvents were evaporated to dryness. The product was purified by column chromatography (silica, CH_2Cl_2/petroleum ether 1:1, v/v) to yield **14** as a purple crystalline solid (67 mg, 63%), together with disubstituted BODIPY **15** (17 mg, 15%); m.p. of **14**: 87 °C

Stille Coupling: BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in toluene (2 mL) and the resulting solution was purged with nitrogen. Tetraphenyltin (96 mg, 0.22 mmol, 1.1 equiv.) was added, followed by tetrakis(triphenylphosphane)palladium (11 mg, 0.01 mmol, 5 mol-%) and Na_2CO_3 (2 mL, 1 M solution in H_2O). The mixture was heated at reflux for 16 h, allowed to cool to room temperature, and poured into diethyl ether (150 mL). The organic layer was washed with water (3 × 200 mL), dried and filtered, and the solvents were evaporated to dryness. The product was purified by column chromatography (silica, CH_2Cl_2/petroleum ether 1:1, v/v) to yield **14** as a purple crystalline solid (76 mg, 72%).

^{1}H NMR (300 MHz): δ = 9.22 (s, 1 H, 1′-H), 7.87 (d, J = 4.5 Hz, 4 H), 7.73 (d, J = 6.6 Hz, 2 H), 7.33–7.45 (m, 9 H), 6.67 (d, J = 3.3 Hz, 2 H), 6.59 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 167.0, 162.2, 160.2, 158.9, 136.2, 136.1, 134.8, 132.1, 131.1, 130.1, 129.7, 129.0, 128.9, 128.4, 125.6, 122.1 ppm. MS (EI): *m/z* = 532. HRMS: calcd. for $C_{31}H_{20}BClF_2N_4$ 532.14376; found 532.14381.

8-(4,6-Diphenylpyrimidin-5-yl)-3,5-diphenyl-BODIPY (15): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in DMF (1 mL) and the resulting solution was purged with nitrogen. Phenylboronic acid (29 μL, 0.26 mmol, 1.3 equiv.) was added, followed by tetrakis(triphenylphosphane)palladium (11 mg, 0.02 mmol, 10 mol-%) and CuI (3.8 mg, 0.02 mmol, 10 mol-%). The mixture was irradiated at 130 °C and 150 W for 15 min, allowed to cool to room temperature and poured into diethyl ether (150 mL). The organic layer was washed with water (3 × 200 mL), dried and filtered, and the solvents were evaporated to dryness. The product was purified by column chromatography (silica, CH_2Cl_2/petroleum ether 1:1, v/v) to yield **15** as a purple crystalline solid (102 mg, 89%); m.p. 140 °C. ^{1}H NMR (300 MHz): δ = 9.51 (s, 1 H, 1′-H), 7.80 (s, 4 H), 7.64 (s, 2 H), 7.36 (m, 12 H), 6.62 (s, 2 H), 6.43 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 166.4, 159.1, 159.0, 137.8, 137.5, 136.8, 132.1, 130.2, 129.9, 129.6, 129.4, 128.7, 128.3, 124.4, 121.7 ppm. MS (EI): *m/z* = 574. HRMS: calcd. for $C_{37}H_{25}BF_2N_4$ 574.2140; found 574.21.

8-(4-Chloro-6-phenylethynylpyrimidin-5-yl)-3,5-diphenyl-BODIPY (16): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in THF (2 mL)

and iPr$_2$NEt (1 mL) and the resulting solution was purged with nitrogen. Phenylacetylene (29 μL, 0.26 mmol, 1.3 equiv.) was added, followed by tetrakis(triphenylphosphane)palladium (11 mg, 0.01 mmol, 5 mol-%) and CuI (1.9 mg, 0.01 mmol, 5 mol-%). The mixture was heated at reflux for 3 h and allowed to cool to room temperature, after which the solvent was stripped. The product was purified by column chromatography (silica, CH_2Cl_2/petroleum ether 1:1, v/v) to yield **16** as a purple crystalline solid (76 mg, 69%); m.p. 193 °C. ^{1}H NMR (300 MHz): δ = 9.12 (s, 1 H, 1′-H), 7.90 (d, J = 4.2 Hz, 4 H), 7.43 (s, 6 H), 7.34 (m, 3 H), 7.26 (m, 2 H), 6.76 (s, 2 H), 6.65 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 160.7, 160.6, 159.1, 152.6, 135.7, 133.7, 133.0, 132.2, 130.9, 130.1, 129.6, 129.4, 129.1, 128.7, 128.5, 122.1, 120.2, 102.2 (C≡C), 85.5 (C≡C) ppm. MS (EI): m/z = 556. HRMS: calcd. for $C_{33}H_{20}BClF_2N_4$ 556.1438; found 556.14355.

8-[4,6-Bis(phenylethynyl)pyrimidin-5-yl]-3,5-diphenyl-BODIPY (17): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in THF (2 mL) and iPr$_2$NEt (1 mL), and the resulting solution was purged with nitrogen. Phenylacetylene (29 μL, 0.26 mmol, 1.3 equiv.) was added, followed by tetrakis(triphenylphosphane)palladium (11 mg, 0.02 mmol, 10 mol-%) and CuI (3.8 mg, 0.02 mmol, 10 mol-%). The mixture was heated at reflux for 3 h and allowed to cool to room temperature, after which the solvent was stripped. The product was purified by column chromatography (silica, CH_2Cl_2/petroleum ether 1:1, v/v) to yield **17** as a purple crystalline solid (69 mg, 56%); m.p. 218 °C. ^{1}H NMR (300 MHz): δ = 9.31 (s, 1 H, 1′-H), 7.92 (d, J = 4.5 Hz, 4 H), 7.44 (m, 6 H), 7.33 (m, 6 H), 7.27 (m, 4 H), 6.89 (d, J = 3.6 Hz, 2 H), 6.64 (d, J = 2.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 160.2, 159.4, 150.9, 136.2, 135.7, 132.9, 132.4, 131.7, 130.6, 130.0, 129.8, 129.6, 128.7, 128.5, 121.9, 120.6, 101.1 (C≡C), 85.9 (C≡C) ppm. MS (EI): m/z = 622. HRMS: calcd. for $C_{41}H_{25}BF_2N_4$ 622.2140; found 622.21376.

8-(4-Chloro-6-piperidinopyrimidin-5-yl)-3,5-diphenyl-BODIPY (18): BODIPY **5c** (98 mg, 0.2 mmol) was dissolved in toluene (2 mL) and the resulting solution was purged with nitrogen. Piperidine (13 μL, 0.26 mmol, 1.3 equiv.) was added, followed by trisdibenzylidene-acetone-dipalladium (9 mg, 0.02 mmol, 10 mol-%), BINAP (24.9 mg, 0.04 mmol, 20 mol-%) and KHMDS (30 mg, 0.03 mmol, 1.5 equiv.). The mixture was flushed with nitrogen and heated at 110 °C in a closed vessel for 1 h. The vessel was allowed to cool to room temperature, after which the solvent was stripped. The product was purified by column chromatography (silica, CH_2Cl_2/petroleum ether 1:1, v/v) to yield **18** as a purple crystalline solid (54 mg, 51%); m.p. 200 °C. ^{1}H NMR (400 MHz): δ = 8.48 (s, 1 H, 1′-H), 7.89 (d, J = 4.5 Hz, 4 H), 7.43 (m, 6 H), 6.88 (d, J = 4.28 Hz, 2 H), 6.64 (d, J = 4.28 Hz, 2 H), 3.66 (t, J = 5.28 Hz, 4 H), 1.57 (m, 2 H), 1.41 (m, 4 H) ppm. ^{13}C NMR (100 MHz): δ = 161.9, 160.7, 159.9, 127.6, 1237.4, 135.9, 132.3, 129.9, 129.7, 129.6, 129.6, 129.2, 128.4, 121.6, 109.0, 48.7, 25.8, 24.5 ppm. MS (EI): m/z = 622. HRMS: calcd. for $C_{30}H_{25}BClF_2N_5$ 539.1859; found 539.18545.

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