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ARTICLE TYPE

Negishi reaction in BODIPY dyes. Unprecedented alkylation by palladium-catalyzed C–C coupling in boron dipyrromethene derivatives†

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Negishi reactions of 3-halogen and 3,5-dihalogen substituted BODIPYs with different organozinc reagents are reported as the first examples of this valuable palladium-catalyzed C–C coupling reaction into the family of the BODIPY dyes. It is demonstrated that the Negishi coupling is especially useful for obtaining interesting alkylated BODIPYs, including synthetically-valuable asymmetrically-3,5-disubstituted BODIPYs.

BODIPY (boron dipyrrin or boron dipyrromethene) dyes constitute one of the most important families of luminophores, due to their easily tunable absorption and emission properties.[1] These systems are highly interesting for the development of valuable photonic applications, such as chemosensors and probes, biological labels, laser dyes, potential photodynamic therapy agents, and a plethora of photonic devices, including solar light harvesting antennas or solar cells.[2] Additionally, chiral BODIPYs exhibiting some particular chiroptical properties (e.g., a clearly bisignated dichroic signal in the visible region) have been recently highlighted as interesting dyes for the development of useful technologies (e.g., CPL-based sensing).[3] There is, therefore, an understandable interest in the synthesis of new BODIPY derivatives, not only for improving useful photonic properties, but also for revealing the key structural factors ruling them.

BODIPY dyes can be obtained by using two general methodologies: (1) functionalization of pyrroles which are used as precursors of the desired BODIPY after final boron complexation (pre-functionalization),[1a,c,4] and (2) functionalization of the BODIPY core (post-functionalization).[1a-c,4b-d,5] The post-functionalization methodology is highly attractive for expanding the diversity of the BODIPY family, especially for some typologies which are difficult to obtain directly by pre-functionalization.[2e,6] However, functionalizing the BODIPY core is not trivial, and in many cases critical problems arise concerning the control of the BODIPY reactivity (lack of reactivity, uncontrolled reactivity, etc.).

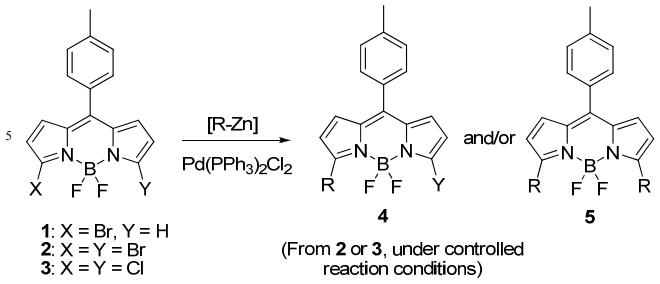
Many of the most important BODIPY functionalization reactions are based on the use of halogen-substituted BODIPYs. Significantly, 3-halo and 3,5-dihaloBODIPYs have been extensively used, because they can be easily prepared by controlled electrophilic aromatic substitution (S_EAr) reactions in dipyrromethane precursors[7] and, afterwards, submitted to nucleophilic substitution with alcohols, amines or enolates to give rise to the corresponding substituted BODIPYs.[3,7a-c,8] Moreover, 3-halo and 3,5-dihaloBODIPYs have been also used as convenient precursors of interesting carbon-substituted BODIPYs through palladium-catalyzed C-C coupling reactions. Thus, Dehaen et al. have reported the use of the Stille, Suzuki, Heck and Sonogashira reactions for the preparation of valuable aryl, alkenyl and alkynyl BODIPYs, with fluorescence spanning the visible spectrum, from a 3,5-dichloroBODIPY.[9] On the other hand, Ravikanth et al. have recently reported the preparation of several symmetric and asymmetric BODIPY derivatives, with interesting photophysical and electrochemical properties, by Sonogashira and Suzuki reactions of the corresponding 3,5-dihaloBODIPYs precursor.[10]

It should be noted that, to the best of our knowledge, only aryl, alkenyl or alkynyl derivatives were obtained by aplying the above-mentioned palladium-catalyzed C-C couplings in BODIPYs.[1a-c,9-11] Strikingly, alkyl BODIPYs were not reported by using those reactions, despite these derivatives are very interesting dyes for many different technological applications (*e.g.*, biological labelling and molecular probing), being mainly prepared through to complex pre-functionalization routes instead.[12]

On the other hand, Negishi reaction in BODIPYs is unprecedented, although it would allow the preparation of alkyl derivatives, as the Suzuki one would, but with the valuable advantage of a high functional-group compatibility (including the labile BODIPY BF_2 group), due to the nature of the Negishi-required organozinc reagents.[13]

The above mentioned facts prompted us to essay the workability of the Negishi reaction in the BODIPY family, specially directed to the synthesis of alkyl BODIPYs.

Herein we report the coupling reaction of 3-bromo, 3,5-dibromo and 3,5-dichloroBODIPYS **1-3** with different organozinc reagents ([R-Zn], Scheme 1), and demonstrate its versatility for obtaining carbon-substituted BODIPYs, including alkylated and asymmetric derivatives.



Scheme 1 Negishi reactions tested in BODIPYs.

HaloBODIPYs **1-3** (Scheme 1) were obtained straightforwardly by previously described pre-functionalization routes based on S_EAr reactions.[7a,b-d] Highly accessible [R-Zn] and common $Pd(PPh_3)_2Cl_2$ were used for the Negishi reactions tested. The results obtained are shown in Table 1.

Table 1 Results for the Negishi reactions tested.

Entry	Halo-BODIPY	[Zn-R] (reaction conditions)[a]	Major product (R/Y or R/R)	Yield (%)[b]
1	**1**	$ZnEt_2$ (N)	**4a** (Et/H)	64
2	**2**	$ZnEt_2$ (N)	**5a** (Et/Et)	86
3	**2**	$ZnEt_2$ (C)	**4b** (Et/Br)	61
4	**3**	$ZnEt_2$ (N)	**5a** (Et/Et)	73
5	**3**	$ZnEt_2$ (C)	**4c** (Et/Cl)	75
6	**3**	$ZnMe_2$ (N)	**5b** (Me/Me)	80
7	**3**	$ZnMe_2$ (C)	**4d** (Me/Cl)	77
8	**3**	BuZnBr (N)	**5c** (Bu/Bu)	52
9	**3**	BuZnBr (C)	**4e** (Bu/Cl)	62
10	**3**	$Zn(iPr)_2$ (C)	**4f** (iPr/Cl) / **4g** (Pr/Cl)[c]	70[c]
11	**3**	BnZnBr (N)	**5d** (Bn/Bn)	20
12	**3**	BnZnBr (C)	**4h** (Bn/Cl)	18
13	**3**	PhZnBr (N)	**5e** (Ph/Ph)	56
14	**3**	PhZnBr (C)	**4i** (Ph/Cl)	70
15	**3**	PhC≡CZnBr (N)	**5f** (PhC≡C/PhC≡C)	54
16	**3**	PhC≡CZnBr (C)	**4j** (PhC≡C/Cl)	56
17	**3**	TMSC≡CZnBr (N)	**5g** (TMSC≡C/TMSC≡C)	70
18	**4d**	BuZnBr (N)	**5h** (Me/Bu)	65

[a]See reaction conditions in ESI†. [b]Isolated yield. [c]**4f**/**4g** = 2/1, determined by ^1H NMR (see ESI†).

Negishi reactions were conducted under standard reaction conditions to reach the highest level of C-C coupling (normal conditions, N), or under controlled conditions (C, mainly by controlling the stoichioimetry and the reaction time) to reach the highest level of mono-coupling when 3,5-dibromoBODIPY **2** or 3,5-dichloroBODIPY **3** are used as starting halogenated BODIPYs (see experimental details in ESI†).

Most of the Negishi alkylations tested took place satisfactorily with high yields (Table 1, entries 1-10), demonstrating that reaction control for mono-coupling of 3,5-dihaloBODIPY **2** and **3** (entries 3, 5, 7 and 9) is possible. No significant differences in reactivity were found between starting 3,5-dibrominated and 3,5-dichlorinated BODIPYs (entries 2-5). For BODIPY isopropylation (entry 10), the expected isopropyl to propyl isomerization was detected, which could be avoided by using an appropriated, more sophisticated palladium catalyst (Pd-PEPPSI-$IPent^{Cl}$).[14] In contrast, benzylations took place with low yields (entries 11 and 12), although conversion of starting 3,5-dihaloBODIPY was almost complete. This can be accounted for by the high reactivity (methylene acidity) of the obtained benzylated **5d** and **4h**. Nonetheless, this reactive property could be used in the future for the easy preparation of new BODIPY derivatives, following the carbanion based BODIPY post-functionalization methodology described by Ziessel *et al.*[5b] It must be noted that, according to our knowledge, **5d** and **4h** are the first benzylated BODIPYs described up to date.

Arylations and alkynylations by Negishi reaction (entries 13-17 in Table 1) were also conducted for the comparison with other related palladium-catalyzed C-C coupling reactions. Thus, the yields in the preparation of phenylated **5e** and **4i** by Negishi reactions (entries 13 and 14) were only slightly higher than those reported previously by Stille reactions by Dehaen *et al.*[9] (56 *vs.* 50%, and 70 *vs.* 63%, respectively), but avoiding the use of the more toxic organotin reagent required for the latter. On the other hand, the yields in the preparation of phenylethynylBODIPYs **5f** and **4j** by Negishi reactions (entries 15 and 16) were similar to those obtained previously by Sonogashira reactions[9] (54 *vs.* 57%, and 56 *vs.* 59%, respectively). Finally, the yield in preparing (trimethylsilyl)ethynylated **5g** from **3** by Negishi reaction (entry 17) was higher than that the reported by Ravikanth *et al.*,[10] starting from **2** and using the Sonogashira reaction (70 *vs.* 60%).

An interesting application of the Negishi coupling is the preparation of asymmetrically substituted 3,5-dialkylBODIPYs. As an example, methylated chloroBODIPY **4d** (entry 7 in Table 1) was used as intermediate in the preparation of asymmetrically dialkylated (5-methyl and 3-butyl) **5h** (entry 18 in Table 1), which was obtained with high overall yield (50%), from readily available 3,5-dichloroBODIPY **3**.

Finally, the study of the photophysical properties for the novel alkylated BODIPYs was also conducted (Figure 1 and Figure S1 in ESI†).

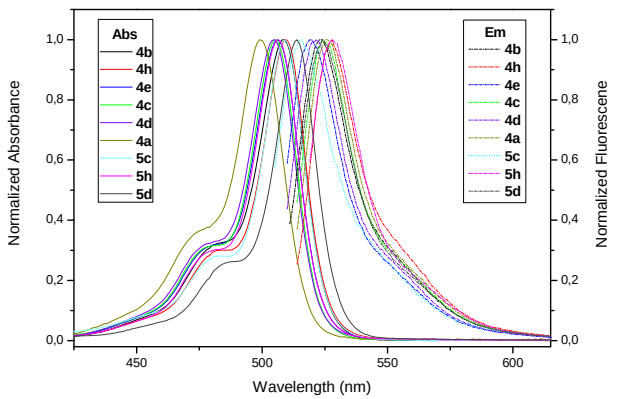


Figure 1 A selection of the normalized visible absorption spectra and corresponding fluorescence emission spectra of the new compounds in AcOEt.

The narrow absorption and emission spectra of the dyes in ethyl acetate (AcOEt) solution are in full accord with those of classic BODIPY dyes,[1,15] with absorption and emission maxima around 500 and 520 nm, respectively. As found for common

difluoroboron dipyrrins, the Stokes shifts are quite small.[15] The fluorescence quantum yields (Φ) are lower than the measured for commercial PM546, which is used as reference (Table 2). The rather low Φ values can be accounted for by the enhanced deactivation of the singlet excited state, due to the rotational mobility of the *p*-tolyl group at the 8-position.[16]

Table 2. Photophysical properties of the BODIPY dyes in AcOEt

BODIPY	λ_{abs}(max) (nm)	λ_{em}(max) (nm)	Δν (cm^{-1})	Φ
PM546	494	504	400	0.85
4a	500	516	620	0.02
4b	509	528	707	0.07
4c	505	522	645	0.14
4d	505	519	534	0.11
4e	506	523	642	0.12
4h	509	523	526	0.17
5c	509	525	599	0.12
5d	514	524	371	0.13
5h	506	521	569	0.13

Absorption (λ_{abs}) and fluorescence emission (λ_{em}) wavelength at the maximum, Stokes shift (Δν) and fluorescence quantum yield (Φ).

In summary, we report the first examples of the Negishi C-C coupling reaction in BODIPYs (3-halo and 3,5-dihaloBODIPYs), highlighting its workability for obtaining alkylated BODIPY dyes, including synthetically-valuable asymmetrically-3,5-disubstituted derivatives. We are convinced that the well-known functional group compatibility of the organozinc reagents augurs a promising future for the Negishi reaction when applied to the preparation of functionalized BODIPY dyes (*e.g.*, useful *ω*-substituted alkyl BODIPYs for biomolecular probing).

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† Electronic Supplementary Information (ESI) available: Experimental Section, Figure S1, as well as ^{1}H and ^{13}C NMR spectra of new compounds. See DOI: 10.1039/b000000x/

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