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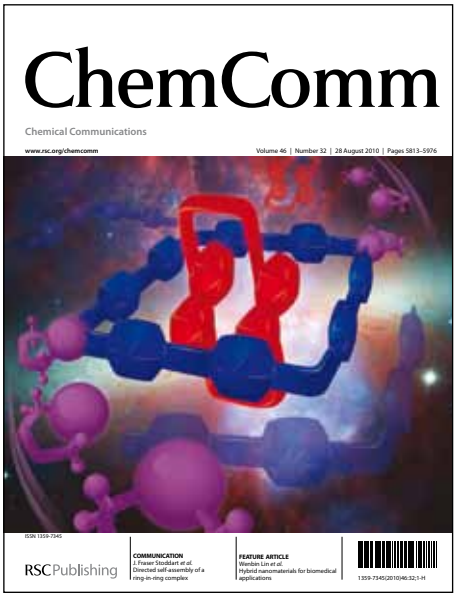

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ARTICLE TYPE

Direct palladium-catalysed C–H arylation of BODIPY dyes at the 3- and 3,5-positions†

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A new one-step synthetic method towards 3- and 3,5-arylated BODIPY dyes via palladium-catalysed C–H arylation has been developed and its scope has been investigated.

Boron complexes of dipyrromethenes, or 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes (BODIPY), are valuable fluorophores because of their many excellent characteristics, such as bright fluorescence, robustness towards light and chemicals, and excitation/emission wavelengths in the visible spectral range.[1] Therefore, they have numerous applications, including the use as chemosensors.[2] Since the spectroscopic and photophysical properties of these boron complexes can be simply tuned by substituting the BODIPY nucleus, much investigation is ongoing on the synthesis and functionalisation of these fascinating molecules. Most strategies to derivatise the core of boron dipyrromethenes either start from functionalised pyrroles,[3] use halogenated BODIPYs[4] or utilise the Liebeskind-Srogl reaction.[5]

A more efficient method to derivatise molecules is the use of transition-metal-catalysed C–H functionalisation reactions.[6] During the last decade, these atom economical reactions have become an increasingly attractive alternative to traditional cross-coupling reactions. Thanks to the advancements in this area, heteroaromatic systems now can be easily functionalised *via*, for instance, direct arylations.[7]

In the case of BODIPY, only a few examples of direct functionalisations are known, namely nucleophilic substitution of hydrogen at the 3,5-positions,[8] and direct alkenylation[9] and direct borylation[10] at the 2,6-positions. Also, previously our group successfully used an intramolecular direct arylation to synthesize ring-fused BODIPY dyes.[11]

Such transition-metal-catalysed C–H functionalisations are interesting alternative strategies to substitute the BODIPY core and to create fluorophores with red-shifted electronic spectra. Therefore, we set out to investigate the feasibility of direct intermolecular palladium-catalysed C–H arylation on readily available *meso*-substituted BODIPY dyes **1** *via* reaction with arylhalides.

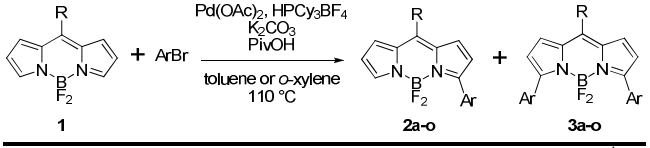
The condition previously optimized by our group for the intramolecular direct β-arylation,[11] was used to test the intermolecular C–H arylation of boron dipyrromethenes **1** with bromobenzene. To our delight, the desired phenyl-BODIPY **2a** was indeed formed after 48 h, although in a low yield. Due to the slow speed of the reaction the majority of the starting material was recovered.

Characterisation of the formed product **2a** showed that bromobenzene had reacted at the electrophilic 3-position. Therefore, the most likely mechanism for this C–H activation is a concerted metallation-deprotonation involving the carbonate as an intramolecular base.[12] Since pivalate (i.e. 2,2-dimethylpropanoate) is known to accelerate C–H functionalisation proceeding *via* this mechanism,[13] addition of a substoichiometric amount of pivalic acid (PivOH, i.e., 2,2-dimethylpropanoic acid) to the reaction mixture was tested. As expected, this sped up the C–H arylation. The estimated *in situ* yield determined *via* NMR spectroscopy increased from 4% after 4 days without pivalic acid (Table S1, entry 2, ESI) to 17% with this additive (Table S1, entry 4).

However, further improvement was needed (Table S1) and hence, other reaction conditions were tried. By changing the ligand with more electron rich or bidentate ligands (entries 4-7) and by altering the palladium source (entries 8 and 9), it was found that palladium(II) acetate and tricyclohexylphosphine were the best catalyst and ligand combination. Furthermore, different bases were tested (entries 10-13), including more soluble bases and a pivalate salt, but all were inferior to K_2CO_3. Varying the solvent (entries 14-18) showed that apolar solvents like toluene and *o*-xylene gave the best results. Of different arylhalides tested (entries 19 and 20), bromoarenes were the best reagents.

Under these conditions the arylation was tried with different bromoarene reagents (Table 1). The yields were only fair, largely because diarylation is an important side reaction and because separating mono- **2** and diaryl-BODIPYs **3** is cumbersome, leading to product loss due to mixed column chromatography fractions. Electron rich (entries 2 and 4), heteroaromatic (entry 4), sterically hindered (entry 5) and ring-fused bromoarenes (entry 6) can be used in this arylation reaction. However, reaction with 4-bromo-*N*,*N*-dimethyl-aniline (entry 3) resulted only in decomposition of the starting BODIPY. Interestingly, reaction with sterically hindered 2-bromo-1,3,5-trimethylbenzene (entry 5) did not produce a diarylated product and only monoarylation, albeit in a lower yield, occured. Disappointingly, the reaction of electron poor bromoarenes (entries 7 and 8) proceeded very slowly under the current reaction conditions. After 2 days there was not enough product formed to allow a complete characterisation, although TLC analysis showed product formation.

Table 1 Scope of the direct C–H arylation of *meso*-substituted BODIPY with different bromoarenes



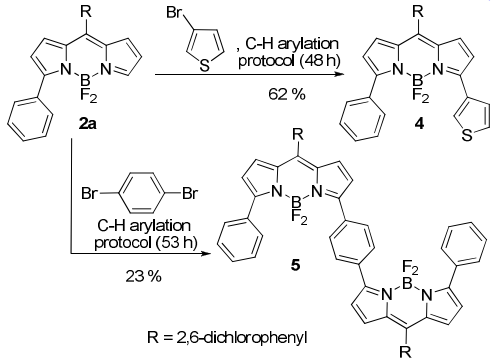
Entry	Compound	Ar[a]	Reaction time	Yield (%)[b] 2	3
1	a	Phenyl[c,d]	24 h	44	17
2	b	4-Anisyl[d]	43 h	42	10
3	c	4-(Dimethylamino)-phenyl[d]	48 h	-[k]	-[k]
4	d	3-Thienyl[d]	27 h	55	10
5	e	Mesityl[d]	43 h	35	0
6	f	1-Naphthyl[c,d]	24 h	20[l]	16
7	g	4-Cyanophenyl[d]	48 h	-[m]	-[m]
8	h	3-Nitrophenyl[d]	48 h	-[m]	-[m]
9	i	Phenyl[c,e]	28 h	31[l]	32
10	j	Phenyl[c,f]	46 h	28	18
11	k	Phenyl[d,g]	4 days	13	43
12	l	Phenyl[c,d,h]	4 days	-[n]	39
13	m	Phenyl[d,i]	3 h	39	40
14	n	3-Thienyl[d,i]	3 h	26	-[n]
15	o	Phenyl[d,i,j]	3,5 h	28	46

[a] Experimental condition: 5 mol% $Pd(OAc)_2$, 10 mol% $HPCy_3BF_4$, 30 mol% PivOH, 3 equivalents K_2CO_3, 1.1 equivalents bromoarene, toluene at 110 °C. [b] All yields are isolated yields. [c] *o*-xylene is used as solvent at 110 °C. [d] R is 2,6-dichlorophenyl. [e] R is phenyl. [f] R is *p*-nitrophenyl. [g] 2.2 equivalents of bromobenzene were used. [h] 10 equivalents of bromobenzene were used. [i] Microwave irradiation, irradiated at 110 °C. [j] 5 equivalents of bromobenzene were used. [k] Only decomposition occurs. [l] Low yield because of difficult purification. [m] Very slow reaction, only starting material retrieved. [n] No pure compound could be obtained.

Next, it was tested whether diaryl-BODIPY **3** could be selectively synthesized by using two equivalents of bromobenzene over a longer reaction time. This resulted in an acceptable yield of the desired diaryl product **3k** (entry 11). Unfortunately, the monoaryl-BODIPY **2k** was still present, which made the purification rather difficult. The use of a significant excess of bromobenzene (entry 12) was not helpful.

Since these C–H arylations require rather long reaction times, the use of microwave irradiation to accelerate the reaction was investigated. Both the monoarylation (entries 13 and 14) and the diarylation (entry 15) protocol became significantly faster under this type of heating. In the case of monoarylation with bromobenzene (entry 13), a similar yield as with conventional heating (entry 1) was obtained for the mono product, although a larger amount of diarylation occurred thus resulting in a higher conversion. However, applying this microwave protocol to arylate with 3-bromothiophene (entry 14), the highest yielding reagent with conventional heating, resulted in a large amount of decomposition and thus a lower yield. In the case of diarylation (entry 15), a similar yield was obtained as with conventional heating (entries 11 and 12) but in a significantly shorter amount of time. Attempts to push this reaction further by irradiating at 150 °C for 3 h resulted only in decomposition.

To demonstrate the generality of this C–H arylation protocol, this reaction was performed with different *meso*-substituted BODIPYs. This showed that not only the *meso*-2,6-dichlorophenyl derivative (entry 1), but also the phenyl



Scheme 1 Synthesis of an asymmetric BODIPY and a BODIPY dimer using the developed C–H arylation method

(entry 9) and *p*-nitrophenyl (entry 10) derivatives, were reactive in this type of arylation albeit with slightly lower yields.

Lastly, to illustrate the possibilities of this novel reaction, an asymmetric dye **4** and a BODIPY dimer **5** were prepared using the developed direct arylation. The asymmetric system **4** was prepared by performing two successive C–H arylations, the first with bromobenzene (entry 1), the second with 3-bromothiophene (Scheme 1). The second arylation proceeded in a much higher yield (62%) than the previous reactions, because the diarylation side reaction was not an issue with the 3-substituted dye **2a**. Because this phenyl-substituted dye **2a** reacted with such a good yield, it was chosen as the substrate for a double C–H arylation with 1,4-dibromobenzene, resulting in the BODIPY dimer **5** in 23% yield (Scheme 1). Indeed, the unsymmetrical dye **4** or dimer **5** would be difficult to prepare from substituted pyrrole building blocks.

The variety of the aromatic groups at the 3,5,8-positions of the BODIPY nucleus of **1**–**5** provides a set of dyes with absorption and fluorescence emission spectra covering a broad range of the visible spectrum (Figure 1). Here we summarize the key results of the spectroscopic investigation. Full details will be described elsewhere.

The spectra display the characteristic narrow absorption and fluorescence emission bands of classic difluoroboron dipyrromethenes. As a function of the solvent, the spectral maxima are located within a very narrow wavelength range and are slightly red-shifted with increasing solvent polarizability, which is the crucial parameter affecting the wavelength position of the maxima. The broadest spectral bands are found for the 1-naphthyl substituted derivatives **2f** and **3f**, and bis-BODIPY **5**. The Stokes shifts are generally quite small with exceptions for **2f**, **3f** and **5**. The extended π-conjugation in the 3,5-diaryl products **3** always leads to bathochromically shifted absorption and emission spectra compared to those of the 3-substituted analogues **2**. Derivative **2e** (with 3-mesityl substituent) has blue-shifted spectra compared to **2a** (with 3-phenyl group), reflecting the diminished π -conjugation in **2e** and indicating that steric hindrance (between 2-H of BODIPY and mesityl *o*-Me) rotates the mesityl group out of the BODIPY plane. The nature of the *meso*-substituent has only a small effect on the spectral positions. The majority of the dyes have high fluorescence quantum yields ($\Phi > 0.85$), except for the analogues with *meso*-phenyl (**2i** and **3i**) and *meso*-*p*-nitrophenyl (**2j** and **3j**) substituents. Free rotation of the 8-aryl

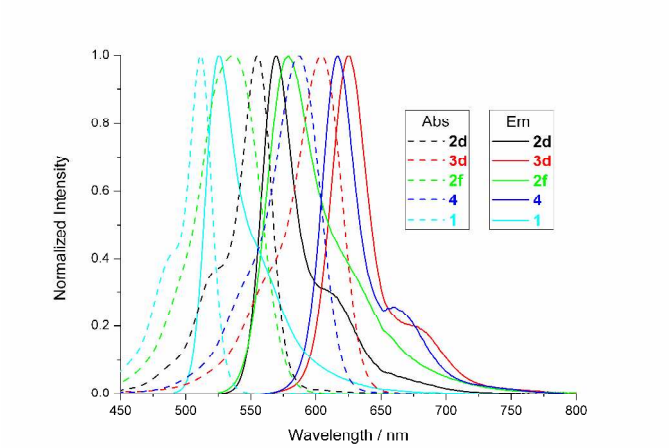


Fig. 1 Normalized, visible absorption spectra and corresponding normalized fluorescence emission spectra of a selection of *meso*-(2,6-dichlorophenyl) substituted BODIPY dyes (**1**, **2d**, **2f**, **3d**, **4**) in THF.

group in the latter dyes enhances nonradiative deactivation of the S_1 excited state, yielding low Φ values, whereas restriction of rotation of the 8-(2,6-dichlorophenyl) group leads to high Φ values.[14] The presence of a nitro function in **2j** and **3j** contributes extra to fluorescence quenching. Since the number of known bis-BODIPY dyes is rather limited, extra information on such derivatives is valuable. Therefore, Table S2 (ESI) lists some relevant spectroscopic data on compound **5**.

In conclusion, a general method for the preparation of brightly fluorescent 3,5-arylated BODIPY dyes with red-shifted electronic spectra utilizing C–H functionalisation has been developed, thus avoiding the tedious synthesis of substituted pyrrole building blocks and unstable intermediates. We are currently working towards conditions to improve the selectivity of monoarylation over diarylation and to expand the scope of this reaction.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, synthesis optimisation study, characterisation data and UV–vis spectroscopic data. See DOI: 10.1039/b000000x/

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