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Regioselective 2,6-dihalogenation of BODIPYs in 1,1,1,3,3,3-hexafluoro-2-propanol and preparation of novel *meso*-alkyl polymeric BODIPY dyes†

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Regioselective 2,6-halogenation of BODIPYs in hexafluoro-2-propanol (HFIP) afforded products in less than 5 min. Halogenated BODIPYs were subjected to Pd-catalyzed cross-coupling reactions to form novel *meso*-alkyl polymeric BODIPY dyes.

4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) represents an important class of fluorescent dyes because of their excellent photophysical and electrochemical properties such as high photoluminescent quantum yields, large molar absorption coefficients, narrow emission bands, high chemical stability, and good bioavailability.[1,2] They have broad applications as labels for reagents and biomarkers,[3,4] chemosensors,[5,6] energy transfer cassettes,[7,8] supramolecular polymers[9] and for photodynamic therapy.[10] A significant amount of effort has been spent on the synthesis of BODIPYs dyes to modify their spectroscopic and electronic properties. Halogenated BODIPYs are common precursors for further functionalization.[11] For example, 3,5-halogenated BODIPYs (Fig. 1, A) could be used for S_NAr reactions and palladium-catalyzed cross-coupling reactions.[12–16] The 2,6-halogenated BODIPYs (Fig. 1, B) are potential sensitizers for photodynamic therapy (PDT).[17,18] They can also be derivatized by metal-catalyzed cross-coupling reactions.[19–21]

Direct electrophilic halogenation of BODIPYs is well-documented in the literature. *N*-Bromosuccinimide (NBS),[20] bromine,[22] NBS-AIBN, and $CuBr_2$[23] have been used for the bromination of BODIPYs. Regioselective bromination has also been reported in the synthesis of tetra- and hexa-brominated *meso*-thienyl BODIPYs,[24] mono- to hepta-brominated pyrrolic-unsubstituted BODIPYs,[25] and 2,6-dibromoBODIPYs.[26] Introduced in this paper is a new process for regioselective 2,6-dihalogenation of BODIPYs using fluorinated alcohol as a solvent. Fluorinated alcohols have unique properties such as low toxicity, low nucleophilicity, high polarity, strong hydrogen bond donating capability, and good solvation capability with water. They have been used as green solvents for many organic transformations.[27–30]

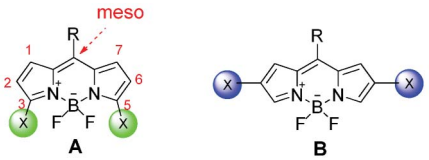
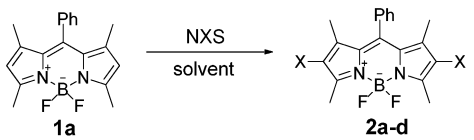


Fig. 1 3,5- and 2,6-dihalogenated BODIPYs.

A range of solvents were screened for the direct halogenation of 1,3,5,7-tetramethyl BODIPY **1a** with *N*-halosuccinimide (NXS). It was found that solvents have a dramatic impact on the reaction time and product yield (Table 1). NCS reactions in common

Table 1 Optimization of reaction conditions for the dihalogenation of **1a**[a]



Entry	NXS (equiv.)	Solvent	Additive (equiv.)	Time	Product	Yield (%)[b]
1	NCS (4.0)	CH_2Cl_2	—	12 h	**2a**	42
2	NCS (4.0)	EtOAc	—	12 h	**2a**	trace
3	NCS (4.0)	CH_3CN	—	12 h	**2a**	13
4	NCS (4.0)	MeOH	—	12 h	**2a**	27
5	NCS (2.4)	MeOH	thiourea (0.05)	30 min	**2a**	82
6	NCS (2.4)	HFIP	—	5 min	**2a**	100
7	NBS (2.4)	HFIP	—	5 min	**2b**	100
8	NIS (2.4)	HFIP	—	1 min	**2c**	100
9	NCS (1.2)	HFIP	—	5 min	**2d**[c]	90

[a] Reaction conditions: **1a** (0.2 mmol), NXS, solvent (2 mL), 25 °C. [b] Yield was determined by ^1H NMR. [c] mono-chlorinated product.

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organic solvents such as CH_2Cl_2, EtOAc, CH_3CN and MeOH at room temperature for 12 h gave the dichlorinated product **2a** in less than 42% yield (Table 1, entries 1–4). Addition of a catalytic amount of thiourea in MeOH increased the yield to 82% and reduced the reaction time to 30 min (Table 1, entry 5). Using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent, the NCS and NBS reactions were completed in 5 min to give product **2a** or **2b** in quantitative yield (Table 1, entries 6 and 7). The reaction with the more active NIS gave **2c** in less than 1 min (Table 1, entry 8). In addition, reaction with 1.2 equiv. of NCS afforded monochloroBODIPY **2d** in 90% yield together with a small amount of dichloroBODIPY. These results are attributed to the hydrogen bonding effect between HFIP and NXS which makes X^+ more electrophilic.[31,32]

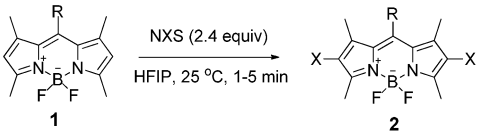
The regioselectivity of halogenation of unsubstituted BODIPY **1b** was also studied. The reaction gave 2,6-dibromoBODIPY **2e** in 90% isolated yield. No 3- or 5-bromoBODIPYs were detected in the reaction mixture (Scheme 1).

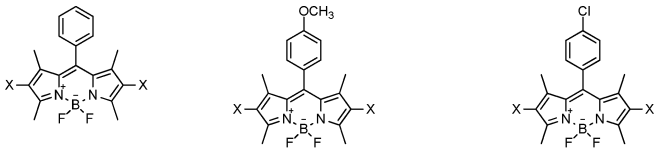
The scope of dihalogenation of BODIPYs was also examined. Dibromination and diiodination reactions were conducted since bromo- and iodoBODIPYs are reactive intermediates and could be used for further modifications. The results shown in Table 2 indicate that BODIPYs with *meso*-aryl and *meso*-alkyl groups gave the corresponding products in good to excellent yields. BODIPYs modified with morpholine, bis(chloromethyl)amine, and schiff base have good compatibility. A diBODIPY was tetrabrominated in the presence of 4.8 equiv. of NBS.

There are several reports on the preparation of polymeric BODIPY dyes by Pd-catalyzed coupling reactions.[33–35] The linkers could be 1,4-phenylenebisboronic acid, 1,4-diethynylbenzene and related structures. Complementary to the polymeric *meso*-aryl BODIPY dyes, we prepared four novel polymeric *meso*-alkyl BODIPY dyes by Pd-catalyzed coupling reactions of dihalogenated BODIPYs (Scheme 2). Thus, a reaction mixture of 2,6-dibromo- or 2,6-diiodoBODIPYs **2** was distilled to remove HFIP and the residue was reacted with 1,4-phenylenebisboronic acid under general Suzuki reaction conditions to give polymeric BODIPY dyes **3a–d** bearing different lengths of *meso*-alkyl chain. The HFIP solvent could be reused in up to four cycles.

Unsubstituted *meso*-alkyl BODIPY **1c** has a strong absorption band at 492 nm and an emission band at 513 nm, and a high Φ_f of 0.949 (Fig. 2). Its 2,6-diborominate analog **2l** has a red-shift of 28 nm for the absorption band and 32 nm for the emission band. Its Φ_f is decreased to 0.471. The results are similar to those reported for bromoBODIPYs due to the heavy-atom effect[36,37] The polymeric BODIPY dye **3a** (M_n = 17 110 g mol^{-1}, polydiversity: 1.17) has bathochromic shifts of 53 and 61 nm for the absorption and emission bands, respectively. The Φ_f is increased to 0.601 due to the enhanced conjugation relative to **2l**. In all cases the polarity of the solvents had little effect on the spectra of the *meso*-alkyl BODIPYs, the dihalogenated BODIPYs, and the polymeric BODIPY dyes.

Table 2 Dihalogenation of BODIPYs (**1**) in HFIP[a]

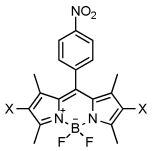




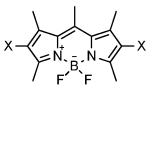
2b, X = Br, 92%
2c, X = I, 90%

2f, X = Br, 82%[b]
2g, X = I, 80%[b]

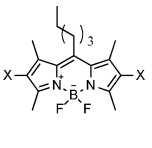
2h, X = Br, 88%
2i, X = I, 86%



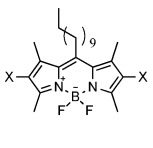
2j, X = Br, 95%
2k, X = I, 92%



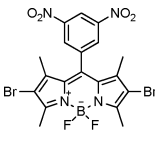
2l, X = Br, 95%
2m, X = I, 93%



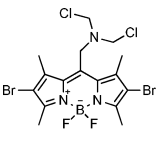
2n, X = Br, 91%
2o, X = I, 90%



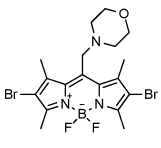
2p, X = Br, 90%
2q, X = I, 85%



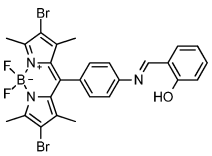
2r, 91%



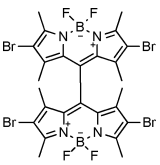
2s, 84%



2t, 83%

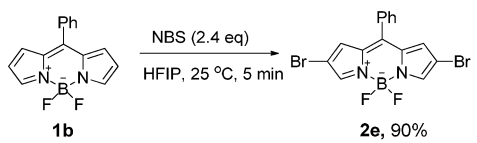


2u, 81%

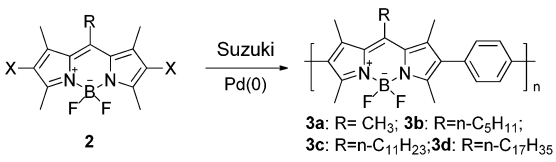


2v, 87%[c]

[a] Reaction conditions: **1** (0.2 mmol), NBS or NIS (2.4 equiv.), HFIP (2 mL), 25 °C, 5 min for bromination or 1 min for iodination, isolated yields. [b] 15 min reaction time. [c] 4.8 equiv. of NBS.



Scheme 1 Regioselective dibromination of BODIPY **1b**.



Scheme 2 Synthesis of polymeric BODIPY dyes.

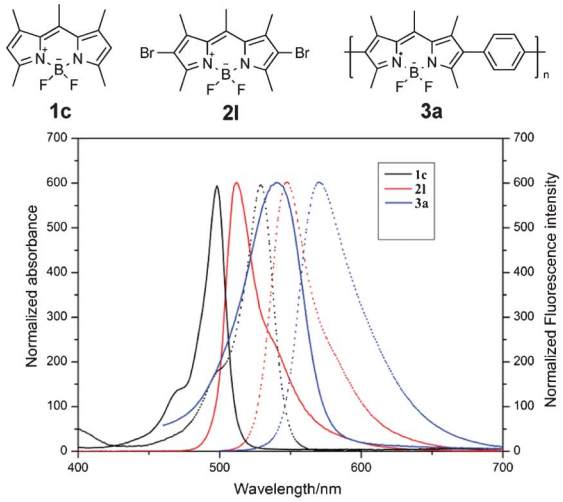


Fig. 2 Normalized absorption (solid lines) and emission (dashed lines) spectra of BODIPYs **1c** (black), **2l** (red) and **3a** (blue) in dichloromethane.

The thermal stabilities of the monomers **1c**, **2l** and polymer **3a** were evaluated by thermogravimetric analysis (TGA). Fig. 3 showed that **1c** and **2l** lost 5% of their weight at 270 °C and 310 °C, respectively. The polymeric BODIPY dye **3a** did not decompose until 335 °C, which suggests it has improved thermal stability.

Different alkyl groups such as *n*-C_5H_{11}, *n*-$C_{11}H_{23}$, *n*-$C_{17}H_{35}$ were incorporated into the *meso*-position and their photophysical properties were investigated (Table 3). It was found that the polymeric BODIPYs **3a–d** have a red-shift of about 50–60 nm compared to the corresponding monomeric BODIPYs. The polarity of the solvents and chain length of the alkyl groups at the *meso*-position have no significant impact on their photophysical properties, while the fluorescence quantum yield is decreased when the chain length of the alkyl group is increased. BromoBODIPY monomers with a longer alkyl chain have higher solubility which resulted in polymers with increased molecular weight. Good thermal stabilities were also found for the polymeric BODIPYs **3b–d** (see ESI†).

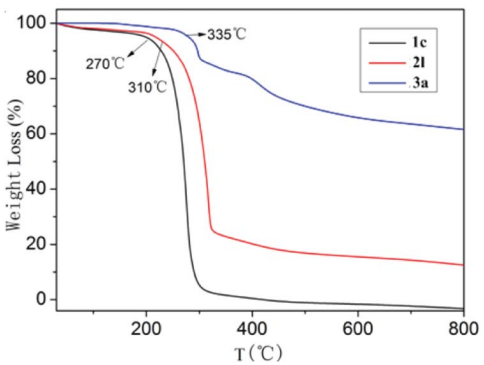


Fig. 3 Thermogravimetric analysis of BODIPYs **1c** (black), **2l** (red) and **3a** (blue) in dichloromethane.

Table 3 Photophysical properties of *meso*-alkyl BODIPY polymeric dyes

Polymer	Solvent	λ_{abs}(nm)	λ_{em} (nm)	Stokes shift (nm)	Φ_f[a]
3a	hexane	546	573	27	0.615
	CH_2Cl_2	545	574	29	0.601
	THF	545	577	32	0.593
	ethanol	543	578	35	0.566
3b	hexane	548	578	30	0.515
	CH_2Cl_2	547	580	33	0.501
	THF	547	581	34	0.493
	ethanol	545	581	36	0.466
3c	hexane	548	577	29	0.485
	CH_2Cl_2	546	578	32	0.471
	THF	546	580	34	0.453
	ethanol	546	581	35	0.426
3d	hexane	548	577	29	0.485
	CH_2Cl_2	546	578	32	0.471
	THF	546	580	34	0.453
	ethanol	544	579	35	0.426

[a] Fluorescence quantum yields (Φ) were calculated using Rhodamine B in anhydrous ethanol (Φ = 0.73).

Solid-state polymeric BODIPY fluorescence dyes **3a–d** were obtained to evaluate the effect of polymer aggregation and their optical properties. The fluorescence spectra of the polymers in the solid state retained most of their spectral features in solution and exhibited significant red shift for both absorption and emission maxima in CH_3CN solution (**3a**: 585 and 617 nm; **3b**: 562 and 603 nm; **3c**: 571 and 602 nm; **3d**: 656 and 608 nm). The results indicate the presence of intermolecular electronic interactions and/or increased coplanarity of the polymer in the solid state.

In summary, we have developed a new process for regioselective 2,6-dihalogenation of BODIPYs in HFIP using *N*-halosuccinimide as the halogen source. The reactions were completed in 1–5 min to give the corresponding products in excellent yields. Fast reaction times, additive-free synthesis and ease of operation make this protocol complementary to the existing literature methods. The non-toxic and green HFIP solvent could be readily recycled by distillation. Further modifications of 2,6-dihalogenated BODIPYs *via* Suzuki coupling reactions generated novel *meso*-alkyl polymeric BODIPYs. They have improved thermal stability and have potential for use as fluorescent materials. Other functionalization of BODIPYs is currently underway in our group and will be reported in due course.

Acknowledgements

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References

1 A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891.
2 G. Ulrich, R. Ziessel and A. Harriman, *Angew. Chem., Int. Ed.*, 2008, **47**, 1184.

3 R. West, C. Panagabko and J. Atkinson, *J. Org. Chem.*, 2010, **75**, 2883.
4 Z. J. Zhang, N. Kwiatkowski, H. Zeng, S. M. Lim, N. S. Gray, W. Zhang and P. L. Yang, *Mol. BioSyst.*, 2012, **8**, 2523.
5 O. A. Bozdemir, R. Guliyev, O. Buyukcakir, S. Selcuk, S. Kolemen, G. Gulseren, T. Nalbantoglu, H. Boyaci and E. U. Akkaya, *J. Am. Chem. Soc.*, 2010, **132**, 8029.
6 T. Cheng, T. Wang, W. Zhu, X. Chen, Y. Yang, Y. Xu and X. Qian, *Org. Lett.*, 2011, **13**, 3656.
7 S. Diring, F. Puntoriero, F. Nastasi, S. Campagna and R. Ziessel, *J. Am. Chem. Soc.*, 2009, **131**, 6108.
8 Y. Ueno, J. Jose, A. Loudet, C. Perez-Bolivar, P. Anzenbacher and K. Burgess, *J. Am. Chem. Soc.*, 2011, **133**, 51.
9 Ö. A. Bozdemir, O. Büyükcakir and E. U. Akkaya, *Chem.–Eur. J.*, 2009, **15**, 3830.
10 S. Atilgan, Z. Ekmekci, A. L. Dogan, D. Guc and E. U. Akkaya, *Chem. Commun.*, 2006, 4398.
11 M. Baruah, W. Qin, N. Basarić, W. M. De Borggraeve and N. Boens, *J. Org. Chem.*, 2005, **70**, 4152.
12 M. Baruah, W. Qin, R. A. L. Vallée, D. Beljonne, T. Rohand, W. Dehaen and N. Boens, *Org. Lett.*, 2005, **7**, 4377.
13 T. Rohand, M. Baruah, W. Qin, N. Boens and W. Dehaen, *Chem. Commun.*, 2006, 266.
14 V. Leen, T. Leemans, N. Boens and W. Dehaen, *Chem. Commun.*, 2009, 4515.
15 V. Leen, E. Braeken, K. Luckermans, C. Jackers, M. Van derAuweraer, N. Boens and W. Dehaen, *Eur. J. Org. Chem.*, 2011, 4386.
16 J. Han, O. Gonzalez, A. Aguilar-Aguilar, E. Peña-Cabrera and K. Burgess, *Org. Biomol. Chem.*, 2009, **7**, 34.
17 T. Yogo, Y. Urano, Y. Ishitsuka, F. Maniwa and T. Nagano, *J. Am. Chem. Soc.*, 2005, **127**, 12162.
18 S. Atilgan, Z. Ekmekci, A. L. Dogan, D. Guc and E. U. Akkaya, *Chem. Commun.*, 2006, 4398.
19 D. Zhang, Y. Wen, Y. Xiao, G. Yu, Y. Liu and X. Qian, *Chem. Commun.*, 2008, 4777.
20 L. Bonardi, G. Ulrich and R. Ziessel, *Org. Lett.*, 2008, **10**, 2183.
21 J. Goday, G. Vives and J. M. Tour, *Org. Lett.*, 2010, **12**, 1464.
22 S. Atilgan, Z. Ekmekci, A. L. Dogan, D. Guc and E. U. Akkaya, *Chem. Commun.*, 2006, 4398.
23 J.-H. Ye, G. Wang, C. Huang, Z. Hu, W. Zhang and Y. Zhang, *Synlett*, 2012, 104.
24 S. H. Choi, K. Kim, J. Jeon, B. Meka, D. Bucella, K. Pang, S. Khatua, J. Lee and D. G. Churchill, *Inorg. Chem.*, 2008, **47**, 11071.
25 Y. Hayashi, S. Yamaguchi, Y. W. Cha, D. Kim and H. Shinokubo, *Org. Lett.*, 2011, **13**, 2992.
26 L.-J. Jiao, W.-D. Pang, L.-Y. Zhou, Y. Wei, X.-L. Mu, G.-F. Bai and E.-H. Hao, *J. Org. Chem.*, 2011, **76**, 9988.
27 R. Ben-Daniel, S. P. de Visser, S. Shaik and R. Neumann, *J. Am. Chem. Soc.*, 2003, **125**, 12116.
28 M. Westermaier and H. Mayr, *Org. Lett.*, 2006, **8**, 4791.
29 M. O. Ratnikov, V. V. Tumanov and W. A. Smit, *Angew. Chem., Int. Ed.*, 2008, **47**, 9739.
30 K. De, J. Legros, B. Crousse and D. Bonnet-Delpon, *J. Org. Chem.*, 2009, **74**, 6260.
31 Y. J. Mei, P. A. Bentley and J. Du, *Tetrahedron Lett.*, 2008, **49**, 3802.
32 L. Wang, C. Cai, D. P. Curran and W. Zhang, *Synlett*, 2010, 433.
33 V. R. Donuru, S. Zhu, S. Green and H. Liu, *Polymer*, 2010, **51**, 5359.
34 A. Nagai and Y. Chujo, *Macromolecules*, 2010, **43**, 193.
35 S. Zhu, N. Dorh, J. Zhang, G. Vegesna, H. Li, F. T. Luo, A. Tiwari and H. Liu, *J. Mater. Chem.*, 2012, **22**, 2781.
36 T. Rohand, M. Baruah, W. Qin, N. Boens and W. Dehaen, *Chem. Commun.*, 2006, 266.
37 V. Lakshmi and M. Ravikanth, *J. Org. Chem.*, 2011, **76**, 8466.

