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Axially chiral BODIPYs†

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The synthesis and resolution of a class of chiral organic fluorophores, axially chiral 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacenes (Ax*-BODIPY), is described. Ax*-BODIPYs were prepared through a modular synthesis combined with a late stage Heck functionalisation. Resolution was achieved by preparative chiral HPLC. Absolute stereochemical assignment was performed by comparison of experimental ECD spectra with TD-DFT calculations.

The boron-dipyrromethene dyes (BODIPY)[1] are among the most widely used organic fluorophores, finding utility in an array of applications including photodynamic therapy,[2] biological imaging[3] and fluorescence sensing.[4] The continuing popularity of the BODIPYs derives from the combination of robust synthetic protocols with desirable physical properties such as thermal, chemical and photochemical stability, high fluorescence quantum yield, low intrinsic triplet-state formation, high extinction coefficients and good solubility (Fig. 1).[5]

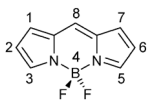

Fig. 1 General structure of a boron-dipyrromethane dye (BODIPY).

Chiral fluorophores have been explored for the selective sensing of chiral molecules,[6] including attempts to determine the enantiomeric excess of a solution by optical measurements.[7] A number of chiral fluorophores have been reported, the most widely studied being the lanthanide coordination complexes,[8] 1,1′-bi-2-naphthols (BINOL) and helicenes.[9] Chiral molecules containing the BODIPY fluorophore have been synthesised, typically through the decoration of the BODIPY core with chiral appendages.[10] An example of a resolved BODIPY based around an asymmetric boron atom (B*-BODIPY) with the chirality embedded in the core structure of the fluorophore itself has been described (**1**),[11] whilst a number of unresolved boron-centred chiral BODIPYs have been reported based on the intramolecularly B–O bonded BODIPY and the closely related aza-BODIPY systems (**2–4**) (Fig. 2).[12]

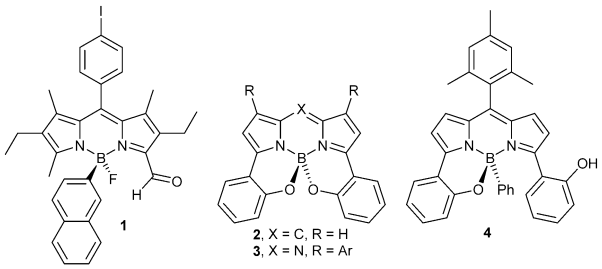

Fig. 2 Chiral BODIPY and aza-BODIPYs.

In this manuscript we present a general approach for the synthesis, resolution and absolute stereochemical determination of a class of axially chiral BODIPYs (Ax*-BODIPY), based on restricted rotation of aromatic substituents in the *meso*-position (or 8-position).

The rotation of aryl substituents at the *meso*-position of BODIPYs has been previously studied because of the influence this has on both the S_1 lifetime and the fluorescence quantum yield of the fluorophore.[13] These results have been applied in the development of BODIPY "rotors" for fluorescence sensing of microenvironment viscosity.[14]

Our design strategy for a resolvable atropisomeric Ax*-BODIPY system therefore involved provision for (a) a high rotational barrier for an aryl substituent at the *meso*-position (b) chemically differentiable groups on the *ortho*-positions of the *meso*-aryl

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† Electronic supplementary information (ESI) available: UV/Vis and fluorescence spectra for **8-(*rac*)**, **9-(*rac*)** and **10-(*rac*)**, ECD spectra of **10-(+)** and **10-(−)**, computational approaches towards predicted ECD and VCD spectra of **10-(+)** and **10-(−)**, HPLC trace for the resolution of **10-(*rac*)**, experimental procedures for compounds **6–10**, ^{1}H and ^{13}C spectra for compounds **6–10**. Crystallographic data for **9-(*rac*)** and **10-(*rac*)**. CCDC 984417 and 984418. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00851k

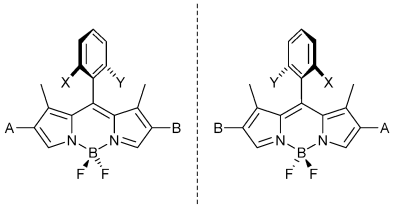
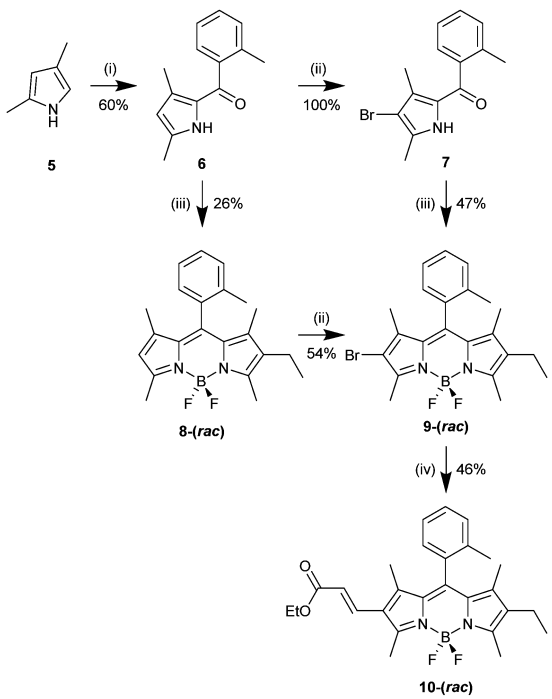


Fig. 3 General design of Ax*-BODIPYs.

substituent (X and Y) and (c) chemically differentiable groups on the 2/6-positions (A and B) of the BODIPY core (Fig. 3).[15]

In order to ensure a high rotational barrier for *ortho*-substituted *meso*-aryl groups we opted to include methyl groups in both the 1- and 7-positions of the BODIPY fluorophore. The introduction of *ortho*-functionalised *meso*-aryl substituents was anticipated to be straightforward, through the application of condensation-based synthetic routes towards BODIPY systems. Finally to allow synthetic flexibility we decided to chemically differentiate at the 2/6-positions *via* a late stage metal-catalysed cross-coupling reaction.

Synthesis of **10-(*rac*)** started with the deprotonation of 2,4-dimethyl-1*H*-pyrrole (**5**) with EtMgBr and subsequent C-2 selective acylation with 2-methylbenzoyl chloride to give (3,5-dimethyl-1*H*-pyrrol-2-yl)(*o*-tolyl)methanone (**6**). Pyrrole **6** was then brominated at the 4-position to give (4-bromo-3,5-dimethyl-1*H*-pyrrol-2-yl)(*o*-tolyl)-methanone (**7**), followed by acid-catalysed condensation with 3-ethyl-2,4-dimethyl-1*H*-pyrrole and subsequent BF_2 chelation to give **9-(*rac*)**. A complementary route to **9-(*rac*)** was also investigated involving condensation of pyrrole **6** with 3-ethyl-2,4-dimethyl-1*H*-pyrrole, BF_2 chelation to give **8-(*rac*)** and subsequent bromination. **9-(*rac*)** is a useful starting point for the synthesis of different axially chiral BODIPY systems through the use of metal-catalysed cross-coupling reactions. In our case we chose to functionalise **9-(*rac*)** *via* a Heck reaction with ethyl acrylate, differentiating the 2- and 6-positions, to give the target **10-(*rac*)** (Scheme 1).



Scheme 1 Synthesis of **10-(*rac*)**. (i) (a) EtMgBr, Et_2O, reflux, 1 h (b) 2-methylbenzoyl chloride, rt, 24 h (ii) Br_2, DCM, rt, 24 h (iii) (a) 2,4-dimethyl-3-ethylpyrrole, TFA, DCM, rt, 18 h (b) i-Pr_2NEt, BF_3OEt_2, rt, 12 h (iv) ethyl acrylate, Et_3N, $Pd(OAc)_2$, PPh_3, DMF, 100 °C, 12 h.

Compounds **8-(*rac*)**, **9-(*rac*)** and **10-(*rac*)** gave UV/Vis absorbance (λ_{max} = 515, 526, 538 nm) and fluorescence (λ_{max} = 525, 540, 555 nm) spectra typical of the BODIPY class of fluorophores, with high extinction coefficients and moderate to good fluorescence quantum yields (ESI†).

The asymmetry of compounds **8-(*rac*)**, **9-(*rac*)** and **10-(*rac*)** was observable by NMR spectroscopy, the ^{1}H NMR spectrum showing five different methyl environments in each case. Restricted rotation of the *meso*-aryl group imposes a diastereotopic relationship on the two fluorine atoms. This was observable in the ^{19}F NMR spectrum as an ABX coupling pattern, each fluorine peak showing both geminal ^{19}F–^{19}F and ^{19}F–^{11}B coupling (ESI† and Fig. 4).[16]

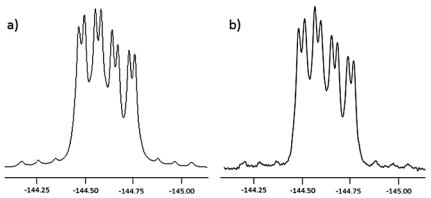


Fig. 4 (a) Simulated (using gNMR)[17] and (b) experimental ^{19}F NMR spectra of **10-(*rac*)**. Note the asymmetry in the spectra due to ^{10}B coupling.

Crystallisation of both **9-(*rac*)** and **10-(*rac*)** by slow diffusion (DCM/petrol) gave single crystals suitable for X-ray analysis. **9-(*rac*)** and **10-(*rac*)** gave monoclinic crystals, both with the centrosymmetric space group $P2_1/c$. In both cases four molecules are present per unit cell, two of each of the (*R*)- and (*S*)-enantiomers (ESI† and Fig. 5).

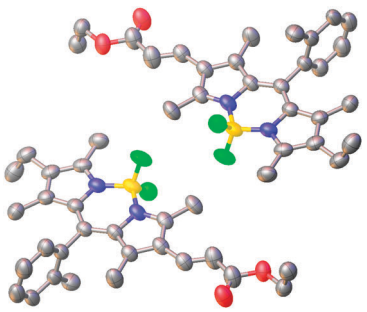


Fig. 5 Part of the crystal structure of **10-(*rac*)** showing both **(*R*)-10** and **(*S*)-10**.

The planes defined by the *ortho*-methylphenyl group and the 1,2-dihydro-1,3λ^4,2λ^4-diazaborinine ring in both **9-(*rac*)** and **10-(*rac*)** are close to orthogonal, with twist angles of 85.9 and 85.7 degrees, respectively, suggesting significant steric hindrance around the chiral axis.

10-(*rac*) was well resolved by semi-preparative chiral HPLC (Chiralpak AD-H, Heptane/IPA 85/15) giving sufficient of both enantiomers of **10** for further study (ESI†). Both enantiomers of **10** gave identical ^{1}H NMR spectra to that of **10-(*rac*)**, whilst giving

weak but opposite $[\alpha]_D$ values of +13.0 and −13.0 respectively (henceforth labelled **10-(+)** and **10-(−)**).

To assign absolute configuration of the enantiomeric samples **10-(+)** and **10-(−)** vibrational circular dichroism (VCD), Raman optical activity (ROA) and electronic circular dichroism (ECD) measurements were performed. In agreement with DFT calculations, VCD spectroscopy showed no significant signals for **10-(+)**/**10-(−)**, preventing the use of VCD for absolute configuration determination (see ESI† for further discussion).[18] Because of intense fluorescence, no useful ROA data could be measured;[19] however, good experimental ECD spectra of both **10-(+)** and **10-(−)** were obtained in the range 175–500 nm using a Chirascan-plus spectrometer (Applied Photophysics Ltd).

Boltzmann-weighted ECD spectra for the postulated **(*R*)-10** enantiomer were obtained from TD-DFT calculations at the cam-B3LYP/6-311++G(2d,p) level.[20] First a low-energy conformation library was generated, followed by calculation of the individual ECD spectra for each of the low-energy conformations. The combined Boltzmann-weighted spectrum was then blue-shift corrected by 10 nm, to compensate for the typical underestimation of transition energies by TD-DFT (ESI†).[20]

Comparison of the corrected Boltzmann-weighted ECD spectrum obtained for **(*R*)-10** showed that, for the near-UV, good agreement is obtained with the experimental ECD spectrum of **10-(+)**, whilst at longer wavelengths, the smaller ECD features are less well reproduced (Fig. 6). The agreement between experiment and theory in the 175–275 nm region allows the absolute stereochemistry of **10-(+)** to be assigned as **(*R*)-10-(+)** and thus **10-(−)** must have opposite stereochemistry, **(*S*)-10-(−)**.

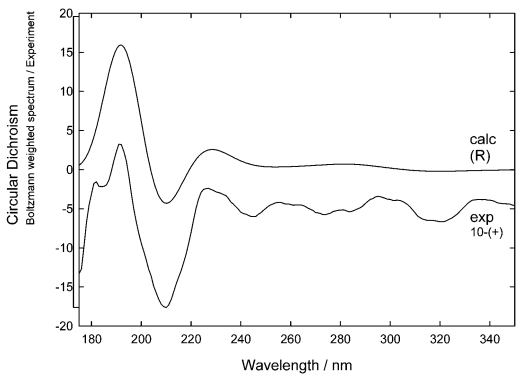


Fig. 6 Comparison of calculated ECD spectra of **(*R*)-10** [top] and experimentally measured ECD **10-(+)** [bottom].

In conclusion, we have reported a synthetically flexible route to a class of axially chiral fluorophores (Ax*-BODIPYs), including resolution and absolute stereochemical determination by combined ECD/TD-DFT. Further research will focus on the interactions of Ax*-BODIPYs with chiral analytes in solution and applications to sensing.

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Notes and references

1 A. Treibs and F.-H. Kreuzer, *Justus Liebigs Ann. Chem.*, 1968, **718**, 208.
2 A. Kamkaew, S. Hui Lim, H. B. Lee, L. V. Kiew, L. Y. Chung and K. Burgess, *Chem. Soc. Rev.*, 2013, **42**, 77.
3 (*a*) I. Johnson and M. T. Z. Spence, *Molecular Probes Handbook, A Guide to Fluorescent Probes and Labeling Technologies*, Life Technologies Ltd, 11th edn, 2010; (*b*) A. Hendricks, E. J. Keliher, D. Wan, S. A. Hilderbrand, R. Weissleder and R. Mazitschek, *Angew. Chem., Int. Ed.*, 2012, **51**, 4603.
4 N. Boens, V. Leena and W. Dehaen, *Chem. Soc. Rev.*, 2012, **41**, 1130.
5 (*a*) G. Ulrich, R. Ziessel and A. Harriman, *Angew. Chem., Int. Ed.*, 2008, **47**, 1184; (*b*) A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891.
6 Y. Zhouab and J. Yoon, *Chem. Soc. Rev.*, 2012, **41**, 52.
7 (*a*) F. Miao, J. Zhou, D. Tian and H. Li, *Org. Lett.*, 2012, **14**, 3572; (*b*) G. Beer, K. Rurack and J. Daub, *Chem. Commun.*, 2001, 1138; (*c*) J. Jiao, X. Liu, X. Mao, J. Li, Y. Cheng and C. Zhu, *New J. Chem.*, 2013, **37**, 317.
8 D. Parker, R. S. Dickins, H. Puschmann, C. Crossland and J. A. K. Howard, *Chem. Rev.*, 2002, **102**, 1977.
9 (*a*) L. Pu, *Chem. Rev.*, 2004, **104**, 1687; (*b*) H. Maeda, Y. Bando, K. Shimomura, I. Yamada, M. Naito, K. Nobusawa, H. Tsumatori and T. Kawai, *J. Am. Chem. Soc.*, 2011, **133**, 9266; (*c*) Y. Sawada, S. Furumi, A. Takai, M. Takeuchi, K. Noguchi and K. Tanaka, *J. Am. Chem. Soc.*, 2012, **134**, 4080.
10 (*a*) G. Beer, C. Niederalt, S. Grimme and J. Daub, *Angew. Chem., Int. Ed.*, 2000, **39**, 3252; (*b*) A. Gossauer, F. Nydegger, T. Kiss, R. Sleziak and H. Stoeckli-Evans, *J. Am. Chem. Soc.*, 2004, **126**, 1772; (*c*) E. M. Sánchez-Carnerero, F. Moreno, B. L. Maroto, A. R. Agarrabeitia, J. Bañuelos, T. Arbeloa, I. López-Arbeloa, M. J. Ortiz and S. de la Moya, *Chem. Commun.*, 2013, **49**, 11641; (*d*) E. M. Sánchez-Carnerero, F. Moreno, B. L. Maroto, A. R. Agarrabeitia, M. J. Ortiz, B. G. Vo, G. Muller and S. de la Moya, *J. Am. Chem. Soc.*, 2014, **136**, 3346–3349.
11 A. Haefele, C. Zedde, P. Retailleau, G. Ulrich and R. Ziessel, *Org. Lett.*, 2010, **12**, 1672.
12 (*a*) H. Kim, A. Burghart, M. B. Welch, J. Reibenspies and K. Burgess, *Chem. Commun.*, 1999, 1889; (*b*) A. Loudet, R. Bandichhor, K. Burgess, A. Palma, S. O. McDonnell, M. J. Hall and D. F. O'Shea, *Org. Lett.*, 2008, **10**, 4771; (*c*) C. Ikeda, T. Maruyama and T. Nabeshima, *Tetrahedron Lett.*, 2009, **50**, 3349.
13 (*a*) K. Yamada, T. Toyota, K. Takakura, M. Ishimaru and T. Sugawara, *New J. Chem.*, 2001, **25**, 667; (*b*) M. A. H. Alamiry, A. C. Benniston, J. Hagon, T. P. L. Winstanley, H. Lemmetyinen and N. V. Tkachenko, *RSC Adv.*, 2012, **2**, 4944; (*c*) H. L. Kee, C. Kirmaier, L. Yu, P. Thamyongkit, W. J. Youngblood, M. E. Calder, L. Ramos, B. C. Noll, D. F. Bocian, W. R. Scheidt, R. R. Birge, J. S. Lindsey and D. Holten, *J. Phys. Chem. B*, 2005, **109**, 20433.
14 (*a*) M. K. Kuimova, G. Yahioglu, J. A. Levitt and K. Suhling, *J. Am. Chem. Soc.*, 2008, **130**, 6672; (*b*) M. K. Kuimova, S. W. Botchway, A. W. Parker, M. Balaz, H. A. Collins, H. L. Anderson, K. Suhling and P. R. Ogilby, *Nat. Chem.*, 2009, **1**, 69; (*c*) N. A. Hosny, G. Mohamedi, P. Rademeyer, J. Owen, Y. Wu, M.-X. Tang, R. J. Eckersley, E. Stride and M. K. Kuimovaa, *PNAS*, 2013, **110**, 9225; (*d*) M. A. H. Alamiry, A. C. Benniston, G. Copley, K. J. Elliott, A. Harriman, B. Stewart and Y.-G. Zhi, *Chem. Mater.*, 2008, **20**, 4024; (*e*) A. C. Benniston, A. Harriman, V. Whittle and M. Zelzer, *Eur. J. Org. Chem.*, 2010, 523.
15 During the preparation of this manuscript a related atropisomeric BODIPY oligomer system was reported: S. Kolemen, Y. Cakmak, Z. Kostereli and E. U. Akkaya, *Org. Lett.*, 2014, **16**, 660–663.
16 (*a*) A. C. Benniston, G. Copley, K. J. Elliott, R. W. Harrington and W. Clegg, *Eur. J. Org. Chem.*, 2008, 2705; (*b*) M. Bröring, R. Krüger, S. Link, C. Kleeberg, S. Köhler, X. Xie, B. Ventura and L. Flamigni, *Chem. – Eur. J.*, 2008, **14**, 2976; (*c*) A. C. Benniston, G. Copley, A. Harriman, D. Howgego, R. W. Harrington and W. Clegg, *J. Org. Chem.*, 2010, **75**, 2018.
17 *gNMR V5*, Adept Scientific plc, Letchworth Herts, UK, 2003.
18 Sampling for 72 hours and combination of the spectra of **10-(+)** and **10-(−)** for improved baseline correction using a BioTools Chiral*IR*-2X spectrometer gave no detectable VCD signals with a significant signal-to-noise ratio.
19 ROA measurements were attempted using a BioTools ChiralRaman spectrometer.
20 J. Autschbach, in *Comprehensive Chiroptical Spectroscopy, Volume 1: Instrumentation, Methodology and Theoretical Simulations*, ed. N. Berova, P. L. Polavarapu, K. Nakanishi and R. W. Woody, John Wiley & Sons, 2012, ch. 21, p. 593.

