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Axially chiral BODIPYs†

Reinner I. Lerrick,a,b Thomas P. L. Winstanley,a Karen Haggerty,a Corinne Wills,a William Clegg,a Ross W. Harrington,a Patrick Bultinck,b Wouter Herrebout,c Andrew C. Bennistona and Michael J. Hall*a

The synthesis and resolution of a class of chiral organic fluorophores, axially chiral 4,4-difluoro-4-bora-5a,4a-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)† are among the most widely used organic fluorophores, finding utility in an array of applications including photodynamic therapy,2 biological imaging3 and fluorescence sensing. 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).

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

Chiral fluorophores have been explored for the selective sensing of chiral molecules,4 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 S1 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
substituent (X and Y) and (c) chemically differentiable groups on the 2/6-positions (A and B) of the BODIPY core (Fig. 3). In order to ensure a high rotational barrier for the asymmetry of compounds 8-(rac), 9-(rac) and 10-(rac) was observable by NMR spectroscopy, the 1H 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 19F NMR spectrum as an ABX coupling pattern, each fluorine peak showing both geminal 19F–19F and 19F–11B coupling (ESI† and Fig. 4).

The planes defined by the ortho-methylphenyl group and the 1,2-dihydro-1,3,4,2,1-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 1H NMR spectra to that of 10-(rac), whilst giving
weak but opposite \([z]_D\) 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(+)\(\text{/}10(−)\), preventing the use of VCD for absolute configuration determination (see ESI† for further discussion).19 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-shifted corrected by 10 nm, to compensate for the typical underestimation of transition energies by TD-DFT (ESI†).

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, \((S)-10(−)\).

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. The authors thank the Indonesian Ministry of National Education (R.I.L.) for funding, ESPRC for X-ray facilities at Newcastle University [EP/F03637X/1] and Dr Mike Probert (Newcastle) for crystallographic support, the EPSRC National Mass Spectrometry Service, Diamond Light Source for access to beamline I19, Bernard Costello, James Law and Dick Fielding (Applied Photophysics Ltd.) for ECD measurements and Prof. William McFarlane (Newcastle) for NMR support.

Notes and references

15 During the preparation of this manuscript a related atropisomeric BODIPY oligomer system was reported: S. Kolemen, Y. Cakmak, Z. Kostereki and E. U. Akkaya, Org. Lett., 2014, 16, 660–663.
18 Sampling for 72 hours and combination of the spectra of 10(+) and 10(−) for improved baseline correction using a BioTools ChiralUR-2X spectrometer gave no detectable VCD signals with a significant signal-to-noise ratio.
19 ROA measurements were attempted using a BioTools ChiralRaman spectrometer.