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Chirality

Circularly Polarized Luminescence from Helically Chiral *N,N,O,O*-Boron-Chelated Dipyrromethenes

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Abstract: Helically chiral *N,N,O,O*-boron chelated dipyrromethenes showed solution-phase circularly polarized luminescence (CPL) in the red region of the visible spectrum (λ_{em}(max) from 621 to 663 nm). The parent dipyrromethene is desymmetrised through O chelation of boron by the 3,5-*ortho*-phenolic substituents, inducing a helical chirality in the fluorophore. The combination of high luminescence dissymmetry factors ($|g_{lum}|$ up to 4.7×10^{-3}) and fluorescence quantum yields (Φ_F up to 0.73) gave exceptionally efficient circularly polarized red emission from these simple small organic fluorophores, enabling future application in CPL-based bioimaging.

Molecules that display circularly polarized luminescence (CPL), the spontaneous emission of right- or left-circularly polarized light, do so as a consequence of the intrinsic chirality of the excited state.[1] CPL-capable molecules and materials are of interest due to their ability to generate optical signals, which include not only wavelength and intensity but also chirality information. CPL from the condensed phase is employed in numerous applications,[2] whilst in the field of solution-phase CPL chiral lanthanide complexes[3] have proved to be popular due to their high luminescence dissymmetry factors.[4,5] However, low fluorescence quantum yields (Φ_F) and thus low CPL efficiency limits their application. Therefore, there is considerable interest in new small organic molecules, which display efficient (high $|g_{lum}|$ ($\geq 10^{-3}$) and high Φ_F) CPL (CPL-SOMs).[6] In particular, CPL-SOMs with efficient emission in the red region of the visible spectrum could be used to create new dye conjugates for CPL-based in vivo bioimaging.[7] The majority of current CPL-SOMs are based on either a BINOL or helicene scaffold. However, despite significant advances in the area,[8,9] these systems still pose significant synthetic challenges, making straightforward tuning of their photophysical or chiroptical properties difficult. Conversely, the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes are stable, tunable organic fluorophores with red to near-IR emission, high extinction coefficients and quantum yields,[10] and have been widely used in in vivo imaging,[11] photodynamic therapy,[12] analyte sensing,[13] light-harvesting arrays[14] and solar cells,[15] but have seen very limited use as chiroptical dyes. Although non-chiral BODIPYs have been co-polymerized with chiral monomers to form CPL emissive polymer materials,[16] resolved BODIPYs, which encompass an intrinsically chiral fluorophore, are rare.[17] Recently, de la Moya and co-workers reported an elegant desymmetrisation of an achiral BODIPY, by boron chelation with either (*S*)- or (*R*)-1,1′-bi-2-naphthol (BINOL).[18] The resulting long-range chiral perturbation of the fluorophore by the chelated enantiopure BINOL resulted in the first reported solution-phase CPL from the direct excitation of a BODIPY chromophore, albeit with modest efficiency ($|g_{lum}| \approx 8 \times 10^{-4}$ and $\Phi_F = 0.46$).[19]

Therefore, our aim was to develop new chiral BODIPYs capable of high-efficiency CPL (high $|g_{lum}|$ and Φ_F) in the red region of the visible spectrum (>600 nm), through the use of a direct desymmetrisation approach to induce a helical chirality in the fluorophore. Our design was inspired by the redshifted *N,N,O,O*-boron-chelated BODIPYs first reported by Burgess and co-workers,[20] involving the bonding of two 3,5-*ortho*-phenolic substituents to the central boron atom to desymmetrise our target BODIPYs **1a–d** and enforce the desired helicity. We postulated that a sterically unobtrusive, minimal substituent at the 8-position together with 1,7-di-*H*-substitution would aid in maximizing the helical pitch, increasing the $|g_{lum}|$, whilst simultaneously minimizing non-radiative decay from the S_1 excited state. Therefore, we included in our design substituents at the 8-position, which would span a range of sizes: H- (**1a**), Me- (**1b**) and two aryl groups, *p*-tolyl- (**1c**) and 2-pyridyl (**1d**; Figure 1).

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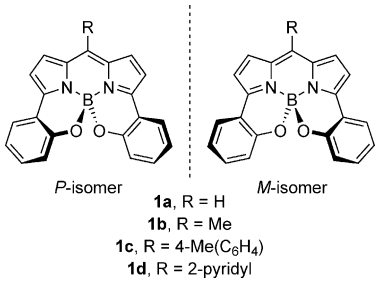


Figure 1. Target helically chiral *N,N,O,O*-boron-chelated BODIPYs **1 a–d**.

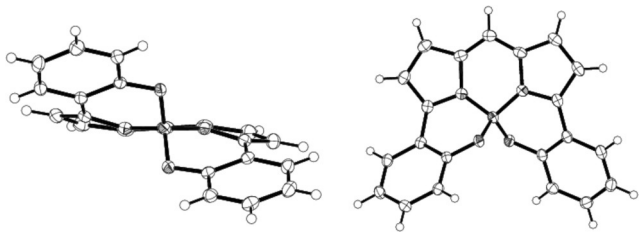
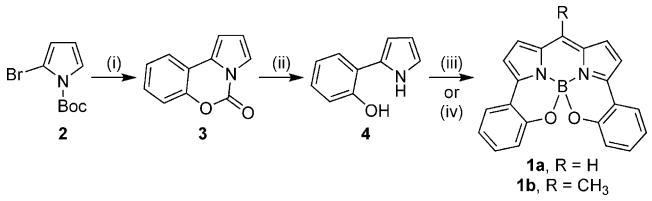


Figure 2. Two views of one molecule in the crystal structure of (***rac***)-**1 a** showing the helical chirality of the molecule (H atoms are omitted for clarity).

Our synthetic work commenced by examining routes to racemic BODIPYs **1 a–b**, which would incorporate an H or Me at the 8-position. *tert*-Butyl 2-bromo-1*H*-pyrrole-1-carboxylate (**2**) underwent Suzuki coupling with (2-hydroxyphenyl)boronic acid.[21] At high temperatures (>80 °C), only low yields of the desired Suzuki product could be obtained; however, decreasing the reaction temperature to 65 °C gave access to 5*H*-benzo[*e*]pyrrolo[1,2-*c*][1,3]oxazin-5-one (**3**), resulting from a Suzuki coupling and in situ intramolecular carbamate formation. Mild basic hydrolysis of **3** gave 2-(1*H*-pyrrol-2-yl)phenol (**4**), which was condensed with triethyl orthoformate or orthoacetate under acidic conditions and reacted with boron trifluoride to give racemic BODIPYs **1 a** and **b** (Scheme 1).



Scheme 1. Reaction conditions: i) (2-hydroxyphenyl)boronic acid, 5 mol% $[Pd(PPh_3)_4]$, K_2CO_3, toluene/EtOH/H_2O, 65 °C, 16 h, (54%); ii) NaOH, EtOH, r.t., 1 h, (72%); iii) (a) $HC(OEt)_3$, TFA, CH_2Cl_2, r.t., 45 min; (b) $BF_3{\cdot}OEt_2$, TEA, CH_2Cl_2, r.t., 2 h, (**1 a** 18%); iv) (a) $CH_3C(OEt)_3$, TFA, CH_2Cl_2, r.t., 45 min; (b) $BF_3{\cdot}OEt_2$, DIPEA, CH_2Cl_2, r.t., 2 h, (**1 b** 43%).

To improve overall yields and to avoid the practical difficulties associated in handling electron-rich pyrrole intermediates (such as **2**), we next examined an alternative route to the aryl-substituted BODIPYs **1 c–d**, in which the two *ortho*-phenolic groups would be introduced through a late-stage Suzuki coupling. BF_3-mediated condensation of *p*-tolualdehyde or picolinaldehyde with pyrrole gave the corresponding dipyrromethanes, which were regioselectively dibrominated at the 3,5-positions, oxidised to the dipyrromethenes with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and reacted with BF_3 to give dibromo-BODIPYs **5 a–b**. Suzuki coupling with 2-methoxyphenylboronic acid gave 3,5-diaryl-BODIPYs **6 a–b**, which were converted, through boron tribromide demethylation, to the racemic BODIPYs **1 c** and **d** (Scheme 2).

Crystallization experiments gave single crystals of **1 a–c** suitable for X-ray analysis (see the Supporting Information).[22] In all cases, a significant twisting of the fluorophore was observed; the twist angle between the planes defined by the two pyrrolic rings: **1 a** 11.2°, **1 b** 9.0° and **1 c** 9.8° (Figure 2).[23]

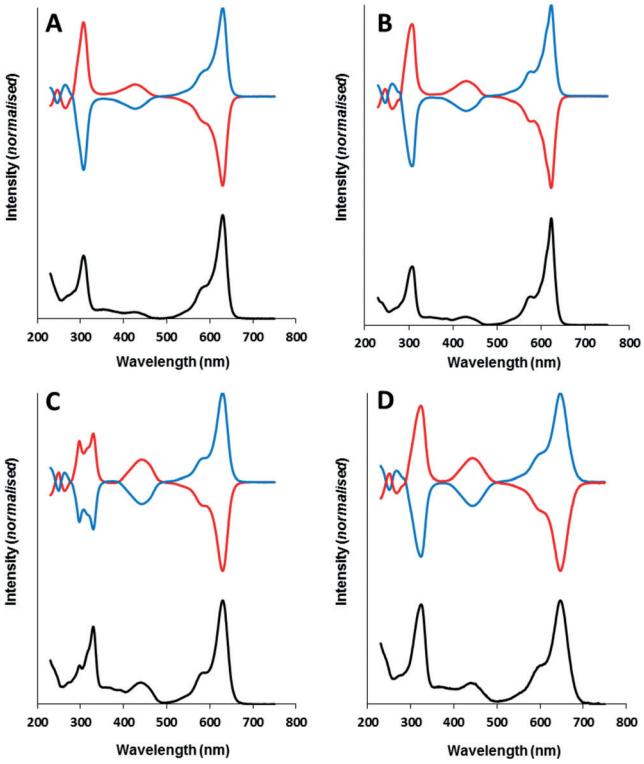
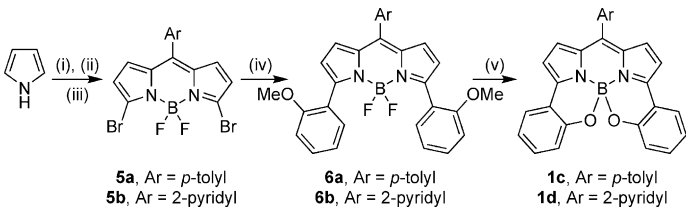


Figure 3. Normalised ECD (red and blue) and UV/Vis absorption spectra (black): a) (*M*)-**1 a** (red) and (*P*)-**1 a** (blue) [$CHCl_3$]: b) (*M*)-**1 b** (red) and (*P*)-**1 b** (blue) [hexane]: c) (*M*)-**1 c** (red) and (*P*)-**1 c** (blue) [hexane]; d) (*M*)-**1 d** (red) and (*P*)-**1 d** (blue) [$CHCl_3$].



Scheme 2. Reagents: i) 4-methylbenzaldehyde or picolinaldehyde, $BF_3{\cdot}OEt_2$, r.t., 30 min; ii) NBS, THF, −78 °C, 1 h; DDQ, THF, −78 °C to r.t.; iii) $BF_3{\cdot}OEt_2$, DIPEA, CH_2Cl_2, r.t., 2 h, (**5 a** 47%, **5 b** 24% over three steps); iv) 2-$(MeO)C_6H_4B(OH)_2$, $[Pd(PPh_3)_4]$ (5 mol%), Na_2CO_3, toluene/H_2O, reflux, 4 h, (**6 a** 98%, **6 b** 81%); v) BBr_3, CH_2Cl_2, r.t., 5 h, (**1 c** 96%, **1 d** 60%).

Both enantiomers of BODIPYs **1a–d** were then resolved by semi-preparative chiral HPLC to examine their chiroptical properties (see the Supporting Information). Electronic circular dichroism (ECD) spectra were measured for each of the enantiomeric samples of **1a–d**, in hexane or $CHCl_3$ as appropriate, using an Applied Photophysics Ltd. Chirascan-plus spectrometer. In each case, mirror image ECD spectra were obtained from the corresponding enantiomers, the major peaks of the ECD spectra aligning well with those of the absorption spectra (Figure 3).

Assignment of absolute configuration to the resolved enantiomers of **1a–d** was performed by a comparison of the experimental ECD with that calculated for the *P*-isomer of **1a–d**. Boltzmann-weighted ECD spectra for the *P*-isomers **1a–d** were obtained by TD-DFT calculations at the cam-B3LYP/6-311++G(3df,2pd) and M06-2X/6-311++G(3df,2pd) levels.[24] Generation of a low-energy conformation library was followed by calculation of the individual ECD spectra for each of the low-energy conformations (Figure 4). Comparison of features of the calculated ECD spectra of the *P*-isomers to the experimental spectra allowed the assignment of the absolute configuration of each of the enantiomeric samples of **1a–d**.

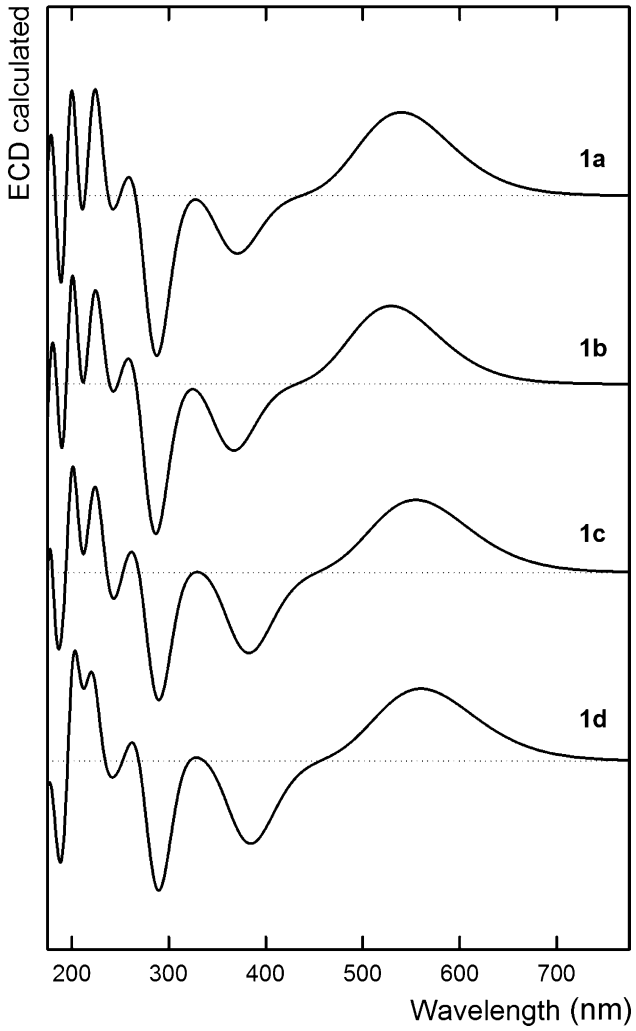


Figure 4. Boltzmann-weighted ECD spectra for the *P*-isomers **1a–d**, calculated at the cam-B3LYP/6-311++G(3df,2pd) level.

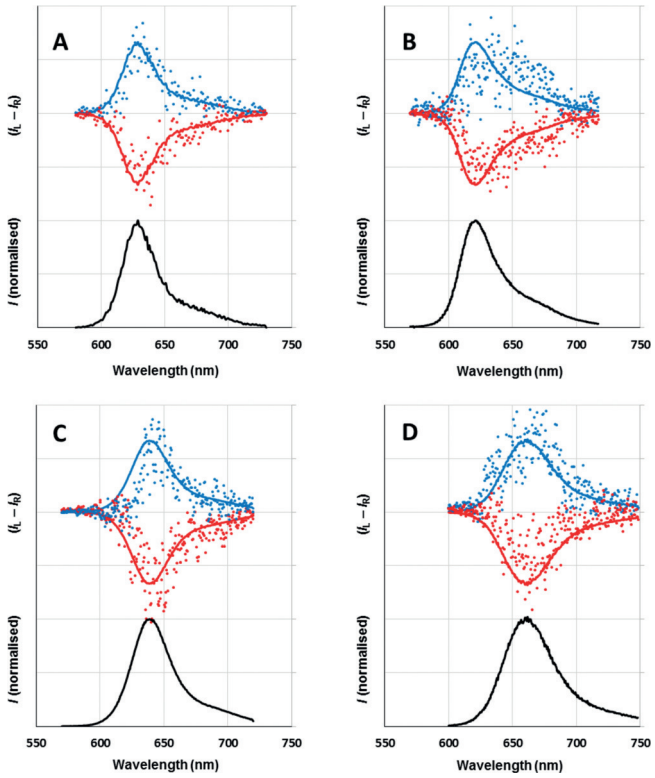


Figure 5. Normalised CPL spectra (red and blue) and normalised fluorescence spectra (black) shown (MeCN, excitation 540 nm): a) (*M*)-**1a** (red) and (*P*)-**1a** (blue); b) (*M*)-**1b** (red) and (*P*)-**1b** (blue); c) (*M*)-**1c** (red) and (*P*)-**1c** (blue); d) (*M*)-**1d** (red) and (*P*)-**1d** (blue).

CPL spectra were then measured for each pair of enantiomeric samples of **1a–d** (Figure 5). The *P*- and *M*-isomers of **1a–d** gave mirror image CPL spectra with high $|g_{lum}|$ (**1a** 0.0047 (623 nm), **1b** 0.0033 (635 nm), **1c** 0.0043 (637 nm) and **1d** 0.0042 (675 nm)). The $|g_{lum}|$ values for this series of compounds include the largest reported to date for a simple BODIPY fluorophore in solution. In the case of BODIPY **1a**, the inclusion of H- at the 8-position resulted in both a large luminescence dissymmetry factor and fluorescence quantum yield ($|g_{lum}| = 4.7 \times 10^{-3}$, $\Phi_F = 0.65$ in MeCN), making it the most efficient single-fluorophore, red-emitting CPL-SOM reported to date.[6]

In conclusion, we have shown that the helical *N,N,O,O*-boron-chelated dipyrromethenes are a privileged molecular scaffold for the creation of redshifted solution-phase CPL-SOMs and are promising motifs for future chiral fluorophore development.

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Keywords: absolute stereochemistry · BODIPYs · chirality · circularly polarized luminescence · luminescence

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