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Multicomponent synthesis of stereogenic-at-boron fluorophores (BOSPYR) from boronic acids, salicylaldehydes, and 2-formylpyrrole hydrazones†

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This work describes one-step syntheses of various stereogenic-at-boron fluorochromes (BOSPYR) via multicomponent reactions involving readily accessible boronic acids, salicylaldehydes, and 2-formylpyrrole hydrazones. The dyes absorb and emit in the visible region of the electromagnetic radiation, and are characterized by large Stokes shifts (2850–4930 cm⁻¹) with weak fluorescence emissions (Φ_f : 1.5–9.1%). Notably, the dimmed fluorescence of BOSPYRs recovers upon transition to viscous media (21-fold for 1a). The representative compound 1a exhibits clear Cotton effects with dissymmetry factors of ca. $|g_{\text{abs}}| \sim 1.9 \times 10^{-3}$ in the visible region, indicating efficient asymmetry induction to the chromophore. The X-ray molecular structure of 1a shows that the chromophore deviates from planarity by 17.2°, which may contribute significantly to the inherent chirality of the fluorophore. A computational examination of excited states by time-dependent density functional theory (TD-DFT) identifies the emission mechanism as arising from a locally-excited (LE) state.

Fluorophores have become indispensable tools across various disciplines, including chemistry, biology, medicine, materials science, and numerous interdisciplinary areas.¹ The element boron (B) plays a crucial role in modern fluorophore design thanks to forming stable tetravalent chelates, thereby restricting internal bond rotations in the π -skeleton of nascent fluorophores, enforcing planarity, and ensuring enhanced π -conjugation throughout the dye.² This can be well exemplified by the archetypal boron dipyrromethene (BODIPY, Fig. 1) dyes³ or similar heterocyclic architectures, locked typically with a difluoro boron bridge.² Despite their successful application as functional dyes in diverse fields, from probes/labels to photosensitizers for photodynamic

action, the synthesis of such functional BODIPYs often involves intricate, long linear routes.⁴

Unlike conventional synthesis approaches, multicomponent reactions (MCRs) offer a convergent synthesis approach, assembling often readily available starting materials in a single step. This has recently sparked growing interest in the development of functional organic dyes through MCRs.^{5,6} In contrast to the commonly used BF₃, the group of Gois & Pischel has employed arylboronic acids as the boron source for the MCR-based development of intriguing BASHY fluorophores (Fig. 1),⁶ which exhibit photophysical properties highly comparable to BODIPYs.^{6–12} Notably, the sp³ hybridized boron atom in these dyes, accommodating four distinct ligands, creates asymmetry around it, imparting chirality to the dye.⁹

This remains a challenge in BODIPYs due to their highly symmetric nature (point group: C_{2v}),^{13–15} particularly for those with chiral-at-boron arrangements.¹⁵ Therefore, currently, the majority of chiral-at-boron chromophores/fluorophores, although rare in number, generally rely on other miscellaneous heterocyclic systems with a tetravalent boron center.¹⁶ The visible light-absorbing BASHY fluorophores, as solely stereogenic-at-boron dyes, exhibited detectable chiroptical activities in electronic circular dichroism (ECD) and circularly polarized luminescence (CPL) spectroscopy within the visible region.⁹ Similarly, although not a true MCR-type synthesis, research efforts by Hao & Jiao and co-workers employing arylboronic acids as the locking unit have



Fig. 1 BODIPY dyes accessible through conventional synthesis vs. BASHY dyes and BOSPYR dyes (this work) through MCR approach.

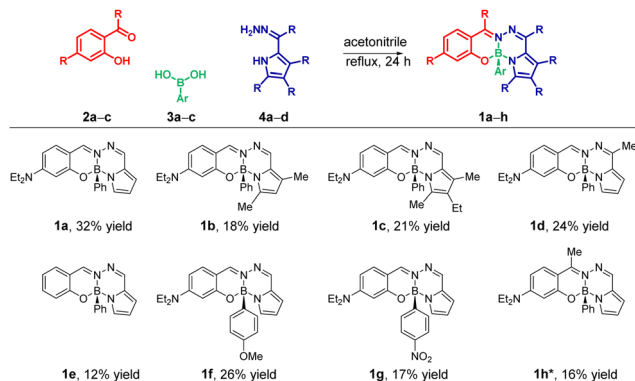
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resulted in a variety of readily accessible BOPBY, BOBHY, and BOSPYPY dyes, offering unique optical behaviors.¹⁷ Although these dyes also share stereogenic-at-boron characteristics similar to those of BASHY, no chiroptical investigation has been conducted yet.

Building on our previous interest in developing chiral dyes,^{15b} in this communication, we describe the development of structurally diverse novel fluorophores (**1a–h**) through a tri-component reactions of commercially available salicylaldehyde derivatives (**2a–c**) and arylboronic acids (**3a–c**) with readily accessible 2-formylpyrrole hydrazones (**4a–d**) in a single step (Scheme 1). The stereogenic boron center in these compounds provides access to unique chiral-at-boron fluorophores (**1a–h**) through enantiomeric resolution on chiral HPLC column.

This assembly system is designed with two key features in mind: ready availability of starting materials and (2) facile diversification potential through the use of substrates with diverse substitution patterns. Capitalizing on these advantages, we successfully synthesized compound **1a** in a reasonable yield of 32% under optimized reaction condition (see ESI†). The reaction involved refluxing an equimolar mixture of 4-(diethylamino)salicylaldehyde (**2a**), phenylboronic acid (**3a**), and the hydrazone of pyrrole-2-carbaldehyde (**4a**) in acetonitrile for 24 hours (Scheme 1). The chemical structure of **1a** was unequivocally confirmed by NMR spectroscopy, high-resolution mass spectrometry (HRMS), and single-crystal X-ray diffraction analysis (see ESI† and Fig. 3). Next, to explore the reaction's versatility, we performed the reaction with structural variations at each component: the pyrrole (**1a–d**), the salicyl-aldehyde/ketone (**1a**, **1e**, and **1h**), and the arylboronic acid (**1a**, **1f**, and **1g**) units. The herein developed one-step, tri-assembly MCRs served as an enabling platform for efficient synthesis of fused tetracyclic boron-chelates **1a–h**, despite the moderate yields (12–32%, Scheme 1), for which conventional synthetic approaches failed to give any trace of product (Scheme S5, ESI†).

The model dye **1a** exhibited very low solvent-dependent absorbance and fluorescence—solvatochromism (Fig. S40, ESI†). It absorbs maximally at around 450 nm and emit at around 530, displaying large Stokes shifts ($\Delta\lambda \sim 3000 \text{ cm}^{-1}$).¹⁸



Fig. 2 (a) Fluorescence emission spectra of **1a** in glycerol–ethanol mixtures with varying glycerol fractions [f_{glycerol} (vol%): 0–99%] at 25 °C. Integrated area ratio of $f_{\text{glycerol}}(0\%)/f_{\text{glycerol}}(99\%) \sim 1/21$. (b) Normalized UV-vis absorption and fluorescence emission spectra of the BOSPYPY dyes (**1a–h**, 2 μM) in DMSO.

Following the work by Hao and coworkers^{17c} on the aggregation-induced emission (AIE) properties of structurally similar BOSPYPY dyes, we investigated the emission properties of our BOSPYPY dyes, in water–DMSO mixtures (Fig. S41, ESI†). The fluorescence intensity exhibits negligible enhancement, gradually increasing up to 50% water fraction, followed by a sharp decrease at higher water fractions, likely due to aggregation or precipitation (Fig. S41, ESI†). To understand the dimmed fluorescence emissions of **1a** in organic solvents, we recorded emission spectra in glycerol–ethanol mixtures with varying glycerol fractions (Fig. 2a). The fluorescence intensity increased by 21-fold when switching from pure ethanol to pure glycerol. The enhanced fluorescence observed in viscous glycerol medium suggests non-radiative vibrational relaxations as a key quenching mechanism for the dye **1a**, making it a promising tool for studying biological processes associated with increased extracellular viscosity.^{19,20}

To understand the influence of structural variations on optical properties, we recorded absorption and fluorescence emission spectra for all BOSPYPY dyes (**1a–h**) in DMSO (Fig. 2b and Table S1, ESI†). All dyes exhibit large Stokes shifts ($2633\text{--}4930 \text{ cm}^{-1}$) and weak emission ($\Phi_{\text{f}}: 1.5\text{--}9.1\%$)²¹ with fluorescence lifetimes ranging from 0.47 to 2.00 ns, all characterized by a monoexponential fit. Alkyl substitution on the pyrrole unit (**1a** to **1c**; entries 1–3, Table S1, ESI†) induces a bathochromic shift (530–573 nm). A more pronounced red-shift is observed for ethyl substitution at the pyrrole's 3-position (**1c**) compared to dimethylation (**1b**). Electrostatic potential surface calculations for compounds **1b** and **1c** (Fig. S51, ESI†) indicate



Fig. 3 (a) X-ray molecular structure of **1a** with the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level. (b) Dihedral angle between chelating mean planes defined by atoms N1–C10–C11–N3 and C13–C18–O1–C12; $\alpha = 17.2^\circ$.





Fig. 4 ESP, charge distribution, HOMO and LUMO surfaces, singlet energy levels and natural transition orbitals of $S_0 \rightarrow S_1$ transition for **1a**.

The HOMO–LUMO energy gap decreased from 2.8 eV to 2.3 eV upon excited state geometry optimization, highlighting the influence of geometry relaxation on the emission spectra (e.g. large $\Delta\lambda$) and supporting the solvent-independent emissions observed experimentally (Fig. S40, ESI[†]). This relaxation also led to a good correlation between the electrochemical bandgap calculated through differential pulse voltammetry (DPV) experiments and the computed optical bandgap (2.27 eV vs. 2.30 eV, Fig. S47 and Table S2, ESI[†]).

In conclusion, this work presents a powerful approach for the synthesis of diverse stereogenic-at-boron BOSPYP fluorochromes through a straightforward one-step MCR. This method offers several advantages: it utilizes readily available starting materials, enables creation of fluorophores with an asymmetry at the boron atom, and yields visible light-absorbing dyes with large Stokes shifts and weak fluorescence that can be significantly enhanced in viscous media, making them promising viscosity imaging probes. Additionally, the inherent chirality of these fluorophores, arising from the bent conformation of the chromophore, evidenced by the large specific rotations and distinct Cotton effects of **1a**, opens exciting possibilities for their development as chiroptical tools. The high configurational stability of B-stereocenter in these chelates further highlight them as reliable chiral fluorochromes. The combination of efficient synthesis, tunable properties, and inherent chirality positions these dyes as versatile, promising building blocks for advanced functional materials.

Data availability

Additional data supporting this article have been included as part of the ESI[†].

Conflicts of interest

There are no conflicts to declare.

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