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Catalytic asymmetric C–N cross-coupling towards boron-stereogenic 3-amino-BODIPYs

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3-Amino boron dipyrromethenes (BODIPYs) are a versatile class of fluorophores widely utilized in live cell imaging, photodynamic therapy, and fluorescent materials science. Despite the growing demand for optically active BODIPYs, the synthesis of chiral 3-amino-BODIPYs, particularly the catalytic asymmetric version, remains a challenge. Herein, we report the synthesis of boron-stereogenic 3-amino-BODIPYs via a palladium-catalyzed desymmetric C–N cross-coupling of prochiral 3,5-dihalogen-BODIPYs. This approach features a broad substrate scope, excellent functional group tolerance, high efficiency, and remarkable enantioselectivities, under mild reaction conditions. Further stereospecific formation of chiral 3,5-diamino-BODIPYs, along with an investigation into the photophysical properties of the resulting optical BODIPYs are also explored. This asymmetric protocol not only enriches the chemical space of chiroptical BODIPY dyes but also contributes to the realm of chiral boron chemistry.

Boron dipyrromethenes (BODIPYs) are one of the most efficient classes of fluorophores, renowned for their exceptional spectroscopic and photophysical properties[1–5]. Their versatility has led to widespread applications across various fields, including biology[6–11], pharmaceuticals[12–16], and materials science[17–25]. Of particular interest is the incorporation of an amine substituent at the α position of BODIPY, giving rise to 3-amino-BODIPYs, which have garnered significant attention. These compounds have found extensive utility as fluorescent sensors and probes for biological imaging and labeling[26–37], as well as in the development of endoplasmic reticulum-targeting reagents[38] and high-performance narrowband red OLEDs[39] (Fig. 1a). However, despite the increasing demand for chiroptical luminophores capable of chiral sensing and labeling[40–51], exploration of chiral 3-amino-BODIPYs has remained limited, with existing studies primarily focusing on chirality at the periphery of the BODIPY core[52–56]. To date, the synthesis of boron-stereogenic 3-amino-BODIPYs has remained unexplored (Fig. 1a). Notably, the construction of boron-stereogenic chirality in a catalytic asymmetric manner has seen limited success until recently due to the lack of effective synthetic tools and the potential instability of ligands attached to the boron atom[57–60]. Given their significant importance and vast potential applications, the development of efficient catalytic asymmetric methods for constructing enantioenriched boron-stereogenic 3-amino-BODIPYs emerges as an enticing and highly desirable objective.

From a retrosynthetic analysis, we devised a synthetic strategy for boron-stereogenic 3-amino-BODIPYs by employing a desymmetric C–N cross-coupling approach starting from prochiral 3,5-dihalogen-BODIPYs (Fig. 1b). In recent years, catalytic asymmetric C–N cross-coupling has emerged as a powerful tool for constructing various amine compounds featuring centered, axial, and planar chirality[61–66]. However, due to the unique reactivity of 3,5-dihalogen-BODIPYs, several side-reactions may occur when attempting the desymmetric C–N

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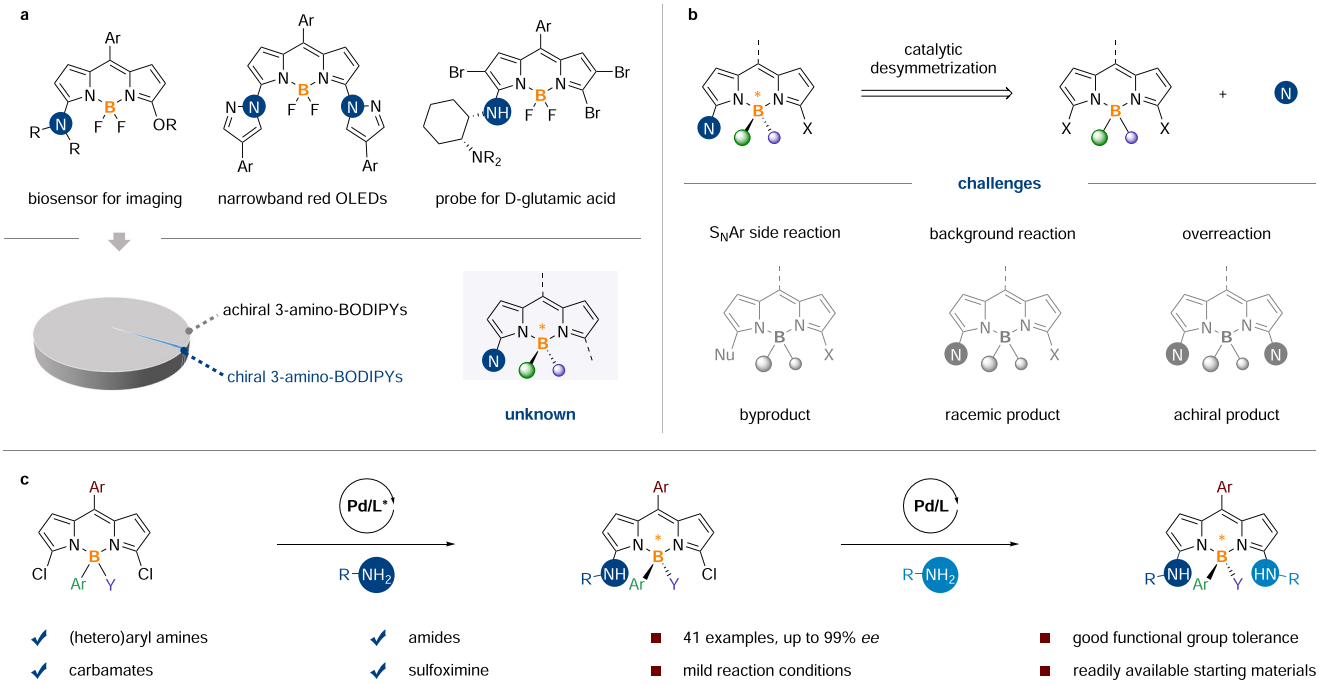

Fig. 1 | Importance and synthesis of boron-stereogenic 3-amino-BODIPYs. a Selected 3-amino-BODIPYs with important applications. **b** Design plan and challenges towards boron-stereogenic 3-amino-BODIPYs. **c** Catalytic asymmetric synthesis of boron-stereogenic 3-amino-BODIPYs (this work).

cross-coupling: (1) S_NAr reaction of 3,5-dihalogen-BODIPYs with strong nucleophilic reagents such as alkoxy bases[67]; (2) direct background reaction of 3,5-dihalogen-BODIPYs with amines, leading to racemic products[68,69]; (3) overreaction resulting in the formation of achiral 3,5-diamino-BODIPYs[70]. Therefore, the selection of an efficient asymmetric catalytic system is crucial for the success of the desired enantioselective transformation. In this study, we report a convenient approach for the synthesis of boron-stereogenic 3-amino-BODIPYs via a palladium-catalyzed asymmetric C–N cross-coupling (Fig. 1c). This transformation features a broad substrate scope, high compatibility with functional groups, and excellent enantioselectivity. In addition, derivatizations and photophysical properties of the obtained chiral 3-amino-BODIPYs are also investigated to illustrate the utility of this asymmetric protocol.

Results and discussion

Reaction development

Our study commenced with the evaluation of the C–N cross-coupling between prochiral 3,5-dichlorinated BODIPY (**1a**) and *p*-toluidine (**2a**). After numerous trials and careful analysis, we found that the occurrence of S_NAr side reaction and overreaction could be circumvented by employing a non-nucleophilic base such as Cs_2CO_3 under mild conditions. In addition, the background reaction occurred in the absence of a catalyst giving the racemic **3a** in an 85% yield after 12 h (Table 1, entry 1). Encouragingly, by shortening the reaction time to 2 h, the background reaction was significantly diminished (Table 1, entry 2), opening the possibility of achieving enantiocontrol when an effective chiral catalyst was employed. Initial attempts using $Pd(dba)_2$ (4 mol%) as the catalyst precursor and *R*-BINAP (**L1**) (10 mol%) as the ligand, in the presence of Cs_2CO_3 (2.0 equiv) in toluene at 60 °C, the target boron-stereogenic 3-amino-BODIPY **3a** could be obtained in a 29% yield with 18% *ee* (enantiomeric excess) (Table 1, entry 3). To assess the impact of different ligands on this asymmetric C–N cross-coupling reaction, a variety of chiral phosphine ligands were examined. The use of electron-rich bidentate phosphine ligands such as Segphos (**L2**) and Josiphos (**L3**) provided similar yields but lower enantioselectivities (Table 1, entries 4 and 5). Employing an electron-rich monodentate phosphine ligand, MeO-MOP (**L4**), yielded a high yield of **3a** but low enantioselectivity (Table 1, entry 6). Then, various electron-deficient chiral ligands including TADDOL-derived phosphoramidite (**L5**) and BINOL-derived phosphoramidites (**L6**-**L9**) were further evaluated (Table 1, entries 7–11). The results demonstrated a correlation between increased enantioselectivity and enhanced steric hindrance of the chiral ligand. In this way, we finally established the optimal conditions wherein **3a** was obtained in a 99% yield with 98% *ee* within 2 h using phosphoramidite **L9** as the ligand (Table 1, entry 11). Notably, the use of a phosphoramidite ligand without axial chirality (**L10**) resulted in lower enantioselectivity (Table 1, entry 12). When K_2CO_3 was used instead of Cs_2CO_3, both yield and *ee* were reduced dramatically (Table 1, entry 13). The use of THF as the solvent led to a similar yield of **3a** with lower enantioselectivity, while lowering the temperature to room temperature resulted in a trace amount of **3a** (Table 1, entries 14 and 15).

Substrate scope

Having established the optimal reaction conditions, we proceeded to investigate the scope of amines in the catalytic asymmetric C–N cross-coupling reaction and the results are summarized in Fig. 2. In general, both electron-donating and electron-withdrawing substituents at the ortho, meta, or para positions of anilines were well accommodated in this transformation. Anilines with electron-donating substituents, such as methyl, methoxy, and diphenylamino groups (**3a, 3c, 3d, 3j, 3l**), underwent smooth asymmetric C–N cross-coupling, affording the desired products in excellent yields with high enantioselectivities. Similarly, anilines with electron-withdrawing substituents, including ester, trifluoromethyl, and cyano groups (**3e, 3g, 3k**), were compatible with this asymmetric C–N cross-coupling and successfully delivered the desired products in excellent yields with high enantioselectivities. Remarkably, susceptible substituents such as alkynyl (**3h**) and hydroxymethyl groups(**3i**), as well as halogen substituents such as chloride (**3n, 3x**) and bromide (**3f, 3m, 3o, 3p**), were all well-tolerated in this transformation, making further downstream functionalization feasible. Furthermore, anilines bearing multiple substituents exhibited good compatibility in this asymmetric cross-coupling reaction (**3n**–**3p**). The absolute configuration of the enantioenriched **3o** was

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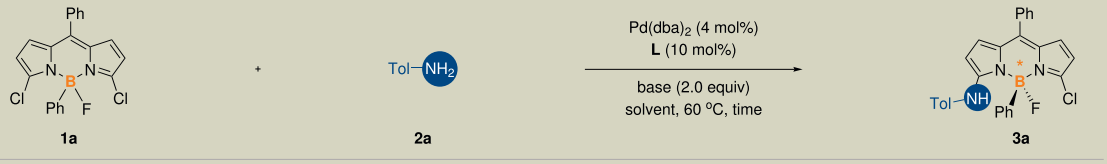
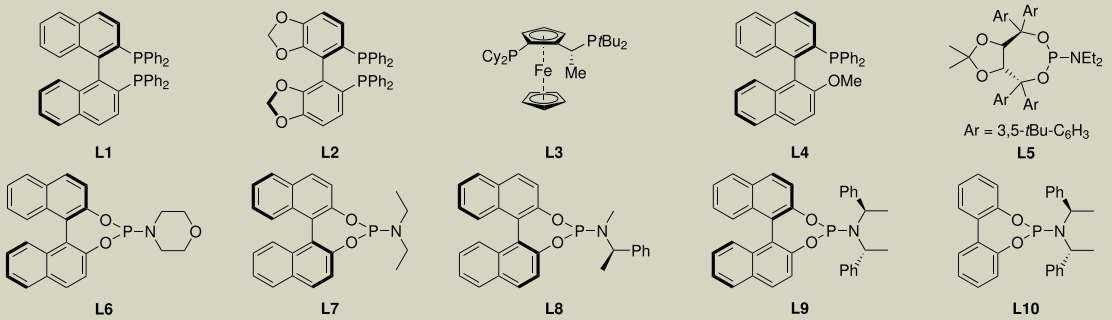
Table 1 | Optimization of the reaction conditions.[a]





Entry	[Pd]/L	Time	Base	Solvent	Yield of 3a (%)	ee of 3a (%)
1	–	12 h	Cs_2CO_3	toluene	85	–
2	–	2 h	Cs_2CO_3	toluene	6	–
3	$Pd(dba)_2$/**L1**	2 h	Cs_2CO_3	toluene	29	18
4	$Pd(dba)_2$/**L2**	2 h	Cs_2CO_3	toluene	20	2
5	$Pd(dba)_2$/**L3**	2 h	Cs_2CO_3	toluene	25	6
6	$Pd(dba)_2$/**L4**	2 h	Cs_2CO_3	toluene	94	22
7	$Pd(dba)_2$/**L5**	2 h	Cs_2CO_3	toluene	74	44
8	$Pd(dba)_2$/**L6**	2 h	Cs_2CO_3	toluene	37	40
9	$Pd(dba)_2$/**L7**	2 h	Cs_2CO_3	toluene	91	72
10	$Pd(dba)_2$/**L8**	2 h	Cs_2CO_3	toluene	70	89
11	$Pd(dba)_2$/**L9**	2 h	Cs_2CO_3	toluene	99	98
12	$Pd(dba)_2$/**L10**	2 h	Cs_2CO_3	toluene	97	58
13	$Pd(dba)_2$/**L9**	2 h	K_2CO_3	toluene	12	16
14	$Pd(dba)_2$/**L9**	2 h	Cs_2CO_3	THF	99	74
15[b]	$Pd(dba)_2$/**L9**	2 h	Cs_2CO_3	toluene	4	–

[a]Standard conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), $Pd(dba)_2$ (4 mol%), **L** (10 mol%), base (2.0 equiv), in 1.0 mL of solvent under argon atmosphere at 60 °C. The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. The *ee* values were determined by chiral HPLC; [b]Reaction at room temperature for 2 h. Ph, phenyl; Tol, *p*-tolyl.

determined through X-ray crystallographic analysis (CCDC 2323832). Additionally, aromatic amines with fused aromatic cores (e.g., naphthalene and pyrene) and heteroaromatic cores (e.g., benzodioxole, benzothiophene, indole, carbazole, quinoline, and pyrimidine) proved to be successful substrates (**3q**–**3x**). Moreover, this catalytic asymmetric C–N cross-coupling was also applicable to amides. Both alkyl-amides and aryl-amides underwent smooth asymmetric C–N cross-coupling, yielding the corresponding products in moderate to good yields with good to excellent enantioselectivities (**3y**–**3aa**). Notably, the reaction of N-Boc and N-Cbz amides produced the desired chiral 3-amino-BODIPYs in 88 and 92% yield with 98% *ee*, respectively (**3ab, 3ac**). To our delight, sulfoximine **2ad** was also a suitable substrate for this reaction, delivering the corresponding product **3ad** in excellent result (91% yield, >99% *ee*). In addition, an interesting 1,4-bisphenylenediamine-bridged BODIPY dimer **3ae** was also assembled in a smooth manner with 63% yield and 99% *ee*. Several unsuccessful amine examples are shown in Fig. S1.

After evaluating the scope of amines, we then assessed the generality of this process concerning the BODIPY scaffold (Fig. 3). The catalytic asymmetric C–N cross-coupling of BODIPYs bearing various aryl substituents at the meso position proceeded smoothly, providing the corresponding boron-stereogenic 3-amino-BODIPYs in good yields with high enantioselectivities(**4a**–**4d**). It is worth mentioning that, this C–N cross-coupling occurred chemoselectively, leaving the aromatic C–Cl bond in the meso aryl substituent intact (**4b**). Notably, the substituents on the boron atom of the BODIPY framework were not limited to phenyl and fluorine. Substituents on boron with diverse steric and electronic effects, including naphthyl, 4-fluorophenyl, thienyl, and methyl groups, were well tolerated, leading to the desired products in good to excellent yields with excellent enantioselectivities (**4e, 4f, 4h, 4i**). BODIPYs featuring methoxy and 4-cyanophenyl substituents on the boron atom exhibited slightly lower enantioselectivities (**4g, 4j**).

To showcase the synthetic potential of this approach, a gram-scale experiment was carried out involving the reaction between **1a** and **2a**, which resulted in the desired product **3a** in a yield of 91% with 94% *ee* (Fig. 4). Furthermore, the remaining chlorine group in **3a** could be further converted into various amino groups, allowing access to chiral 3,5-diamino-BODIPYs in a stereospecific manner. In the presence of a Pd/Xphos catalytic system, the C–N cross-coupling of **3a** with diverse aromatic and aliphatic amines proceeded smoothly, affording the desired chiral 3,5-diamino-BODIPYs in moderate to good yields without the loss of ee (**5a**–**5f**). In addition to the C–N coupling reaction, the Suzuki cross-coupling reaction also proceeded smoothly, yielding the corresponding C–C cross-coupling products **5g** and **5h** in good yields without the loss of *ee*.

Photophysical properties investigations

With a diverse array of enantioenriched boron-stereogenic 3-amino BODIPYs in hand, we proceeded to investigate the photophysical

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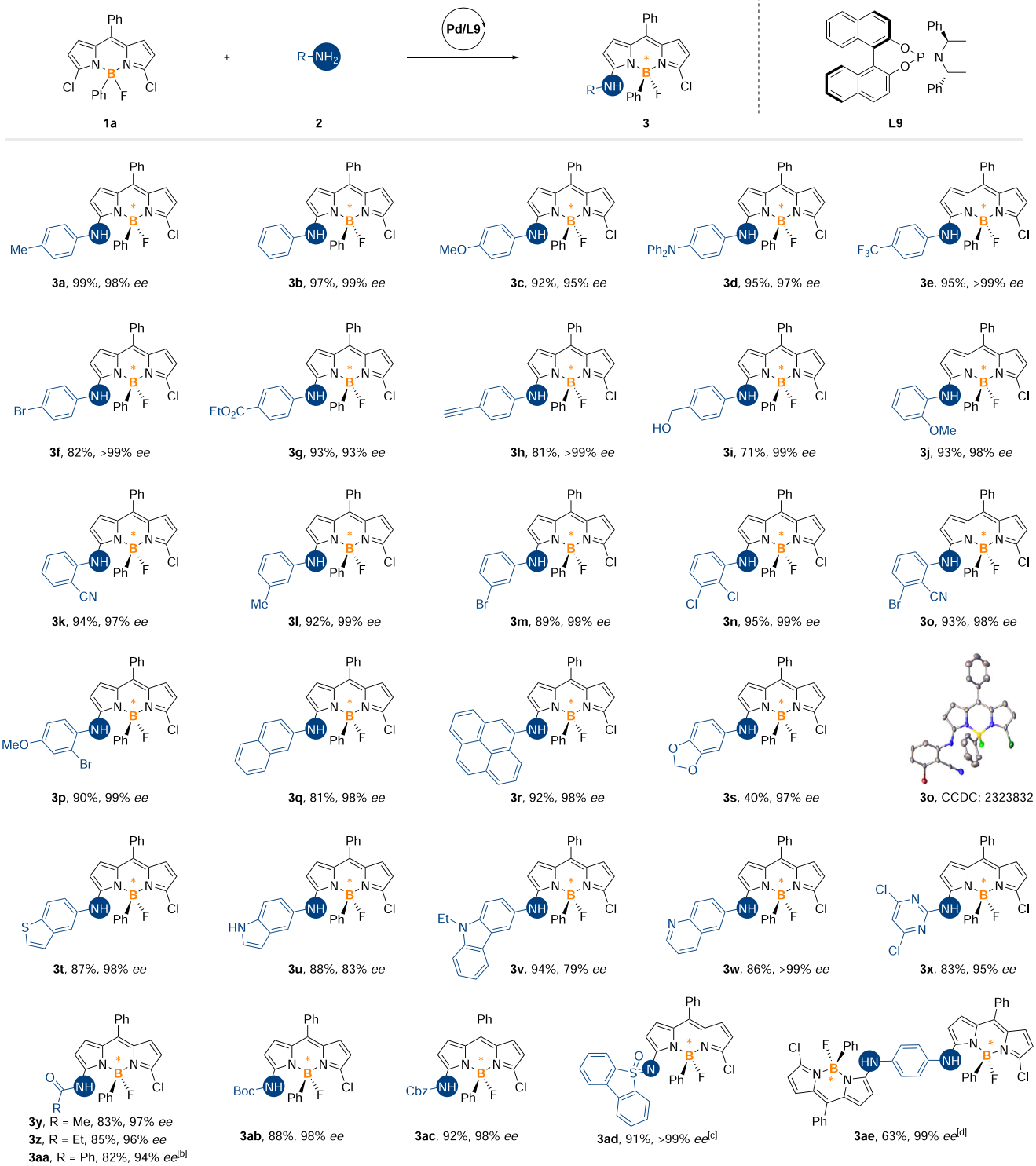

Fig. 2 | Substrate scope for amines. a Standard conditions: **1a** (0.1 mmol), **2** (0.1 mmol), $Pd(dba)_2$ (4 mol%), **L9** (10 mol%), Cs_2CO_3 (2.0 equiv), in 1.0 mL of toluene under argon atmosphere at 60 °C for 2 h. Isolated yields. The *ee* values were determined by chiral HPLC; (**b**) 2.0 equiv of **2** was used. X-ray crystallographic analysis determined that the absolute configuration of **3o** is (*R*). **c** 1.0 equiv of sulfoximine was used. **d 1a** (0.2 mmol), **2** (0.1 mmol), a 25% yield of *meso* isomer was also detected (mixture). Ph phenyl, Boc *tert*-butoxycarbonyl, Cbz benzyloxycarbonyl.

properties of selected products (Fig. 5). In comparison to the 3-amino-BODIPYs (**3a, 3r**, and **3y**), the 3,5-diamino-BODIPYs (**5c, 5e**) exhibited a remarkable red shift in both absorption and emission maxima (Fig. 5a, b). Notably, compounds **3r, 5c**, and **5h** displayed emission maxima in the first near-infrared region (NIR-I), rendering it potentially suitable for various applications such as labeling reagents, photodynamic therapy, and chemosensors. Additionally, the chiroptical properties of **3r, 5g, 5h**, and their enantiomers were investigated using circular dichroism (CD) spectroscopies. The CD spectra exhibited mirror images of each other, demonstrating clear Cotton effects at approximately 512, 565 and 556 nm, respectively (Fig. 5c). To our delight, **5g** and **5h** also exhibited CPL activity from 500 to 750 nm, with $|g_{lum}|$ up to 2.6×10^{-4} (634 nm) and 4.5×10^{-4} (648 nm), respectively (Fig. 5d). Moreover, we also investigated the fluorescence quantum yields and fluorescence lifetimes of

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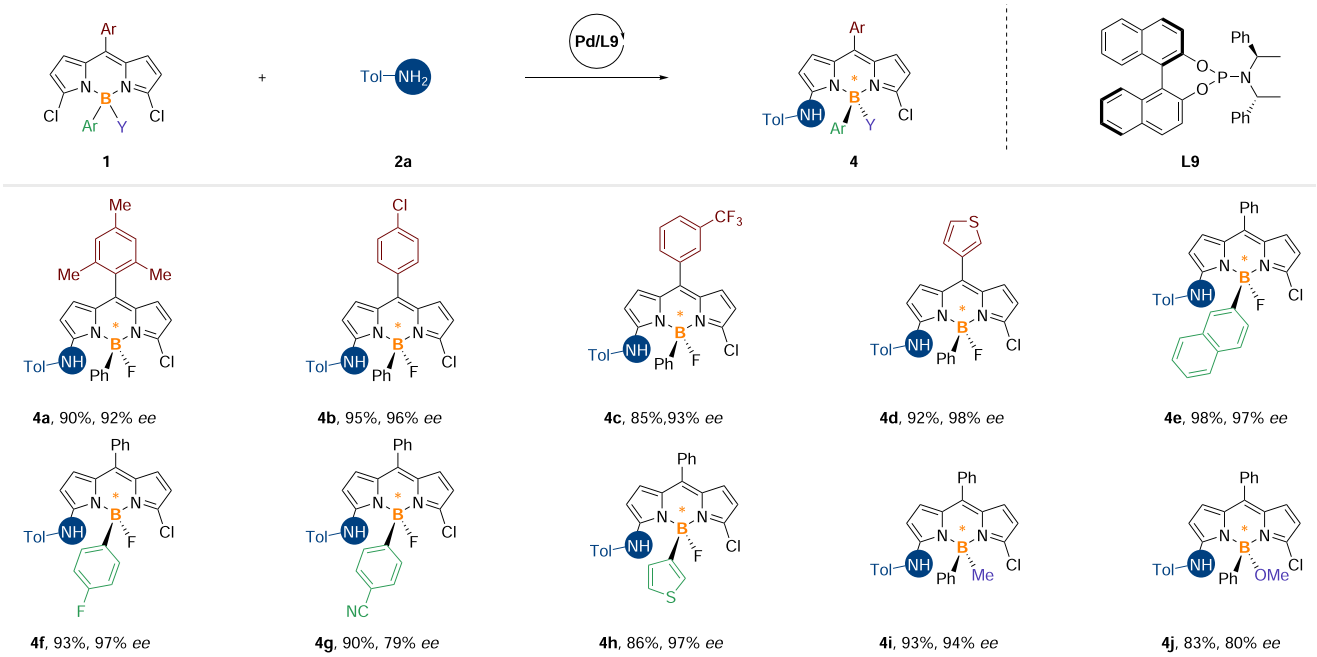

Fig. 3 | Substrate scope for BODIPYs. a Standard conditions: **1** (0.1 mmol), **2a** (0.1 mmol), $Pd(dba)_2$ (4 mol%), **L9** (10 mol%), Cs_2CO_3 (2.0 equiv), in 1.0 mL of toluene under argon atmosphere at 60 °C for 2 h. Isolated yields. The *ee* values were determined by chiral HPLC. Ar aryl, Ph phenyl, Tol *p*-tolyl.

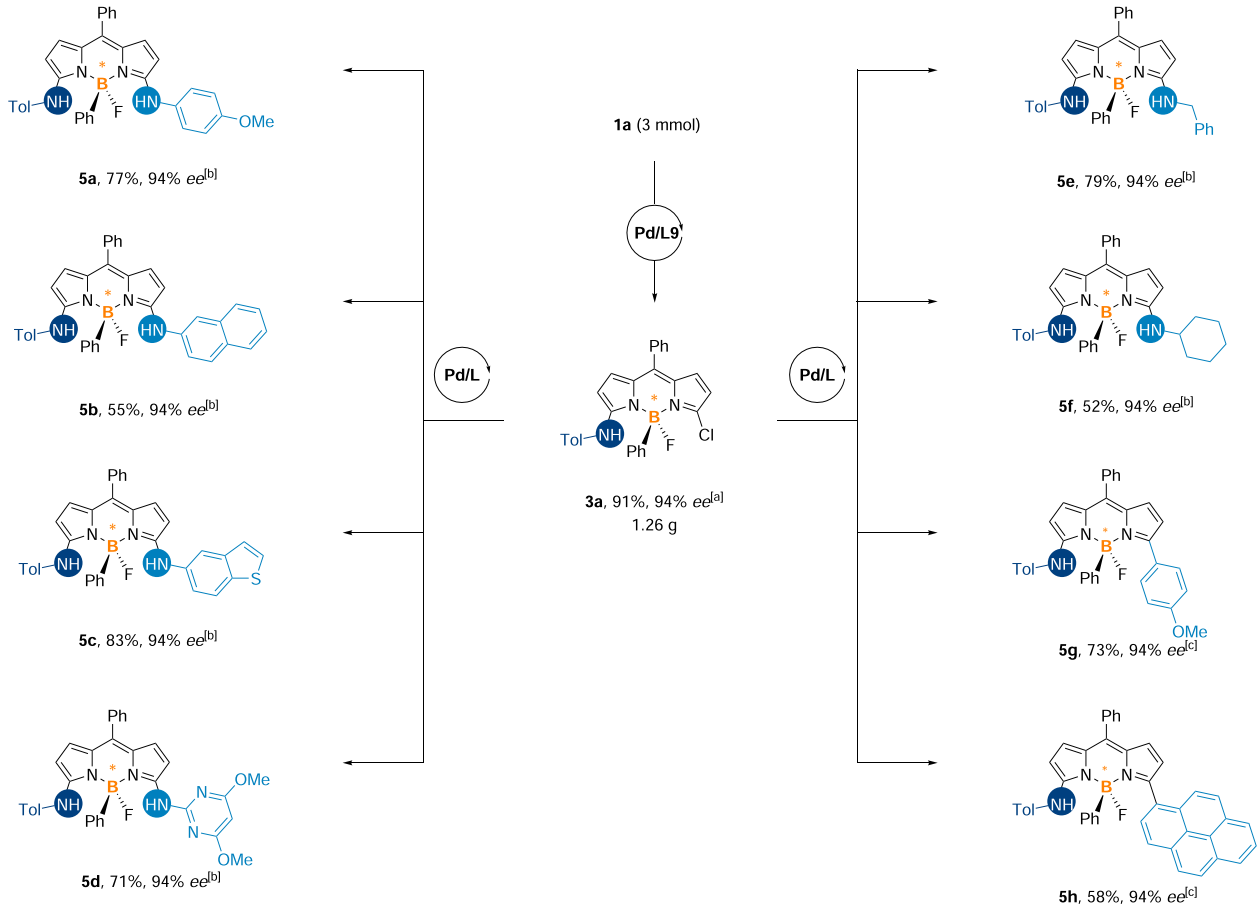

Fig. 4 | Derivatization of boron-stereogenic 3-amino-BODIPYs. a 1a (3 mmol), **2a** (3 mmol), $Pd(dba)_2$ (2 mol%), **L9** (5 mol%), Cs_2CO_3 (2.0 equiv), in 10 mL of toluene under argon atmosphere at 60 °C for 12 h. **b 3a** (0.1 mmol), amine (2.0 equiv), $Pd(OAc)_2$ (10 mol%), Xphos (30 mol%), Cs_2CO_3 (2.0 equiv), in 1.0 mL of toluene under argon atmosphere at 100 °C for 4 h. **c 3a** (0.1 mmol), arylboronic acid (1.0 equiv), $Pd(OAc)_2$ (10 mol%), Sphos (10 mol%), Et_3N (2.0 equiv), in 1.0 mL of TBME (*t*-butyl methyl ether) under argon atmosphere at 80 °C for 24 h. Isolated yields. The *ee* values were determined by chiral HPLC. Ph phenyl, Tol *p*-tolyl.

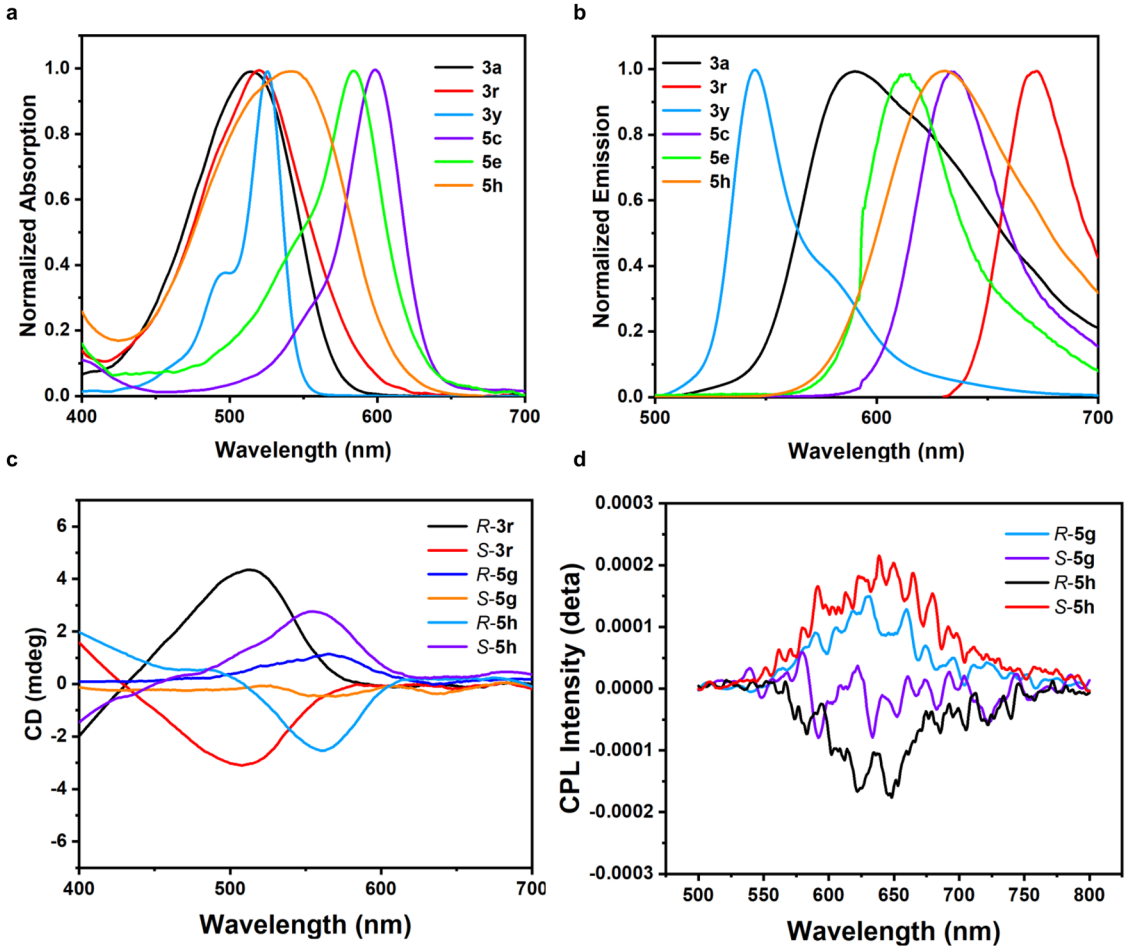

Fig. 5 | Photophysical property investigations. a Absorption spectra of **3a, 3r, 3y, 5c, 5e, and 5h** in CH_2Cl_2 (10^{-5} M). **b** Emission spectra of **3a, 3r, 3y, 5c, 5e, and 5h** in CH_2Cl_2 (10^{-5} M). **c** CD spectra of **3r, 5g** and **5h** in CH_2Cl_2 (10^{-5} M). **d** CPL spectra of **5g** and **5h** in CH_2Cl_2 (2×10^{-5} M).

several representative examples (Fig. S3). The 3,5-diamino-BODIPYs (**5c** and **5e**) exhibit higher fluorescence quantum yields than those of 3-amino-BODIPYs (**3a, 3y, 4h**, and **4i**). Compounds **4h, 5c**, and **5e** showed longer fluorescence lifetimes (≥3.60 ns). These characteristics expand the diversity of the chiroptical BODIPY dye platform, making it potentially appealing in the fields of biological, medicinal, and material chemistry as chiroptical luminophores.

In summary, we have developed a straightforward approach for achieving boron-stereogenic chirality through catalytic asymmetric C–N cross-coupling. This method enables the synthesis of a wide range of boron-stereogenic 3-amino-BODIPYs in decent yields with excellent enantioselectivities, which could be further converted to chiral 3,5-diamino-BODIPYs via a second stereospecific C–N cross-coupling. Additionally, we have investigated the photophysical properties of the obtained chiroptical BODIPYs. We believe this work not only enriches the chemical diversity of chiroptical BODIPY dyes but also inspires further advances in chiral boron chemistry.

Methods

General procedure for the enantioselective synthesis of boron-stereogenic BODIPY 3

Inside an argon-filled glovebox, an oven-dried 5 mL microwave reaction tube was charged with $Pd(dba)_2$ (2.2 mg, 0.004 mmol), **L9** (5.4 mg, 0.01 mmol), and anhydrous toluene (0.5 mL). After stirring for 5 min, Cs_2CO_3 (65.2 mg, 0.2 mmol), **1a** (39.5 mg, 0.1 mmol), and primary amine (1.0 equiv to 2.0 equiv) were added, followed by the addition of toluene (0.5 mL). The tube was capped and taken outside of the glovebox. The resulting mixture was placed into a pre-heated (60 °C) aluminum block and stirred for 2 h. Then the reaction mixture was concentrated and purified by column chromatography using preparative TLC (petroleum ether/ethyl acetate, from 10:1 to 3:1) as the eluent to afford the target product.

Data availability

The data that support the findings of this study are available within the paper and its Supplementary Information. Data supporting the findings of this manuscript are also available from the corresponding author upon request. Details about materials and methods, experimental procedures, characterisation data, ^{1}H, ^{13}C, ^{19}F, ^{11}B NMR spectra and mass spectrometry data are available in Supplementary Information. Crystallographic data for the structure reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 2323832 (**3o**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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C.H., B.Z., and L.Q.R. conceived the project. B.Z., L.Q.R., and J.Z. designed and performed the synthetic experiments. C.H. H.Z. and B.Z. prepared the manuscript. Correspondence should be sent to H.Z. (huazhang@scuec.edu.cn), C.H. (hec@sustech.edu.cn).

Competing interests

The authors declare no competing interests.

Additional information

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