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Diversity-Oriented Facile Access to Highly Fluorescent Membrane-Permeable Benz[*c,d*]indole *N*-Heteroarene BF_2 Dyes

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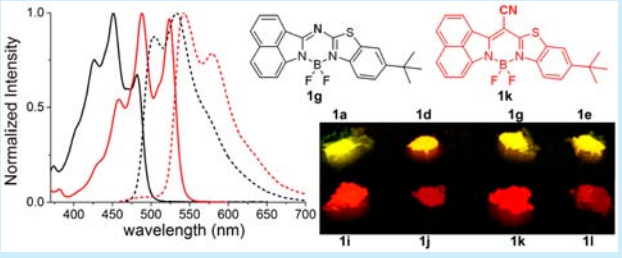
Supporting Information

ABSTRACT: A diversity-oriented one-pot synthesis of a series of membrane-permeable BF_2-rigidified benz[*c,d*]indole *N*-heteroarene BBN and BBC dyes has been achieved from the condensation of two commercial components (benz[*c,d*]indol-2-one and a set of *N*-heteroarene derivatives that can be selected from thousands of commercially available sources) and the subsequent in situ BF_2 complexation reaction. These dyes enjoy a set of excellent photophysical properties including the large Stokes shift, high solution and solid-state fluorescence, and excellent photostabilities.



Multidisciplinary research on novel organic fluorescent dyes is propelled by their potential applications in plastic electronics and biomedical sciences.[1] Ideally, a fluorescent dye suitable for these applications should be high chemically/photochemically stable and meet the profiles of high molar absorption coefficients, high fluorescence quantum yields, large Stokes shifts, and tunable absorption/emission. Despite continuous efforts devoted to their development,[2] in reality, few currently available dyes meet all of these criteria. For example, the most popular (aza)BODIPY (Figure 1) dyes[3−5] enjoy a set of outstanding optical properties but generally show small Stokes shifts (5−30 nm).

The construction of sophisticated fluorescent dyes around a tetrahedral boron(III) center[6] is a practical approach to achieve a specific set of properties including the large Stokes shift addressed here. Rational design of novel ligands has already been demonstrated as a key issue in this approach by some recent elegant research on the desymmetrical bidentate nitrogen ligands.[7−10] As part of our efforts toward large Stokes shift fluorophores, our[11a] and Ziegler's[11b] research groups very recently have independently developed the hydrazine−Schiff base linked bispyrrolic ligands, which upon BF_2 rigidification show improved Stokes shifts up to 70 nm yet suffer from limited structural versatility due to limitations from pyrrole starting materials.

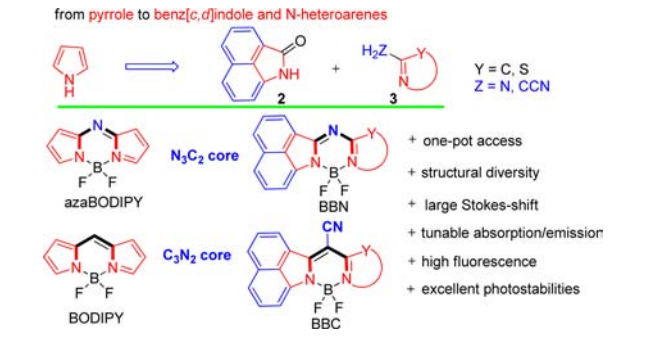


Figure 1. Chemical structures of BODIPY/azaBODIPY core and our rationally designed BF_2 rigidified benz[*c,d*]indole *N*-heteroarene (BBN/BBC) dyes in this work.

In our conceptual design of novel ligands to address this issue, we were attracted to two nonpyrrolic components, *N*-heteroarenes **3** and benz[*c,d*]indole **2** (Figure 1), because they both have good stability and easy accessibility (thousands of commercially available 2-amino-*N*-heteroarenes). This would render the desired structural versatility of dye **1**. In addition, *N*-heteroarenes have recently been used as heterocycles in building locked π-conjugated luminescent materials,[7a,10] and benz[*c,d*]-indole has been applied in the construction of NIR dyes.[12] Herein, we reported a diversity-oriented one-pot synthesis and properties of a library of membrane-permeable BBNs **1a−h** and BBCs **1i−l** (Scheme 1). Most of the synthesized dyes showed excellent solid-state fluorescence, which is in contrast to most BODIPY dyes. In addition, our cell-imaging results indicated that dye **1e** was highly cell permeable and could clearly highlight oil droplets of adipocytes.

Initially, we have attempted to condense benz[*c,d*]indol-2-one **2a** with 2-aminopyridine **3a** in refluxing toluene. No reaction was

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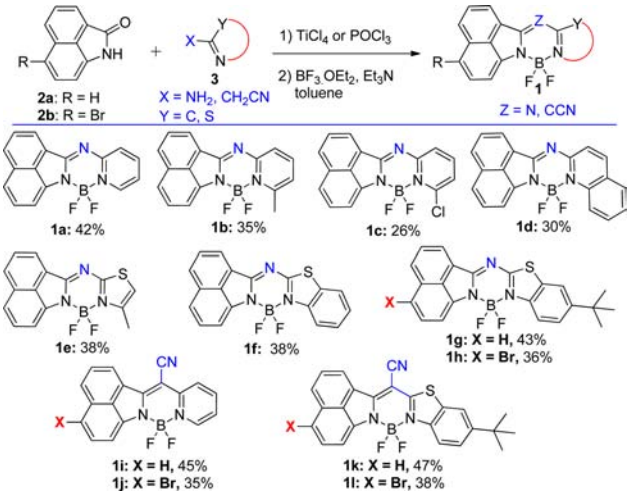
Scheme 1. Synthesis of BBNs and BBCs 1 from Benz[*c*,*d*]indol-2-ones 2 and *N*-Heteroarenes 3



observed, which may be attributed to the low reactivity of the carbonyl group. By adopting a literature procedure initially developed by Hall et al.,[13] $TiCl_4$ and triethylamine were added into the mixture, and the desired BBN **1a** (Scheme 1) was smoothly generated in 42% isolated yield after subsequent in situ BF_2 complexation. We further extended this one-pot process to a set of commercial *N*-heteroarenes, including 2-amino-*N*-pyridines **3a**−**d**, 2-amino-*N*-thiazoles **3e**−**g**, and even heteroarene acetonitriles **3h**,**i** (Chart S1, Supporting Information), from which the desired BBN series of dyes **1b**−**h** and the BBC series of dyes **1i**−**l** were efficiently synthesized in fair to good (26−47%) isolated yields (Scheme 1). It is worth noting that $POCl_3$ was also able to promote this reaction with a comparably isolated yield, and it gave a much cleaner reaction in case of 2-amino-6-chloro-*N*-heteroarene **3c**. The chloro substituent on the resultant BBN **1c** provides valuable reactive site for the facile postfunctionalization with various functionalities. For example, it readily underwent nucleophilic substitution reactions with common nucleophiles like 1-dodecanamine or 2-mercaptoethanol (a model compound of biothiols) in refluxing acetonitrile to give BBNs **4a**,**b** in 82% and 53% yields, respectively (Scheme 2).

Scheme 2. Synthesis of BBNs 4a and 4b

A similar reaction has found many applications on 3,5- or 8-halogenated BODIPYs.[14] These resultant dyes were characterized by high-resolution mass spectrometry and the NMR analysis. In addition, the structures of BBNs **1a**,**c**,**e**,**g** and BBCs **1i**,**j**,**l** were further confirmed by single-crystal analysis.

In the solid state, these dyes exhibit similarly planar structures (Figures 2 and 3) with the dihedral angles between benz[*c*,*d*]-indole moiety and *N*-heteroarene (pyridine or thiazole) moiety less than 7.6° (Tables S1 and S2, Supporting Information). The boron is coordinated in a tetrahedral geometry by two nitrogen and two fluorine atoms. These dyes all showed well ordered packing structures due to the multiple intermolecular C−H···F hydrogen bonds (Figures S1−S8, Supporting Information).

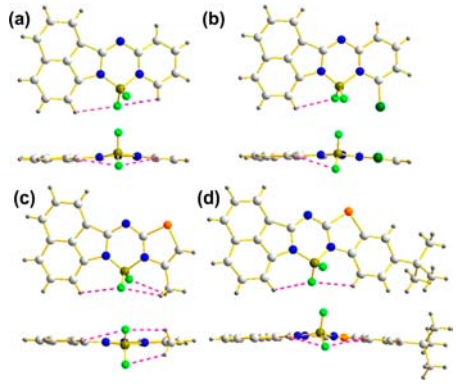


Figure 2. X-ray structures of **1a** (a), **1c** (b), **1e** (c), and **1g** (d). Key: C, light gray; H, gray; N, blue; B, dark yellow; F, bright green; Cl, green; Br, dark green; S, orange.

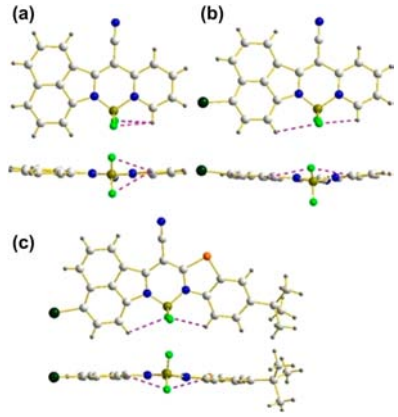


Figure 3. X-ray structures of **1i** (a), **1j** (b) and **1l** (c). Key: C, light gray; H, gray; N, blue; B, dark yellow; F, bright green; Br, dark green; S, orange.

Most of dyes formed slipped dimers except BBC **1l**, in which the blue molecules and red molecules are arranged in a columnar fashion in the crystal packing structure (Figures S7 and S8, Supporting Information).

BBNs **1a**−**h** showed one absorption maximum (440−460 nm), while their BBC analogues **1i**−**l** exhibited two well-split absorption maxima (480−540 nm) in dichloromethane (Table 1 and Figures S10−27 in the Supporting Information). All these dyes show two broad emission bands (centered within the range of 520−560 nm), most of which are not the mirror images of their absorption bands. This indicates differentiation in the vibration energy patterns at the ground and excited states. In contrast to their benz[*c*,*d*]indole *N*-heteroarene ligands, which hardly showed any fluorescence, these BBN dyes showed good to excellent fluorescence quantum yields (close to unity) in dichloromethane, comparable to commercial BODIPYs 505/515 and PM567 (Table 1). Large Stokes shifts were observed for these dyes (over 3000 cm^{-1} for BBNs and over 2000 cm^{-1} for BBC dyes, respectively), which are much larger in magnitude than those observed for typical BODIPY dyes (generally within 400−1000 cm^{-1}). Tunable absorption/emission profiles were observed for these dyes via the simple variation of the *N*-heteroarenes or their postfunctionalizations. For example, BBN **1d** showed an ∼20 nm red shift in both the absorption and the emission maxima in comparison with those of BBN **1a** due to the extended π-conjugation (Table 1 and Figure S10, Supporting Information). Strong electron-donating substituents, like 1-

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Table 1. Photophysical Properties of Dyes 1a–l and 4a,b in Dichloromethane at Room Temperature[a]

	λ_{ab}[b] (nm)	ε[b] (M^{-1} cm^{-1})	λ_{fl}[b] (nm)	Φ	τ (ns)	$\Delta\upsilon_{St}$[c] (cm^{-1})
1a	438	26300	518	>0.99	7.1	3526
1b	441	28600	521	>0.99	7.1	3482
1c	447	31700	526	>0.99	6.4	3360
1d	455	39200	536	>0.99	6.1	3321
1e	445	25500	527	0.95	6.5	3497
1f	448	30100	529	0.85	6.6	3418
1g	451	33300	534	0.86	5.7	3446
1h	463	34300	552	0.72	5.0	3482
1i	478, 511	36200	530	0.88	8.7	2053
1j	488, 523	34300	546	0.67	7.8	2177
1k	488, 524	40000	543	0.70	6.0	2076
1l	501, 538	44900	560	0.60	6.0	2103
4a	467	28200	522, 556	0.25	2.5	2256
4b	453	26200	501, 530	>0.99	7.3	3207
BDP[d]	506	87100	519	0.95	6.1	495

[a]For full detailed data, see Table S5 in the Supporting Information. [b]Data correspond to the strongest absorption (or emission) peaks. [c]Stokes-shifts for BBNs **1i–l** refer to the difference between the higher energy absorption maximum and the emission maximum. [d]BODIPY 505/515.

dodecanamine on **4a** and 2-mercaptoethanol on **4b**, lead to a large red shift in the absorption (30–40 nm) and an ~10 nm red shift in the emission maximum over their unsubstituted analogue **1a** (Figure 4a).

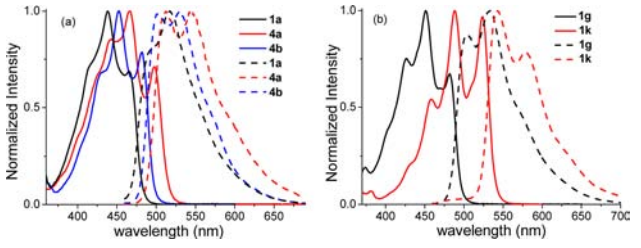

Figure 4. Overlaid normalized absorption (solid lines) and fluorescence emission (dashed lines) spectra in dichloromethane: (a) BBNs **4a,b** and **1a**; (b) BBC **1k** and its analogue BBN **1g**.

BBC **1k** showed significant bathochromic shift in the absorption (~40 nm in the *higher energy* absorption maxima and ~70 nm in the *lower energy* ones, Table 1 and Figure 4b) and ~10 nm in the emission maximum with respect to those of its BBN analogue **1g**. Similar red shifts were observed in BBCs **1i** and **1l** (Table S5, Supporting Information). This may be attributed the strong electron-withdrawing properties of the nitrile group. As summarized in the electrochemical data in Table S7 in the Supporting Information, this nitrile group reduced the HOMO–LUMO band gaps (around 0.2 eV) in BBCs **1i**, **1k**, and **1l** with respect to those of their BBN analogues **1a**, **1g**, and **1h** via the decrease of the LUMO and the increase of the HOMO energy levels. In addition, the HOMO energy values (between −5.64 and −5.93 eV) observed in these dyes are also lower than that of BODIPY 505/515 (−5.49 eV), indicating the more electron-deficient nature in these dyes in comparison with common BODIPYs.

In great contrast to most BODIPY dyes, which barely exhibit fluorescence in their solid-state due to the small Stokes-shifts,[10] most of these BBN and BBC dyes show strong solid-state fluorescence emission covering the range of visible to near IR regions (Figure 5). The fluorescence emission bands in solid

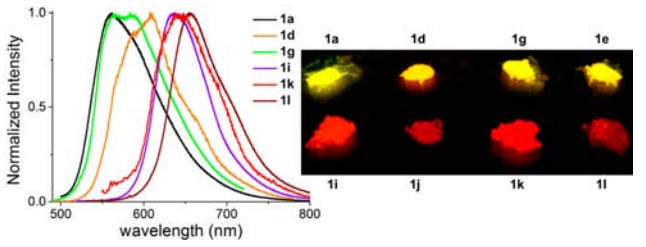

Figure 5. Spectral overlap of the normalized solid-state fluorescence emission of BBNs **1a,d,g** and BBCs **1i,k,l** (left); solid-state fluorescence images of these dyes, BBN **1e** and BBCs **1j**, under 365 nm UV-light irradiation (right).

state are less structured but still tunable via the variation of the *N*-heteroarenes. For example, BBNs **1a**, **1d**, **1e**, and **1g** each showed strong solid-state fluorescence at 561 nm (ϕ = 0.37), 607 nm (ϕ = 0.16), 566 nm (ϕ = 0.15), and 583 nm (ϕ = 0.16), respectively. Interestingly, BBCs **1i–l** each showed moderate to strong red solid-state fluorescence at 637 nm (ϕ = 0.18), 626 nm (ϕ = 0.06), 648 nm (ϕ = 0.17) and 656 nm (ϕ = 0.09), respectively. The relatively low fluorescence of BBCs **1j** and **1l** may be attributed to the heavy-atom effect of bromo-substituent. In addition, dyes **1d**, **1i**, **1k**, and **1l** each showed over 70 nm red shifts of the fluorescence emission maximum in the solid state over those observed in dichloromethane.

All these dyes were stable as solids toward light, humidity, and air. Like the BODIPY fluorophores, their solutions are stable toward extended ambient light and handhold UV light (365 nm) irradiation conditions for days in the presence of air. As demonstrated by **1a**, these dyes are more resistant to photobleaching than commercial *meso*-unsubstituted BODIPY 505/515, *meso*-methyl BODIPY PM567, and fluorescein: Only 75% of BODIPY 505/515, 85% of BODIPY PM567, and 56% of fluorescein remained, respectively after a specific period of strong irradiation in toluene (1 h) or in the aqueous solution (DMSO/H_2O = 1/1, v/v, 30 min), while the absorption profile of **1a** was essentially unchanged under the same condition (Figures S38 and S39, Supporting Information).

Decreasing the polarity of the system from acetonitrile to toluene/hexane led to a slight to moderate red shift of the absorption/emission maxima with little variation of the fluorescence quantum yields for most of these dyes, which is a favorite in bioimaging. Lipid droplets are responsible for the storage of neutral lipids and are associated with a multitude of metabolic syndromes, including obesity and diabetes. BODIPY dyes have been used for staining oil droplets of adipocytes. For example, BODIPY493/505 is a standard dye for cell imaging of differentiated 3T3-L1 adipocytes.[15a] However, it suffers limitation of photostability in solution.[15b] We applied BBN **1e** for the preliminary cellular imaging of lipid droplets. As shown in Figure 6, BBN **1e** can readily enter into the lipid droplets and exhibit strong green fluorescence with FITC filter set. Cells remained viable after treatment. We further evaluated the cytotoxicity of BBN **1e** using the MTT assay by varying the probe concentration from 0.25 to 2.5 μM. As demonstrated in Figure S9 in the Supporting Information, 2.5 μM BBN **1e** used for the cell loading shows low toxicity to cells.

In summary, starting with a set of widely commercially available starting materials, we have developed a diversity-

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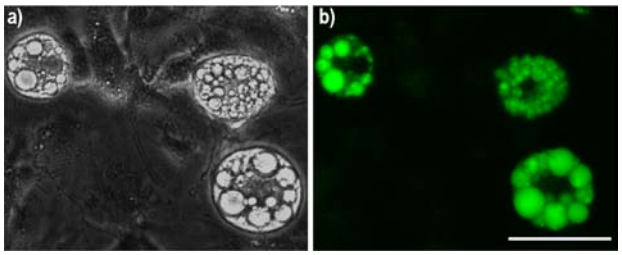

Figure 6. Staining patterns of differentiated 3T3-L1 cells with BBN **1e**: (a) bright field image; (b) BBN **1e** staining fluorescence image of oil droplets using FITC excitation/emission filters. Scale bar: 50 μm.

oriented one-pot synthesis of a small library of membrane-permeable fluorescent benz[*c*,*d*]indole *N*-heteroarene BF_2 dyes featuring large Stokes shifts, high solution- and solid-state fluorescence, good photostability, and tunable absorption/emissions. We believe these dyes have great potential as new fluorescent materials and cell-imaging probes. In addition, we have shown that some dyes could be easily functionized. Conceivably, these dyes could be easily conjugated with ligands of various receptors for biomedical imaging.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, NMR data, additional photophysical data, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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