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Regioselective Decarboxylative Direct C−H Arylation of Boron Dipyrromethenes (BODIPYs) at 2,6-Positions: A Facile Access to a Diversity-Oriented BODIPY Library

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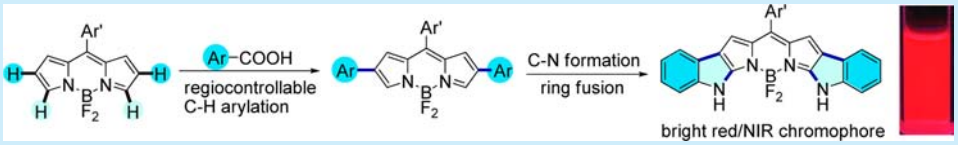
Supporting Information

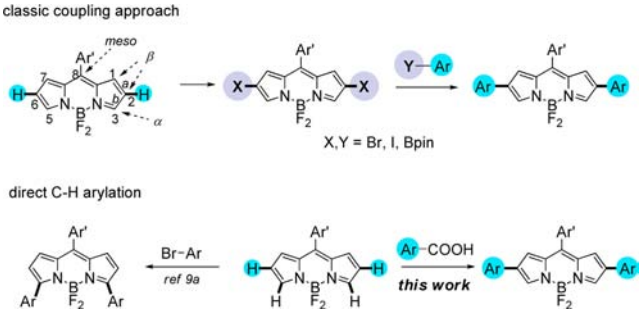


ABSTRACT: A palladium-catalyzed regioselective decarboxylative direct C−H arylation of boron dipyrromethenes (BODIPYs) at the 2,6-positions has been developed as a late-stage approach to rapidly assemble a diversity-oriented BODIPY library. With the complement of this protocol, the direct C−H arylation of BODIPYs becomes regiocontrollable at α- and β-positions. A new type of indole-fused BODIPY exhibiting bright red/NIR fluorescence with a large molar extinction coefficient (145 500 M^{-1} cm^{-1}) and a high quantum yield (71%) has been synthesized for the first time.

Boron dipyrromethene (BODIPY) is a well-known versatile fluorescent dye that plays important roles in many fields such as luminescent solar concentrators, reaction mechanistic studies, *in vivo* biomolecular probing, labeling, and imaging.[1] A plethora of efforts have been made to modify BODIPYs to pursue various properties such as high quantum yield, red/NIR emission, large Stokes shift, and photostability.[2] Modifications at α- and β-positions of BODIPYs have proven more effective in altering the electronic spectroscopies compared with those at the *meso*-position. However, the differentia of the substituent effects between α- and β-C of BODIPY still remains underrepresented. Due to limited types of β-modified BODIPYs, there is only one example to distinguish these effects by comparing β- and α-alkenylated BODIPYs, wherein the former exhibits a wider full width at half-maximum (fwhm) and larger Stokes shift.[3] Therefore, it is highly desirable to develop a rapid and concise route to β-substituted BODIPYs.

Conventional approaches to β-functionalized BODIPYs, such as Suzuki, Heck, and Sonogashira coupling reactions as well as Knoevenagel condensations, often require multistep synthesis (Scheme 1).[2d,3−6] However, some prefunctionalized pyrroles and BODIPYs are easily subjected to instability or even unavailability, which limits the rapid establishment of a diversity-oriented BODIPY library with functional significance. Direct C−H functionalization circumvents the use of unwelcomed intermediates and/or environmentally risky organometallic reagents and would be an ideal alternative to the late-stage diversification of BODIPY frameworks.[7] However, despite the wealth of methods for direct C−H functionalization, there are only a few examples involving late-stage modification of BODIPYs.[8,9] Especially, the direct C−H arylation at the 2(,6)-position(s) of BODIPY remains elusive. The major challenge

Scheme 1. Arylation and Regioselectivity at 2(,6)-Position(s) of BODIPY



exists in the regioselectivity issue incurred from the coexistence of multiple inequivalent C−H bonds on the ready-made BODIPYs.

In continuation of our efforts to extend π-conjugated systems via C−H functionalization of (hetero)arenes,[10] we herein turned our attention to the late-stage arylation of BODIPYs. Carboxylic acids possess advantages of wide availability, high stability, easy handling, and low prices, and the byproduct coming from the C−COOH bond cleavage is relatively eco-friendly carbon dioxide, which render the decarboxylative cross-coupling reaction attractive.[11] Initially, 2-nitrobenzoic acid was chosen as the coupling partner of **8-Ph-BODIPY** to investigate the reaction (eq 1; Table S1). After rational screening, the best result was obtained in the presence of $Pd(OAc)_2$ as the palladium source,

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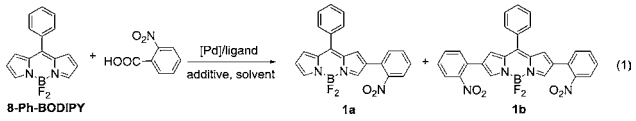


$PCy_3{\cdot}HBF_4$ as the ligand, Ag_2CO_3, and 4 Å molecular sieves (4 Å MS) as the additive in DMSO/diglyme (1:20 v/v) at 140 °C for 24 h. The desired monoarylated **1a** and diarylated **1b** were produced in 32% and 35% yields, respectively (Table S1, entry 11). The arylation exclusively occurred at the 2(,6)-position(s), which was confirmed by ^{1}H, ^{13}C, and ^{1}H−^{1}H NOESY NMR (see the Supporting Information).

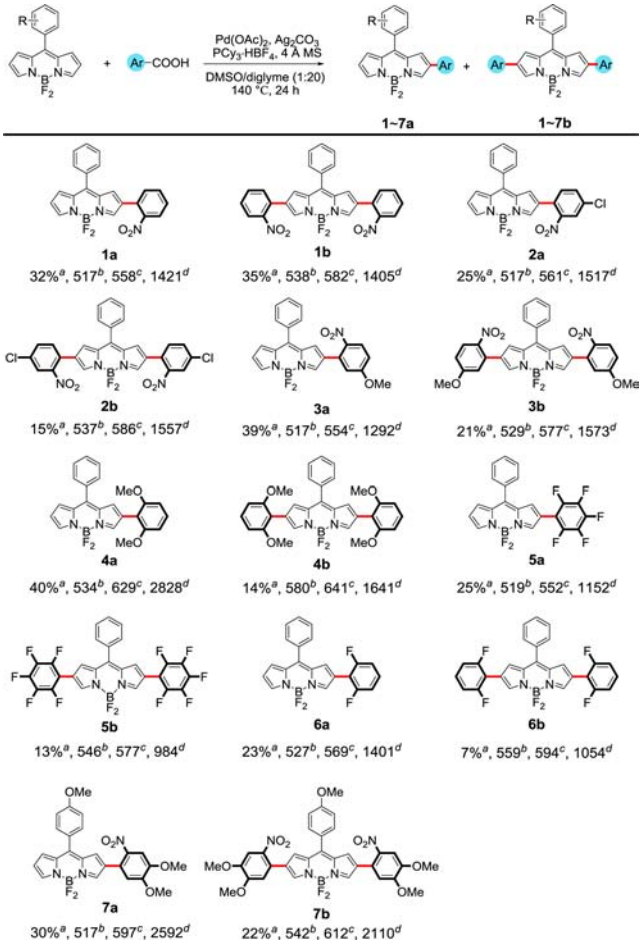
It is notable that, in a previous report, the palladium-catalyzed C−H arylation of BODIPYs with aryl bromides preferentially occurred at the α-position(s) of BODIPY (Scheme 1).[9a] The C−C bond formation via regioselective direct β-C−H functionalization of BODIPYs remains unknown unless the other positions are blocked by inert groups.[2b,8a] The regioselectivity is assumed to stem from the electronic difference in the carbon atoms, among which the least positively charged C-2,6 atoms are most susceptible to electrophilic attack through an electrophilic aromatic substitution (S_EAr) pathway (for Mulliken charge distribution of **8-Ph-BODIPY**; see Figure S1).[2b,4c,e,8a,11h,i] Considering the coexistence of six types of chemically distinct C−H bonds around **8-Ph-BODIPY**, the total yield of up to 67% implied satisfying regioselectivity and efficiency. With the complement of this novel protocol, the direct C−H arylation of BODIPYs becomes regiocontrollable at α- and β-positions.

With the optimized reaction conditions in hand, the scope of benzoic acids was examined. Gratifyingly, the benzoic acids investigated smoothly underwent the reaction to give synthetically useful yields. Benzoic acids with either electron-deficient, electron-rich, or sterically hindered groups were compatible (Scheme 2, **1**−**7**). The amounts of mono- and diarylated products could be tuned easily by varying the ratio of the two coupling partners. For example, the ratios of mono-/diarylated BODIPYs spanned over the range 0.9/1.0 to 3.0/1.0 when the ratios of 2-nitrobenzoic acid/BODIPY varied from 3.0/1.0 to 1.0/1.5 (Table S2).

Based on the established BODIPY library, the photophysical properties were investigated preliminarily. Generally, the absorption maxima were red-shifted by 17−34 nm by monoarylation and further red-shifted by 12−46 nm by the second arylation with reference to **8-Ph-BODIPY** (Figure 1). The bathochromic effects were much more pronounced in fluorescence spectra. In addition, the electron-rich substituent on the phenyl ring generally had a more substantial effect than the electron-deficient one. The most notable red shift of the emission maximum was observed for **4b** (123 nm). As presented in Scheme 2, the monoarylated **4a** and **7a** exhibited larger Stokes shifts (2828 and 2592 cm^{-1}, respectively) than the corresponding symmetrically diarylated **4b** and **7b** (1641 and 2110 cm^{-1}, respectively), which was attributed in part to the electronic desymmetrization.[2d]

D−π−A (donor−π−acceptor) structures have interesting properties including bathochromic spectra, low band gaps, and large Stokes shifts. The decarboxylative C−H arylation allowed the resulting monoarylated BODIPYs to be further arylated by using a different aryl carboxylic acid without preactivation, blockage, protection, and deprotection that are almost inevitable in traditional strategies. Treatment of monosubstituted **5a** with 2,6-dimethoxybenzoic acid afforded the unsymmetrically diarylated **8** in 44% yield (Scheme 3). Crystal structure determination

Scheme 2. Diversified 2(,6)-Modified BODIPY Library Built up through Direct C−H Arylation



[a]Isolated yields. [b] λ_{abs}. [c] λ_{em}. [d] Stokes shift (cm^{-1}) in CH_2Cl_2 (1.6×10^{-5} M).

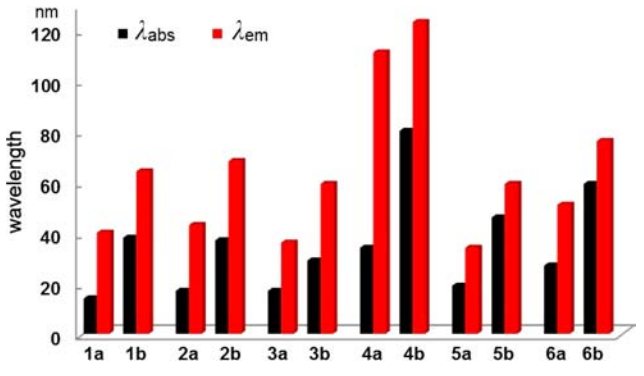


Figure 1. Bathochromic effects of aryl substituents in **1**−**6** with reference to **8-Ph-BODIPY**. λ_{abs} and λ_{em} of **8-Ph-BODIPY** in CH_2Cl_2 (1.6×10^{-5} M) are 500 and 518 nm, respectively.

confirmed the regioselectivity at the 2,6-positions (Figure 2). Subsequently, the fluorescence solvatochromism of the D−π−A compound **8** was investigated. The unsymmetrical substitution of **8** led to a remarkable red shift with the increasing polarity of solvent. The emission peaks red-shifted from 618 nm in cyclohexane to 658 nm in DMF (Figure S4). Compared with **5a**, the D−π−A molecule **8** exhibited a red shift of 90 nm in the emission band (642 and 552 nm for **8** and **5a**, respectively) and a

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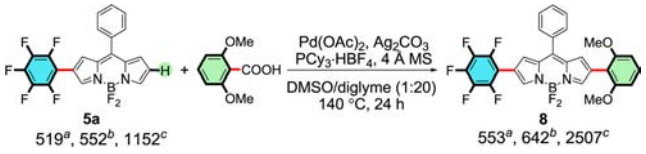
Scheme 3. D−π−A Motif Built through Further C−H Arylation of Monoarylated BODIPY



[a] λ_{abs}. [b] λ_{em}. [c] Stokes shift (cm^{-1}) in CH_2Cl_2 (1.6×10^{-5} M).

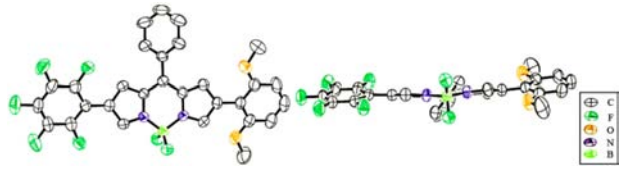


Figure 2. Top (left) and side (right) views of **8** by ORTEP drawings with 50% probability thermal ellipsoids. H atoms were omitted for clarity.

larger Stokes shift (2507 and 1152 cm^{-1} for **8** and **5a**, respectively) in CH_2Cl_2. The red/NIR emission and the large Stokes shift would make **8** a promising fluorecent dye.

Ring fusion to achieve a highly extended π-conjugation system is a powerful strategy to acquire interesting properties such as red/NIR emission as exhibited by benzene-, (benzo)furan-, and (benzo)thiophene-fused BODIPYs.[8b,12] The calculation studies disclosed indole[*b*]-fused BODIPY **10** as a rigid and nearly planar conformation composed of seven fused rings with fully delocalized charge distribution (Figure 3a−c; for calculation

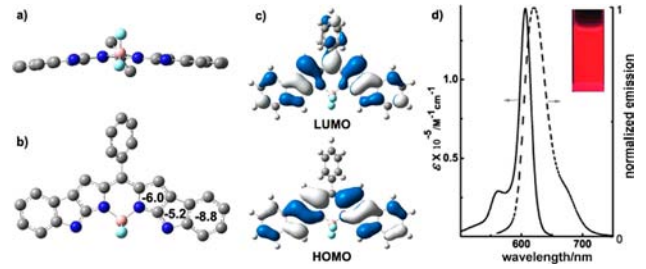
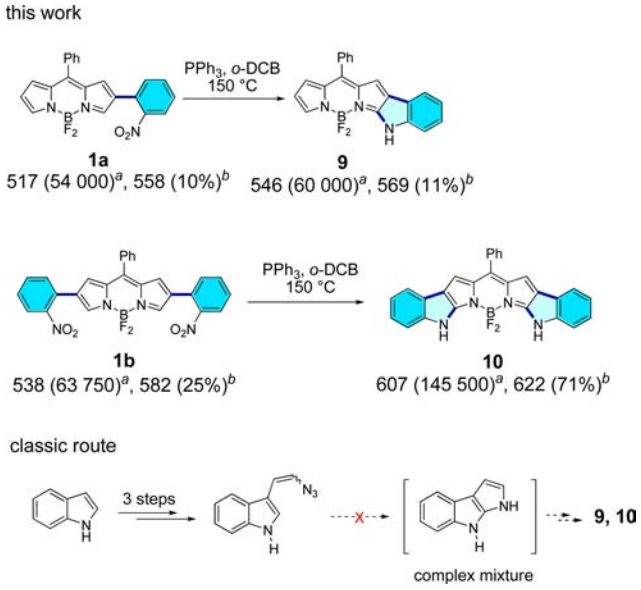


Figure 3. Structure and photophysical properties of **10**. (a) Side view and (b) top view with NICS(0) values (ppm) at the geometric center points of corresponding five-/six-membered rings. H atoms were omitted for clarity. (c) LUMO and HOMO obitals; (d) UV−vis−NIR absorption and emission spectra. The picture inserted was the photograph under UV irradiation (365 nm). All were measured in CH_2Cl_2 (4.0×10^{-6} M).

details, see Supporting Information). NICS(0) values of −6.0, −5.2, and −8.8 ppm at the center points of five-/six-membered (hetero)rings predicted by Nucleus-Independent Chemical Shifts (NICS) showed that **10** exhibited good aromacity (Figure 3b), indicating this new extended π-conjugated system would have strong and red-shifted absorption and emission bands.[13] However, the synthesis of multiring-fused BODIPYs is a challenging task mainly due to inconvenient or even unavailable precursors, especially for the heteroaromatic ring[*b*]-fused BODIPYs. For example, indole-fused pyrrole was disclosed to be not stable enough to purify, thus hindering the classic synthetic route of Lewis acid catalyzed condensation to build **9** and **10** (Scheme 4).[14] The protocol developed herein provided a rapid and concise access to the multiring-fused BODIPYs.

Scheme 4. Access to Indole-Fused BODIPYs



[a] λ_{abs} (nm) with ε_{max} (M^{-1} cm^{-1}) inside parentheses. [b] λ_{em} (nm) with ϕ inside parentheses. All were measured in CH_2Cl_2 ($c = 1.6 \times 10^{-5}$ M) except λ_{abs} of **10** ($c = 4.0 \times 10^{-6}$ M). *o*-DCB: *ortho*-dichlorobenzene.

Following the direct C−H arylation, the *ortho*-nitro group(s) on the 2(,6)-phenyl substituent(s) of BODIPY were employed as a useful handle to regioselectively form C−N bond(s) via an intramolecular reductive cyclization, namely the Cadogan reaction (Scheme 4).[15] **1a** and **1b** were transformed into indole[*b*]-fused BODIPYs **9** and **10** in 65% and 31% yields, respectively. X-ray crystallographic analysis of **9** confirmed the molecular structure (Figure 4). Compound **10** exhibited

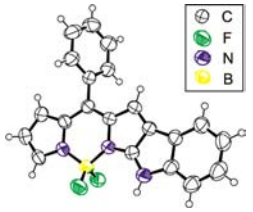


Figure 4. Top view of **9** by ORTEP drawings with 50% probability thermal ellipsoids.

remarkably red-shifted absorption and emission maxima (λ_{abs} = 607 nm, λ_{em} = 622 nm). A large molar extinction coefficient ε_{max} (145 500 M^{-1} cm^{-1}) and a high quantum yield ϕ (71%) of **10** would qualify it as a bright red/NIR flourecent dye (Figure 3d, Scheme 4, and Table S3). To our knowledge, here is the first example of indole-fused BODIPYs.

In conclusion, we have introduced the Pd-catalyzed decarboxylative C−H arylation into the late-stage functionalization of BODIPYs with regioselectivity at the C-2(,6) position(s). The amounts of mono- and diarylated products can be adjusted by altering the ratio of the coupling partners. This protocol offers a rapid and convenient approach to a diversity-oriented BODIPY library including mono- and diarylated BODIPYs, D−π−A motifs, and multiring-fused skeletons. Through two steps of regioselective transformations, the indole-fused BODIPY **10** with prominent flourecent properties has been conveniently achieved for the first time. We envision that the current

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methodology will facilitate the discovery of high performance fluorescent materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of NMR spectra and X-ray crystallographic files, in CIF format, for **8** (CCDC-1005230) and **9** (CCDC-1031858). 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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