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# Highly Regioselective α-Chlorination of the BODIPY Chromophore with Copper(II) Chloride

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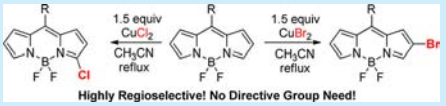
Supporting Information

**ABSTRACT:** A general and efficient method for α-chlorination of 4,4′-difluoro-4-bora-3a,4a-diaza-*s*-indacenes (BODIPYs) has been developed using $CuCl_2$ as chlorination reagent. The reaction is characterized by complete 3/5-positions of BODIPY regioselectivity. This unusual highly regioselective α-halogenation of BODIPY is in sharp contrast to previously reported halogenation methods which preferred to occur first at the 2,6-positions of BODIPY. This approach provides a straightforward, facile, and economical route to 3- and/or 5-chloroBODIPYs with various *meso*-groups (H, alkyl, and aryl) and their derivatives.




BODIPY (4,4′-difluoro-4-bora-3a,4a-diaza-*s*-indacene) dyes have found applications in highly diverse research fields, for example, as labeling reagents, chemosensors, and energy-transfer cassettes, due to their remarkable properties, including large molar absorption coefficients, sharp fluorescence emissions, high fluorescence quantum yields, and high photophysical stability.[1−3] The development of efficient synthetic methods for the facile functionalization of the BODIPY chromophore to achieve a set of desired specific optical properties has attracted intense research interest lately.[4,5] Among those, facile access to core-halogenated BODIPYs is particularly attractive, since they allow the introduction of a variety of functionalities on the BODIPY core.[6]

Traditionally, the postfunctionalization of the BODIPY core with halogen agent is mainly achieved via the blocking effects from the preinstalled substituents on the core.[7] Recently, direct regioselective halogenations of BODIPY using various reagents were developed by us and others (Figure 1a).[8] These direct halogenation methods generate 2,6-(β-)halogenated BODIPYs (for example, **A** and **B** in Figure 1) since the 2,6-positions of the BODIPY core bear the least positive charge based on the electronic structure features of BODIPY and are most susceptible to electrophilic attack. Thus, direct access to 3- and/or 5-haloBODIPYs,[9a−f] 1- and/or 7-haloBODIPYs,[9g] and 8-haloBODIPYs[9h] instead of total synthesis was not possible. For example, 3- and/or 5-chloroBODIPYs **C** and **E** were first developed by Dehaen and Boens via chlorination of dipyrromethane **D**[9a−c] or pyrrole precursors[9d] using NCS at −78 °C (Figure 1b,c). Those 3- and/or 5-haloBODIPYs are very useful for fine-tuning the optical properties of BODIPYs as already demonstrated via the preparation of a series of 3- and/or 5-aryl-, alkenyl-, and alkynyl-functionalized BODIPYs through $S_NAr$ and palladium-catalyzed cross-coupling reactions (e.g., Stille, Negishi, Heck, Suzuki, and Sonogashira).[9]

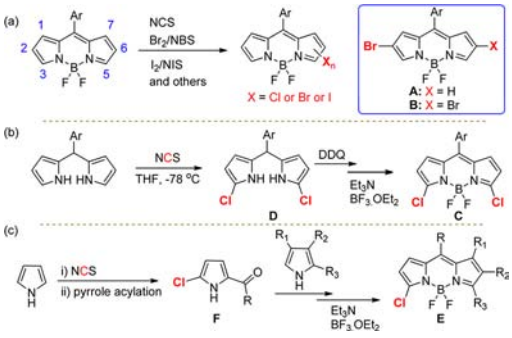



**Figure 1.** Reported regioselective synthesis of the halogenated BODIPYs **A**/**B**,[8a−c] **C**,[9a−c] and **E**.[9d]

Herein, we report an unusual highly regioselective α-chlorination of the BODIPY core with $CuCl_2$ in $CH_3CN$ with good versatility for various *meso*-aryl-, *meso*-H-, and *meso*-alkylBODIPYs. The regioselectivity of this chlorination reaction was confirmed by X-ray analysis and may come through a cation radical pathway in the single-electron-transfer (SET) processes and the nucleophilic addition by chloride anion. The resultant regioselective 3- and/or 5-(di)chloroBODIPYs are valuable synthetic precursors for the preparation of various α-functionalized BODIPYs as demonstrated in the preparation of the analogues of commercial labeling reagents, BODIPY 630/650 and 650/665.

Inspired by the wide applications of copper salt as oxidation reagents for C−H bond activation,[10] we attempted the direct oxidative dimerization of BODIPY via Cu(II) salts. Our initially investigation explored the reactivity of *meso*-mesityl BODIPY **3a** in this Cu(II)-catalyzed reaction. No reaction took place with a catalytic amount of $CuCl_2{\cdot}2H_2O$. However, when a stoichiometric amount of $CuCl_2{\cdot}2H_2O$ was used for this reaction in $CH_3CN$ (entry 1, Table S1), one major product was isolated (28% yield). To our surprise, HRMS and NMR spectroscopic

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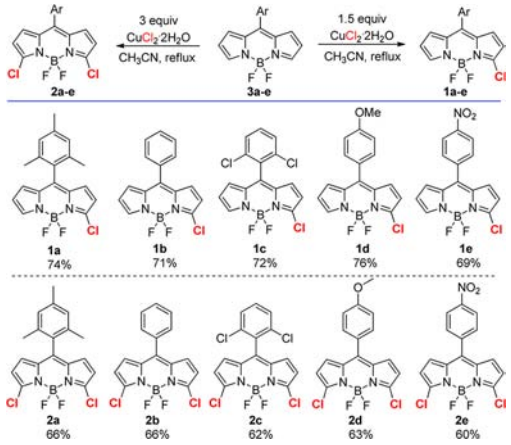
analysis results show that it is 3-chloroBODIPY **1a** instead of the desired BODIPY dimer. $CH_3CN$ is the best solvent for this reaction among a set of common organic solvents (entries 6−10, Table S1). After optimization of this reaction, we found that the reaction with 1.5 equiv of $CuCl_2·2H_2O$ in $CH_3CN$ at 80 °C in 2 h gave the best result for **1a** (74% yield, entry 4, Table S1). A further increase of the amount of $CuCl_2·2H_2O$ to 3 equiv with extended reaction time to 6 h afforded regioselectively the corresponding 3,5-dichloroBODIPY **2a** in 66% isolated yield (Scheme 1). Increasing further the amount of $CuCl_2·2H_2O$ and the reaction time only led to the decrease of the yield of the target compound, and no oligochloroBODIPYs were obtained.

**Scheme 1. Synthesis of Mono- and DichloroBODIPYs 1 and 2 Using $CuCl_2·2H_2O$ from *meso*-arylBODIPYs 3**[a]



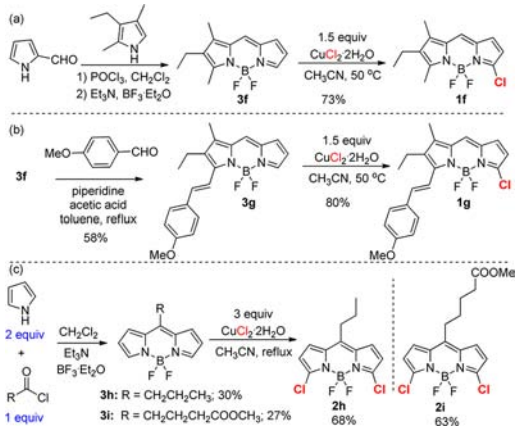

[a]The Ar substituent is shown for the specific compounds.

To test the versatility of this unique highly regioselective α-chlorination of BODIPY, we further applied a set of pyrrolic unsubstituted *meso*-arylBODIPYs **3b−e** (Figure S1) containing electron-donating substituents (like the methoxyl group in **3d**) or an electron-withdrawing group (like the chloro and nitro group in **3c** and **3e**) for this reaction. This reaction is compatible with these functionalities. At 1.5 equiv of $CuCl_2·2H_2O$, the desired 3-chloroBODIPYs **1b−e** (Scheme 1) were isolated in good yields (69−72%). By raising the ratio of $CuCl_2·2H_2O$ to 3 equiv, the corresponding 3,5-dichloroBODIPYs **2b−e** were obtained as the major product in 60−66% isolated yields in 6 h.

The unsymmetrical *meso*-H BODIPY **3f** that contains only one free α-position shows even better reactivity in this regioselective α-chlorination reaction with respect to those *meso*-arylBODIPYs **3a−e**. For example, with the same amount (1.5 equiv) of $CuCl_2·2H_2O$, it only requires 50 °C and 2 h for the completion of the reaction, from which the desired 3-chloroBODIPY **1f** was obtained in 73% yield (Scheme 2a). This method provides a straightforward and economical route to **1f** and avoids the tedious preparation of chlorinated pyrrole **F** (Figure 1c).

Currently, the synthesis of 3,5-dichloro-*meso*-alkylBODIPY remains a challenge since 5-alkyldipyrromethane as the key synthetic precursor for the regioselective α-chlorination reaction (Figure 1b) is highly unstable and readily undergoes oxidation to form the corresponding dipyrromethene. The success of regioselective α-chlorination of *meso*-arylBODIPYs leads us to further investigate the reactivity of other pyrrolic unsubstituted *meso*-alkylBODIPYs **3h** and **3i** and $CuCl_2·2H_2O$ in $CH_3CN$ (Scheme 2c). BODIPYs **3h** and **3i**, which were synthesized in 27

**Scheme 2. Synthesis of *meso*-H BODIPYs 1f,g and *meso*-alkylBODIPYs 2h,i**



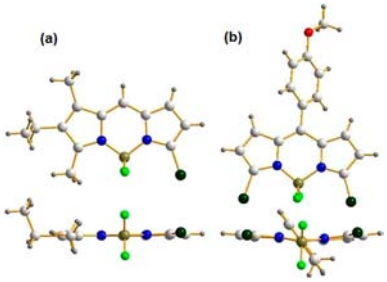




**Figure 2.** X-ray structures of **1f** (a) and **2d** (b): C, gray; H, light gray; O, red; N, blue; B, dark yellow; F, green; Cl dark green.

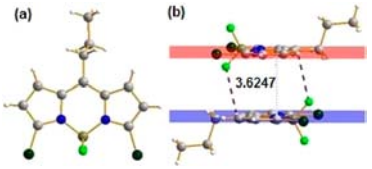



**Figure 3.** X-ray structure of **2h** (a) and its packing dimer (b).

and 30% yields from a one-pot stoichiometry reaction between pyrrole and acyl chloride in diluted dichloromethane, also showed good reactivity in this α-chlorination reaction and gave the corresponding 3,5-dichloroBODIPYs **2h** and **2i** in 68% and 63% isolated yields (Scheme 2c).

The α-selectivity in this chlorination reaction was confirmed by X-ray structures of 3-chloroBODIPY **1f** (Figure 2a), 3,5-dichloroBODIPY **2d** (Figure 2b), and **2h** (Figure 3). Crystals suitable for X-ray analysis were obtained via the slow diffusion of petroleum ether into the dichloromethane solutions of these dyes under atmospheric pressure. As usual, all three BODIPYs show an almost planar structure for the BODIPY core (the central six-membered $C_3N_2B$ ring with two adjacent five-membered pyrrole rings) with the plane defined by F−B−F atoms perpendicular to that of BODIPY core. The dihedral angle between the *meso*-phenyl group and the BODIPY core in **2d** is around 53°, similar to that of 2-bromo-*meso*-(*p*-methoxyphenyl)BODIPY (with a dihedral angle 51°).[8a] The B−N distance for these BODIPYs is within 1.55−1.56 Å, which indicates the usual delocalization of the positive charge. In the solid state, there are multiple C−H···F intermolecular hydrogen bonds between F atoms and methyl hydrogens (with the bond distance in the range of 2.39−2.85 Å, Table S3). This strong intermolecular hydrogen bonding helps



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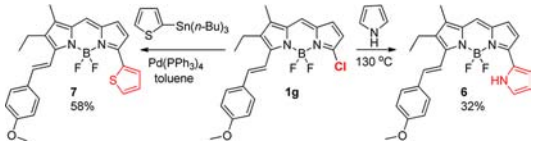
the establishment of the crystal-packing structure and leads to the formation of interesting hydrogen-bonding networks. A dimeric packing as a repeated unit was observed in the three crystals in which the two BODIPY cores are nearly parallel to each other in a head-to-tail orientation with the distance between the two BODIPY cores at 3.56, 3.71, and 3.62 Å, respectively (Figure 3b and Figure S2), similar to that of parent BODIPY.[2d]

BODIPYs 630/650 and 650/665 as commercial biological fluorescent labeling agents[8g] are only available in small quantities due to their synthetic difficulties. For example, the current synthesis of BODIPY 650/665 generally involves complicated reaction steps and the usage of expensive precursors (Figure S1). The success of our regioselective $\alpha$-chlorination of *meso*-alkylBODIPYs promotes us to further study its application in the construction of dyes **6** and **7** (Scheme 3), the analogues of

**Scheme 3. Synthesis of BODIPYs 6 and 7**




BODIPYs 630/650 and 650/665. The key synthetic precursor BODIPY **3g** (Scheme 2b) was obtained from the Knoevenagel condensation between BODIPY **3f** and 4-methoxybenzaldehyde and was directly applied for the subsequent chlorination reaction with 1.5 equiv of $CuCl_2 \cdot 2H_2O$ in $CH_3CN$ at 50 °C for 2 h from which the desired 3-chloroBODIPY **1g** was obtained in 80% yield. The further application of **1g** in a simple aromatic nucleophilic substitution ($S_NAr$) using neat pyrrole[11] or a Stille-coupling reaction using 2-(tributylstannyl)thiophene generated the corresponding BODIPYs **6** and **7** in 32% and 58% yields (Scheme 3).

As shown in Figure 4, a 66 and 72 nm bathchromic shift was observed in the absorption and emission maximum of the

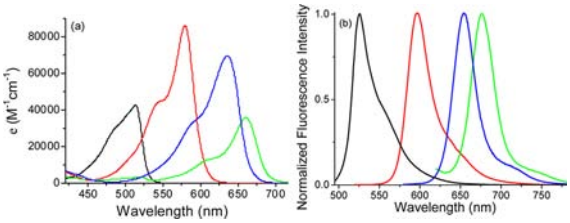
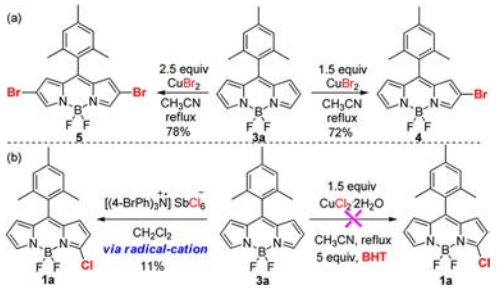



**Figure 4.** Overlaid absorption (a) and normalized fluorescence emission (b) spectra of BODIPYs **1f** (black), **1g** (red), **6** (green), and **7** (blue) in dichloromethane at room temperature.

Knoevenagel condensation product of **1g** with respect to those of **1f** in dichloromethane. Both dyes show comparable fluorescence quantum yields around 0.54 in dichloromethane (Table S2). The further installation of a pyrrole moiety at the 3-position of the BODIPY core (in **6**) leads to a larger red shift of the spectra with respect to a thiophene substituent (in **7**). In comparison with that of **1g**, $\alpha$-thiophene-BODIPY **7** and the $\alpha$-pyrroloBODIPY **6** each showed a 56 and 81 nm red-shift in the absorption maximum and 57 and 79 nm bathochromic shift in the fluorescence emission maximum. In comparison with those of commercial BODIPYs 650/665 and 630/650, BODIPYs **6** and **7** each showed a 15 and 11 nm red-shift in the absorption and a 16 and 14 nm red-shift in the fluorescence emission maximum with good fluorescence quantum yields in the range of 0.35−0.45 in dichloromethane.

The successful regioselective $\alpha$-chlorination of BODIPY chromophore with $CuCl_2 \cdot 2H_2O$ also raised the possibility of achieving regioselective bromination of BODIPY with $CuBr_2$. The reaction of BODIPY **3a** with 1.5 equiv of $CuBr_2$ in refluxing acetonitrile for 2 h indeed generated a major product, which was confirmed to be the $\alpha$-brominated BODIPY **4** in 72% isolated yield (Scheme 4a). Under the same reaction conditions, simply

**Scheme 4. Synthesis of Mono- and DibromoBODIPYs 4 and 5 and Mechanism Studies**




raising the amount of $CuBr_2$ to 2.5 equiv gave the corresponding 2,6-dibromoBODIPY **5** in 78% isolated yield. Notably, $CuBr_2$ acetonitrile combination is a milder and more convenient reagent than previously reported $Br_2$ and NBS for the regioselective bromination of BODIPY at 2- and 6-positions due to the ease of handling this complex system.[8]

We attributed the different regioselectivity by different types of copper salt ($CuCl_2 \cdot 2H_2O$ vs $CuBr_2$) to the different reaction mechanisms. As described in the literature,[12] the bromination of arenes with $CuBr_2$ is believed to operate through formation of $Br_2$ in which the copper catalyst facilitates the aerobic oxidation of bromide to molecular bromine. In our case, a red color was observed during the bromination reaction under heating, which possibly indicates the formation of molecular bromine in solution. This in situ formed bromine then undergoes electrophilic aromatic substitution to generate the corresponding $\beta$-bromoBODIPY which is in good agreement with our previously reported bromination with liquid bromine.[8a] In comparison with that of $CuBr_2$, it is hard to decompose $CuCl_2$ into CuCl and $Cl_2$ as previously reported by Stahl during the chlorination and bromination of arenes.[12a]

We also investigated the ability of other metal salts to promote the chlorination reaction. $ZnCl_2$, $MgCl_2$, $FeCl_3$, $AlCl_3$, and $TiCl_4$ did not provide any of the chlorinated product. Two main pathways have been postulated for $CuCl_2$-mediated chlorination and related oxidation reactions. These involve either a SET process or organometallic mechanism.[13] Based on the above chlorination and bromination results, we began to speculate that this new reaction might proceed by initial oxidation of BODIPY to a cation radical by $CuCl_2$. To test this hypothesis, we first investigated the impact of the addition of the radical inhibitors 2,6-di-*tert*-butyl-4-methylphenol (BHT) to this reaction (Scheme 4b). The reaction between **3a** and $CuCl_2$ was completely suppressed by adding 5 equiv of BHT, without any desired product being identified, even after an extended reaction time. Next, we treated **3a** with 1 equiv of $(4\text{-BrPh})_3N \cdot SbCl_6$, a stable aminium salt known to promote cation radical mediated reactions.[14] The reaction between **3a** and $(4\text{-BrPh})_3N \cdot SbCl_6$ proceeded smoothly in dichloromethane at room temperature



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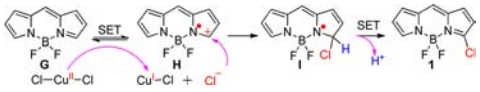
(Scheme 4b). Product **1a** was obtained in 11% yield, providing initial evidence that these reactions may proceed via cation radical intermediates. Based on these findings, we propose that this $\alpha$-chlorination of BODIPY probably occurs through a SET process from one pyrrole unit in BODIPY **G** to $CuCl_2$, which leads to the formation of a cation radical **H**. This in situ formed cation radical **H** then immediately undergoes an electrophilic addition by a chloride anion at the $\alpha$-position that possesses the highest positive charge to give radical **I**. The target $\alpha$-chloroBODIPY **1** was then formed through another SET process from **I** (Scheme 5).

**Scheme 5. Plausible Mechanism for Chlorination of BODIPY G**




In conclusion, we reported the unusual highly regioselective $\alpha$-chlorination of a series of BODIPYs including the *meso*-H-, *meso*-aryl-, and *meso*-alkylBODIPYs with $CuCl_2$. These $\alpha$-chloroBODIPYs can be easily applied to the further functionalization of BODIPY as demonstrated in this work via the substitution or coupling reaction to achieve the analogues of commercial BODIPYs 650/665 and 630/650. The use of $CuBr_2$ for this halogenation reaction leads to the regioselective $\beta$-bromination of BODIPY under mild conditions. A plausible mechanism was proposed for this unusual $\alpha$-chlorination reaction as the first functionation of BODIPY through a SET process.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02383.

Experimental details, tables, and additional spectra (PDF)
X-ray data for **1j**, **2d**, and **2h** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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