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Unusual Intramolecular Hydrogen Transfer in 3,5-Di(triphenylethylenyl) BODIPY Synthesis and 1,2-Migratory Shift in Subsequent Scholl Type Reaction

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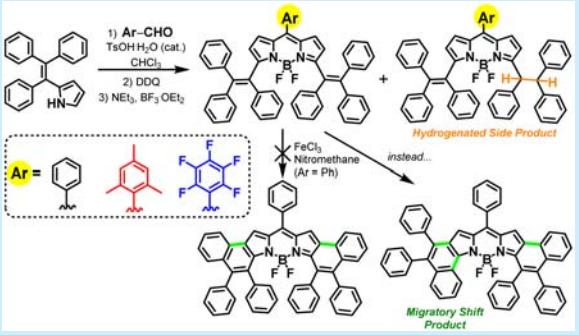
Supporting Information

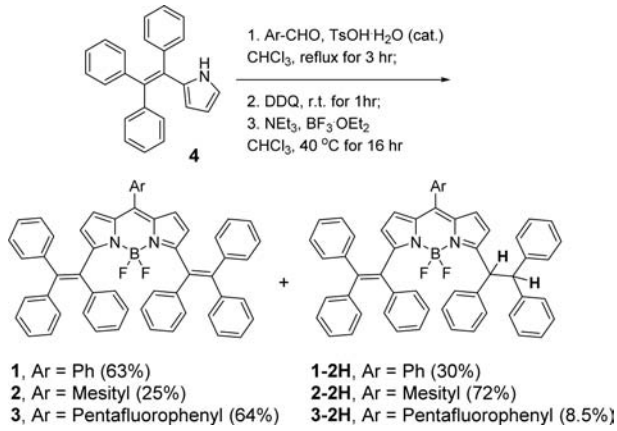
ABSTRACT: The straightforward synthesis of 3,5-di(triphenylethylenyl) BODIPYs **1**−**3** from the condensation of 2-(triphenylethylenyl) pyrrole with aryl aldehydes are surprisingly found to produce side products that are hydrogenated at one of the two triphenylethylene substituents. It was also observed that the subsequent Scholl type reaction of **1** resulted in a "1,2-migratory shift" of one triphenylethylene substituent in addition to a ring closing reaction. Preliminary investigations, including DFT calculations and isolation of intermediates, were conducted to study these unusual observations on BODIPY chemistry.



BODIPY dyes are a widely studied class of luminogens that have been developed into many useful applications.[1] Recently, much focus has been given to the development of far-red and near-infrared (NIR) BODIPY dyes for *in vivo* biological imaging applications[2] because they have the advantages of low phototoxicity, low autofluorescent background, and ability toward deeper tissue penetration, over visible emitting bioprobes.[3] Like conventional luminophores, the structurally planar BODIPY core subjects the dyes to strong $\pi-\pi$ stacking in the event of aggregation, thus the aggregation-caused quenching (ACQ) effect. This posed some problems to potential applications of the luminogen. Such a tricky issue can, however, be overcome by introducing the concept of aggregation-induced emission (AIE) to the dyes and luminogens.[4] AIE luminogens were reported to be superior over conventional ACQ ones in many applications, including bioimaging.[5]

While there are several reports of AIE-active BODIPY dyes to date, most of them adopted the strategy of functionalizing the *meso*-position with AIE-active or bulky moieties.[6] We recently reported the successful synthesis of triphenylethylenyl (TPE) functionalized *meso*-ester BODIPYs with the AIE property.[7] When we adopted the same synthetic strategy for the synthesis of *meso*-aryl analogues, we observed the recurring formation of a side product and the yields of the side products were affected by the electron-richness of the aryl aldehyde precursors (Scheme 1). On further analysis, the side products formed were identified to be BODIPYs with only one of its two TPE-moieties hydrogenated. In addition, we performed a

Scheme 1. Synthesis of 3,5-Di(triphenylethylenyl) BODIPYs and the Formation of Hydrogenated Side Products



Scholl type reaction on BODIPY **1** using $FeCl_3$ to fuse the phenyl rings with the BODIPY core with the aim of extending the conjugation, hence red-shifting its absorption and emission wavelength toward NIR region. Surprisingly, single-crystal XRD analysis suggested a "1,2-migratory shift" occurred on one side of the TPE moieties instead, in addition to a ring fusing reaction taking place. We are extremely intrigued with these unusual observations associated with 3,5-di(triphenylethylenyl)

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BODIPYs and herein would like to report our preliminary investigations on these two phenomena.

Following a general synthetic protocol for BODIPY dyes, a one-pot reaction by first condensing **4**[7] with aryl aldehydes, followed by oxidation with DDQ and eventually $-BF_2$ coordination with $BF_3{\cdot}OEt_2$, gave the *meso*-phenyl, mesityl, and pentafluorophenyl 3,5-di(triphenylethylenyl) BODIPYs **1**–**3** in 63%, 25%, and 64% yield, respectively (Scheme 1). Interestingly, apart from the main BODIPY product, the dihydrogenated side products **1-2H**, **2-2H**, and **3-2H** were also isolated in 30%, 72%, and 8.5% yield, respectively (Scheme 1). The structural identities of the side products were revealed by single-crystal XRD analysis of **1-2H** and **3-2H**, showing one hydrogenated ethylene bond with a much larger bond length (1.495 Å in **1-2H** and 1.546 Å in **3-2H**) (Figure 1). The structures were further confirmed by NMR and APCI-MS analysis (see Supporting Information (SI)).

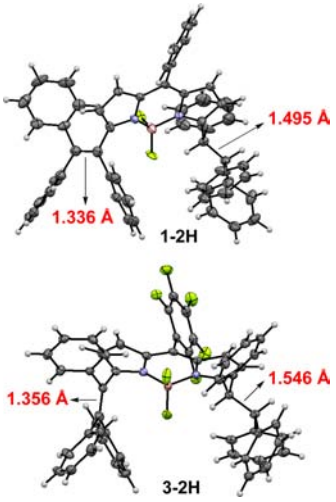
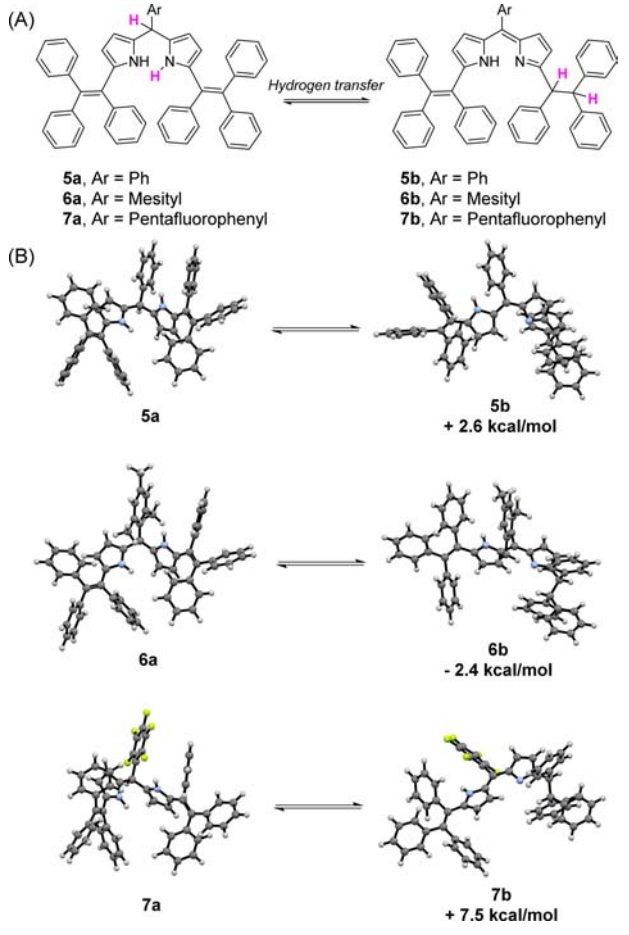


Figure 1. X-ray crystallographic structures of **1-2H** and **3-2H**.

Extending the initial condensation duration between aryl aldehyde and **4** under reflux conditions in chloroform overnight did not yield any product with both triphenylethene moieties hydrogenated. The emergence of side products dihydrogenated at only one of the two TPE substituents was extremely intriguing, which prompted further investigations. The typical one-pot synthesis of BODIPY from pyrrole and benzaldehyde involves the following sequential steps: an acid-catalyzed condensation between the reagents to form dipyrrolephenylmethane, which is oxidized in the second step on addition of the oxidant, and addition of amine base in the final step deprotonates the pyrrole to allow coordination with boron on addition of $BF_3{\cdot}OEt_2$. We thus sought to determine in which step of the one-pot BODIPY synthesis the hydrogenation took place and how it took place.

It is reasonable to propose that the dipyrrolearylmethanes **5a**/**6a**/**7a** are formed in the first-step condensation reaction in our case (Scheme 2A). Taking the synthesis of **2** as an example, it was found that replacing the DDQ oxidant with milder *p*-chloranil did not yield much difference in yield for both main and side products. However, performing the one-pot reaction without the use of DDQ gave only hydrogenated side product **2-2H** without any formation of **2**. This gave us the clue that hydrogenation took place in the initial condensation step which does not require the addition of an oxidant prior to boron

Scheme 2. (A) Proposed Intramolecular Hydrogen Transfer Process; (B) Calculated Geometry and Energy of Two Different Forms (5a/6a/7a *versus* 5b/6b/7b)



coordination. We postulated that an intramolecular hydrogen transfer could have occurred on dipyrrolearylmethane intermediates **5a**–**7a** resulting in the formation of hydrogenated ligands **5b**–**7b**, respectively (Scheme 2A). This logically explained why only one of the two TPE moieties got hydrogenated. We further postulated that the possible driving force for this unusual process taking place could be due to the ease of steric strain over the TPE moiety. The sp^2-hybridized carbons on C=C bonds would prefer a planar geometry, but this is not possible due to the steric strain posed by the three phenyl rings and the BODIPY core. Hydrogenation would thus render the two carbon atoms sp^3-hybridized (tetrahedral geometry) and thus release the steric strain about the C–C bond.

We then attempted to isolate both dipyrrolearylmethane intermediates **5a**–**7a** and the corresponding hydrogenated ligands **5b**–**7b** by performing only the condensation reaction. TLC of the crude products showed formation of both intermediates and ligands, but purification was challenging. Only **5a** and **5b** could be purified via column chromatography. Hydrogenated ligands **6b** and **7b** cannot be purified but nonetheless be detected via APCI-MS (SI). Dipyrrolephenylmethane intermediate **5a** is readily oxidized on standing and thus cannot be characterized whereas hydrogenated ligand **5b** is more stable and can be identified by NMR in THF-d_8. Daily monitoring of ^{1}H NMR spectra of **5b** for up to a week did not

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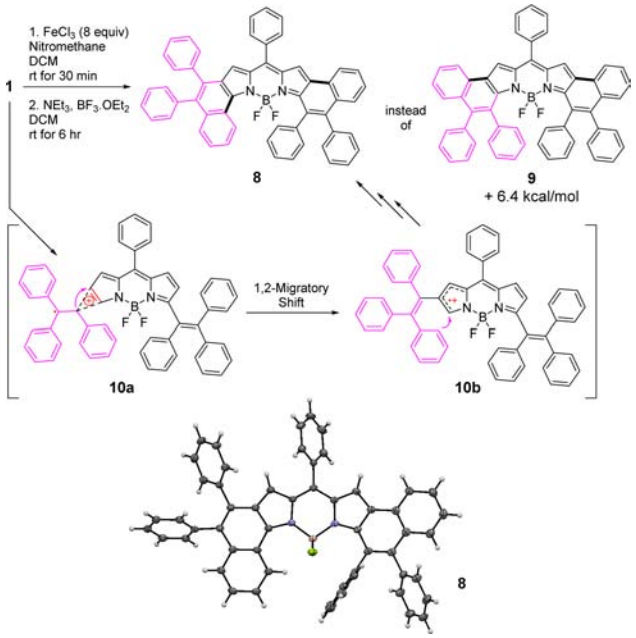
show any signs of change or converting back to intermediate **5a**.

DFT calculations (B3LYP/6-31G*) were performed, and it was found that **5b** and **7b** are 2.6 and 7.5 kcal/mol higher in energy than the respective **5a** and **7a**, while **6b** is 2.4 kcal/mol lower in energy than **6a** (Scheme 2B). These data are in agreement with the observed relative yields of the main and side products. The equilibrium can be correlated to the electron-richness and -poorness of the *meso*-aryl group since the intramolecular transfer process can be also regarded as a redox process, i.e., oxidation of the dipyrrolemethane unit and reduction of the TPE moiety. Thus, electron-rich mesityl substituted intermediate **6a** has a higher tendency to become the dihydrogenated intermediate **6b**, and the trend is reverse for electron-deficient pentafluorophenyl substituted **7a**/**7b**.

To further red-shift the absorption and emission wavelengths of BODIPY **1**, we performed a Scholl type reaction using $FeCl_3$ in an attempt to increase the extent of conjugation by fusing two phenyl rings to the BODIPY core (Scheme 3).

Scheme 3. Scholl Reaction of 1 and Proposed Mechanism for the Unexpected Product 8; Shown at the Bottom Is the Single-Crystal Structure of BODIPY 8



Surprisingly, the partially fused BODIPY isomer **8** was obtained in 46% yield instead of the target product **9**, which was confirmed by X-ray crystallographic analysis. It seems that **1** has undergone a 1,2-migratory shift of one of its TPE moieties from the 3- to 2-position of the BODIPY core under the Scholl reaction conditions. It is usually believed that a radical cation intermediate is formed in an $FeCl_3$-mediated oxidative cyclodehydrogenation reaction,[8] and we can hypothesize the first formation of triphenylethene radical cation, followed by a 1,2-migration process and subsequent ring fusing reaction (Scheme 3). 1,2-Migragation was also observed in the Scholl reaction of oligophenylenes, but it is hard to rationalize an exact mechanism due to the complexity of the reaction.[9] Similar Scholl reactions were performed on BODIPYs **2** and **3**, but the reactions were messy and no main products could be isolated. DFT calculations predicted that **8** was 6.3 kcal/mol lower in energy than that of target compound **9**, which may partially explain the formation of **8** rather than **9**.

The normalized absorption and emission spectra of BODIPYs **1**−**3**, **8**, and hydrogenated BODIPYs **1-2H**−**3-2H** are shown in Figure 2, and the data are summarized in Table S1

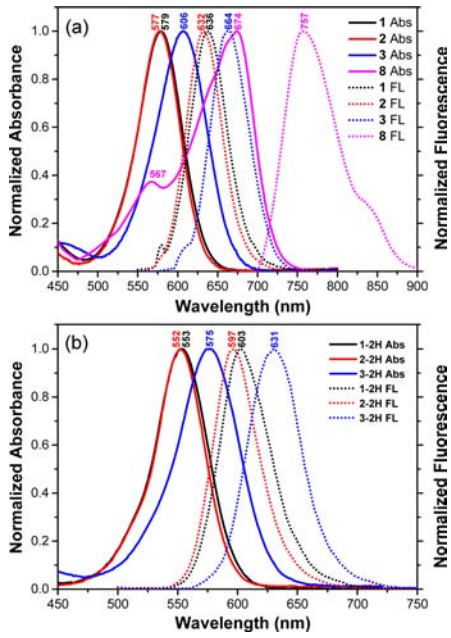


Figure 2. (a) Normalized UV−vis absorption and fluorescence spectra of **1**−**3** and **8** in THF solution; (b) normalized UV−vis absorption and fluorescence spectra of the hydrogenated BODIPY side products **1-2H**, **2-2H**, and **3-2H** in THF solution.

(SI). The absorption and emission wavelengths of BODIPY side products **1-2H**−**3-2H** are generally blue-shifted compared to their corresponding main products **1**−**3**, as expected due to a decreased extent of conjugation arising from hydrogenation of one of the two TPE moieties. Their relative quantum yields are generally higher than those of the main products as well (SI). An electron-deficient *meso*-pentafluorophenyl group resulted in **3** and **3-2H** being red-shifted in both absorption and emission wavelengths compared to their electron-richer counterparts, presumably due to intramolecular donor−acceptor interaction. In spite of the presence of AIE-active TPE moieties substituted to the BODIPY cores, all BODIPY main products **1**−**3** and hydrogenated side products **1-2H**−**3-2H** do not exhibit AIE properties on investigation (SI). Scholl reaction product BODIPY **8** experienced a significant red shift in both maximum absorption (674 nm) and emission wavelengths (757 nm) with respect to its precursor **1** due to an increase in extent of conjugation. Time-dependent DFT (B3LYP/6-31G*) calculations predicted a similar absorption spectrum for **1** with the absorption maximum at 577.6 nm (oscillator strength f = 0.3054). While the calculated maximum wavelength for **8** occurs at 552.3 nm (f = 0.8463) which is slightly shorter than the actual measurement at 567 nm (SI).

In summary, we unraveled an unusual phenomenon in the synthesis of 3,5-di(triphenylethylenyl) BODIPYs by isolating corresponding BODIPY side products with one of the two triphenylethene moieties hydrogenated at the C═C bond. Preliminary investigations showed that hydrogenation occurred in the initial condensation step between aryl-aldehydes and 2-(triphenylethylenyl)pyrrole. The ratio between the yield of the

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main and side products depended on the electron-richness and -poorness of the BODIPY *meso*- aryl group, and this was supported by DFT calculations. The subsequent Scholl reaction of BODIPY **1** also resulted in an unusual "1,2-migratory shift" occurring on top of the expected ring fusing between the BODIPY core and the adjacent phenyl rings. Even though we did not achieve AIE-activity for the synthesized BODIPY dyes, we were excited to report the above preliminary findings, and we look forward to further possible detailed mechanistic investigations (e.g., isotopic labeling), to shed more light on the mechanisms behind this unusual phenomenon.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01916.

General experimental and synthetic methods with characterization data; photophysical properties and AIE investigation data; DFT calculation details; single-crystal XRD data; NMR spectra and mass spectra of all intermediates and products (PDF)
Crystallographic data for **1-2H** (CIF)
Crystallographic data for **3** (CIF)
Crystallographic data for **3-2H** (CIF)
Crystallographic data for **8** (CIF)

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Notes

The authors declare no competing financial interest.

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