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Conjugated Thiophene-Fused Isatin Dyes through Intramolecular Direct Arylation

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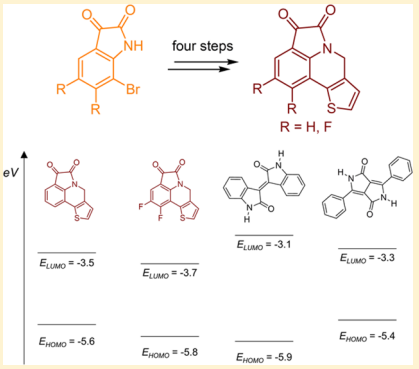
Supporting Information

ABSTRACT: We report on the design, synthesis, and properties of innovative, planar, π-conjugated compounds in which a thiophene ring is fused with the skeleton of the naturally occurring dye isatin. The synthesis is achieved in high yields making use of an intramolecular direct arylation reaction as the key step, making the overall process potentially scalable. The synthetic sequence has been demonstrated also for an isatin bearing fluorine substituents on the aromatic ring. NMR and X-ray studies demonstrate the crosstalk occurring between the fused, coplanar, and conjugated moieties, making these novel dyes with a donor−acceptor character. Cyclic voltammetry and UV−vis studies confirm very interesting HOMO−LUMO levels and energy gaps for the new compounds.



INTRODUCTION

Organic dyes constitute a large and important class of industrial products. They are generally characterized by good optical absorption and mechanical properties and by solution processability and stability. These properties are also desirable for solid-state applications; therefore major classes of industrial dyes and pigments (phthalocyanines, naphthalene diimides, diketopyrrolopyrroles, indigos and isoindigos, squaraines) have already found applications in the broad world of organic electronics.[1] In fact, organic dyes such as diketopyrrolopyrrole or naturally occurring isoindigo, when incorporated in a π-conjugated polymer scaffold, have yielded efficient materials to be used in the field of organic photovoltaics (OPV).[2]

Isatin (1*H*-indole-2,3-dione) and its derivatives are synthetically versatile natural dyes, extensively used in organic synthesis. The advances in the use of isatins for organocatalysis, as well as their biological and pharmacological properties, have been recently reviewed.[3] Although isatin is the synthetic precursor of isoindigo (Figure 1), its direct incorporation into functional fragments for OPV or organic electronic applications has been far from fully explored.[4] The isatin skeleton contains formally an amide functionality, linked to the aromatic ring, combined with an electron-withdrawing C3 ketone functionality, *ortho*-linked to the aromatic ring with respect to the amide; it thus possesses a donor−acceptor structure giving the compound a bright red color. The C3 ketone possesses orthogonal reactivity with respect with the C2 carbonyl amide, and its derivatization occurs with relative ease.[3] Since low-band gap polymers for OPV are currently engineered by alternating electron-rich and electron-deficient units in order to match and optimize solar photon harvesting,[5] suitable isatin derivatives can be ideal monomers. Simple and efficient synthetic protocols are of the foremost importance in the design of π-conjugated polymers for OPV, demanding the removal of synthetic steps requiring organometallic chemistry.[6]

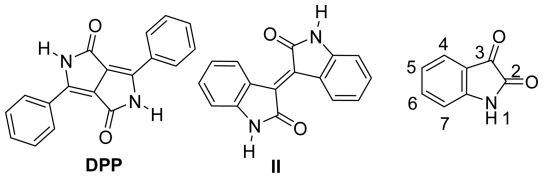


Figure 1. Most popular dyes used for OPV applications (diketopyrrolopyrrole (DPP), right, isoindigo (II), center, and the isatin core structure with numbering).

In this paper, we present the design, synthesis, and evaluation of a series of fully π-conjugated dyes in which a thiophene ring is fused into the isatin core. The synthesis adopts an intramolecular, direct heteroarylation (DHA) cyclization protocol as the key step, in order to ensure potential for industrial scalability.[5,6]

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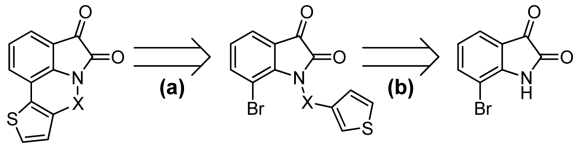
RESULTS AND DISCUSSION

Molecular Design and Synthesis. Our retrosynthetic analysis is presented in Scheme 1. It develops starting from

Scheme 1. Retrosynthetic Analysis for the Synthesis of Target Dyes

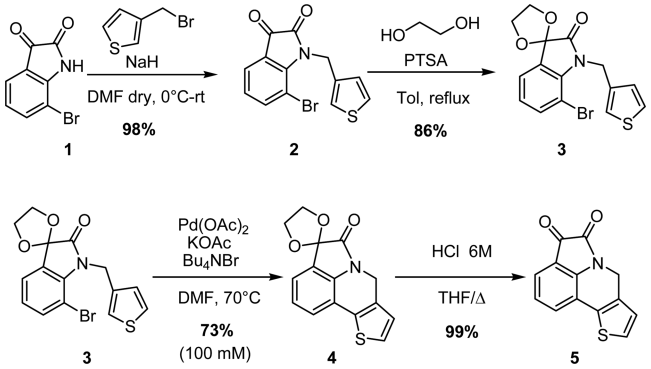


commercially available 7-bromoisatin, possessing a bromine atom at a suitable position for intramolecular DHA reaction, forming a stable six-membered ring system. The introduction of the thiophene moiety (step b in Scheme 1) takes advantage of the amide nitrogen at position 1, which has been reported to be acylated[7] or alkylated.[8]

Regarding the acylation approach, the reaction between 7-bromoisatin and 3-thiophenecarbonyl chloride was explored under several conditions, by changing the nature of the reaction solvent and base and adapting protocols reported in the literature,[7] but in all cases the conversion of the isatin starting material was minimal (see Supporting Information).

We thus turned our attention to the *N*-alkylation of 7-bromoisatin (**1**) with 3-bromomethylthiophene (Scheme 2).[8]

Scheme 2. Synthesis of Thiophene-Fused Isatin Dye 5

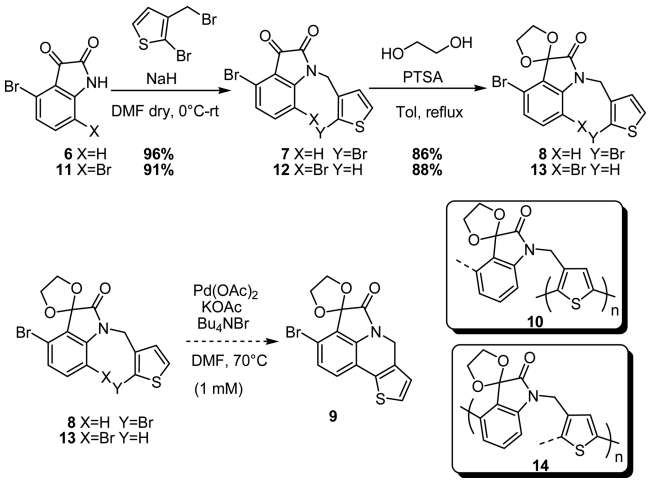


The reaction was successfully carried out in the presence of NaH in dry DMF at 0 °C to give compound **2** in excellent yields (98%). *N*-Alkyl isatin derivative **2** was then protected on C3 keto-carbonyl group with ethylene glycol to give *spiro*-dioxolane **3** (86% yield). The key DHA ring closing reaction was carried out in the presence of $Pd(OAc)_2$ as catalyst and an excess of potassium acetate as base and in moderate dilution conditions (100 mM for reagent **3** in dry DMF). The desired compound **4** was isolated after purification by flash chromatography in good yields (73%). The reaction was also carried out under substantially different dilution conditions (10 mM), but yields were essentially the same. Finally, deprotection under acidic conditions, and purification by flash chromatography afforded isatin-based dye **5** as a red solid (Scheme 2).

The protection at the C3 carbonyl was adopted because similar substrates were identically protected before DHA reaction using palladium as the catalyst.[9] Avoiding the protection/deprotection steps would advantageously lower the number of synthetic steps and raise the total yield of the final compound; however, the DHA ring closing protocol, successfully applied on protected compound **3**, did not work at all when attempted directly on compound **2**. Presumably, since all starting material was recovered, the oxophilicity of the Pd(II) catalyst, which can coordinate to the C2 and C3 neighboring carbonyls was detrimental in this case. We also attempted recently reported[10] organocatalytic DHA reaction protocols (*o*-phenantroline, *t*-BuOK,), for the ring closing reaction of **2** to afford **5** directly, but in this case degradation of the isatin lactam ring could be detected.[11]

Encouraged by the successful synthetic route presented in Scheme 2, we aimed at obtaining fused substrates presenting a bromine atom at position 4 of the isatin core. Compound **9** (Scheme 3), presenting a nucleophilic (the carbon linked to the

Scheme 3. Attempted Synthesis of DHA Polymerizable Monomer 9 and Probable Structures of the Obtained Polymers 10 and 14



bromine atom) and an electrophilic (the α-carbon on the thiophene residue) site on the same molecule, could be an interesting monomer to be polymerized or copolymerized head to tail using a DHA protocols. The *spiro*-dioxolane protecting group, with its quaternary carbon atom, could be advantageous in solubilizing the growing polymer chains, preventing π-stacking, aggregation, and precipitation from the reaction mixture.[12]

Our first approach to compound **9** was elaborated by implementing the use of commercially available 4-bromo-1*H*-indole-2,3-dione, **6** (Scheme 3). We envisaged it could be possible, by utilizing high dilution reaction conditions, to activate a regioselective intramolecular DHA between position 7 of the isatin core and the position 2 of the thiophene ring.

4-Bromo-1*H*-indole-2,3-dione, **6**, was alkylated with 2-bromo-3-bromomethylthiophene under conditions identical to those used for **1**, to give compound **7** in excellent yields (96%). Protection with ethylene glycol gave *spiro*-dioxolane **8** (86% yield), but the key intramolecular DHA ring closing reaction, attempted in high dilution conditions, did not yield the desired compound **9**, but rather an insoluble oligomeric or polymeric baseline red material. Since intermediate **8** presents a thiophene ring with α positions orthogonally reactive in the DHA reaction, a plausible hypothesis provides for a polythiophene-type structure **10** (boxed in Scheme 3) of the polymer formed. The negligible but probably not suppressed reactivity of the

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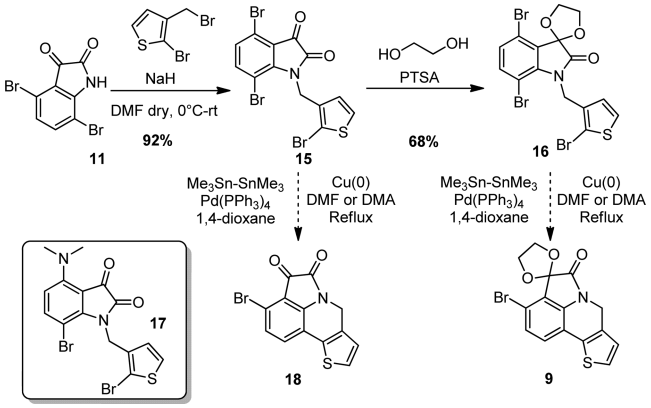
isatin carbon atom in position 4, linked to the bromine, in the carbon−carbon bond formation with DHA, results in the cross-linking of the structure and in the resulting insolubility properties.

We pursued a further possibility to obtain **9**, in which both bromine atoms (the one needed for the intramolecular DHA ring closing step, and the one to be remaining in the final product for subsequent polymerization), are placed on the isatin core. Derivative **11** is not commercially available and was synthesized starting from 2,5-dibromoaniline following a general reported procedure for isatins.[13]

Alkylation with 3-bromomethylthiophene, to afford compound **12** (91% yield), and protection, for compound **13** (88% yield), went smoothly as before, but again the key intramolecular DHA ring closing reaction, attempted in high dilution conditions, did not yield even trace amounts of the desired compound **9** (Scheme 3). Also in this case an insoluble oligomeric or polymeric baseline red material was formed; it is likely in this case that the nucleophilic character of the bromine in position 4 is much higher than of the one in position 7 of the isatin core, so that intermolecular DHA reaction, on either of the α-carbons of the appended thiophene residue is competitive with the intramolecular DHA ring closing, thus affording cross-linking and intractability of the resulting material. An indirect proof of the higher reactivity as a nucleophile in metal-catalyzed cross-coupling reactions of the carbon atom at the 4-position with respect to the 7-position is reinforced by the results illustrated in Scheme 4, where further attempts were made by

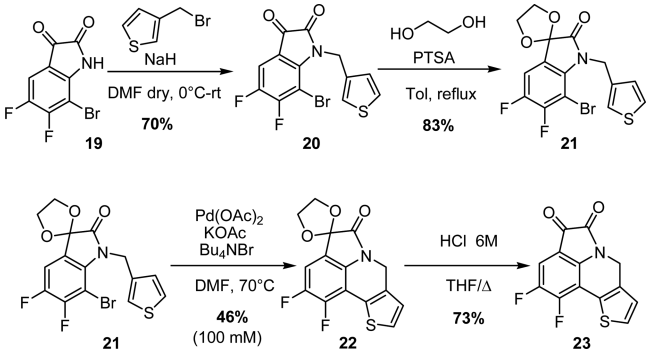
Scheme 4. Attempted synthesis of DHA Polymerizable Monomer 9 and 18 through Ulmann or Stille/Kelly Coupling



synthesizing derivatives with three bromine atoms, in order to develop Ulmann[14] or Stille−Kelly[15] ring closing strategies. However, when attempted on compounds **15** or **16**, both methodologies failed to give the desired, cyclized dyes **9** or **18**. Interestingly, when the Ulmann protocol was adopted on compound **15** in the presence of solvents such as DMF or DMA, derivative **17**, in which a dimethylamino group has *regioselectively* substituted the bromine atom in position 4, was obtained in high yields. Both compounds **15** and **17** have been characterized by X-ray crystallography, and their crystal data, plots showing thermal ellipsoids and crystallographic details are reported in the Supporting Information.

Held by the success of the DHA route presented in Scheme 1, we set out to demonstrate its feasibility with other isatin derivatives. In particular, we considered isatin **19**, bearing two fluorinated atoms on the aromatic ring, for two reasons: (a) the availability of the precursor 2-bromo-3,4-difluoroaniline for its synthesis;[13] (b) the fact that the aromatic ring has only one aromatic hydrogen, possibly allowing a selective late stage further introduction of a bromine atom through electrophilic aromatic substitution once dye **23** has been synthesized (Scheme 5). Indeed, alkylation, protection, intramolecular

Scheme 5. Completion of the Synthesis of Thiophene-Fused Isatin-Based Dye 23



DHA, and deprotection occurred smoothly to generate dye **23**, although in sensibly reduced yields when compared to **5**. Attempts to use Pd(0) sources, namely, by employing $Pd_2(dba)_3$, resulted in negligible yields of the desired compound, probably because of the increased steric hindrance around the Pd catalytic center.

NMR, UV/vis and Cyclic Voltammetry. Characterization by ^{1}H NMR spectroscopy was able to substantiate the interaction between the thiophene and isatin moieties, placed in direct conjugation. We report in Figure 2 a comparison between the ^{1}H NMR spectra of compounds **2** and **5** on one side and **20** and **23** on the other. In both cases, peaks related to the isatin core in **2** and **20** above 7.5 ppm, markedly shift to higher fields in **5** and **23**, probably also as a consequence of the loss of the bromine atom as a substituent on the aromatic ring. Peaks of the thiophene moieties (labeled 5 and 6 for compounds **2** and **5**, 3 and 4 for compounds **20** and **23**) shift in opposite directions upon ring closure. A large shift upon cyclization is also detected for the benzylic CH_2 proton resonances (labeled 4 for compounds **2** and **5**, 3 and 2 for compounds **20** and **23**) demonstrating an effective charge transfer and cross-talk between the moieties within the fully π-conjugated molecular structure.

Such cross talk is also evidenced by the UV/vis spectra of compounds **5** and **23** (Figure 3, left). Whereas the λ_{max} is centered around 320 nm (ε = 4000−9000 M^{-1} cm^{-1} in $CHCl_3$), a weaker intramolecular charge transfer band centered around 490 nm is detected in both compounds (ε = 600−1000 M^{-1} cm^{-1} in $CHCl_3$). The latter band showed solvent dependence in the case of compound **5** (the maximum shifting from 490 nm in $CHCl_3$ to 478 nm in toluene, see Figure S1). Compound **5** proved to be weakly emissive (Figure 2, right) when excited at 318 nm, and nonemissive when excited on the charge-transfer band at 480 nm.

Data for the HOMO−LUMO gaps of the final compounds **5** and **23**, could be determined by both optical and electrochemical methods, and they are compared with isoindigo (II) and diketopyrrolopyrrole (DPP), for which literature data are available (Table 1). The effect of the introduction of the

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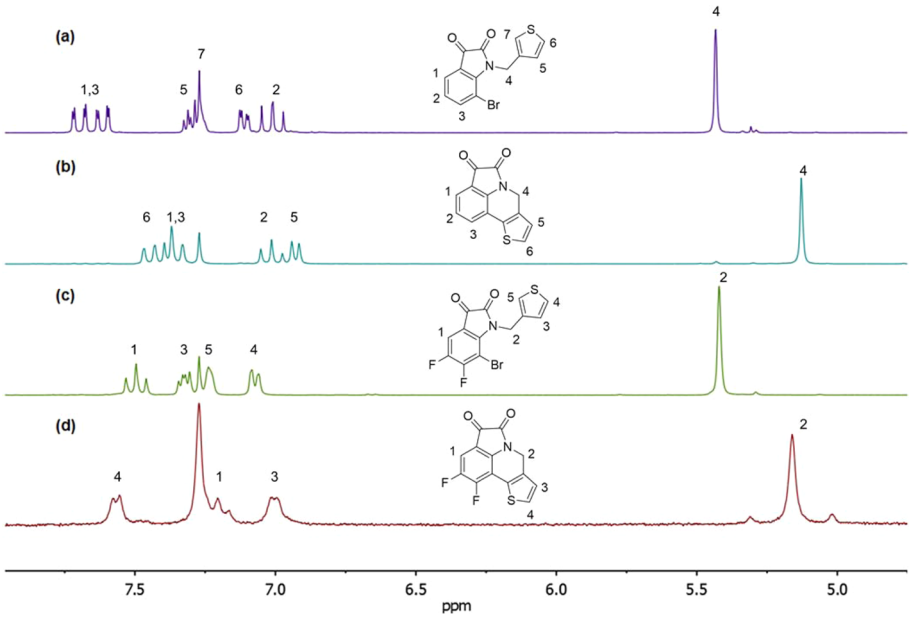

Figure 2. Stacked ^{1}H NMR spectra (200 MHz, $CDCl_3$) of compounds: (a) **2**, (b) **5**, (c) **20**, and (d) **23**.

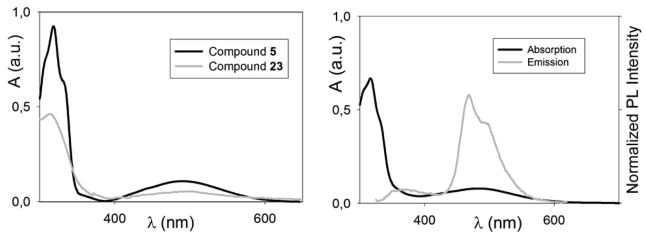

Figure 3. (left) UV/vis spectra of compounds **5** and **23** (10^{-4} M in $CHCl_3$). (right) Absorption and emission spectra (λ_{ex} = 318 nm) of compound **5** (5×10^{-5} M in MeCN).

Table 1. Experimental Values for Semiconducting Properties of the New Dyes Synthesized and Comparison with Literature Values of Relevant Compounds

compd	HOMO−LUMO gap (eV) CV	HOMO−LUMO gap (eV) optical	HOMO (eV)	LUMO (eV)
DPP[a]	2.1	2.1	−5.4	−3.3
II[b]	2.8	2.5	−5.9	−3.1
5[c]	2.1[d]	2.1	−5.6	−3.5
23[c]	2.1[d]	2.1	−5.8	−3.7

[a]Data taken from ref 16. [b]Data taken from ref 17. [c]UV/vis and CV spectra are shown in Figures S1 and S2, respectively. [d]HOMO−LUMO values obtained by the analysis of the first cycle.

fluorine substituents is to lower both HOMO and LUMO levels, thus maintaining the band gap at 2.1 eV. For both compounds **5** and **23**, the reduction peak is reversible, whereas it is not reversible in the oxidation mode, indicating that the compound does not polymerize electrochemically, even by lowering the scan rate from 200 to 20 mV/s. A slight shift of the cathode potential is observed upon successive reduction cycles.

X-ray Crystal Structure of 5. The dye **5** originates in the solid state two polymorphs: the **5_1** crystal, triclinic, and the **5_2** crystal, monoclinic. In both crystals, the asymmetric units contain two very similar but crystallographically independent molecules of **5**; all of them are essentially planar. Plots showing thermal ellipsoids are drawn in Figure S3, and relevant bond distances in each independent molecule **5** are reported in Table S2.

The bond distances for the thiophene moiety change slightly but significantly upon fusion with the isatin core with respect to those observed in the isolated system. In all molecular structures **5**, the sp^2 thiophene carbon atoms directly connected to the isatin groups originate thiophene C−C and C−S bonds significantly longer (by 0.02−0.05 Å) than the symmetrically placed C−C and C−S bonds, linked with CH groups. All bonds are significantly different than those in isolated thiophene.[18] A transfer of electron density toward the C−C bonds connecting the thiophene rings and the isatin aromatic groups is also evident by their shortening (1.451 for **5_1** and 1.457 Å for **5_2**) with respect to a C_{sp^2}−C_{Ar} single bond (1.470 Å) observed in related structures.[18]

In the solid state, the two polymorphs of compound **5** differ in the dihedral angle between the two independent molecules forming the crystal: in **5_1**, the dihedral angle between the two independent polycyclic compounds is 21°, whereas in **5_2** the dihedral angle is 89°. In the **5_1** crystal, the two independent molecules originate two face-to-face π-stacked molecular rows extending along the direction of the *a* crystallographic axis. Each row is made by centrosymmetrically related molecules, as shown in Figure 4. The stacked molecules are placed on overlying planes having interplanar distances in the range 3.41−3.56 Å. Molecular rows are kept together by weak nonconventional C−H···O interactions involving the CH group of the thiophene unit linked to the sulfur atom (H-donor) and one oxygen atom of isatin (H-acceptor) of adjacent molecules of **5**. Features of these interactions are shown in Figure S4.

In the **5_2** crystal, the two independent molecules of the polycyclic compound originate two molecular rows already characterized by face-to-face π-stacking interactions: the stacked molecules are placed on overlying planes having interplanar distances of 3.31 and 3.32 Å. However, the stacked units along the two independent molecular rows are the pentagonal rings of the polycyclic compound **5**, that is, the thiophene group and the pyrrole subunit of the isatin group. In

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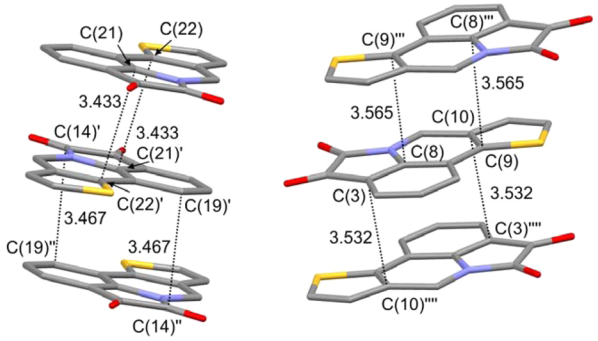

Figure 4. A simplified sketch of the molecular rows made by face-to-face π-stacked molecules in the **5_1** crystal. The shortest intermolecular contacts are drawn with dashed lines (values are in Å). H atoms are omitted for clarity.

particular, as shown in Figure 5, each molecule has the pyrrole subunit placed above the thiophene group of a symmetrically

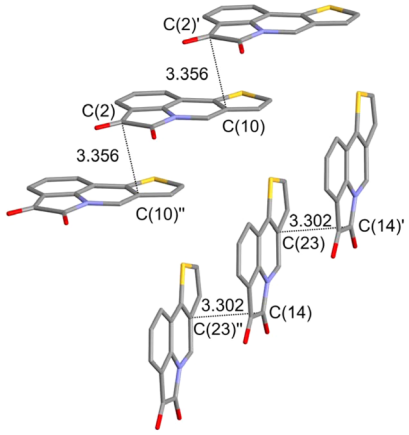

Figure 5. A simplified sketch of the molecular rows made by face-to-face π-stacked molecules in the **5_2** crystal. H-Atoms were omitted for clarity.

equivalent molecule placed in the underlying plane, whereas it has the thiophene group placed below the pyrrole subunit of a symmetrically equivalent molecule placed in the overlying plane. The molecular offset promotes the formation of zigzag like molecular rows extending along the direction of the *a* crystallographic axis. The molecular rows are interconnected by weak nonconventional C−H···O interactions having as H-acceptor species the O atoms of isatin groups and as H-donor groups three different groups: the CH group of thiophene rings bonded to the sulfur atom; one CH group of the phenyl ring of the isatin moiety; the CH group of the C_{sp^3} atom of the fused rings. Features of these interactions are shown in Figure S5.

CONCLUSIONS

We have successfully synthesized fully conjugated molecular hybrids in which the core of the naturally occurring dye isatin has been fused with a thiophene residue. We have demonstrated that the synthesis is feasible using the mild and scalable conditions associated with the DHA reaction, used as the key intramolecular ring closing step. The DHA reaction has however to be performed with the correct set up in terms of nucleophilic and electrophilic atom, that is, the halogen atom on the isatin residue and hydrogen atoms on both the α-positions of the thiophene residue, to avoid intermolecular propagation and cross-linking, which cannot be suppressed using high dilution reaction conditions. We have also demonstrated that the synthetic protocol is adaptable to other substituents, namely, fluorine atoms, on the aromatic isatin residue. The synthetic flexibility has afforded tunable energy levels of the final dyes, with the fluorinated compound **23** having identical bandgap with respect to **5**, but lower HOMO and LUMO levels. We are currently engaged in tuning reaction protocols for late stage dibromination of both **5** and **23**, to afford isatin-based conjugated monomers capable of polymerization for organic photovoltaic applications.

EXPERIMENTAL SECTION

General Experimental Methods. All commercially available reagents and solvents were used as received. THF (Na, benzophenone) and CH_2Cl_2 (CaH_2) were dried and distilled before use. Analytical thin layer chromatography was performed on chromophore loaded, commercially available silica gel plates. Flash chromatography was carried out using silica gel (pore size 60 Å, 230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ or DMSO-d_6 on 200 or 300 spectrometers using the solvent residual proton signal or tetramethylsilane as the internal standard. Samples for the mass spectrometry were analyzed with GC-MS and ESI-MS conventional instrumentation. The UV/vis and emission spectroscopic studies were recorded using conventional spectrophotometers, with a scanning speed of 50 nm/min at 20 °C. Photoluminescence studies were conducted using an excitation slit of 2.0 nm, and emission slit of 3.0 nm with a scanning speed of 50 nm/min at 20 °C.

Cyclic voltammetry was performed with the sample at a concentration of 10^{-3} M (in the case of **5**) or 0.6×10^{-3} M (in the case of **25**) in *o*-DCB/MeCN (1:10 by volume) solution in the presence of Bu_4NBF_4 0.1 M as the supporting electrolyte. A stationary glassy carbon (GC) disk electrode was used as the working electrode. Silver electrode $Ag/AgNO_3$ served as the reference electrode and the potential sweep rate was 200 mV s^{-1}. Measurements were carried out under thermostatic conditions (20 °C) in a nitrogen atmosphere.

Diffraction data for **5_1** (reddish brown color, $0.60 \times 0.43 \times 0.36$ mm^3) and for **5_2** (dark brown color, $0.51 \times 0.43 \times 0.36$ mm^3) were collected by means of a conventional diffractometer, working at ambient temperature with graphite-monochromatized Mo Kα X-radiation (λ = 0.71073 Å). Data reductions were performed with the WinGX package;[19] absorption effects evaluated with the ψ-scan method[20] were negligible, and absorption correction was not applied to the data. All crystal structures were solved by direct methods (SIR 97)[21] and refined by full-matrix least-squares procedures on F^2 using all reflections (SHELXL 2014).[22] Anisotropic displacement parameters were refined for all non-hydrogen atoms; hydrogens were placed at calculated positions with the appropriate AFIX instructions and refined using a riding model. Crystal data are reported in Table S2. Melting points were measured on commercially available instrumentation and are uncorrected.

3-Bromomethylthiophene.[23] A suspension of *N*-bromosuccinimide (NBS; 1.78 g, 10 mmol) and benzoyl peroxide (3 mg, 0.001 mmol) in CCl_4 (10 mL) was heated at 40 °C for 30 min, then 3-methylthiophene (10 mmol) was added dropwise. The mixture was refluxed for 2 h. The precipitate was filtered and washed with hexanes. The organic solvent was removed and the crude reaction was distilled *in vacuo* to yield the desired product (1.54 g, 87%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.31 (m, 2H), 7.14 (d, J = 5.0 Hz, 1H), 4.54 (s, 2H).

2-Bromo-3-methylthiophene.[24] NBS (1.74 g, 9.8 mmol) was added slowly to solution of 3-methylthiophene (10 mmol) in glacial AcOH (7 mL) at 0 °C. The mixture was maintained at room temperature for 1 h. The reaction mixture was then quenched with water and extracted with ether. The organic solvent was removed, and the crude material was purified by flash column chromatography using hexanes as eluent. 2-Bromo-3-methylthiophene was obtained as a pale

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yellow oil (1.47 g, 83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (d, J = 5.6 Hz, 1H), 6.79 (d, J = 5.5 Hz, 1H), 2.21 (s, 3H).

2-Bromo-3-bromomethylthiophene.[23] A suspension of 2-bromo-3-methylthiophene (1.77 g, 10 mmol), NBS (1.78 g,10 mmol) and benzoyl peroxide (3 mg, 0.001 mmol) in CCl_4 (10 mL) was heated to reflux for 8 h. The reaction mixture was filtered, and precipitate was washed with hexanes. The organic solvent was removed, and organic crude was distilled *in vacuo* to yield the desired product as a pale colorless oil (2.93 g, 87%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (d, J = 5.6 Hz, 1H), 7.01 (d, J = 5.7 Hz, 1H), 4.47 (s, 1H).

General Procedure for the Synthesis of *N*-Benzylisatins. *Example for the Synthesis of **2**.* 7-Bromoisatin (226 mg, 1 mmol) and dry DMF (5 mL) were introduced at 0 °C, under nitrogen, in a flame-dried Schlenk flask. NaH (60 mg, 1.5 mmol) was added slowly, and the reaction mixture was stirred at 0 °C for 30 min. 3-Bromomethylthiophene (194 mg, 1.1 mmol) was then added via syringe, and the reaction mixture was stirred at room temperature. After full conversion of the starting material (5 h, TLC monitoring), the reaction mixture was quenched with water. The aqueous phase was extracted with ethyl acetate, the solvent was removed from the combined organic extracts *in vacuo*, and the crude material was purified by flash chromatography (SiO_2; *n*-hexanes/ethyl acetate, 8:2) to afford pure *N*-benzylisatin **2** as a red solid (315 mg, 98%).

*7-Bromo-1-(thiophen-3-ylmethyl)indoline-2,3-dione (**2**).* Obtained as a red solid (315 mg, 98%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.69 (dd, J = 8.1 and 1.3 Hz, 1H), 7.61 (dd, J = 7.3 and 1.3 Hz, 1H), 7.35−7.21 (m, 2H), 7.11 (dd, J = 4.8 and 1.5 Hz, 1H), 7.06−6.94 (m, 1H), 5.43 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.2, 158.7, 147.4, 144.0, 136.5, 126.8, 126.4, 125.1, 124.7, 122.8, 120.8, 104.3, 40.3. MS-ESI: m/z 322 $[M + H]^+$, 345 $[M + Na]^+$, 644 $[2M]^+$. GC-MS (EI) rt: 16.94 min, m/z 323 $[M]^+$. Anal. Calcd for $C_{13}H_8BrNO_2S$: C 48.5; H 2.5. Found: C 48.2; H 2.2. Mp > 300 °C (dec.).

*4-Bromo-1-((2-bromothiophen-3-yl)methyl)indoline-2,3-dione (**7**).* Obtained as an orange solid (385 mg, 96%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45−7.20 (m, 3H), 6.92−6.81 (m, 2H), 4.88 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3, 157.1, 151.6, 138.4, 133.8, 128.8, 127.3, 127.3, 121.7, 111.5, 109.5, 109.3, 38.6. MS-ESI: m/z 400 $[M + H]^+$,422 $[M + Na]^+$, 798 $[2M]^+$. Anal. Calcd for $C_{13}H_7Br_2NO_2S$: C 38.9; H 1.8. Found: C 38.6; H 1.9. Mp > 300 °C (dec.).

*4,7-Dibromo-1-(thiophen-3-ylmethyl)indoline-2,3-dione (**12**).* Obtained as an orange solid (365 mg, 91%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (d, J = 8.7 Hz, 1H), 7.30 (dt, J = 5.5 and 2.7 Hz, 1H), 7.24 (s, 1H), 7.14 (d, J = 8.7 Hz, 1H), 7.11−7.04 (m, 1H), 5.45 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 157.8, 149.0, 143.7, 136.1, 129.9, 126.7, 126.5, 122.8, 121.4, 118.9, 102.9, 40.4. MS-ESI: m/z 400 $[M + H]^+$,422 $[M + Na]^+$, 798 $[2M]^+$. Anal. Calcd for $C_{13}H_7Br_2NO_2S$: C 38.9; H 1.8. Found: C 38.7; H 2.0. Mp > 250 °C (dec.).

*4,7-Dibromo-1-((2-bromothiophen-3-yl)methyl)indoline-2,3-dione (**15**).* Obtained as an orange solid (442 mg, 92%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49 (d, J = 8.7 Hz, 1H), 7.24 (d, J = 5.7 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.66 (d, J = 5.7 Hz, 1H), 5.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.6, 157.8, 149.0, 143.7, 136.1, 129.9, 126.7, 126.5, 122.8, 121.4, 118.9, 102.9, 40.4. MS-ESI: m/z 400 $[M + H]^+$, 422 $[M + Na]^+$, 798 $[2M]^+$. single crystals suitable for X-ray crystallography were obtained by slow evaporation of a solution of compound in CH_2Cl_2. Mp > 250 °C (dec.).

*7-Bromo-5,6-difluoro-1-(thiophen-3-ylmethyl)indoline-2,3-dione (**20**).* Obtained as a pale orange solid, (251 mg, 70%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (t, J = 7.2 Hz, 1H), 7.32 (dd, J = 4.9 and 3.0 Hz, 1H), 7.24 (s, 1H), 7.07 (d, J = 4.9 Hz, 1H), 5.42 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3, 158.5, 156.1, 152.7, 149.1, 145.8, 136.0, 126.8, 126.5, 122.8, 113.8, 95.9, 40.5, 29.6. Anal. Calcd for $C_{13}H_6BrF_2NO_2S$: C 43.6; H 1.7. Found: C 43.4; H 1.6. Mp > 250 °C (dec.).

General Procedure for the Synthesis of *N*-Benzylisatin Ethylenedioxy Ketals. *Example for the Synthesis of **3**.* A solution of compound **2** (322 mg,1 mmol), ethylene glycol (1 mL, 18 mmol), and *p*-toluenesulfonic acid (few crystals) in toluene (5 mL) was heated at reflux for 6 h with Dean−Stark equipment. The solvent was then removed, the solid was treated with a sat. $NaHCO_3$ aqueous solution, and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were concentrated *in vacuo*, and the solid was purified by flash chromatography (SiO_2; CH_2Cl_2) to afford pure product **3** as a white solid (315 mg, 86%).

*7′-Bromo-1′-(thiophen-3-ylmethyl)spiro[[1,3]dioxolane-2,3′-indolin]-2′-one (**3**).* Obtained as a white solid, (315 mg, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45 (dd, J = 8.1 and 1.3 Hz, 1H), 7.34 (dd, J = 7.3 and 1.3 Hz, 1H), 7.27 (dd, J = 4.9 and 3.1 Hz, 1H), 7.15 (dd, J = 2.9 and 1.3 Hz, 1H), 7.06 (dd, J = 5.0, 1.3 Hz, 1H), 6.95 (dd, J = 8.2, 7.3 Hz, 1H), 5.31 (s, 2H), 4.72−4.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 141.1, 137.3, 127.4, 126.5, 126.0, 124.5, 124.1, 121.8, 102.9, 100.9, 65.9, 40.1. GC-MS (EI) rt: 17.94 min, m/z 268 $[M]^+$. Anal. Calcd for $C_{15}H_{12}BrNO_3S$: C 49.2; H 3.3. Found: C 49.0; H 3.5.

*4′-Bromo-1′-((2-bromothiophen-3-yl)methyl)spiro[[1,3]-dioxolane-2,3′-indolin]-2′-one (**8**).* Obtained as a white solid (383 mg, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19 (td, J = 6.7, 6.2, 4.0 Hz, 3H), 6.81 (d, J = 5.7 Hz, 1H), 6.72 (dd, J = 6.5 and 2.2 Hz, 1H), 4.75 (s, 2H), 4.72−4.37 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.3, 157.1, 151.6, 138.4, 133,8, 128.8, 128.6, 121.6, 116.4, 111.5, 109.6, 66.7 38.6. MS-ESI: m/z 444 $[M + H]^+$, 466 $[M + Na]^+$, 886 $[2M]^+$. Anal. Calcd for $C_{15}H_{11}Br_2NO_3S$: C 40.5; H 2.5. Found: C 40.9; H 2.2. Mp > 200 °C (dec.).

*4′,7′-Dibromo-1′-(thiophen-3-ylmethyl)spiro[[1,3]dioxolane-2,3′-indolin]-2′-one (**13**).* Obtained as a white solid, (392 mg, 88%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35−7.23 (m, 2H), 7.18−6.97 (m, 3H), 5.31 (s, 2H), 4.74−4.36 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 142.9, 138.2, 137.0, 128.7, 126.4, 126.2, 125.4, 121.8, 119.2, 102.0, 101.6, 66.7, 40.2. MS-ESI: m/z 444 $[M + H]^+$, 466 $[M + Na]^+$, 886 $[2M]^+$. Anal. Calcd for $C_{15}H_{11}Br_2NO_3S$: C 40.5; H 2.5. Found: C 40.1; H 2.8.

*4′,7′-Dibromo-1′-((2-bromothiophen-3-yl)methyl)spiro[[1,3]-dioxolane-2,3′-indolin]-2′-one (**16**).* Obtained as a white solid (356 mg, 68%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 5.7 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 5.7 Hz, 1H), 5.18 (s, 2H), 4.62−4.46 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 142.9, 138.2, 137.0, 128.7, 126.4, 126.2, 125.4, 121.8, 119.2, 102.0, 101.6, 66.7, 40.2. MS-ESI: m/z 444 $[M + H]^+$,466 $[M + Na]^+$, 886 $[2M]^+$. Anal. Calcd for $C_{15}H_{10}Br_3NO_3S$: C 34.4; H 1.9. Found: C 34.8; H 2.1.

*7′-Bromo-5′,6′-difluoro-1′-(thiophen-3-ylmethyl)spiro[[1,3]-dioxolane-2,3′-indolin]-2′-one (**21**).* Obtained as a white solid (334 mg, 83%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.29 (dd, J = 4.9 and 2.9 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.11 (s, 1H), 7.01 (d, J = 6.0 Hz, 1H), 5.28 (s, 2H), 4.68−4.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 149.4, 148.5, 146.1, 145.1, 130.6, 128.4, 116.6, 116.5, 111.7, 103.0, 65.9, 41.7. MS-ESI: m/z 402 $[M + H]^+$,425 $[M + Na]^+$, 804 $[2M]^+$. Anal. Calcd for $C_{15}H_{10}BrF_2NO_3S$: C 44.8; H 2.5. Found: C 44.7; H 2.9.

General Procedure for the Intramolecular DHA Reaction. *Example for the Synthesis of **4**.* A suspension of *N*-benzylisatin ketal **3** (366 mg, 1 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), KOAc (294 mg, 3 mmol), and Bu_4NBr (322 mg, 1 mmol) in dry DMF (5 mL) was stirred and heated to reflux. After full conversion of the starting material (8 h, TLC monitoring), the reaction mixture was quenched with water, and the aqueous phase was extracted with ethyl acetate. The organic extracts were concentrated *in vacuo*, and the solid was purified by flash chromatography (SiO_2; *n*-hexanes/ethyl acetate, 8:2) to afford the pure product **4** as a white solid (208 mg, 73%).

*Spiro[[1,3]dioxolane-2,4′-pyrrolo[3,2,1-ij]thieno[3,2-c]quinolin]-5′(7′H)-one (**4**).* Obtained as a white solid (208 mg, 73%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31−7.20 (m, 2H), 7.15 (dd, J = 7.5 and 1.0 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 5.1 Hz, 1H), 4.99 (s, 2H), 4.67−4.23 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 138.6, 130.4, 129.5, 126.2, 125.3, 123.4, 123.3, 121.9, 115.4, 103.5, 65.7, 41.5. GC-MS (EI) rt: 18.37 min, m/z 285 $[M]^+$. Anal. Calcd for $C_{15}H_{11}NO_3S$: C 63.1; H 3.9. Found: C 63.4; H 3.9.

*1′,2′-Difluorospiro[[1,3]dioxolane-2,4′-pyrrolo[3,2,1-ij]thieno[3,2-c]quinolin]-5′(7′H)-one (**22**).* Obtained as a white solid (148 mg, 46%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.47 (d, J = 5.2 Hz, 1H), 7.09−6.88 (m, 2H), 5.02 (s, 2H), 4.67−4.22 (m, 4H). ^{13}C NMR (75 MHz,

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$CDCl_3$): δ 172.6, 149.3, 148.5, 146.1, 145.1, 130.6, 128.4, 125.4, 116.5, 111.8, 106.4, 102.9, 65.9, 41.7. MS-ESI: *m/z* 322 $[M + H]^+$, 344 $[M + Na]^+$, 642 $[2M]^+$. Anal. Calcd for $C_{15}H_9F_2NO_3S$: C 56.1; H 2.8. Found: C 56.4; H 2.9.

General Procedure for the Deprotection. *Example for the Synthesis of* ***5****.* A solution of compound **4** (285 mg, 1 mmol) in THF (2.5 mL) and aqueous HCl 6 M (2.5 mL) was stirred and heated to reflux for 6 h. THF was removed *in vacuo*, and the resulting aqueous phase was extracted with ethyl acetate. The combined organic extracts were concentrated *in vacuo*, and the resulting crude material was purified by chromatography (SiO_2; *n*-hexanes/ethyl acetate, 9:1) to afford pure product **5** in quantitative yield.

*4H-Pyrrolo[3,2,1-ij]thieno[3,2-c]quinoline-4,5(7H)-dione (**5**).* Obtained as a red solid (241 mg, 99%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.53−7.29 (m, 3H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 5.2 Hz, 1H), 5.13 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.6, 167.4, 155.6, 143.6, 127.5, 126.8, 124.3, 124.2, 121.8, 121.1, 114.6, 113.4; 40.0. MS-ESI: *m/z* 242 $[M + H]^+$, 264 $[M + Na]^+$. Single crystals suitable for X-ray crystallography were obtained by slow evaporation of a solution of compound in CH_2Cl_2. Mp > 300 °C (dec.).

*1,2-Difluoro-4H-pyrrolo[3,2,1-ij]thieno[3,2-c]quinoline-4,5(7H)-dione (**23**).* Obtained as a red solid (202 mg, 73%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.56 (d, *J* = 4.0 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 4.5 Hz, 1H), 5.16 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 171.4, 157.2, 152.1, 130.9, 129.6, 125.5, 122.6,117.6 111.2, 110.9, 110.2, 42.0. MS-ESI: *m/z* 278 $[M + H]^+$. Anal. Calcd for $C_{13}H_5F_2NO_2S$: C 56.3; H 1.8. Found: C 56.6; H 2.0. Mp > 300 °C (dec.).

*4,7-Dibromoindoline-2,3-dione **11**.*[25] Chloral hydrate (14.7 g, 88.8 mmol) was added to a suspension of hydroxylamine hydrochloride (18.5 g, 0.266 mol), sodium sulfate (84 g, 0.59 mol), and 2,5-dibromoaniline (74.0 mmol) in water (500 mL) and 2 M HCl (25 mL). The mixture was then heated at 55 °C overnight with stirring. After cooling to room temperature, the hydroxyiminoacetanilide intermediate was collected by filtration, washed with water, and dried under vacuum. The intermediate was added in small portions, with stirring, to concentrated H_2SO_4 (45 mL), which had been heated to 55 °C. The temperature of the reaction mixture was maintained below 70 °C during the addition. The dark-colored solution was heated at 80 °C for an additional 10 min and then cooled to room temperature, poured onto crushed ice, and allowed to stand for 30 min. The precipitate was collected by filtration, washed three times with water, and dried under vacuum to yield isatin **11** to be used directly in the next step without further purification. ^1H NMR (200 MHz, DMSO-d_6) δ 7.54 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H).

*7-Bromo-1-((2-bromothiophen-3-yl)methyl)-4-(dimethylamino)-indoline-2,3-dione (**17**).* Cu powder (0.10 g, 1.67 mmol) was added to a solution of compound **15** (0.10 g, 0.21 mmol) in dry DMF (10 mL) under nitrogen. The reaction mixture was heated under stirring at 130 °C for 3 days. The reaction mixture was quenched with water, and the resulting aqueous phase was extracted with ethyl acetate. The combined organic extracts were removed of the solvent *in vacuo*, and the crude material was purified by flash chromatography (SiO_2; *n*-hexanes/ethyl acetate, 8:2) to afford pure compound **17** as a red solid (43 mg, 73%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.29 (d, *J* = 9.2 Hz, 1H), 7.19 (d, *J* = 5.7 Hz, 1H), 6.68 (d, *J* = 5.7 Hz, 1H), 6.47 (d, *J* = 9.4 Hz, 1H), 5.28 (s, 2H), 3.16 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 160.7, 151.2, 146.7, 143.1, 136.4, 129.5, 126.4, 124.0, 114.1, 108.6, 90.3, 43.3, 41.0. MS-ESI: *m/z* 284 $[M + H]^+$. Single crystals suitable for X-ray crystallography were obtained by slow evaporation of a solution of compound in CH_2Cl_2. Mp > 300 °C (dec.).

General Procedure for the Stille−Kelly Reaction for the Attempted Synthesis of Compounds 9 and 18. *Example for the Synthesis of* ***18****.* $Pd(PPh_3)_4$ (0.013 g, 10%mol) was added to a solution of compound **16** (0.061 g, 0.12 mmol) in dry 1,4-dioxane (3 mL). The reaction mixture was purged with nitrogen for 5 min; then hexamethylditin (0.076 g, 0.24 mmol) was added under nitrogen. The reaction mixture was quenched with water after 1 d (TLC monitoring), and solvents were removed *in vacuo*. The resulting crude solid was extracted with ethyl acetate, and the organic extracts were concentrated *in vacuo*. ^1H NMR spectrum of the crude of reaction did not show the expected signals of compound **9**.

7-Bromo-5,6-difluoroindoline-2,3-dione (19). Chloral hydrate (477 mg, 5.8 mmol) was added to a suspension of hydroxylamine hydrochloride (584 mg, 16.8 mmol), sodium sulfate (2.05 g, 28.8 mmol), and 2-bromo-3,4-difluoroaniline (500 mg, 2.4 mmol) in 2 M aqueous HCl (5 mL). The mixture was refluxed overnight with vigorous stirring. After cooling to room temperature, the hydroxyiminoacetanilide intermediate was collected by filtration as a yellow solid, which was washed with water and dried under vacuum. The intermediate was added in small portions, with stirring, to concentrated H_2SO_4. The temperature of the reaction mixture was maintained below 70 °C during the addition. The dark-colored solution was heated at 80 °C for 3 h and then cooled to room temperature, poured onto crushed ice, and allowed to stand for 30 min. The precipitate was collected by filtration, washed with water and toluene, and purified by flash chromatography (SiO_2; *n*-hexanes/ethyl acetate, 8:2) to give the analytically pure product as a pale orange solid (290 mg, 46%). ^1H NMR (200 MHz, DMSO- d_6): δ 11.41 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 181.8, 159.8, 154.3, 150.9, 144.4, 114.5, 113.2, 94.3. GC-MS (EI) rt: 9.94 min, *m/z* 261 $[M]^+$. Anal. Calcd for $C_8H_2BrF_2NO_2$: C 36.8; H 0.8. Found: C 36.6; H 0.9.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01922.

Copies of ^1H, ^{13}C NMR, ESI-MS, and GC-MS spectra for new compounds and additional figures and tables about UV/vis spectroscopy, cyclic voltammetry, and X-ray crystallography (PDF)

Crystallographic structures of **5_1**, **5_2**, **15**, and **17** CIF)

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Notes

The authors declare no competing financial interest.

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