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Palladium-Catalyzed Direct C-H Arylations of Dioxythiophenes Bearing Reactive Functional Groups: A Step-Economical Approach for Functional π-Conjugated Oligoarenes†

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† Electronic supplementary information (ESI) available:

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Abstract

A Pd-catalyzed and single-step C-H arylation of dioxythiophene derivates bearing unprotected reactive functional groups (-OH, -COOH, -N_3) in a phosphine-free manner has been developed. Various dioxythiopene-based oligoarenes with extended π-conjugation are obtained with good yields (up to 90%). These oligoarenes display suitable optical properties (absorption and emission maxima, quantum yields) and contain reactive functional groups suitable for further conjugations with bioactive molecules. This new methodology is step economical (fewer synthetic steps), environmental friendly (no toxic metal-containing side-poducts) and the oligoarenes synthesized are potentially applicable for bio-labeling, bioimaging, and biosensing.

Keywords: C-H arylation, phosphine-free, π-conjugated materials, oligothiophene, organic electronic material.

Introduction

Oligoarenes originated from thiophene moieties with extended π-conjugation attract a lot of research interests due to their exceptional electrical and optical properties. They have been used in various organic electronic and optoelectronic applications, including light-emitting diodes,[1] field-effect transistors[2] and photovoltaic cells.[3] On top of these established applications in organic electronics, thiophene-based poly-/oligoarenes exhibit potential applications in biological/biomedical research as molecular probes because they can provide optical or electrical signals.[4] For these areas, it is preferred that the probes contain reactive functional groups, e.g. hydroxyl, carboxylic acid, or azide, because such groups can be linked to bioactive building blocks by simple chemical transformations, including esterification, amidation and copper-catalyzed azide-alkyne cycloaddition.[5] As a result, specific or enhanced bio-labeling/-imaging will be achieved.[6] Therefore, simple, direct and efficient synthetic approaches to extend thiophene conjugation with arenes bearing reactive functional groups is of highly significance.

Traditional approaches for thiophene-containing oligoarene synthesis often employ expensive, reactive and environment unfriendly thienyl organometallic reagents.[7] Moreover, these reagents are often synthesized from protonated thiophene precursors. Therefore, the synthetic routes utilized are neither atom-economical nor environmentally benign although these approaches were efficient to construct various oligoarenes at early stage to understand the potential of these materials. Considering the pit-falls, synthesis of thiophene containing oligoarenes through direct C-H arylations has become a viable and convenient alternative.[8] To date, direct C-H arylations catalyzed by Pd, Ir and Rh complexes have been well reported.[9] In addition, there are often tedious protection and deprotection steps in order to synthesize thiophene-contaning oligoarenes bearing reactive functional groups.

Although direct arylations of oligothiophenes bearing unprotected -OH or -NH_2 groups have been disclosed, these reactions usually proceed with an excess amount of starting materials at a high temperature (120-160 ^{o}C) for a long reaction time (16-20 h).[10] Therefore, there is an urgent need to discover more efficient and milder conditions to extend the π-conjugation of thiophene moieties with unprotected functional groups.

Results and discussion

We reported previously a Pd-catalyzed direct arylation of 3, 4-ethylenedioxythiophene (EDOT), which avoided the tedious preparation of the required organometallic coupling partners and provided an efficient route to a variety of EDOT-based functional π-conjugated molecules.[11] Considering all the plausible applications of thiophene-based oligoarenes for bio-related research, we report herein significant advances on a Pd-catalyzed and one-step synthetic approach for the preparation of extended π-conjugated oligoarenes containing dioxythiophenes with unprotected functional groups as illustrated in **Scheme 1**. In order to expand the substrate scope and overcome the limitations of the functional group tolerance, we anticipate that the dioxythiophene derivatives **1**-**4** would undergo the Pd-catalyzed direct C-H bond arylations with aryl halides in the presence of unprotected hydroxyl, carboxylic acids, and azides to yield dioxythiophene-based oligoarenes **5**. Furthermore, this new approach provides another advantageous feature with no environmental unfriendly metal-containing by-products.

We first examined the direct arylation of hydroxymethyl-functionalized EDOT **1** because hydroxyl group are less reactive comparing to other functional groups. Oligothiophenes displayed promising performance for organic thin film transistors so we would like to first target on the synthesis of those molecules bearing functional groups as shown in **Table 1**. Similar to the optimized reaction condition reported previously,[11] **1** was treated with 2-bromothiophene in the presence of $Pd(OAc)_2$ (5 mol%), P(*m*-tolyl)$_3$ (10 mol%), and Cs_2CO_3 (2.4 equiv.) in toluene at 110 °C. Unfortunately, only 5% of the desired product **5a** was isolated after the reaction was carried out for 24 hours. We continued to test other reaction conditions. Schipper and Fagnou reported the synthesis of thiophene-based organic optoelectronic molecules by using the combination of PCy_3HBF_4 ligand, pivalic acid and

K_2CO_3.[8a] However, we did not obtain any product when carrying out reaction under this condition. After several unsuccessful attempts, we observed that a greatly enhanced isolated yield was obtained using $Pd(OAc)_2$ catalyst under a phosphine-free condition.[12] Using potassium acetate as base and tetrabutylammonium bromide (nBu$_4$NBr) as a phase-transfer agent, several earlier reports demonstrated efficient C-H arylation on thiophenes bearing electron-donating groups to form corresponding oligothiophenes or polythiophenes.[12] When we performed C-H arylation using this condition in DMF, the isolated yield of **5a** reached 77% after heating at 90 °C for only 1.5-2 h. These preliminary results encouraged us to further investigate the reaction scope using various kinds of aryl bromides which are promising building blocks for organic electronic or optoelectronic materials.

With the optimized reaction condition at hand, we commenced our investigation from EDOT derivate **1** as summarized in **Table 2**. Anisole derivative **5b** could be readily prepared in 75% yield by using the phosphine-free reaction condition shown in **Table 1**. Likewise, treating **1** with the ethyl 4-bromobenzoate afforded the desired product **5c** in good yield (85%). Oligoarene **5d** bearing triphenylamines, which is of particular interest as hole injection/transport layer in organic electronic devices[13], was efficiently synthesized and isolated in 83% yield. A potential candidate **5e** for the n-type organic field-effect transistors (OFET)[14] was produced in 82% yield under similar reaction condition. In addition, the easily obtained diarylated adducts **5f**-**g** bearing alkyl end groups (80% and 46%) could exhibit interesting optoelectronic properties[15] or be applied as liquid crystals[16] as well as organic crystal transistors.[17] A sensitive methyl ketone functionality is also compatible with the mild C-H arylation conditions and the expected diketone **5h** was isolated in good yield (82%). We have also found a straightforward synthesis of the fluorene- and spirobifluorene-capped EDOT derivatives **5i**-**j** (77% and 90%) which could be used as efficient emitters for organic

light-emtting diodes.[18]

Opposite to asymmetric oligoarenes from EDOT **1**, oligoarenes from hydroxyl-functionalized 3,4-propylenedioxythiophene (ProDOT) **2** exhibited plane symmetry and different optical and electrical properties might present. As shown in **Table 2**, different bromoarenes reacted efficiently with **2** in the presence of $Pd(OAc)_2$ under identical reaction conditions to yield the corresponding ProDOT-based π-conjugated molecules (**5k-5m**) in moderate to good isolated yields (48-79%). It should be noted that good yields were obtained regardless of the electron-donating or electron-withdrawing substituents on bromoarenes.

Optical properties of these new reactive dioxythiophene-based oligoarenes **5b-5m** were also examined and the results were summarized under each molecule. As the result of extended π-conjugation after diarylation, the absorption and emission maxima of the compounds fell in the range of 340 ~ 480 nm and 389 ~ 475 nm, respectively. The Strokes-shift of these products fell in the range of 47 ~ 97 nm. The smallest Strokes-shift was observed for compound **5e** (47 nm) and the biggest Strokes-shift was observed for compounds **5l** and **5m** (74 nm). When the coupled arenes contained only alkyl or no substituents, the products from diarylation (**5f**, **5i** and **5j**) displayed higher quantum efficiency (Φ = 0.26~0.34). In contrast, both electron-donating and electron-withdrawing groups (**5b**, **5c**, **5d**, **5e** and **5h**) lead to reduced quantum efficiency (Φ = 0.03~0.15). It is also observed that diarylation adducts (**5k-m**) from hydroxyl-ProDOT **2** displayed absorption and emission maxima at shorter wavelength compared to similar adducts from EDOT **1**. For example, the absorption maximum of **5k** (361 nm) showed a 14 nm blue-shift to the absorption maximum of **5c** (375 nm) with almost identical quantum yields. Similar phenomenon was observed with **5m** and **5f**. One plausible explanation was that the P_z

orbitals of oxygen in EDOTs are more perpendicular with the heterocycle ring plane than in ProDOTs. This results in a less destabilization of the electrons in ProDOT.[19]

The initial success on hydroxyl functionalized dioxythiophenes prompted us to investigate those containing more reactive and suitable functional groups for bioconjugation. We first evaluated the reactivity of the carboxylic acid group bearing EDOT derivate **3**. To our delight, successful C-H arylations were observed and the carboxylic acid group could be well tolerated. As a result, a variety of EDOT-containing molecules bearing a carboxylic acid group **5n**-**t** were readily synthesized in yields of 53-78% (**Table 3**) by means of the direct C-H coupling of the EDOT derivative **3** with various kinds of aryl bromides. The single crystal X-ray analysis of compound **5o** (shown in **Figure 1**) demonstrated the molecule was not sterically congested. The torsional angle between EDOT and phenyl ring was measured to be 16.7°. And the torsional angle between two phenyl rings was measured to be 1.5°. The planar structure would facilitate π-conjugation along the backbone. The single crystal X-ray analysis of compound **5f** and **5h** were also shown in the supporting information.

In most cases, the introduction of carboxylic acid did not change the optical properties (absorption and emission maxima, quantum yields) of the adduct **5**. Only in the synthesis of ethyl benzoate adduct (**5t**), we observed significant shifts on the absorption and emission maxima to longer wavelength comparing to the hydroxyl-functionalized EDOT and ProDOT adducts (**5c** and **5k**). An enhanced quantum yield was also measured.

The Pd-catalyzed direct C-H bond arylation is also possible in the case of azide-substituted EDOT derivative **4** (**Table 3**). Regarding to an azide function group in cross-coupling reactions, our phosphine-free C-H arylation would be a better synthetic alternative than the traditional cross-coupling approach involving phosphine ligands because they may trigger the decomposition/reduction of the azide moiety.[20] In the presence of

$Pd(OAc)_2$, KOAc, and Bu_4NBr in DMF, reaction of **4** with the bromoarenes afforded the desired products **5u**-**z** after 2 h at 90 °C with moderate yields (20-68%, **Table 3**). These compounds **5u**-**z** carrying the azide moiety[21] would be able to undergo the copper-catalyzed azide-alkyne cycloadditions with alkynes to orthogonally conjugate biologically important molecules.[22] It was also noted that azide groups did not change the optical performances of the molecules.

The calculations of frontier orbital of some coupling products were conducted using density functional calculations (B3LYP/6-31G* level) and shown in **Figure 2**. Generally, both HOMO and LUMO orbitals of the compounds (**5a**, **5c**, **5d**, **5e**, **5j**, **5k**, **5r** and **5s**) were observed to localize all through the molecular backbones. The results witnessed good π-conjugation of the molecules. Due to the robust electron donating capability of triphenylamine moiety in compound **5d**, the LUMO was observed to less localize in the triphenylamine group comparing to the HOMO. The partially charge separation suggested compound **5d** could be potentially applied in as hole injection/transport layer in organic electronic devices. Additionally, the UV-vis absorption maxima of the coupling products (**5b** to **5z**) were also calculated. As shown in **Table S1**, the calculation results showed a general red-shift in UV-vis maxima, which is widely seen in the density functional calculations. Furthermore, the detailed DFT calculations of energies and Cartesian coordinates of the optimized structures for all the compounds are shown in supporting information.

Conclusions

In conclusion, we have demonstrated a general and single-step approach for the facile preparation of dioxythiophene-containing molecules with extended π-conjugation bearing reactive functional groups (-OH, -COOH, $-N_3$). Through Pd-catalyzed direct C-H arylations, dioxythiophene derivatives yield relative bis-arylation adducts without the protection of reactive functional groups. The optimized reaction condition is phosphine-free and all reactions proceed under a milder temperature (90 °C) and a much shorter reaction time (1.5-2 h) without the production of environmental unfriendly metal-halide by-products. This approach allows us to synthesize π-conjugated molecules with functional groups suitable for conjugation with biomolecules. Several products displayed favorable absorption/emission at the visible range with reasonable quantum yields. Therefore, they are potentially applicable for biolabeling, bioimaging, and biosensing.

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Scheme 1. Traditional and step-economical synthetic routes of the EDOT-containing functional building blocks.

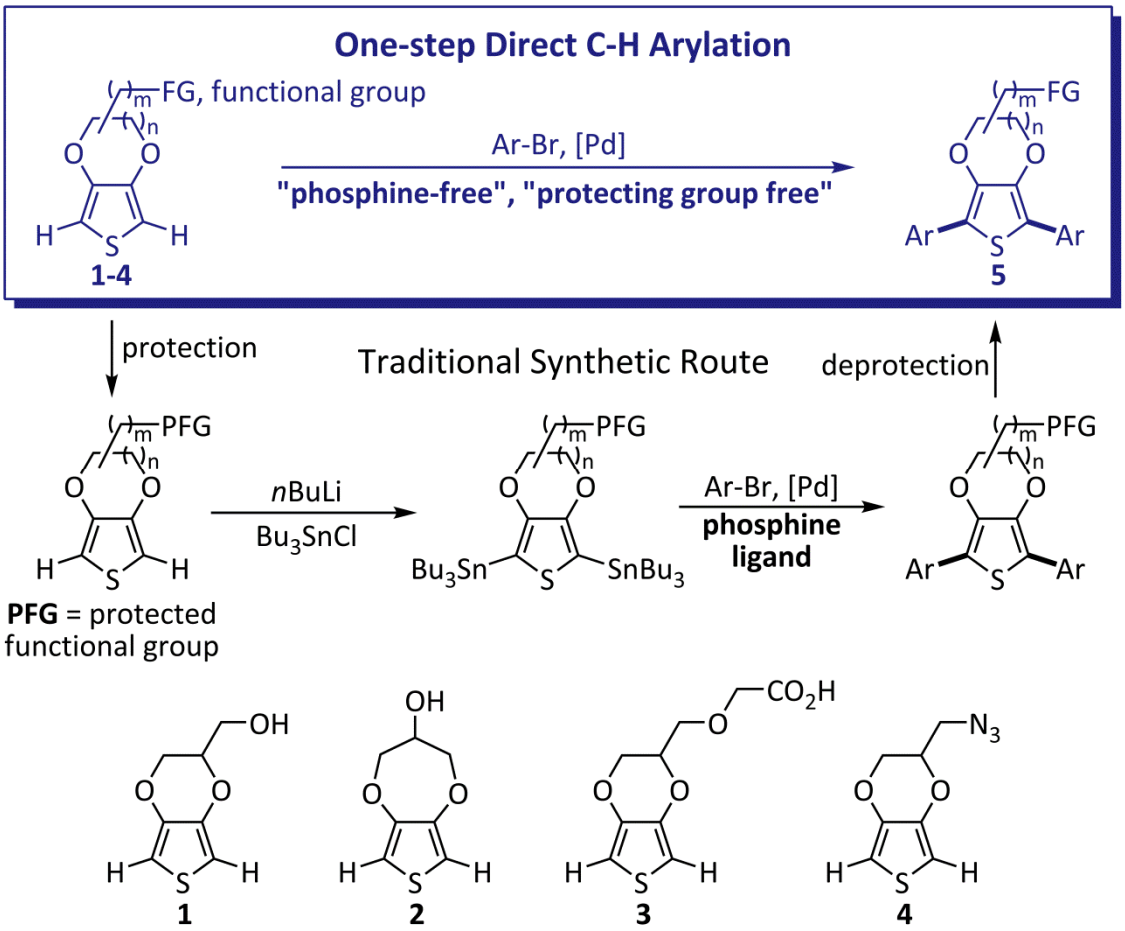
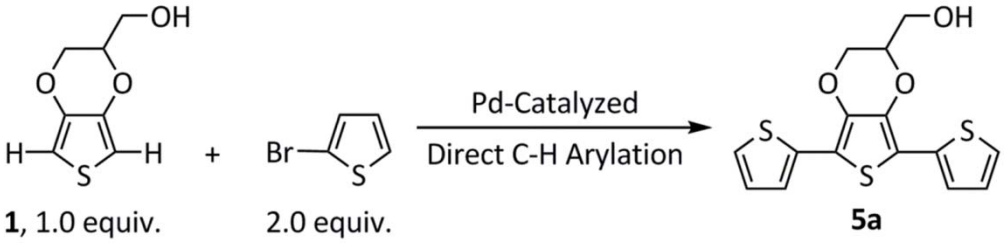


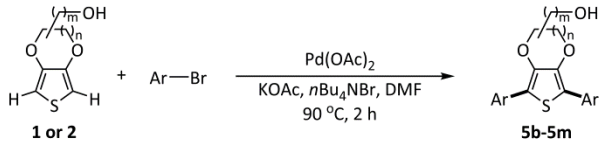
Table 1. Different reaction conditions for Pd-catalyzed direct C-H arylation of EDOT-OH **1** with 2-bromothiophene.



1, 1.0 equiv. 2.0 equiv. **5a**

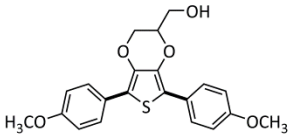
Phosphine Ligand	Additive	Temp.	Time	Yields
P(*m*-Tol)$_3$	Cs_2CO_3	110 ^oC	24 hr	trace
PCy_3HBF_4	PivOH, K_2CO_3	100 ^oC	24 hr	ND
None	KOAc, *n*Bu_4NBr	90 ^oC	1.5 hr	77%

Table 2: Pd-catalyzed direct arylation of the -OH containing dioxythiophenes **1-2** with aryl bromides.[a]

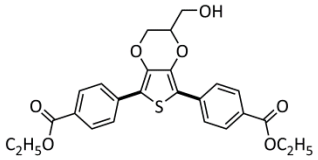


1 or 2 **5b-5m**

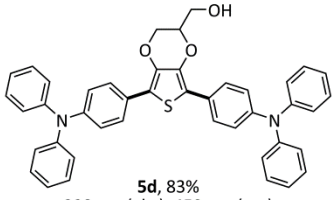
Products (isolate yield, absorption and emission maximum, quantum yield)



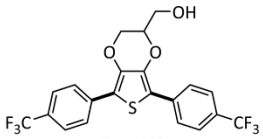
5b, 75%
340 nm (abs), 393, 413 nm (em)
Φ = 0.035



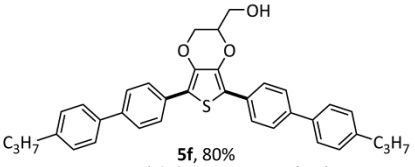
5c, 85%
375 nm (abs), 416, 436 nm (em)
Φ = 0.119



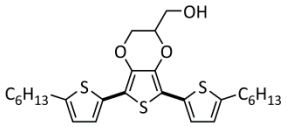
5d, 83%
398 nm (abs), 453 nm (em)
Φ = 0.148



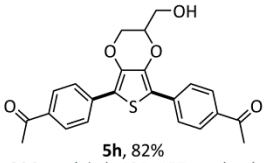
5e, 82%
351 nm (abs), 391, 405 nm (em)
Φ = 0.073



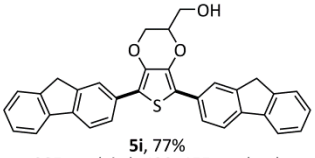
5f, 80%
370 nm (abs), 426, 448 nm (em)
Φ = 0.333



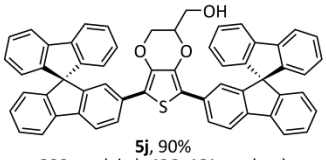
5g, 46%
383 nm (abs), 429, 452nm (em)
Φ = 0.039



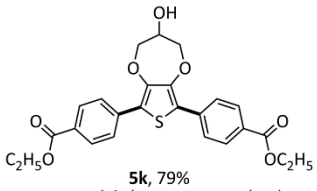
5h, 82%
386 nm (abs), 435, 457 nm (em)
Φ = 0.116



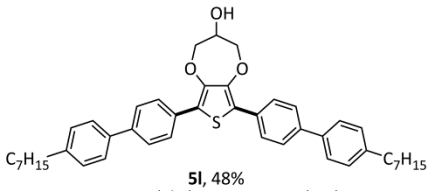
5i, 77%
385 nm (abs), 430, 455 nm (em)
Φ = 0.312



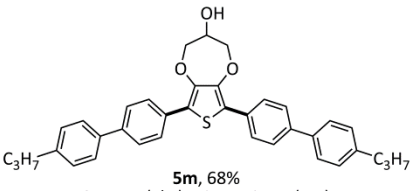
5j, 90%
390 nm (abs), 436, 461 nm (em)
Φ = 0.262



5k, 79%
361 nm (abs), 417, 429 nm (em)
Φ = 0.116



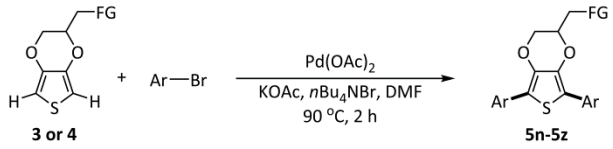
5l, 48%
357 nm (abs), 421, 440 nm (em)
Φ = 0.312



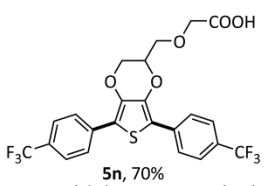
5m, 68%
357 nm (abs), 421, 440 nm (em)
Φ = 0.313

[a] Reaction conditions: -OH functionalized dioxythiophene derivatives **1**-**2** (1.0 equiv.), aryl bromides (2.2 equiv.), $Pd(OAc)_2$ (0.1 equiv.), KOAc (2.4 equiv.), $n$$Bu_4NBr$ (1.0 equiv.), DMF (3 mL $mmol^{-1}$ of EDOT derivatives), 90 °C, 1.5-2 h.

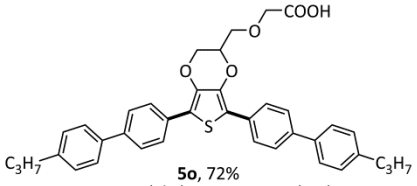
Table 3: Pd-catalyzed direct arylation of the functionalized EDOT derivatives **3-4** with aryl bromides.[a]



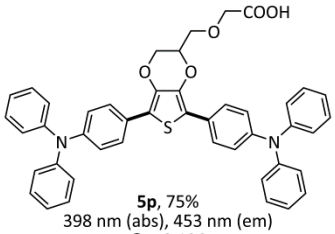
Products (isolate yield, absorption and emission maximum, quantum yield)



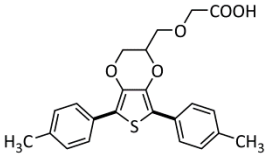
5n, 70%
352 nm (abs), 391, 410 nm (em)
Φ = 0.067



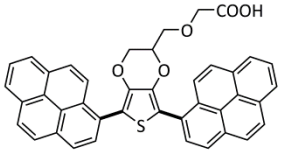
5o, 72%
370 nm (abs), 425, 449 nm (em)
Φ = 0.305



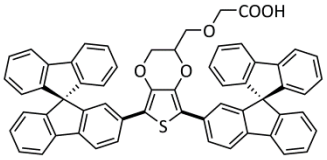
5p, 75%
398 nm (abs), 453 nm (em)
Φ = 0.126



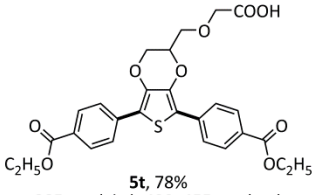
5q, 53%
346 nm (abs), 389, 408 nm (em)
Φ = 0.056



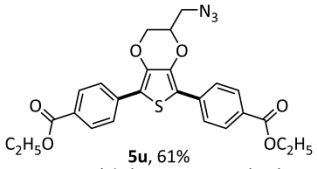
5r, 66%
378 nm (abs), 475 nm (em)
Φ = 0.135



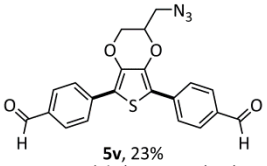
5s, 77%
391 nm (abs), 436, 462nm (em)
Φ = 0.268



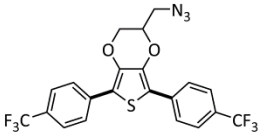
5t, 78%
385 nm (abs), 429, 455 nm (em)
Φ = 0.288



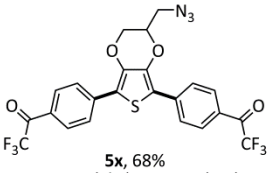
5u, 61%
373 nm (abs), 417, 438 nm (em)
Φ = 0.132



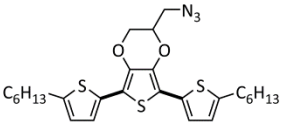
5v, 23%
386 nm (abs), 442 nm (em)
Φ = 0.112



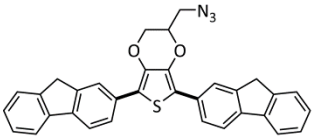
5w, 63%
350 nm (abs), 389, 408 nm (em)
Φ = 0.066



5x, 68%
408 nm (abs), 465 nm (em)
Φ = 0.135



5y, 31%
383 nm (abs), 431, 453 nm (em)
Φ = 0.033



5z, 20%
384 nm (abs), 430, 456 nm (em)
Φ = 0.266

[a] Reaction conditions: EDOT derivatives with carboxylic acid group **3** and azide group **4** (1.0 equiv.), aryl bromides (2.2 equiv.), $Pd(OAc)_2$ (0.1 equiv.), KOAc (2.4 equiv.), nBu$_4$NBr (1.0 equiv.), DMF (3 mL mmol^{-1} of EDOT derivatives), 90 °C, 1.5-2 h.

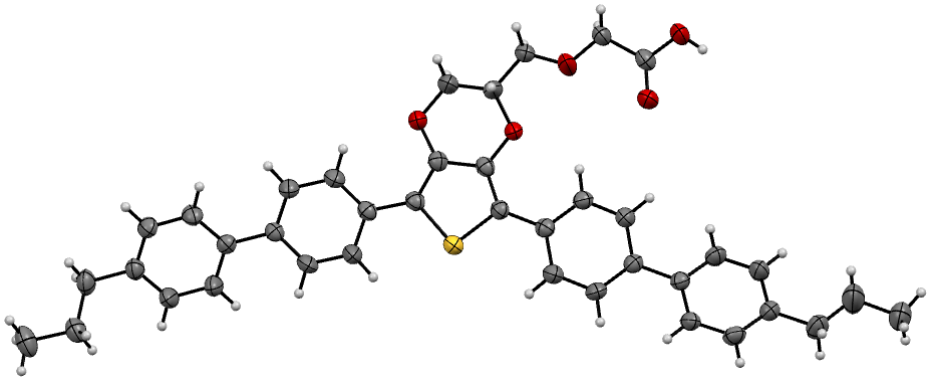


Figure 1: Single crystal structure of compound **5o**.

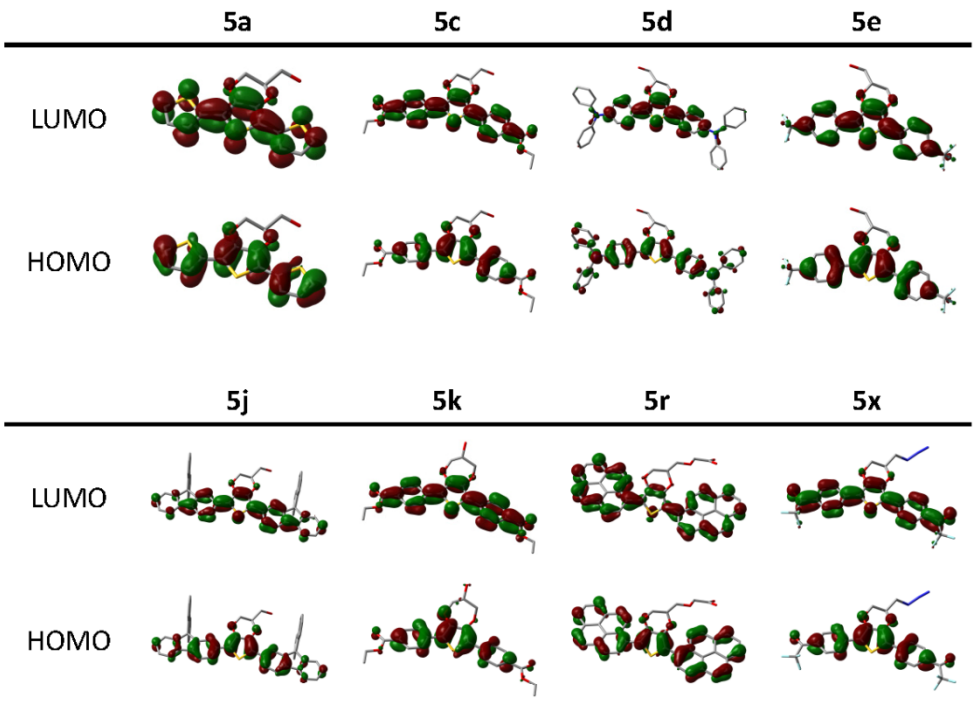


Figure 2: Calculated frontier orbitals of the selected coupling products.

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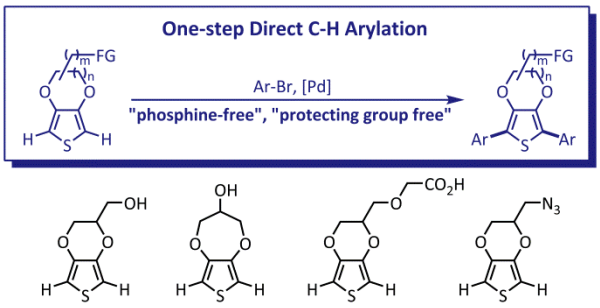

A single-step, phosphine-free C-H arylation of dioxythiophenes bearing unprotected reactive functional groups is developed to afford dioxythiopene-based oligoarenes with good yields.