ORGANIC LETTERS

2011
Vol. 13, No. 15
4068–4071

Efficient Synthesis of 3,4-Ethylenedioxythiophene (EDOT)-Based Functional π-Conjugated Molecules through Direct C−H Bond Arylations

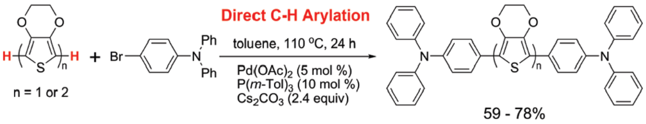
Ching-Yuan Liu, Haichao Zhao, and Hsiao-hua Yu*

Yu Initiative Research Unit, RIKEN Advanced Science Institute, 2-1 Hirosawa, Wako,
Saitama 351-0198, Japan

bruceyu@riken.jp

Received June 11, 2011

ABSTRACT



A variety of 3,4-ethylenedioxythiophene (EDOT)-based π-conjugated molecules were efficiently synthesized in good yields through Pd-catalyzed direct C−H bond arylations, wherein a detailed synthetic investigation, including the screening of various kinds of palladium catalysts, ligands, additives, and solvents, was carried out. In addition, the spectroscopic and electrochemical properties of these EDOT-containing molecules were also investigated.

Syntheses and applications of thiophene-based organic electronic materials have been widely investigated in recent years, and their importance cannot be overemphasized.[1] Very recently, much attention has been drawn to the efficient synthesis of thiophene-containing organic materials due to the importance of atom-economics and green chemistry.[2] As a result, the direct C−H arylation of various (hetero)arenes including thiophenes has become a viable and popular alternative method to conventional cross-coupling reactions.[3] Among all thiophene derivatives, 3,4-ethylenedioxythiophene (EDOT)-based π-conjugated materials have been extensively investigated for the past decade because the incorporation of the EDOT moiety resulted in a smaller intrinsic band gap in polymers,[4] enhanced π-donor ability in tetrathiafulvalene analogues,[5] and improved electrochromic properties.[6] However, in-depth synthetic studies concerning the conjugation extension of EDOT building blocks through atom-economical approaches are quite limited.[7]

Therefore, we report herein a comprehensive synthetic investigation of Pd-catalyzed direct C−H bond arylations

---

(1) Perepichka, I. F.; Perepichka, D. F. *Handbook of Thiophene-Based Materials*; John Wiley & Sons: Chichester, U.K., 2009.

(2) (a) Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23*, 1594 and references cited therein. (b) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (c) Borghese, A.; Geldhof, G.; Antoine, L. *Tetrahedron Lett.* **2006**, *47*, 9249. (d) Masui, K.; Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011. (e) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074.

(3) (a) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946. (b) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (c) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3644. (d) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008**, *64*, 6073. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (f) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (g) Derridj, F.; Roger, J.; Djebbar, S.; Doucet, H. *Org. Lett.* **2010**, *12*, 4320. (h) Roy, D.; Mom, S.; Beaupérin, M.; Doucet, H.; Hierso, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6650. (i) Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749. (j) Tamba, S.; Okubo, Y.; Tanaka, S.; Monguchi, D.; Mori, A. *J. Org. Chem.* **2010**, *75*, 6998. (k) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (l) Li, H.; Sun, C.-L.; Yu, M.; Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *16*, 3593. (m) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044. (n) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (o) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *advanced article.*

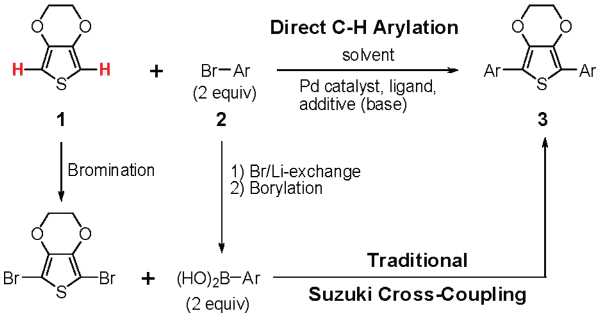
(4) (a) Apperloo, J. J.; Groenendaal, L. B.; Verheyen, H.; Jayakannan, M.; Janssen, R. A. J.; Dkhissi, A.; Beljonne, D.; Lazzaroni, R.; Brédas, J. L. *Chem.—Eur. J.* **2002**, *8*, 2384. (b) Akoudad, S.; Roncali, J. *Chem. Commun.* **1998**, 2081. (c) Huchet, L.; Akoudad, S.; Levillain, E.; Emge, A.; Bäuerle, P.; Roncali, J. *J. Phys. Chem.* **1998**, *102*, 7776.

(5) Akoudad, S.; Frère, P.; Mercier, N.; Roncali, J. *J. Org. Chem.* **1999**, *64*, 4267.

10.1021/ol201571u

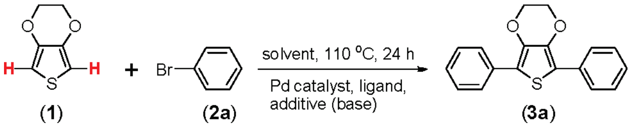
of EDOT through the screening of various palladium catalysts, ligands, bases, and solvents. We envisaged that the reaction of EDOT **1** with aryl bromides **2** under well-optimized reaction conditions would lead to the formation of diarylated EDOT **3** in comparable yields[4a] and the direct C–H arylation of EDOT would become a viable alternative, thus providing a more efficient and atom-economical synthetic approach than the traditional cross-coupling reactions (Scheme 1).

Scheme 1. Synthesis of EDOT-Based Functional π-Conjugated Molecules



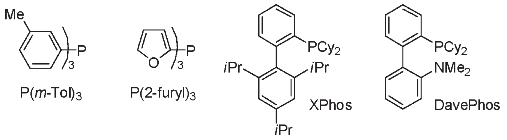
We aimed to develop a general and efficient synthetic method for the Pd-catalyzed direct C–H diarylation of EDOT and EDOT dimer **4**. We selected EDOT **1** as the core and bromobenzene **2a** as the coupling partner for the initial screening of reaction conditions (Table 1). First, the direct diarylation of EDOT **1** was carried out in the presence of $PdCl_2$ (5 mol %) following an early report's reaction condition,[3b] resulting in the diphenyl EDOT **3a** in only 5% yield (entry 1, Table 1).

Table 1. Optimization of the Direct C–H Arylation of EDOT[a]



entry	Pd catalysts[b]	ligands	additives	solvents	yield (%)[c]
1	$PdCl_2$	bipyridyl	Ag_2CO_3	xylene	5
2	$PdCl_2(PPh_3)$	bipyridyl	Ag_2CO_3	xylene	27
3	$Pd(dba)_2$	bipyridyl	Ag_2CO_3	xylene	30
4	$Pd(dba)_2$	PPh_3	Cs_2CO_3	toluene	5
5	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	toluene	88
6	$Pd(OAc)_2$	dppe	Cs_2CO_3	toluene	68
7	$Pd(OAc)_2$	dppb	Cs_2CO_3	toluene	92
8	$Pd(OAc)_2$	dppf	Cs_2CO_3	toluene	73
9	$Pd(OAc)_2$	$P(o\text{-}Tol)_3$	Cs_2CO_3	toluene	62
10	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	Cs_2CO_3	toluene	98
11	$Pd(OAc)_2$	$P(p\text{-}Tol)_3$	Cs_2CO_3	toluene	91
12	$Pd(OAc)_2$	$P(furyl)_3$	Cs_2CO_3	toluene	54
13	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	Cs_2CO_3	toluene	97
14	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$	Cs_2CO_3	toluene	48
15	$Pd(OAc)_2$	XPhos	Cs_2CO_3	toluene	47
16	$Pd(OAc)_2$	bipyridyl	Cs_2CO_3	toluene	39
17	$Pd(OAc)_2$	phenanthroline	Cs_2CO_3	toluene	20
18	$Pd(OAc)_2$	DavePhos	Cs_2CO_3	toluene	33
19	$Pd(OAc)_2$	none	Cs_2CO_3	toluene	0
20	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	K_2CO_3	toluene	79
21	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	K_2CO_3	toluene	0
22	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	Na_2CO_3	toluene	0
23	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	Na_2CO_3	toluene	0
24	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	none	toluene	0
25	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	none	toluene	0
26	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	Cs_2CO_3	xylene	96
27	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	Cs_2CO_3	DMF	97
28	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	Cs_2CO_3	DMA	97
29	$Pd(OAc)_2$	$P(m\text{-}Tol)_3$	Cs_2CO_3	dioxane	94
30	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	Cs_2CO_3	xylene	91
31	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	Cs_2CO_3	DMF	88
32	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	Cs_2CO_3	DMA	83
33	$Pd(OAc)_2$	$P(Cy)_3HBF_4$	Cs_2CO_3	dioxane	68

[a] Unless noted, the reaction was carried out with EDOT **1** (1 equiv) and bromobenzene **2a** (2.1 equiv) in the presence of Pd catalyst (5 mol %), ligand (10 mol %), base (2.4 equiv) in toluene (5 mL) at 110 °C for 24 h. [b] No desired product was obtained when the palladium catalyst was excluded from the direct arylation reaction. [c] Isolated yield.



Improved yields were observed by employing other palladium catalysts such as $PdCl_2(PPh_3)_2$ and $Pd(dba)_2$ (27% and 30%, entries 2 and 3, respectively). In addition to the selection of catalysts, we found that the reaction yields of the diarylated adduct **3a** were also significantly altered due to the use of different ligands, additives, and solvents (entries 1 and 5). These preliminary results encouraged us to search for the optimal reaction conditions for the efficient preparation of these EDOT-based molecules. We focused on $Pd(OAc)_2$ as our catalyst because it gave a promising yield (88%, entry 5). Moreover, $Pd(OAc)_2$ is air stable and less expensive. Hence, a variety of different ligands (10 mol %) were examined in the presence of $Pd(OAc)_2$ (5 mol %) and Cs_2CO_3 (2.4 equiv) in toluene at 110 °C for 24 h (entries 5 to 18). The direct C–H arylation of EDOT using the bidentate phosphine ligands afforded the product in 68–92% isolated yields (entries 6 to 8). In comparison, moderate to excellent yields were obtained when monodentate ligands (47–98%, entries 9 to 15) were used. Among these phosphine ligands, tri-*m*-tolylphosphine ($P(m\text{-}Tol)_3$) and tricyclohexylphosphine

---

(6) (a) Kumar, A.; Reynolds, J. R. *Macromolecules* **1996**, *29*, 7629. (b) Sankaran, B.; Reynolds, J. R. *Macromolecules* **1997**, *30*, 2582. (c) Irvin, D. J.; DuBois, C. J.; Reynolds, J. R. *Chem. Commun.* **1999**, 2121. (d) Gaupp, C. L.; Reynolds, J. R. *Macromolecules* **2003**, *36*, 6305. (e) Thomas, C. A.; Zong, K.; Abboud, K. A.; Steel, P. J.; Reynolds, J. R. *J. Am. Chem. Soc.* **2004**, *126*, 16440. (f) Nielsen, C. B.; Angerhofer, A.; Abboud, K. A.; Reynolds, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 9734.

(7) (a) Mohanakrishnan, A. K.; Amaladass, P.; Clement, J. A. *Tetrahedron Lett.* **2007**, *48*, 539. (b) Amaladass, P.; Clement, J. A.; Mohanakrishnan, A. K. *Tetrahedron* **2007**, *63*, 10363. (c) Borghese, A.; Geldhof, G.; Antoine, L. *Tetrahedron Lett.* **2006**, *47*, 9249.

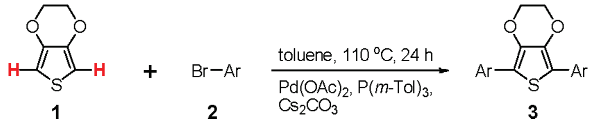
(P(Cy)$_3$•HBF$_4$) yielded **3a** in almost quantitative yields (98% and 97%, entries 10 and 13, respectively). With further screening, we found that P, N- or N, N-ligands were less efficient in the direct arylation reactions and the desired adduct **3a** was produced in only 20−39% yields (entries 16 to 18). In the absence of ligands, the Pd-catalyzed direct diarylation of EDOT did not occur at all (entry 19).

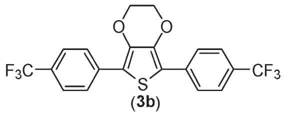
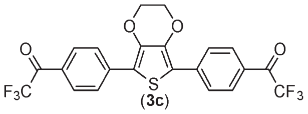
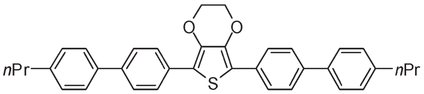
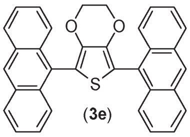
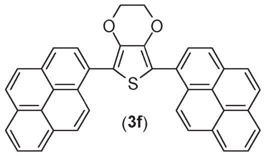
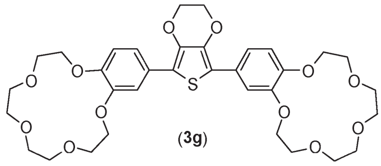
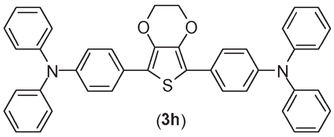
We then focused on the screening of reaction conditions using P(*m*-Tol)$_3$ and P(Cy)$_3$•HBF$_4$ as ligands. In the presence of P(*m*-Tol)$_3$ and K_2CO_3 as base instead of Cs_2CO_3, the reaction resulted in 79% of **3a** (entry 20), whereas the combination of P(Cy)$_3$•HBF$_4$ and K_2CO_3 did not afford any desired product (entry 21). Other combinations such as using Na_2CO_3 or additive-free conditions were shown to be inefficient, and the arylated adducts were not formed (entries 22 to 25). Finally, different kinds of solvents were also evaluated with both ligands. In most cases, the diphenyl EDOT **3a** was readily obtained in good to excellent yields in either nonpolar or polar solvent (68−97%, entries 26 to 33). After trying these reaction conditions, we concluded that the reaction conditions of entry 10 are optimal, and they were further employed to investigate the substrate scope of the direct C−H arylation (Table 2).

The optimized reaction conditions found in Table 1 (5 mol % Pd(OAc)$_2$, 10 mol % P(*m*-Tol)$_3$, 2.4 equiv of Cs_2CO_3 in 5 mL of toluene at 110 °C for 24 h) were subsequently applied to the facile preparation of the EDOT-based π-conjugated molecules **3b**−**3h** starting from EDOT **1** and various bromoarenes **2b**−**2h** (Table 2). Compounds **3b** and **3c** with trifluoromethyl electron-withdrawing groups at the terminal positions could be potentially useful as n-type organic field-effect transistors (OFET).[8] In general, these types of molecules were synthesized using traditional Suzuki[8a] or Stille[8b] coupling reactions; however, **3b** and **3c** were, for the first time, readily obtained through the more straightforward and atom-economical C−H arylations in good yields (77% and 83%, entries 1 and 2, respectively). A biphenyl-incorporated compound **3d** bearing the aliphatic end groups (81%, entry 3) are potentially useful to raise some interesting optoelectronic properties[9] and applied in the preparation of liquid crystals[10] or organic crystal transistors.[11]

The reaction of EDOT **1** with bromoarenes **2e** or **2f** under our optimized reaction conditions led to the formation of the desired products **3e** or **3f** in 75% and 73% yields, respectively (entries 4 and 5). These molecules represent favorable structures for organic electroluminescent devices.[12] In addition, compounds **3g** and **3h** were efficiently synthesized and isolated in good yields (83% and 78%, entries 6 and 7); interestingly, **3g** bearing the macrocyclic ether rings as end caps would be able to act as metal ion sensors,[13] and molecule **3h** is particularly of interest as a hole injection/transport layer in organic electronic devices.[14]

Table 2. Substrate Scope (Bromoarenes) of the Pd-Catalyzed Direct C−H Arylation of EDOT[a]



entry	bromoarenes	products	yield (%)[b]
1	4-bromo-benzotrifluoride (**2b**)	 (**3b**)	77
2	4′-bromo-2,2,2-trifluoro acetophenone (**2c**)	 (**3c**)	83
3	4-bromo-4′-*n*-propylbiphenyl (**2d**)	 (**3d**)	81
4	9-bromo-anthracene (**2e**)	 (**3e**)	75
5	1-bromo-pyrene (**2f**)	 (**3f**)	73
6	4′-bromobenzo-15-crown-5-ether (**2g**)	 (**3g**)	83
7	bromo-triphenylamine (**2h**)	 (**3h**)	78

[a] General reaction conditions: EDOT **1** (1 equiv), bromoarene **2** (2.1 equiv), Pd(OAc)$_2$ (5 mol %), P(*m*-Tol)$_3$ (10 mol %), Cs_2CO_3 (2.4 equiv) in toluene (5 mL) at 110 °C for 24 h. [b] Isolated yield.

The scope of the direct C−H arylation reaction was extended to the use of the EDOT dimer **4** as the core

---

[8] (a) Ando, S.; Nishida, J.; Tada, H.; Inoue, Y.; Tokito, S.; Yamashita, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5336. (b) Ie, Y.; Nitani, M.; Uemura, T.; Tominari, Y.; Takeya, J.; Honsho, Y.; Saeki, A.; Seki, S.; Aso, Y. *J. Phys. Chem. C* **2009**, *113*, 17189.

[9] Katagiri, T.; Ota, S.; Ohira, T.; Yamao, T.; Hotta, S. *J. Heterocycl. Chem.* **2007**, *44*, 853.

[10] Schubert, H.; Sagitdinov, I.; Svetkin, J. V. *Z. Chem.* **1975**, *15*, 222.

[11] Yamao, T.; Miki, T.; Akagami, H.; Nishimoto, Y.; Ota, S.; Hotta, S. *Chem. Mater.* **2007**, *19*, 3748.

[12] (a) Takata, Y.; Iwata, T. *Jpn. Kokai Tokkyo Koho* **2009**, 43. (b) Kido, J.; Osachi, Y.; Yoshizaki, M.; Omae, Y.; Yasuda, H. *Jpn. Kokai Tokkyo Koho* **2008**, 102.

[13] Kadarkaraisamy, M.; Thammavongkeo, S.; Basa, P. N.; Caple, G.; Sykes, A. G. *Org. Lett.* **2011**, *13*, 2364.

[14] (a) Lim, Y.; Park, Y.-S.; Kang, Y.; Jang, D. Y.; Kim, J. H.; Kim, J.-J.; Sellinger, A.; Yoon, D. Y. *J. Am. Chem. Soc.* **2011**, *133*, 1375. (b) Terao, K.; Shinohara, Y.; Shinohara, T. *Jpn. Tokkyo Koho* **2010**, 36.

(Scheme 2). Reaction of **4** with different bromoarenes (**2b**, **2h**, and **2i**) under the optimized reaction conditions provided the desired products **5a**–**5c** in moderate yields (53–66%). We noted that compound **5b** has been used as high-luminance organic electroluminescent devices. However, its preparation, as previously described,[15] required tedious chemical transformations by the traditional synthetic route with the generation of a large number of metal-containing side products. Besides, we speculated that the relatively lower yields of **5a**–**5c** might be due to the partial loss of the products while carrying out the reaction workup and purification because we observed that these molecules displayed poor solubility in commonly used organic solvents.[16]

Scheme 2. Synthesis of EDOT Dimer-Based π-Conjugated Molecules

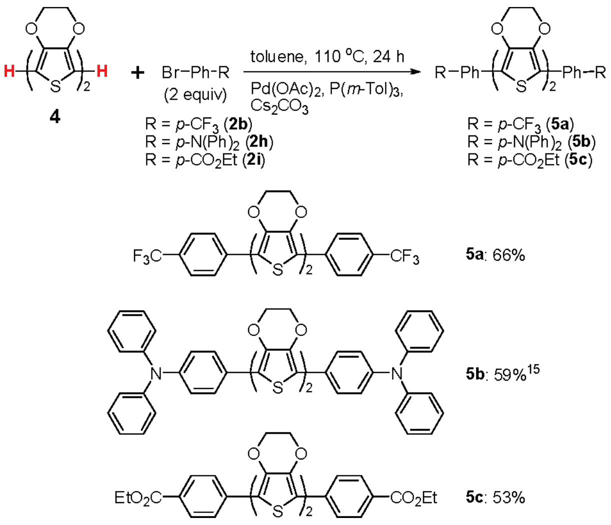


Table 3. Spectroscopic and Electrochemical Properties of the EDOT (**3a**–**h**)- and Bis-EDOT (**5a**–**c**)-Based Molecules

compd	λ_{max} (abs)[a] [nm]	λ_{max} (em)[b] [nm]	$E_{1/2}$ [V][c]
3a	345	380, 399	0.72
3b	353	390, 409	0.97
3c	428	469	−1.71, 1.08
3d	374	422, 447	0.54, 1.04
3e	372, 393	460	0.41
3f	380	470	0.38, 0.63
3g	357	401, 422	0.30
3h	399	449	0.13, 0.30, 1.06
5a	408, 431	454	0.35, 0.90
5b	430	482, 518	−0.03, 0.15, 0.89
5c	427, 452	481, 514	0.34, 0.72

[a] abs = UV–vis absorption (measured in CH_2Cl_2 solution). [b] em = fluorescence emission (measured in CH_2Cl_2 solution). [c] Potential/V vs Fc^+/Fc.

We also examined the spectroscopic and electrochemical characteristics of the synthesized EDOT-based π-conjugated molecules, and the results are summarized in Table 3. All compounds displayed certain color with the absorption peak in the visible range due to the extended conjugation from diarylation, allowing delocalization of π-electrons. When the core EDOT was replaced by the EDOT dimer (from **3b** to **5a** and from **3h** to **5b**), the effect of the longer conjugation length was clearly observed. The main absorption and fluorescence peak in optical measurement shifted to a longer wavelength. The half-wave potential ($E_{1/2}$) was also reduced by 0.07–0.17 V. It was also noted that a film was formed onto the electrodes during the cyclic voltammetric measurements of **3h** and **5b**, indicating that these compounds may undergo electropolymerization and deposit on the surface.[17]

In summary, we have demonstrated a general and atom-economical approach for the syntheses of EDOT-based π-conjugated molecules through Pd-catalyzed direct C–H bond arylations. The optimized reaction conditions obtained after the comprehensive synthetic investigations allow the facile preparation of a variety of functional π-conjugated EDOT- or EDOT-dimer-containing oligoarenes, which are of pronounced importance in materials science. Ongoing studies using this efficient synthetic strategy are focused on the examinations of substrate scope and further applications in organic electronics.

Acknowledgment. This work was supported by the RIKEN Advanced Science Institute and a Grant-in-Aid for Young Scientists (Nos. 22681016 and 23700565) from JSPS/MEXT, Japan. We thank Dr. Takashi Otani, Dr. Liangchun Li, Dr. Tsukasa Matsuo, and Dr. Kohei Tamao (RIKEN Advanced Science Institute) for their help on the spectroscopic measurements. We also thank Prof. Kenichiro Itami (Nagoya University) for useful discussions.

Supporting Information Available. Experimental procedures and full characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(15) Synthesis and applications of molecule **5b** have been previously reported: Seki, M.; Agata, T.; Hirose, E.; Horiba, K.; Imai, A.; Ozaki, T.; Nishino, Y.; Yoneyama, H.; Okuda, D.; Ishii, T.; Mashimo, K.; Sato, K. *Jpn. Kokai Tokkyo Koho* **2008**, 67.

(16) Compounds **5a**–**5c** are almost insoluble in ether, ethyl acetate, chloroform, acetone, benzene, THF, and DMSO. Slightly better solubility was observed in dichloromethane.

(17) (a) Chiang, C. C.; Chen, H. C.; Lee, C. S.; Leung, M. K.; Lin, K. R.; Hsieh, K. H. *Chem. Mater.* **2008**, *20*, 540. (b) Chang, C. C.; Leung, M. K *Chem. Mater.* **2008**, *20*, 5816.

(18) **Typical Procedure: Preparation of Molecule 3h.** To a solution of $Pd(OAc)_2$ (12 mg, 5 mol %), P(*m*-Typical Procedure: Preparation of MoleculTol)$_3$ (31 mg, 10 mol %), and Cs_2CO_3 (782 mg, 2.4 mmol) in toluene (5 mL) in a flame-dried Schlenk tube (20 mL) were added EDOT **1** (142 mg, 1.0 mmol) and bromotriphenylamine **2h** (680 mg, 2.1 mmol) under N_2. The reaction mixture was then heated at 110 °C under N_2 for 24 h. After the reaction mixture had cooled to room temperature, water (10 mL) was added. The mixture was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by reprecipitation from a mixture of dichloromethane and hexane gave the desired product **3h** (489 mg, 78%) as a yellow solid; mp: 279–281 °C.