Composite Tetraheteroarylenes and Related Higher Cyclic Oligomers of Heteroarenes Produced by Palladium-Catalyzed Direct Coupling

Keita Fukuzumi,[1] Yuji Nishii,*[2] and Masahiro Miura*[1]

[1] Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871

[2] Frontier Research Base for Global Young Researchers, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871

y_nishii@chem.eng.osaka-u.ac.jp, miura@chem.eng.osaka-u.ac.jp

Yuji Nishii

Yuji Nishii is an assistant professor of the Graduate School of Engineering, Osaka University. He received his Ph.D. degree from Osaka University in 2015 under the guidance of Prof. K. Mashima. He then assumed the current position. He is a member of Otsu Academy Award Fellow. His current research interests are focusing on the organic synthetic chemistry utilizing organo- and transition metal-catalyses, involving direct functionalization of aromatic compounds. He worked as a visiting researcher with Prof. P. Knochel at Ludwig-Maximilians-Universität München in 2011, and with Prof. T. Agapie at California Institute of Technology in 2014.

Masahiro Miura

Masahiro Miura is a professor of the Graduate School of Engineering, Osaka University. He received his Ph.D. degree from Osaka University in 1983 under the guidance of Prof. S. Kusabayashi and Prof. M. Nojima. He started his academic career as assistant professor at Osaka University in 1984. He was promoted to associate professor in 1994 and to full professor in 2005. He also worked as a Humboldt fellow with Prof. K. Griesbaum at Karlsruhe University of Germany in 1990–1991. His current research interests include transition-metal catalysis and the synthesis of functional molecules, especially new π-conjugated aromatic substances. He received the CSJ award for Creative work for 2012.

Abstract

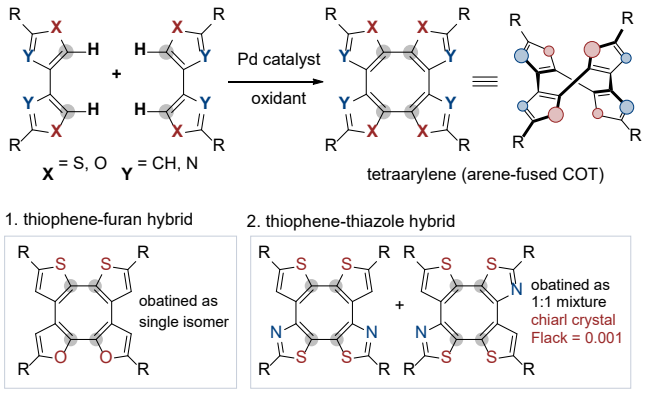
Substantial research interests have been focused on cyclic π-conjugated molecules owing to their unique chemical and physical properties. By constructing hybrid aromatic arrays within these cyclic systems, new series of composite macrocycles would be provided. Our group has been studying the construction of such hybrids by adopting the palladium-catalyzed direct coupling of heteroaromatics. We herein report the synthesis and characterization of thiophene-thiazole composite macrocycles. X-ray diffraction analyses elucidated that some of these coupling products exhibit characteristic helical assemblies in the solid state. Additionally, we synthesized a heteroarene-fused cyclooctatetraene composed of four different heteroaryl fragments.

Keywords: Palladium, Macrocycles, Cross-coupling

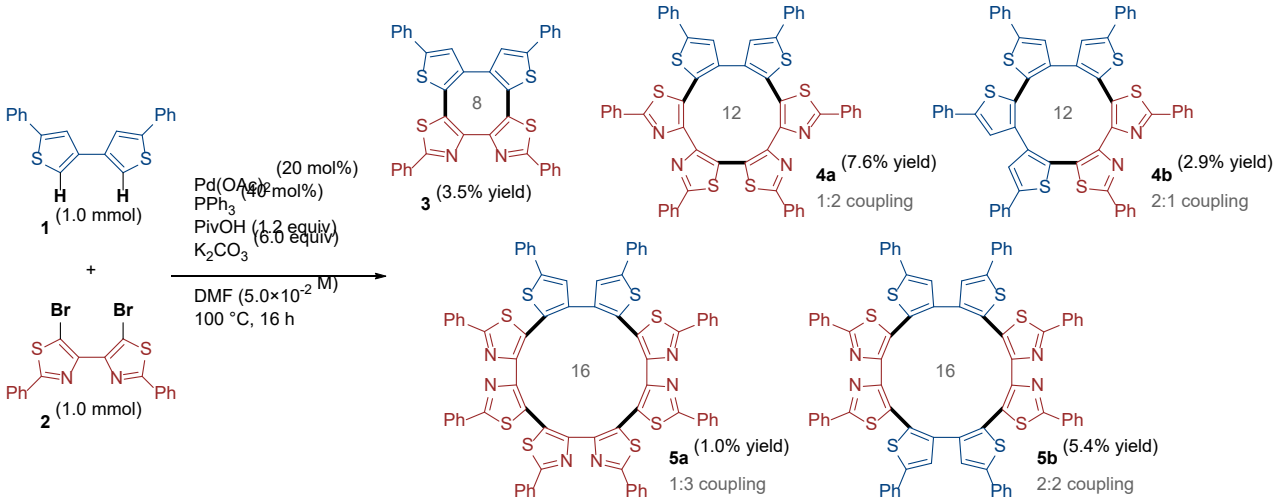
1. Introduction

The construction of cyclic π-conjugated oligomers of arenes has been an intriguing research topic because of their unusual optical, electronic, magnetic, and molecular inclusion properties as contrasted to the parent linear aromatics.[1] Among these macrocycles, tetraarylenes are the smallest class of compounds in which four aromatic fragments are *ortho*-linked each other to establish an arene-fused cyclooctatetraene (COT) core at the center of the molecules. Considerable attention has been paid to these compounds over the decades owing to their unique characteristics involving chirality, conformational flexibility, and redox-active nature of the central ring.[2,3] Notably, a series of arene-fused COTs have been of key motifs for investigating the antiaromaticity[4,5] and the Baird aromaticity.[6]

Meanwhile, construction of hybrid aromatic arrays within such macrocyclic scaffolds would provide a wide variety of novel π-conjugated systems. For example, Sessler, Kim, and Bucher reported an electrochemical synthesis of a novel thiophene-containing cyclo[9]pyrrole as a 34π-electron aromatic expanded porphyrin.[7] Tanaka and Osuka also described a thiophene-pyrrol hybrid macrocycle as a precursor for an aza[8]circulene.[8] The synthesis of these "composite" molecules, however, has been a significant challenge, and thus, their low availability has obstructed the systematic study on their properties. Our group recently reported a Pd-catalyzed synthesis of heteroarene-fused COTs through the dehydrogenative cyclodimerization of biheteroaryls (Scheme 1).[9,10,11] Additionally, the first synthesis and characterization of composite tetraheteroarylenes from unsymmetrical biheteroaryls were achieved. It was worth noting that a thiophene-thiazole hybrid tetraarylene provided chiral crystals via the spontaneous resolution, which was evidenced by a Flack parameter[12] of 0.001(7) in the X-ray crystallographic analysis; however, this compound was only obtained as an inseparable mixture of two regioisomers under the C–H/C–H coupling protocol.



Scheme 1. Tetraarylene synthesis through the Pd-catalyzed dehydrogenative cyclodimerization of biaryls.



Scheme 2. Palladium-catalyzed direct C–H coupling for the synthesis of a composite tetraheteroarylene and related higher heteroarylenes.

To address this issue, we have undertaken the construction of hybrid cyclic skeletons through the Pd-catalyzed C–H/C–Br direct coupling method.[13] In this report, we describe the synthesis and characterization of a series of thiophene-thiazole hybrid macrocyclic compounds. Single crystal X-ray analyses revealed that the created coupling products form characteristic helical assemblies, and among them, the new COT specifically affords chiral crystals. In addition, we have achieved the first synthesis of a tetraarylene which is composed of four different heteroaryl fragments.

2. Results and Discussion

Our study was initiated with the preparation of a thiophene-thiazole composite tetraarylene **3** through the palladium-catalyzed direct coupling of a bithiophene **1** with a dibromo-bithiazole **2**. After screening various reaction parameters, the target compound **3** was found to form up to 6% yield in the presence of $Pd(OAc)_2$, PPh_3, PivOH, and K_2CO_3 in DMF. However, further improvement of the productivity of this compound was difficult because the competing formation of higher cyclic/acyclic oligomers accounted for the majority of the reaction mixture. The higher cyclic oligomers, however, seemed to be invaluable compounds which should be characterized. Thus, we carried out the reaction at a preparative scale and isolated a series of cyclized products using size-exclusion chromatography (Scheme 2). The tetraarylene **3** was given in 3.5% yield. As the 12-membered ring compounds, a 1:2 coupling product **4a** and a 2:1 coupling product **4b** were obtained in 7.6% yield and 2.9% yield, respectively. In addition, 16-membered ring compounds **5a** (1:3 coupling product) and **5b** (2:2 coupling product) could be isolated. The connectivity of **5b**, in which bithiophene and bithiazole fragments are alternately coupled, was confirmed by the highly symmetric signals observed in its NMR measurements, showing only one ^{1}H signal for the thiophene C–H. The structures of **3**, **4a**, and **5a** were unambiguously determined by X-ray crystallographic analyses (Figure 1 and 2). The formation of these cyclic compounds implies that not only thiophene-thiazole (C-H/C-Br) coupling, but also thiophene-thiophene (C-H/C-H) oxidative coupling and thiazole-thiazole (C-Br/C-Br) reductive coupling, possibly via disproportionation or protodebromination, occur under the palladium-catalyzed conditions.

The compound **3** has a tab-shape structure with a bent angle θ[5a] (Chart 1) of 31.2–33.4 degrees in the COT ring. Fascinatingly, the crystal was classified into a space group $P2_1$ (monoclinic), and its absolute configuration was estimated by a Flack parameter of 0.04(2). The chirality was derived from the helical assembly along the a-axis underpinned by two characteristic C–H···N hydrogen bonding interactions (ca. 2.6 Å) between the thiophene and thiazole fragments (Figure 1c). This result contrasts with the fact that each of other tetraarylenes crystallizes into a "Pringles-like" columnar (or slipped columnar) packing structure.[3i,3j] This is probably because the hydrogen bonding interaction is much stronger than the π–π stacking interaction between electronically non-biased aromatic systems.

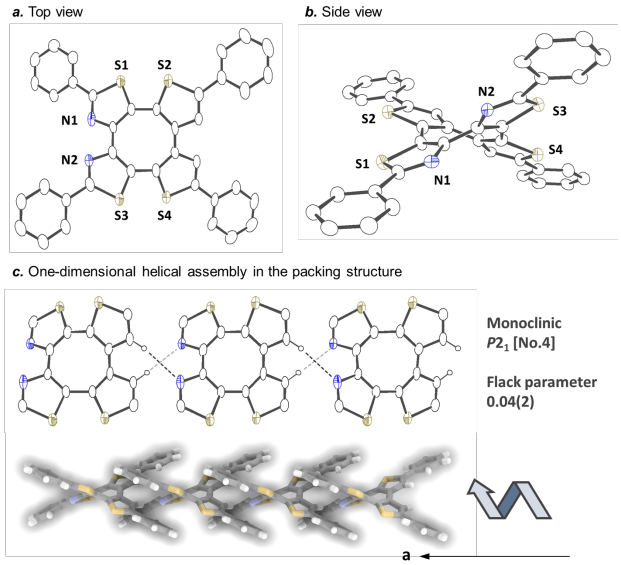


Figure 1. (a,b) Molecular structure of **3** drawn with 40% thermal probability ellipsoids. Hydrogen atoms and solvent molecules are omitted for clarity. (c) Helical pattern in the crystal structure.

Chart 1. Bent angle for the COT skeleton.

On the other hand, no significant C–H···N interaction was found in the structure of **4a** (Figure 2a and 2b). The central 12-membered ring was twisted and folded as an infinity symbol, which is structurally relevant to a previously reported hexa[2,3-thienylene] macrocycle.[14] The compound **5a** exhibited an intramolecular stacking association in between two opposite bithiazole units, and its distance was approximately 3.14–3.15 Å (Figure 2c and 2d). Although the proper location of the bithiophene unit in the structure of **5a** was not feasibly determined by the crystallographic analysis, it should be placed at the edge of the molecule since the crystals of **5a** displayed one-dimensional helical assembly as similar to that found in the structure of **3**. However, **5a** afforded achiral crystals which contain both the right-handed and left-handed helical patterns with a space group *Pba*2 (orthorhombic).

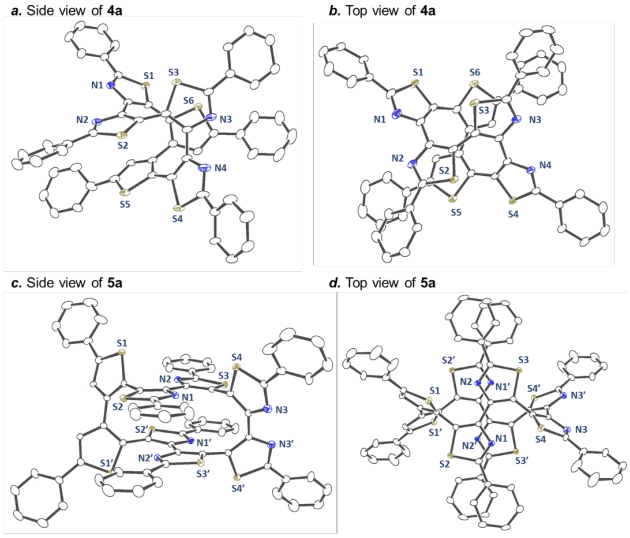


Figure 2. Molecular structure of **4a** (a,b) and **5a** (c,d) drawn with 20% thermal probability ellipsoids. Hydrogen atoms and solvent molecules are omitted for clarity.

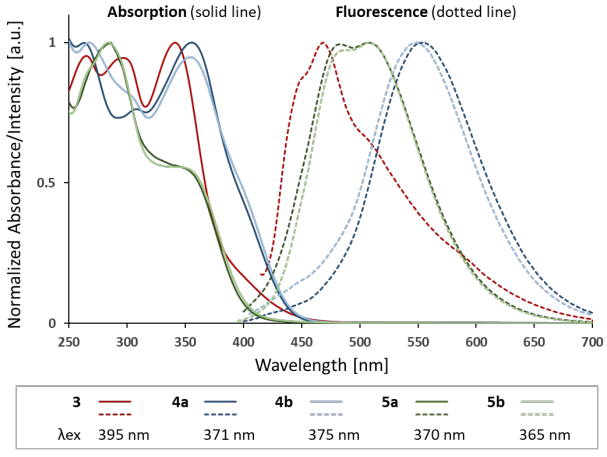
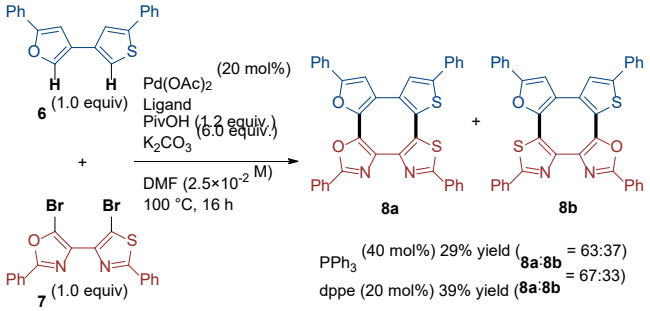


Figure 3. UV-vis absorption and emission spectra of **3** (red), **4a** (blue), **4b** (light blue), **5a** (green), and **5b** (light green) in $CHCl_3$ (5.0×10^{-6} mol/L).

The UV-vis spectra of the cyclic coupling products **3**–**5** were measured for $CHCl_3$ solutions (Figure 3). All of these compounds also exhibited fluorescence in visible region with emission maxima at 460–560 nm, albeit the internal quantum efficiencies were low (Φ = 0.02–0.03). It was obvious that the spectral shapes were primarily influenced by the numbers of arylene units within the central rings, and the thiophene/thiazole compositional ratio had a minimal impact on their optical properties. Substantial bathochromic shifts both in the absorption and fluorescence bands were found for the 12-membered ring compounds **4** as compared to the other cyclo-oligomers. This indicates the relatively high conformational flexibility of **4** which ensures a longer effective conjugation length. In accordance with these observations, ^{1}H NMR spectra of **4a** and **4b** showed two and three nonequivalent thiophene C–H peaks, respectively, probably due to the conformational isomerism. The ratio of these signals were reversibly shifted in valuable-temperature (VT-NMR) measurements (see the Supporting Information). In contrast, quasi-bimodal emission bands were found around 500 nm in the fluorescence spectra of **5** even though these compounds have the largest ring size among the obtained coupling products, suggesting the higher conformational rigidity of these macrocycles.

Finally, we challenged ourselves to synthesize a tetraarylene composed of four different arylene fragments (Scheme 3). Two unsymmetrical biaryls **6** and **7** were prepared as coupling partners, and these were subjected to the standard reaction conditions. To our delight, the desired compound **8** was obtained as a mixture of regioisomers (**8a**:**8b** = 63:37) in 29% combined yield. Replacement of the ligand by 1,2-bis(diphenylphosphino)ethane (dppe) improved both the yield and the selectivity (39%, **8a**:**8b** = 67:33). Interestingly, the competing formation of higher oligomers were fairly retarded in these reactions while the clear explanation for this has not been in hand.[15] After numerous attempts, the major isomer **8a** was successfully isolated by recrystallization, and its structure was confirmed by single-crystal X-ray diffraction analysis. This represents the first synthesis and characterization of tetraarylene with all different aryl subunits.



Scheme 3. Tetraarylene synthesis through the palladium-catalyzed direct C–H coupling.

The positions of two sulfur atoms in **8a** can be explicitly assigned as illustrated in Figure 4, whose structure and unit cell parameters are similar to those of **3**. Bent angles of the COT moiety ranges within 27.3–31.7 degrees, and the largest angle was given to the thiophen unit. This can be attributed to the C–H/C–H as well as S/S repulsive interactions against the adjacent furan and thiazole fragments. The crystal exhibited helical packing pattern along the a-axis as expected; however, the structure was refined as a two-component inversion twin with a Flack parameter of 0.44(7).

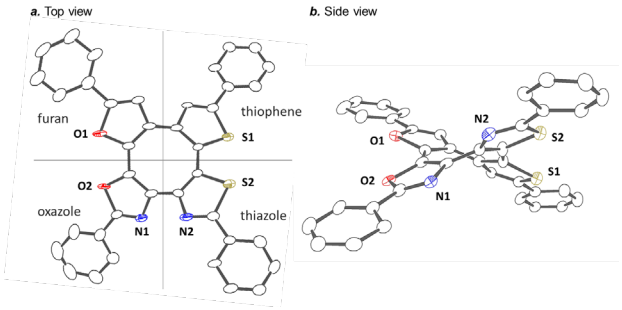


Figure 4. Molecular structure of **8a** drawn with 15% thermal probability ellipsoids. Hydrogen atoms and solvent molecules are omitted for clarity.

3. Conclusion

In summary, as demonstrated in this study, the palladium-catalyzed direct coupling reaction can be a convenient method for the generation of composite heteroarene-fused COTs and higher macrocyclic homologs. Although we should admit that the productivity and generality of the present protocol need to be improved, it has unveiled unique characteristics of these compounds forming helical assemblies and chiral crystals. Further studies on the chiroptical properties of the composite heteroarylenes is in underway.

4. Experimental

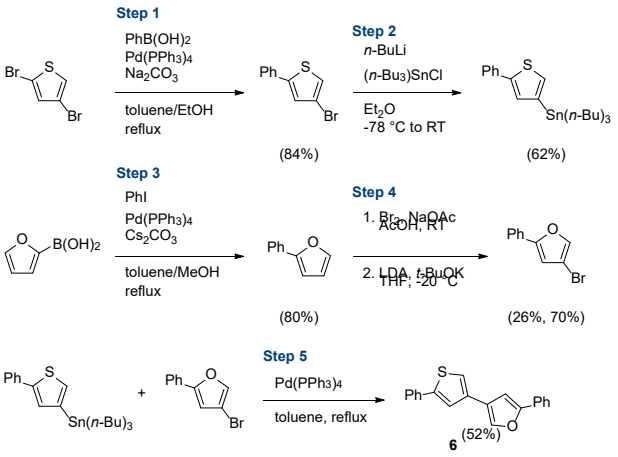
General information

All manipulations were performed under N_2 using standard Schlenk techniques unless otherwise noted. Toluene, DMF, and Et_2O were dried and deoxygenated by a Glass Counter Solvent Dispending System (Nikko Hansen & Co., Ltd.). DCM was degassed with N_2 bubbling and dried over molecular sieves 4A. THF and MeOH were purchased as dehydrated solvent and used as received. Silica gel column chromatography was performed using Wakosil® C-200. Nuclear magnetic resonance spectra were measured at 400 MHz (^{1}H NMR) and at 100 MHz (^{13}C NMR) in 5 mm NMR tubes. ^{1}H NMR chemical shifts were reported in ppm relative to the resonance of TMS (δ 0.00) or the residual solvent signals at δ 7.26 for $CDCl_3$ and at δ 5.32 for CD_2Cl_2. ^{13}C NMR chemical shifts were reported in ppm relative to the residual solvent signals at δ 77.2 for $CDCl_3$. Melting points were measured with Mettler Toledo MP90. High resolution mass spectra (HRMS) were recorded by FAB or APCI-TOF. HPLC analyses were carried out with JASCO EXTREMA (PU-4180/MD4015/CO4065) equipped with an YMC CHIRAL ART Cellulose-SB column at 350 nm detection. GC-MS spectra were recorded on Shimadzu GCMS-QP2010 SE with a CBP-1 column (0.5 mm × 25 m). Preparative gel permeation chromatography (GPC) was conducted with Showa Denko H-2001, H-2002 column (eluent: $CHCl_3$) or YMC T2000 (eluent: EtOAc) column. Absorption spectra were recorded on JASCO V-750 spectrometer. Fluorescence and excitation spectra were recorded on JASCO FP8500 spectrometer. Quantum efficiency was determined using JASCO FP8500 spectrometer equipped with an integration sphere system JASCO ILF-835.

5,5'-dibromo-2,2'-diphenyl-4,4'-bithiazole (2)

A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 2,2'-diphenyl-4,4'-bithiazole (641 mg, 2.0 mmol), NBS (730 mg, 4.1 mmol). DCM (10 mL) was added via syringe, and the mixture was stirred at room temperature overnight. The resulting suspension was diluted with Na_2CO_3aq and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane) to give **2** in 73% yield (698 mg, 1.46 mmol). NMR data was identical with that reported in the literature.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.47 (m, 6H), 7.93-7.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 126.6, 129.2, 130.8, 133.1, 147.5, 167.9.

2-phenyl-4-(5-phenylthiophen-3-yl)furan (6)



[Step 1] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 2,4-dibromothiophene (2.42 g, 10 mmol), phenylboronic acid (1.22 g, 10 mmol), $Pd(PPh_3)_4$ (231 mg, 2.0 mol%), and Na_2CO_3 (1.06 g, 10 mmol). Toluene (20 mL) and ethanol (4 mL) were added via syringe, and the mixture was refluxed overnight. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane) to give 4-bromo-2-phenylthiophene as white solid in 84% yield (2.00 g, 8.4 mmol). NMR data was identical with that reported in the literature.[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 1.4 Hz, 1H), 7.21 (d, J = 1.4 Hz, 1H), 7.30-7.35 (m, 1H), 7.37-7.42 (m, 2H), 7.54-7.58 (m, 2H).

[Step 2] Synthesized according to the literature procedure.[18] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 4-bromo-2-phenylthiophene (1.28 g, 5.38 mmol) and Et_2O (10 mL). To a solution was added *n*-BuLi (1.6 mol/L in hexane, 5.91 mmol) dropwise at -78 °C. The mixture was stirred for 30 min at this temperature, followed by the slow addition of tributyltin chloride (3.8 mL, 5.91 mmol). The resulting solution was allowed to warm to room temperature, and stirred for an additional 2 h. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layers was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel (containing ca. 10wt% K_2CO_3) chromatography (eluent: hexane) to give 2-phenyl-4-(tributylstannyl)thiophene in 62% yield (1.50 g, 3.34 mmol). colorless oil; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 0.88-0.93 (t, J = 7.3 Hz, 9H), 1.07-1.12 (m, 6H), 1.30-1.40 (m, 6H), 1.53-1.61 (m, 6H), 7.24-7.30 (m, 2H), 7.33-7.40 (m, 3H), 7.60-7.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 13.8, 27.4, 29.2, 126.4 (2C), 127.3, 129.0 (2C), 129.5, 131.4, 134.8, 140.1, 144.7; HRMS (FAB$^+$) *m/z* calcd for $C_{22}H_{35}SSn$ $[M+H]^+$ 451.1478, found 451.1478.

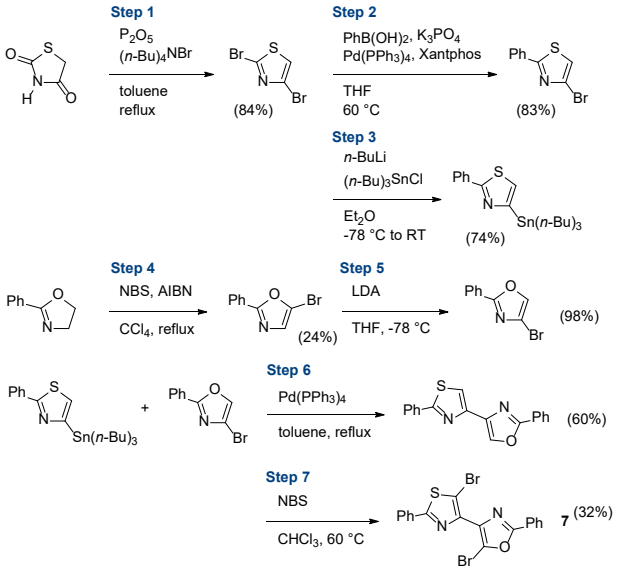
[Step 3] Synthesized according to the literature procedure.[19] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 2-furylboronic acid (1.00 g, 8.93 mmol), iodobenzene (696 mg, 4.47 mmol), $Pd(PPh_3)_4$ (514 mg, 10 mol%), and Cs_2CO_3 (1551 mg, 4.76 mmol). Toluene (10 mL) and methanol (2.5 mL) were added via

syringe, and the mixture was refluxed overnight. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane) to give 2-phenylfuran as pale yellow oil in 80% yield (514 mg, 3.57 mmol). NMR data was identical with that reported in the literature.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, J = 1.8, 3.3 Hz, 1H), 6.64-6.67 (m, 1H), 7.23-7.29 (m, 1H, overlapped with $CDCl_3$), 7.35-7.42 (m, 2H), 7.45-7.50 (m, 1H), 7.65-7.71 (m, 2H).

A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with diisopropylamine (0.26 ml, 1.8 mmol), *t*-BuOK (202 mg, 1.8 mmol), and THF (5 mL). To a solution was added *n*-BuLi (1.6 mol/L in hexane, 1.71 mmol) dropwise at -78 °C, and the mixture was stirred for 30 min. A solution of 5-bromo2-phenylfuran (254 mg, 1.14 mmol) in THF (10 mL) was added dropwise, and the temperature was slowly brought up to -20 °C. After stirring for 2 h at this temperature, the resulting mixture was diluted with H_2O (10 mL) and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane) to give 4-bromo-2-phenylfuran as white solid in 70% yield (176 mg, 0.80 mmol). NMR data was identical with that reported in the literature.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (m, 1H), 7.27-7.33 (m, 1H, overlapped with $CDCl_3$), 7.37-7.42 (m, 2H), 7.46 (m, 1H), 7.60-7.65 (m, 2H).

[Step 5] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 2-phenyl-4-(tributylstannyl)thiophene (356 mg, 0.80 mmol), 4-bromo-2-phenylfuran (176 mg, 0.80 mmol), $Pd(PPh_3)_4$ (45.6 mg, 5 mol%). Toluene (5 mL) was added via syringe, and the mixture was heated at 100 °C for 16 h. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane) and further purification was carried out with GPC (EtOAc) to give **6** in 52% yield (125 mg, 0.42 mmol). NMR data was identical with that reported in the literature.[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 7.27 (d, J = 1.3 Hz, 1H), 7.28-7.34 (m, 2H), 7.38-7.44 (m, 4H), 7.45 (d, J = 1.3 Hz, 1H), 7.62-7.68 (m, 2H), 7.68-7.74 (m, 3H).

5-bromo-4-(5-bromo-2-phenylthiazol-4-yl)-2-phenyloxazole (7)



[Step 1] Synthesized according to the literature procedure.[22] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 1,3-thiazolidine-2,4-dione (834 mg, 7.12 mmol), P_2O_5 (4.78 g, 33.7 mmol), and tetrabutyl-ammonium bromide (5.32 g, 16.5 mmol). Toluene (16 mL) was added via syringe, and the mixture was refluxed overnight. The resulting suspension was diluted with Na_2CO_3aq and was extracted with Et_2O three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 3/1) to give 2,4-dibromothiazole as white solid in 84% yield (1.45 g, 5.97 mmol). NMR data was identical with that reported in the literature.[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H).

[Step 2] Synthesized according to the literature procedure.[23] $Pd(OAc)_2$ (49.8 mg, 2.5 mol%) and Xantphos (129 mg, 2.5 mol%) were dissolved in THF (10 mL) under an N_2 atmosphere. After stirring for 5 min at room temperature, this solution was transferred to a two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap containing 2,4-dibromothiazole (2.16 g, 8.88 mmol), phenylboronic acid (1.16 g, 9.5 mmol), K_3PO_4 (5.66 g, 26.6 mmol), and THF (20 mL). The mixture was heated at 60 °C overnight. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 10/1) to give 4-bromo-2-phenylthiazole as white solid in 83% yield (1.76 g, 7.33 mmol). NMR data was identical with that reported in the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.42-7.47 (m, 3H), 7.91-9.97 (m, 2H).

[Step 3] Synthesized according to the literature procedure.[24] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 4-bromo-2-phenylthiazole (717 mg, 3.0 mmol) and Et_2O (20 mL). To a solution was added *n*-BuLi (1.6 mol/L in hexane, 3.6 mmol) dropwise at -78 °C, and the mixture was stirred at -50 °C for 30 min. Then the reaction mixture was cooled again to -78 °C, followed by the slow addition of tributyltin chloride (1.1 mL, 4.1 mmol). After stirring for 10 min, the resulting solution was allowed to warm to room temperature and stirred for an additional 1 h. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel (containing ca. 10wt% K_2CO_3) chromatography (eluent: hexane/EtOAc = 9/1) to give 2-phenyl-4-(tributylstannyl)thiazole as pale yellow oil in 74% yield (1.00 g, 2.22 mmol). NMR data was identical with that reported in the literature.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72-1.73 (m, 27H), 7.32 (s, 1H), 7.38-7.46 (m, 3H), 7.98-8.03 (m, 2H).

[Step 4] Synthesized according to the literature procedure.[26] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 2-phenyl-4,5-dihydrooxazole (1.47 g, 10 mmol), NBS (5.35 g, 30 mmol), and AIBN (82 mg, 5.0 mol%). CCl_4 (20 mL) was added via syringe, and the mixture was refluxed overnight. The resulting mixture was filtered through a pad of Celite eluting with EtOAc, and the filtrate was washed with saturated $Na_2S_2O_3$aq. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 5/1) to give 5-bromo-2-phenyloxazole as brown solid in 24% yield (540 mg, 2.4 mmol). NMR data was identical with that reported in the literature.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 1H), 7.44-7.50 (m, 3H), 7.97-8.03 (m, 2H).

[Step 5] Synthesized according to the literature procedure.[25] A two-neck round-bottom flask equipped with an

N_2 balloon and a rubber cap was charged with 5-bromo-2-phenyloxazole (540 mg, 2.4 mmol) and THF (10 mL). To a solution was added freshly-prepared LDA (3.63 mmol in 5 mL THF) dropwise at -78 °C, and the mixture was stirred for 2 h at this temperature. The reaction was quenched with H_2O (10 mL), and the resulting suspension was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 20/1) to give 4-bromo-2-phenyloxazole as white solid in 98% yield 530 mg, 2.37 mmol). NMR data was identical with that reported in the literature.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.51 (m, 3H), 7.69 (s, 1H), 7.99-8.06 (m, 2H).

[Step 6] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with 2-phenyl-4-(tributylstannyl)thiazole (1.00 g, 2.22 mmol), 4-bromo-2-phenyloxazole (530 mg, 2.37 mmol), and $Pd(PPh_3)_4$ (128 mg, 5.0 mol%). Toluene (10 mL) was added via syringe, and the mixture was heated at 100 °C for 16 h. The resulting suspension was diluted with H_2O and was extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 5/1) to give the target compound as white solid in 60% yield (400 mg, 1.32 mmol). mp 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.52 (m, 6H), 7.76 (s, 1H), 8.00-8.05 (m, 2H), 8.12-8.16 (m, 2H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.7, 126.8 (2C), 126.8 (2C), 127.5, 128.9 (2C), 129.1 (2C), 130.4, 130.7, 133.6, 135.6, 138.1, 148.7, 162.1, 168.8; HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{13}N_2OS$ $[M+H]^+$ 305.0743, found 305.0752.

[Step 7] A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with thiazole-oxazole biaryl (304 mg, 1.0 mmol), NBS (712 mg, 4.0 mmol). $CHCl_3$ (10 mL) was added via syringe, and the mixture was heated at 60 °C overnight. The resulting suspension was diluted with H_2O and was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 5/1) and further purification was carried out with GPC ($CHCl_3$) to give **7** as white solid in 32% yield (150 mg, 0.32 mmol). mp 188-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.52 (m, 6H), 7.92-7.98 (m, 2H), 8.08-8.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.7, 121.2, 126.6 (4C), 126.6, 129.0 (2C), 129.2 (2C), 130.8, 131.1, 133.0, 134.2, 144.5, 162.5, 168.3; HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{11}N_2OSBr_2$ $[M+H]^+$ 462.8933, found 462.8929.

Pd-catalyzed direct coupling of 1 with 2 (Scheme 2)

A two-neck round-bottom flask equipped with an N_2 balloon and a rubber cap was charged with **1** (318 mg, 1.0 mmol), **2** (476 mg, 1.0 mmol), $Pd(OAc)_2$ (46 mg, 20 mol%), PPh_3 (104 mg, 40 mol%), PivOH (112 mg, 1.2 mmol), and K_2CO_3 (830 mg, 6.0 mmol). DMF (20 mL) was added via syringe, and the mixture was heated at 100 °C for 16 h. The resulting suspension was diluted with H_2O and was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to short-pad silica gel chromatography (eluent: hexane/EtOAc = 3/1) and GPC ($CHCl_3$) to roughly separate the products by the molecular sizes. Further purification was carried out as described below.

Isolation of 3

Analytically pure compound **3** was obtained by washing the crude material with EtOAc (22.0 mg, 3.5% yield). Single crystals suitable for X-ray analysis were obtained from $CHCl_3$ solution layered with hexane. orange solid, mp >300 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 2H), 7.31-7.36 (m, 2H), 7.38-7.46 (m, 10H), 7.57-7.63 (m, 4H), 7.97-8.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.6, 125.9, 126.9, 128.2, 128.5, 129.0, 129.2, 129.7, 130.6, 133.3, 133.5, 138.3, 147.2, 148.3, 169.4; HRMS (APCI$^+$) *m/z* calcd for $C_{38}H_{23}N_2S_4$ [M+H] 635.0739, found 635.0744.

Isolation of 4a and 4b

The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 3/1) to give **4a** (36.2 mg, 7.6% yield) and **4b** (13.8 mg, 2.9% yield). Single crystals of **4a** suitable for X-ray analysis were obtained from DCM solution layered with hexane.

Note: All ^{13}C NMR data were reported as appeared in the spectra. ^{1}H NMR data of **4a** and **4b** were reported as appeared in the spectra because they showed complicated signals due to the conformational isomerism. VT-NMR (variable temperature) measurements of **4** displayed a reversible spectral change (see the Supporting Information).

4a: yellow solid, mp >300 °C; ^{1}H NMR (400 MHz, CD_2Cl_2, -60 °C) δ 6.81-6.93 (m, 4H), 7.12-7.16 (m, 3H), 7.20-7.52 (m, 19H), 7.62-7.67 (m, 3H), 7.98-8.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.8, 124.6, 125.5, 125.5, 125.7, 126.0, 126.3, 126.4, 126.7, 127.1, 127.2, 127.2, 127.4, 127.7, 127.8, 128.1, 128.2, 128.3, 128.6, 128.7, 128.7, 128.8, 129.0, 129.2. 130.1, 130.2, 130.3, 130.4, 130.6, 130.7, 131.2, 133.0, 133.1, 133.2, 133.2, 133.3, 133.4, 133.4, 133.5, 133.5, 133.6, 135.2, 138.3, 144.0, 144.5, 144.6, 145.0, 146.0, 146.4, 147.2, 148.7, 149.6, 166.7, 167.0, 167.2, 167.8, 168.4, 168.9; HRMS (APCI$^+$) *m/z* calcd for $C_{56}H_{33}N_4S_6$ $[M+H]^+$ 953.1024, found 953.1029.

4b: yellow solid, mp >300 °C, ^{1}H NMR (400 MHz, CD_2Cl_2, -60 °C) δ 6.81 (s, 1H), 6.81-7.00 (m, 4H), 7.12-7.50 (m, 24H), 7.64-7.70 (m, 4H), 8.00-8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.4, 124.8, 125.6, 125.7, 125.8, 125.9, 126.0, 126.2, 126.2, 126.3, 126.4, 126.4, 127.1, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.2, 128.6, 128.7, 128.8, 128.9, 128.9, 129.0, 129.0, 129.2, 129.2, 130.0, 130.1, 130.5, 130.9, 131.1, 132.4, 132.7, 133.3, 133.5, 133.6, 133.7, 133.7, 133.7, 133.8, 133.9, 134.1, 134.3, 135.7, 137.0, 138.1, 143.6, 143.8, 144.4, 144.7, 146.0, 146.7, 148.6, 166.4, 167.1, 167.9; HRMS (APCI$^+$) *m/z* calcd for $C_{58}H_{35}N_2S_6$ $[M+H]^+$ 951.1119, found 951.1123.

Isolation of 5a and 5b

The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 3/1) to give **5a** (4.1 mg, 1.0% yield) and **5b** (34.4 mg, 5.4% yield). Single crystals suitable of **5a** for X-ray analysis were obtained from DCM solution layered with hexane.

5a: yellow solid, mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64-6.74 (m, 8H), 6.94-7.00 (m, 4H), 7.00-7.07 (m, 8H), 7.34-7.38 (m, 2H), 7.41-7.47 (m, 4H), 7.48-7.54 (m, 8H), 7.68-7.74 (m, 4H), 8.08-8.15 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 115.3, 122.6, 125.0, 125.6, 125.7, 126.1, 127.1, 128.0, 128.2, 128.2, 129.1, 129.2, 130.4, 132.1, 132.7, 132.7, 133.9, 134.4, 145.3, 146.5, 147.2, 148.5, 166.0, 166.4, 169.3; HRMS (APCI$^+$) *m/z* calcd for $C_{74}H_{43}N_6S_8$ [M+H] 1271.1309, found 1271.1299.

5b: yellow solid, mp >300 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66-6.73 (m, 8H), 6.93-6.99 (m, 4H), 7.02-7.09 (m, 8H), 7.32-7.38 (m, 4H), 7.40-7.47 (m, 8H), 7.50 (s, 4H), 7.70-7.75 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.0, 125.7, 126.1, 126.5, 127.9, 128.2, 128.8, 129.2, 132.5, 133.0, 134.5, 137.3, 145.1, 146.7, 165.7; HRMS (APCI$^+$) *m/z* calcd for $C_{76}H_{45}N_6S_8$ [M+H] 1269.1404, found 1269.1378.

Pd-catalyzed direct coupling of 6 with 7 (Scheme 3)

A vial equipped with a magnetic stir bar was charged with **6** (7.6 mg, 0.025 mmol), **7** (11.6 mg, 0.025 mmol), $Pd(OAc)_2$ (1.1 mg, 20 mol%), dppe (2.0 mg, 20 mol%), PivOH (3.1 mg, 0.03 mmol), K_2CO_3 (20.8 mg, 0.15 mmol) and DMF (1 mL). The vial was refilled with dry N_2 and sealed. The mixture was heated at 100 °C for 16 h. The resulting suspension was diluted with

H_2O and was extracted with $CHCl_3$ three times. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was subjected to silica gel chromatography (eluent: hexane/EtOAc = 9/1) and GPC ($CHCl_3$) to give the product **8** in as a mixture of two isomers (5.9 mg, 39% yield). The ratio of **8a** and **8b** was determined by ^1H NMR analyses. Analytically pure crystals of **8a** were obtained by recrystallization from $CHCl_3$ solution layered with hexane.

8a: orange solid, mp >300 °C, ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1H), 7.22 (s, 1H), 7.31-7.39 (m, 2H), 7.41-7.50 (m, 10H), 7.61-7.66 (m, 2H), 7.69-7.74 (m, 2H), 8.00-8.08 (m, 2H), 8.13-8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.3, 124.2, 124.4, 125.1, 125.2, 125.9, 126.9, 126.9, 127.0, 128.5, 128.7, 128.9, 129.0, 129.0, 129.3, 129.8, 130.7, 131.0, 133.2, 133.4, 135.7, 140.6, 142.9, 146.1, 148.6, 156.8, 163.3, 170.6; HRMS ($APCI^+$) *m/z* calcd for $C_{38}H_{23}N_2O_2S_2$ [M+H] 603.1195, found 603.1195.

Summary of optical properties of the coupling products

compd	λ_{abs} [nm]	ε [$mM^{-1}cm^{-1}$]	λ_{flu} [nm]	Φ
3	341, 297, 265	34360, 33220, 33860	468	0.033
4a	355, 308, 263	50760, 39420, 54420	555	0.024
4b	354, 267	40880, 42840	550	0.033
5a	355, 284	46320, 87860	508, 483	0.030
5b	353, 284	44180, 79660	508, 489	0.031

All measurements were carried out as $CHCl_3$ solution (5.0×10^{-6} M). ε = molar extinction coefficient for each absorption peak Φ = internal quantum efficiency measured with an integration sphere system (JASCO ILF-835)

Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1894799 (**3**), 1894801 (**4a**), 1894802 (**5a**), and 1894918 (**8a**). Copies of the data can be obtained free of charge via CCDC Website.

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Supporting Information

Detailed experimental procedures, identification data, ORTEP drawings with selected parameters, and copy of NMR spectra are described. This material is available on http://dx.doi.org/10.1246/bcsj.***.

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Graphical Abstract

<Title>
Composite Tetraheteroarylenes and Related Higher Cyclic Oligomers of Heteroarenes
Produced by Palladium-Catalyzed Direct Coupling

<Authors' names>
K. Fukuzumi, Y. Nishii, and M. Miura

<Summary>
The synthesis and characterization of a series of thiophene-thiazole hybrid macrocyclic compounds through the Pd-catalyzed direct couping are described. The coupling products form characteristic helical assemblies, and among them, the new tetraheteroarylene specifically affords chiral crystals. Additionally, the first synthesis of a tetraarylene composed of four different heteroaryl fragments is achieved.

<Diagram>