Accounts

Palladium-Catalyzed CH Arylation and Dehydrogenative Homocoupling of Heteroaromatic Compounds and Application to the Design of Advanced Organic Materials

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CH arylation of five-membered heteroaromatic compounds such as thiazoles and thiophenes recently developed by the authors is reviewed. The reaction of thiazole with aryl iodides in the presence of a palladium/copper catalyst system and tetrabutylammonium fluoride causes CH arylation at the 2-position of thiazole. The reaction of 2-arylthiazole with aryl iodide by the catalysis of a palladium complex with silver(I) fluoride induces CH arylation at the 5-position. The reactions allow preparation of a variety of 2,5-diarylthiazoles in a facile manner. Spectroscopic, thermal, and electrochemical characteristics of 2,5-diarylthiazole are summarized. Introduction of the 2,5-diarylthiazole moiety, which exhibits photoluminescent and liquid crystalline characteristics, into the side chain of polymethacrylate is also described. CH arylation of thiophene derivatives are described to occur similarly to the case of thiazole. CH homocoupling of thiophene leading to bithiophene, in which the carbon–bromine bond on the thiophene ring is completely intact in the palladium-catalyzed reaction, is also described. Mechanistic studies on the reactions of thiophene are shown with a stoichiometric use of arylpalladium(II) halide complex and thiophene to undergo electrophilic substitution at the thiphene ring toward the palladium atom and the following reductive elimination of the thus obtained aryl(thienyl)-palladium complex.

Introduction

Heteroaromatic compounds have attracted considerable attention in the field of advanced materials as well as biologically active compounds.[1] Hence, the development of synthetic methodologies for the facile modification of such molecules with substituents is highly important in organic synthesis. Transition-metal-catalyzed cross-coupling,[2] which is the reaction of an organic halide and an organometallic reagent to form a carbon–carbon bond, has been a powerful method for the introduction of substituents at appropriate positions of the heteroaromatic structure. A variety of named coupling reactions of Grignard reagents (Kumada–Tamao),[3] boron (Suzuki–Miyaura),[4] zinc (Negishi),[5] and tin (Migita–Kosugi–Stille)[6] have been employed as a coupling partner to allow the transition-metal-catalyzed reaction forming the carbon–carbon bond. A process that is capable of forming a similar bond avoiding the preparation and use of organometallic reagents is the direct functionalization of a carbon–hydrogen bond of heteroaromatic compounds with transition-metal catalysis, which is an alternative and more straightforward pathway. Development of novel CH substitution reactions with a transition-metal catalyst has recently become important in organic synthesis, accordingly.[7,8] We herein report our recent efforts on transition-metal-catalyzed reactions at the CH bond of five-membered heteroaromatic compounds such as thiazoles and thiophenes to form the corresponding substituted products. Studies on the spectroscopic, thermal, and electrochemical characteristics of the obtained heteroaromatic compounds directed to application to functional organic materials are also described.

CH Arylation of Thiazole Derivatives

We have been studying a new class of coupling reactions of terminal alkynes and have shown that tetrabutylammonium fluoride (TBAF) serves as a novel and excellent activator for the Pd/Cu-catalyzed reaction to undergo the sp CH substitution with organic electrophiles.[9] Hence, we envisaged that sp^2 CH substitution would also take place under similar conditions.

Thiazole **1**, which is a heteroaromatic compound bearing sp^2 CH bonds, was chosen as an initial candidate for the coupling and the Pd/Cu-catalyzed reaction with 4-iodo(methoxy)benzene (**2a**) was examined in the presence of TBAF. The above conditions were previously applied to the coupling of terminal alkynes with aryl halides to undergo the reaction without using excess amounts of amine as a solvent or a cosolvent,[9] which is the conditions commonly employed for Sonogashira coupling.[10] When the reaction was carried out in DMSO at 60 °C, 82% of the product coupled at the 2-position (**3aa**) was obtained[11] (eq 1-1). Worthy of note is the low reaction temperature, which is a remarkably mild condition among tran-

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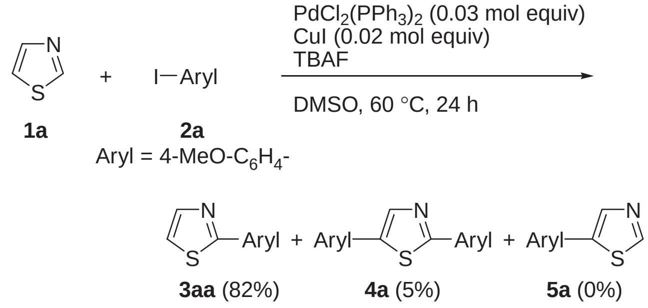
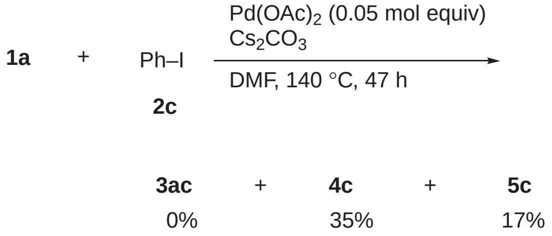
sition-metal-catalyzed CH substitutions with organic electrophiles.[7] The reaction at even lower temperature also proceeded to give **3aa** in 61% (40 °C) or 31% (room temperature) although it took 96 h. It should also be pointed out that the course of regiochemistry was highly controlled with a catalytic amount of CuI, taking place at the 2-position. Only 6% of 2,5-diarylated product **4a** was obtained, while mono-substituted product at the 5-position (**5a**) was not observed at all. On the other hand, a related coupling reaction catalyzed by palladium in the presence of K_2CO_3 or Cs_2CO_3 has been shown by Miura et al.[7d] The reaction is reported to proceed at 140 °C and the regioselectivity is markedly different from our results to give **4** and **5**, while no 2-substituted product **3** is obtained (eq 1-2).



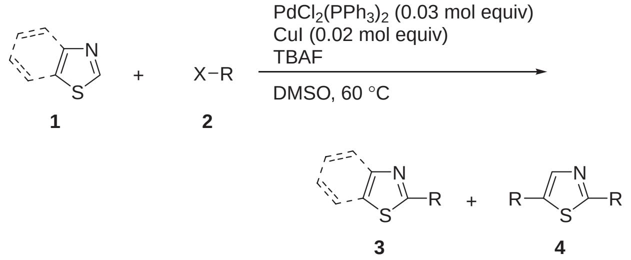
(1-1)

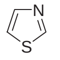
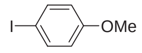
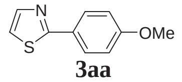
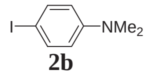
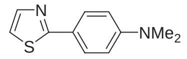
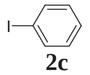
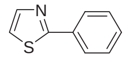
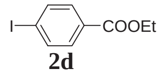
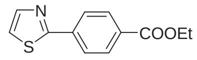
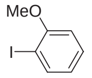
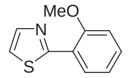
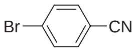
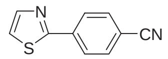
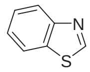
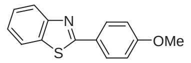
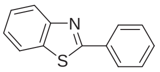
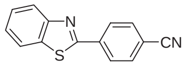
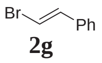
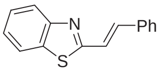


(1-2)

The addition of stoichiometric or excess amounts of copper(I) salt for the coupling reaction of thiazole has been employed to deliver 2-arylated product.[7d,7q,7r] However, catalytic control of the regiochemistry of thiazole has not been shown so far. The observed regioselectivity despite use of catalytic copper would be due to the mild reaction temperature. Table 1 summarizes the results of the CH arylation of thiazole with aryl iodides. The reaction with electron rich iodides proceeded smoothly to give 2-arylated thiazole, while employment of a substrate bearing an electron-withdrawing substituent resulted in lower yields. Benzothiazole was also found to be a favorable substrate for the reaction to afford the corresponding 2-arylated product in excellent yields.[12]

Table 1. CH Substitution Reaction of Thiazoles at the 2-Position

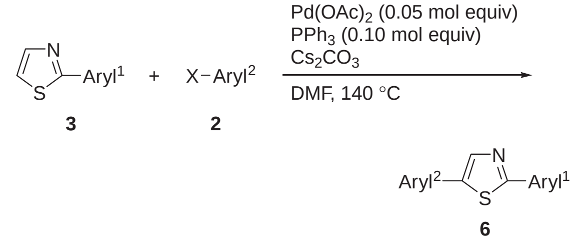


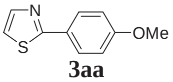
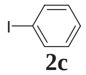
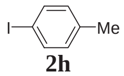
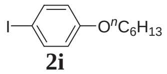
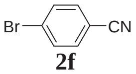
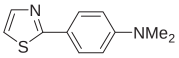
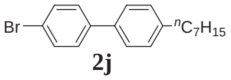
Thiazole	X–R	Product **3**	Yield of **3**/%	Ratio **3**/**4**
 **1a**	 **2a**	 **3aa**	82	15/1
	 **2b**	 **3ab**	80	—
	 **2c**	 **3ac**	59	—
	 **2d**	 **3ad**	25	11/1
	 **2e**	 **3ae**	57	—
	 **2f**	 **3af**	20	—
 **1b**	**2a**	 **3ba**	79	—
	2c	 **3bc**	84	—
	2f	 **3bf**	55	—
	 **2g**	 **3bg**	75	—

Since 2-arylated thiazoles are obtained under mild conditions, we envisaged further coupling of 2-arylthiazoles at the 5-position. The combination of the 2-arylation, which we have shown, with the reaction conditions for arylation at the 5-position developed by Miura et al.[7d] would lead to a facile synthesis of 2,5-diarylthiazoles from unsubstituted thiazole. The method was found to be effective to afford **6** since the alternative reaction site had already been substituted with the preceding reaction. As summarized in Table 2, 2,5-disubstituted derivatives bearing electron-donating and/or -withdrawing substituents were synthesized via the tandem reactions in moderate to excellent yields. The method would be suitable to the combinatorial synthesis of a variety of 2,5-diarylthiazoles highly efficiently.

UV–vis absorption and photoluminescence spectra of the obtained thiazole derivatives are summarized in Table 3. It was found that λ_{max} values of UV–vis absorption spectra of the thiazole derivatives were influenced by the electronic characteristics of the substituent. The absorption λ_{max} of **6bf** bearing dimethylamino and cyano groups was observed at 398 nm, while that of 2-(4-methoxyphenyl)-5-(4-methylphenyl)thiazole **6ah** was 334 nm. In addition, most of these compounds obtained were found to show photoluminescent characteristics.

Table 2. Synthesis of 2,5-Diarylthiazoles



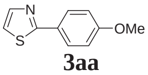
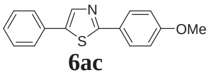
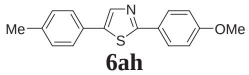
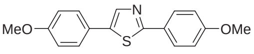
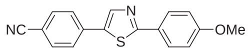
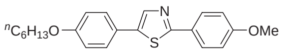
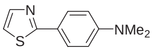
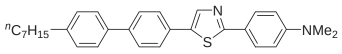
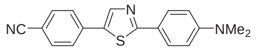
2-Arylthiazole	X-Aryl^2	Product	Yield/%
 **3aa**	 **2c**	**6ac**	69
	 **2h**	**6ah**	94
	 **2i**	**6ai**	76
	 **2f**	**6af**	62
 **3ab**	 **2j**	**6bj**	39
	2f	**6bf**	18

Their wavelengths and intensities also depended on the type of substituents suggesting that the color and strength of emission would be tunable by the electronic properties of the functional group. Considerably high quantum yields (Φ) were observed in thiazoles bearing a dimethylamino group such as **6bj** and **6bf**.

Although synthesis of 2,5-diarylthiazoles has previously been shown by condensation of *N*-phenacylbenzamide derivatives ($Aryl^1COCH_2NHCOAryl^2$) in the presence of P_2S_5, their yields are generally low (25–35%).[1c] By contrast, the tandem coupling strategy allows us to afford 2,5-disubstituted thiazole with various substituents in good yields and in a combinatorial manner, which would be potentially effective for the construction of thiazole libraries.[13]

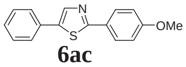
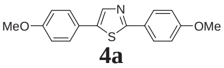
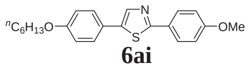
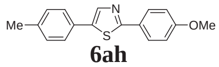
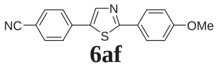
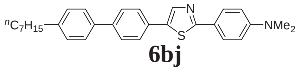
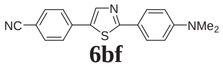
In addition to the strong light emission of 2,5-diarylthiazole derivatives, a number of thiazoles synthesized were found to show liquid crystalline (LC) characteristics,[1c] which were evaluated by means of DSC (heating and cooling rate: 2 °C min^{-1}) analyses and polarizing microscopy observation. Data of LC characteristics are summarized in Table 4 and Figure 1. It should be pointed out that 2,5-diarylthiazoles exhibited a LC phase over a remarkably wide range of temperatures. For example, **6bj** showed LC phase between 150 and 260 °C. The result markedly contrasts to that of 2,5-diaryl-1,3,4-oxadiazoles **7** bearing the same substituents, which has recently been reported to exhibit LC phase between 138–143 °C as well as light-emitting characteristics.[14] It is noteworthy that influence on the thermal characteristics was observed from the structure of the *N*,*N*-dialkylamino moiety. DSC thermograms of **6bf** vs. **6af** and **6bj** exhibited differences in ΔH values of the transition of the liquid crystalline phase to the isotropic indicating a larger value for **6bf** (11.2) than those

Table 3. The Results of UV–Vis Absorption of Arylthiazoles

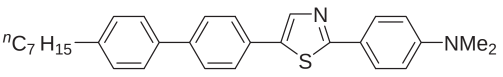
Arylthiazole	Absorption[a)] λ_{max}/nm (ε/M^{-1} cm^{-1})	Emission[a)] λ_{max}/nm (Φ)
 **3aa**	300 (10800)	361 (0.21)
 **6ac**	333 (28000)	406 (0.22)
 **6ah**	334 (22800)	408 (0.17)
 **4a**	339 (22300)	419 (0.17)
 **6af**	350 (30200)	462 (0.27)
 **6ai**	339 (27900)	419 (0.24)
 **3ab**	340 (25400)	401 (0.19)
 **6bj**	376 (38200)	462 (0.49)
 **6bf**	398 (26900)	488 (0.37)

a) Absorption spectra and emission spectra were measured as a chloroform solution (1×10^{-5} and 3×10^{-6} M, respectively).

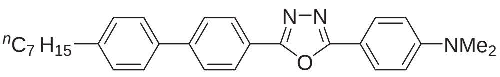
Table 4. Phase Transition Temperatures (°C) and Enthalpies (kJ mol^{-1}, in Parentheses) of 2,5-Diarylthiazoles

2,5-Diarylthiazole	DSC T/°C[a)]
 **6ac**	I 83.3 (27.7) Cr
 **4a**	I 219.9 (0.3) N 126.9 (34.4) Cr
 **6ai**	I 181.8 (0.8) N 82.2 (6.7) Cr
 **6ah**	I 150[b)] N 86.4 (16.7) Cr
 **6af**	I 225 (0.04) N 151.3 (19.6) Cr
 **6bj**	I 258.4 (0.26) N 144.5 (3.4) Cr
 **6bf**	I 204.3 (11.2) S 188.0 (4.0) Cr

a) Cr = Crystal, N = Nematic phase, S = Smectic phase, I = Isotropic. b) Determined by POM.



6bj



7 (C 138 N 143 I)

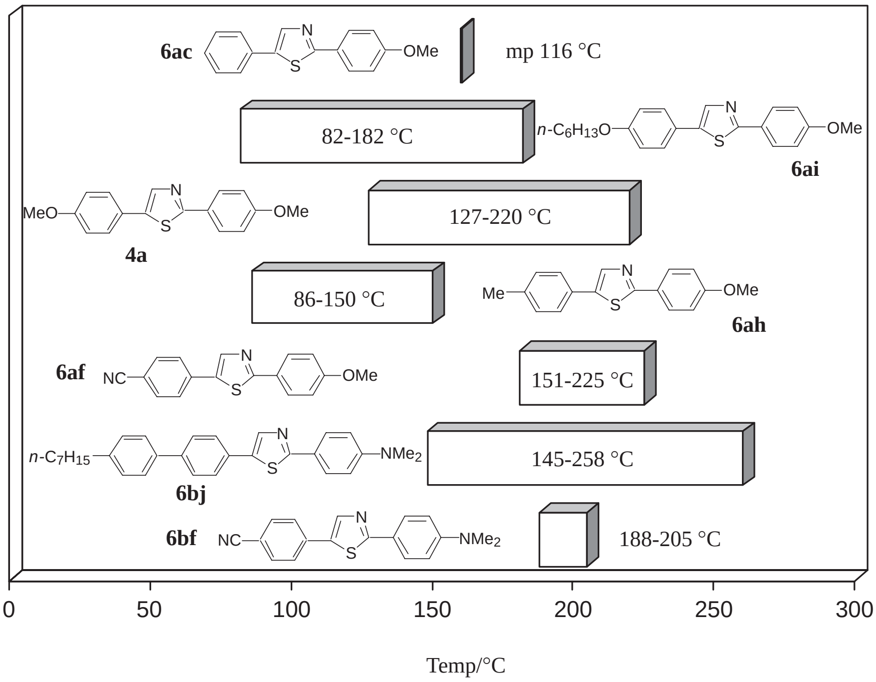


Figure 1. The range of temperature of nematic phase on cooling.

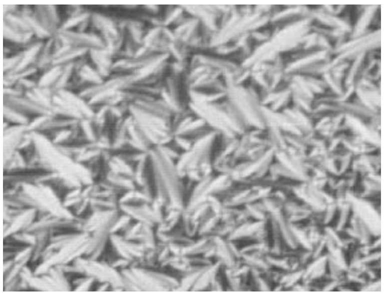


Figure 2. Polarized optical microscopy image of 2,5-diarylthiazole **6bf**.

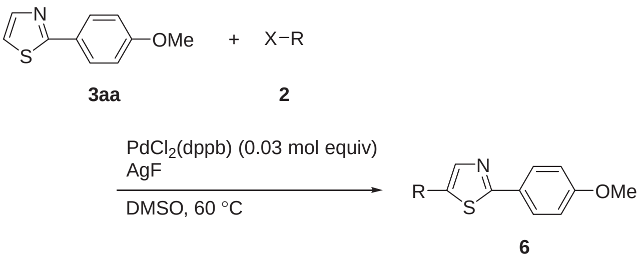
of **6af** and **6bj** (0.04 and 0.26, respectively). These results suggest that donor–acceptor-type 2,5-diarylthiazoles bearing a strong electron-donating dialkylamino group show smectic phase, while **6af** and **6bj**, which possess a less electron-donating methoxy group, are nematic liquid crystal. Polarized optical microscope images of **6bf** in Figure 2, which indicate characteristic batonnet structures, also support the formation of smectic liquid crystal, while observation of the polarized optical micrograph of **6af** and **6bj** indicate the nematic phase.[1c] The remarkable difference would arise from the bimolecular interaction between donor and acceptor substituent moieties of 2,5-diarylthiazole by 4-dialkylaminophenyl and 4-cyanophenyl groups. The interaction would bring about a definite layer width leading to smectic liquid crystal. On the other hand, 2,5-diarylthiazole **6bj** that does not possess an acceptor substituent shows little intermolecular interaction resulting in nematic.[1c] In addition, the donor effect of the methoxy group of **6af** was not found to be strong enough to form the donor–acceptor complex also leading thereby to the nematic phase.

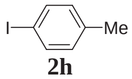
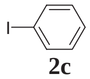
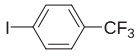
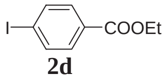
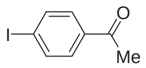
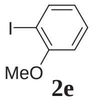
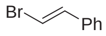
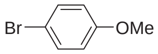
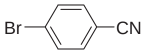
We then set out to develop a new CH arylation of thiazole at the 5-position. The reaction conditions involving the palladium species, effect of ligand, presence of a co-catalyst, and additive effect have been carefully studied. We found that a silver salt such as AgF or Ag_2O was an effective additive (activator) for the reaction.[15] In sharp contrast to the palladium-catalyzed arylation reaction with K_2CO_3 or Cs_2CO_3 at 140 °C,[7d] the reaction was found to proceed at 60 °C. As shown in Table 5, the reaction with aryl iodides gave corresponding diarylthiazoles, while the reaction of alkenyl bromide and aryl bromides resulted in poor yields.[16]

During our studies on the synthesis of 2,5-diarylthiazoles through tandem coupling of unsubstituted thiazole and on the photoluminescent properties of the obtained compounds, we learned that a thiazole derivative bearing donor–acceptor-type substituents at the 2- and 5-positions showed strong light emission. For example, a thiazole derivative **6bf** bearing a 4-(dimethylamino)phenyl group, which showed strong electron-donating characteristics, at the 2-position and a 4-cyanophenyl group as an electron-withdrawing one at the 5-position exhibited $\lambda_{\max}$ values in UV–vis absorption and photoluminescence at 398 and 488 nm ($\Phi = 0.37$), respectively (see Table 3). However, as shown in Figure 1, **6bf** showed LC characteristics in a relatively narrow temperature range compared with other thiazole derivatives. We thereby performed synthesis of the donor–acceptor-type 2,5-diarylthiazoles bearing different alkyl substituents on the nitrogen atom.

Synthesis of a series of 2,5-diarylthiazoles **2n–2p** was carried out with tandem CH substitution reactions of thiazole at the 2- and 5-positions as outlined in Scheme 1.[17] The reaction at the 2-position was performed with thiazole and 4-(dialkylamino)iodobenzene **2** in the presence of TBAF and catalytic amounts of [$PdCl_2(PPh_3)_2$]/CuI. The reaction proceeded smoothly to afford 2-arylated thiazole in good to excellent yields. Preparation of **2** was carried out by iodination of the corresponding *N*,*N*-dialkylaniline. Introduction of the second aryl group was carried out by the palladium-catalyzed reaction in the presence of AgF as an activator or alternatively by the Miura's method,[7d] which is the reaction with $Pd(OAc)_2$–$2PPh_3$ in the presence of Cs_2CO_3 at 140 °C. Although both reactions proceeded smoothly to afford the crude product in almost quantitative yields, 2,5-diarylthiazoles **6** were partially decomposed on silica gel column chromatography, which lowered the isolated yield.

Table 5. Synthesis of 2,5-Diarylthiazoles in the Presence of Silver(I) Fluoride



X–R	Product	Yield[a)]/%
 **2h**	**6ah**	(67)
 **2c**	**6ac**	68(79)
 **2k**	**6ak**	61(85)
 **2d**	**6ad**	58
 **2l**	**6al**	(36)
 **2e**	**6ae**	70(82)
 **2g**	**6ag**	0
 **2m**	**6am**	0
 **2f**	**6af**	(25)

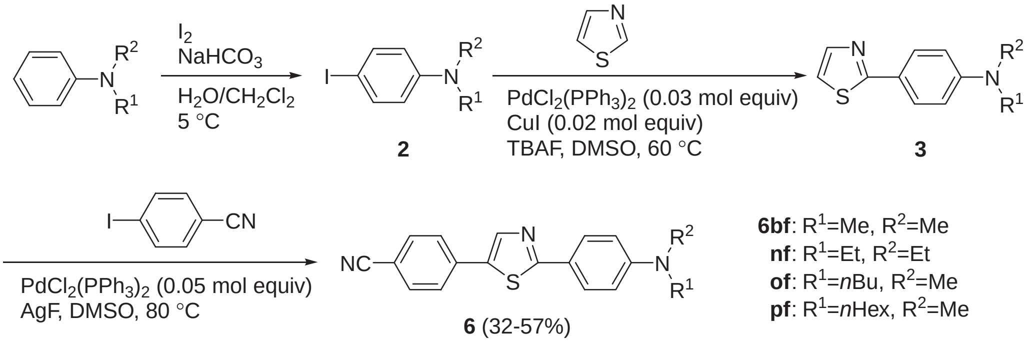
a) Isolated yield. NMR yields are shown in the parenthesis.

The 2,5-diarylthiazoles bearing a dialkylamino group were characterized by UV–vis absorption and photoluminescent spectra to find that the length of the alkyl chain on the nitrogen atom was less influenced to the wavelength of UV–vis and photoluminescent spectra (Table 6).

Thermal characteristics of 2,5-diarylthiazoles are summarized in Table 7. All compounds exhibited liquid crystalline characteristics over a wide range of temperature. Although the chain length of the dialkylamino groups of **6** showed little influence on UV–vis absorption and photoluminescent spectra, the temperature range showing liquid crystalline phase was found to expand as the chain length of the *N*-alkyl group increased. Indeed, **6pf** exhibited smectic phase between 82–166 °C, in comparison to the range of **6bf** as shown to be 188–204 °C. Accordingly, stable liquid crystalline characteristics of 2,5-diarylthiazoles are potentially an advantage for the design of an electroluminescent device with polarized light emission.

We next envisaged the preparation of pendant-type polymers bearing a 2,5-diarylthiazole moiety at the side chain of methacrylate polymer.[18] The CH arylation reaction of thiazole at the 2-position was also carried out with a substrate bearing a hydroxy group at the alkyl end, which were synthesized as shown in Scheme 2. The following arylation reactions of **2** with thiazole and aryl iodides were performed similarly to afford 2,5-diarylthiazole **6**. It was found that arylation reactions at both the 2- and 5-positions occur smoothly without protection of the hydroxy group. The monomers **8a–8c** were obtained by the reaction of 2,5-diarylthiazoles bearing a hydroxy group with methacryloyl chloride in the presence of triethylamine.

Radical polymerization of **8a–8c** with AIBN as an initiator



Scheme 1.

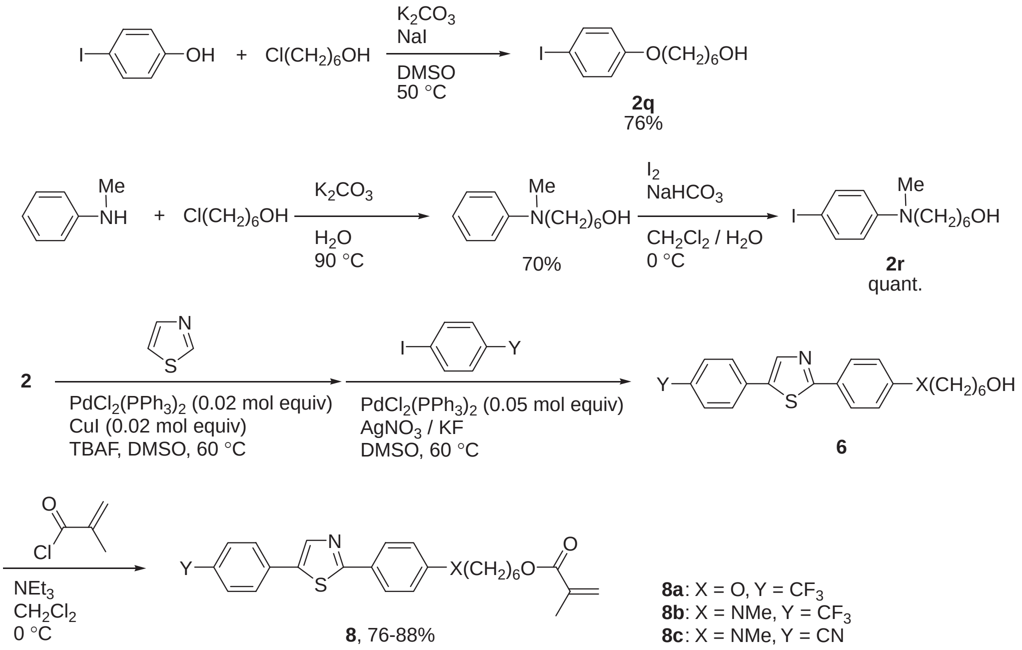
Table 6. Spectroscopic Properties of 2,5-Diarylthiazoles Bearing a Dialkylamino Group[a)]

2,5-Diarylthiazole	UV–vis $\lambda_{\text{em max}}$/nm	$\varepsilon_{\max}$ /$M^{-1}\,cm^{-1}$	Emission $\lambda_{\text{em max}}$/nm	Excitation $\lambda_{\text{ex max}}$/nm	Quantum yield Φ
6bf	398	26900	488	395	0.37
6nf	407	46100	493	405	0.60
6of	404	37700	492	405	0.55
6pf	404	34800	486	406	0.74

a) UV–vis and photoluminescence spectra were recorded as 1×10^{-5} and 1×10^{-6} M solutions in chloroform, respectively.

Table 7. Thermal Characteristics of 2,5-Diarylthiazoles

2,5-Diarylthiazole	DSC T/°C	TGA T_d/°C
6bf	I 204.3 (11.2) S 188.0 (4.0) Cr	297, 196, 206
6nf	I 182.8 (6.7) S 131.5 (17.6) Cr	306
6of	I 180.4 (4.8) S 89.2 (12.4) Cr	300
6pf	I 165.5 (4.5) S 82.3 (9.2) Cr	—

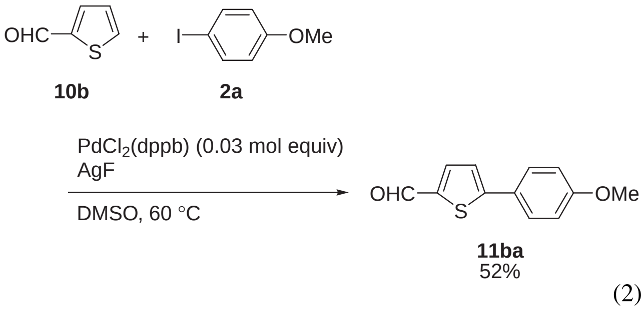


Scheme 2.

took place to afford the corresponding side-chain-type polymers **9a–9c** bearing a 2,5-diarylthiazole moiety in 60%–75% yields.[18] As summarized in Table 8, the molecular weight and molecular weight distribution were estimated by SEC analysis to be $M_n = 3800$–12900 and $M_w/M_n = 1.54$–1.82, respectively. Preliminary measurements of spectroscopic properties of polymers **9a–9c** were similar to those of the corresponding low molecular weight compounds **8a–8c** as summarized in Table 9. The polymers were found to form thin films by spin coating from chloroform solutions of **9a–9c**. The films showed remarkable red-shift in photoluminescent spectra. Further studies on the characterization of the polymers bearing thiazole at the side chain are currently under way.

Reactions at the CH Bond of Thiophene Derivatives

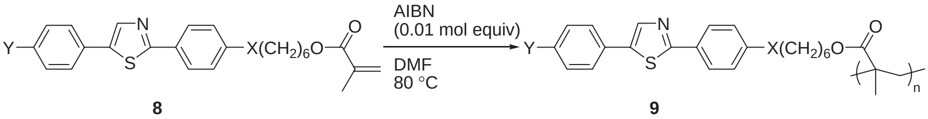
The conditions employed for CH arylation at the 5-position of thiazole were found to be applicable for the reaction of thiophene derivatives. When the reaction of 2-formylthiophene (**10b**) was carried out with 4-iodo(methoxy)benzene (**2a**) in the presence of 0.03 molar equiv of the palladium catalyst and AgF, the arylation took place similarly to afford **11ba** in 52% yield (eq 2).[15]



(2)

As shown in Table 10, the reaction of several thiophene derivatives with aryl iodides bearing various substituents was found to proceed. It should be pointed out that 2-bromothio-

Table 8. Synthesis of Pendant-Type Polymer



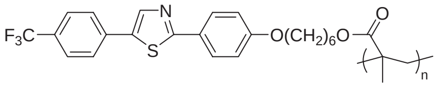
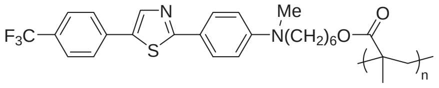
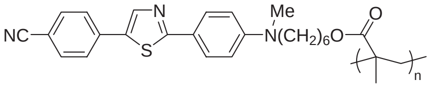
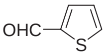
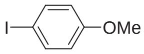
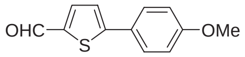
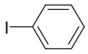
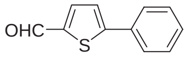
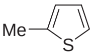
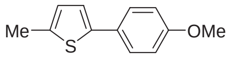
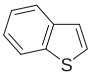
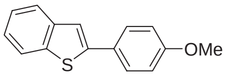
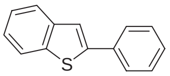
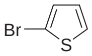
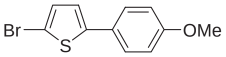
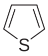
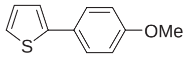
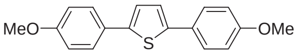
Polymer	Yield/%	M_n	M_w/M_n
 **9a**	75	12900	1.82
 **9b**	67	6500	1.77
 **9c**	60	3800	1.54

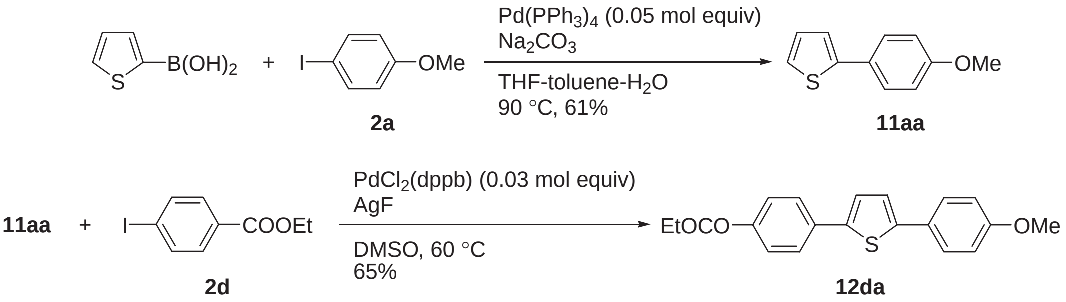
Table 9. Spectroscopic Properties of 2,5-Diarylthiazole Derivatives[a)]

Substrate	UV–vis $\lambda_{\text{em max}}$/nm	ε_{max}/M^{-1} cm^{-1}	Emission $\lambda_{\text{em max}}$/nm	Excitation $\lambda_{\text{ex max}}$/nm	Quantum yield Φ
Monomer **8a**	338	63100	413	342	0.21
Polymer **9a**	338	31200	416	341	0.19
Monomer **8b**	385	32600	460	394	0.77
Polymer **9b**	383	35200	468	393	0.22
Monomer **8c**	401	35200	487	408	0.59
Polymer **9c**	399	34100	491	408	0.21

a) UV–vis and photoluminescence spectra were recorded as 1×10^{-5} and 1×10^{-6} M solutions in chloroform, respectively.

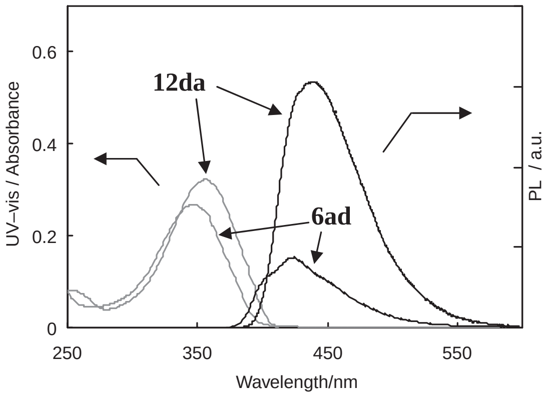
Table 10. CH Substitution Reaction Using Various Thiophene Derivatives

Thiophene	Ar–I	Product	Yield/%
 **10b**	 **2a**	 **11ba**	52
	 **2c**	 **11bc**	58
 **10c**	**2a**	 **11ca**	34
 **10d**	**2a**	 **11da**	54
	2c	 **11dc**	36
 **10e**	**2a**	 **11ea**	60
 **10a**	**2a**	 **11aa**	43
		 **12aa**	6



Scheme 3. Synthesis of 2,5-diarylthiophene.

12da **6ad**



12da:

UV λ_{max}=357 nm (ε = 32200)

E_m=441 nm (ϕ =0.79)

6ad:

UV λ_{max}=347 nm (ε = 26800)

E_m=424 nm (ϕ =0.24)

Figure 3. UV–vis absorption (gray) and PL emission (bold) spectra of **12da** and **6ad**. The spectra were measured in a chloroform solution (1×10^{-5} and 1×10^{-6} M, respectively).

phene (**10e**) also underwent the CH arylation reaction at the 5-position, while the carbon–bromine bond was completely intact. The success of CH arylation of thiophene derivatives allowed the synthesis of 2,5-diarylthiophene by combination of Suzuki–Miyaura coupling[4] and the following palladium-catalyzed CH arylation as shown in Scheme 3.[15]

Accordingly, properties of 2,5-diarylthiophene and 2,5-diarylthiazole were compared. UV–vis absorption spectra showed little difference between thiophene and thiazole. In contrast, the quantum yield of 2,5-diarylthiophene **12da** was almost three times greater than that of the analogous diarylthiazole **6ad** (Figure 3). It was also found that 2,5-diarylthiophene exhibited smectic liquid crystalline phase by measurement of DSC thermogram and observation of polarized micrograph, while the corresponding thiazole showed nematic phase (Figure 4).[15]

Since AgF was shown to be an excellent activator for the CH arylation of thiazoles (5-position) and thiophenes, we screened less expensive and common activators (systems). As summarized in Table 11, the reaction was examined with 2-formylthiophene and 4-iodo(methoxy)benzene using 0.03 molar equiv of $PdCl_2$(dppb) as a catalyst. Combination of silver(I) nitrate and several fluoride ion species was found to be as effective as AgF. Among which, potassium, cesium, and tetra-*n*-butylammonium fluorides effectively underwent the reaction, while sodium fluoride did not effect the reaction at all probably due to the strong affinity of Na and F. Several cationic counter ions of silver(I) such as BF_4, OTf, and $OCOCF_3$ promoted the reaction similarly.[19]

Although the CH arylation reaction of thiophene derivatives took place similarly to that of thiazoles, the yield of the coupling product was relatively lower. Thus, we examined the reaction conditions carefully and found that the fractional addition of additives remarkably improved the yield.[20] When the addition of $AgNO_3$ was carried out in several portions, the yield of the arylation product was dramatically improved. Although the yield of the reaction of 2,3-dibromothiophene (**10f**) with **2a** was only 41% by the addition of $AgNO_3$ (1 molar equiv) in one portion, the addition of $AgNO_3$ in four portions (0.5 molar equiv × 4) with each 2 h improved the yield to 83%. Further optimization revealed that the addition of $AgNO_3$ (0.25 molar equiv × 5) at one hour intervals afforded the coupling product in 87% yield. The addition of TBAF as a solution of DMSO over a period of 5 h also furnished **11fa** in an excellent yield. Table 12 summarizes the results. The effective activator would be in situ formed silver fluoride. The species would cause degradation into unreactive species by light or heat. Hence, a longer reaction period was not effective in achieving higher yield when the reaction did not proceed at a reasonable reaction rate.

The reaction of several bromothiophene derivatives was examined with a variety of aromatic iodides as shown in Table 13. It was found that 2-bromothiophene (**10e**) and 2,3-dibromothiophene (**10f**) reacted with a variety of aryl iodides bearing an electron-donating or electron-withdrawing substituent in moderate to excellent yields. The reaction proceeded with ethyl 4-iodobenzoate (**2d**), 4-iodobenzonitrile (**2s**), 4-iodo(trifluoromethyl)benzene (**2k**), and 2-iodonaphthalene (**2t**) in good yields. Further bromothiophene derivatives such as 2-bromo-3-methylthiophene (**10g**), 5-bromo-2,2′-bithiophene (**10h**), and 2,4-dibromothiophene (**10i**) also underwent the reaction.

Since the obtained CH substitution reaction products **11** possessed a carbon–bromine bond, **11** allowed further substitution reactions with several nucleophilic reagents. Hence, bromothiophenes serve as a chameleon substrate that brings about sequential electrophilic and nucleophilic substitutions, without a protective group, at CH and CBr bonds, respectively. Indeed, when **11ea** was treated with tributyl(2-thienyl)tin in the presence of a palladium/copper catalyst, the corresponding bithiophene **13** was obtained in 81% yield. The reaction of 1-octyne using 2-ethanolamine as an activator[21] also underwent Sonogashira coupling to afford **14** in a reasonable yield and Mizoroki–Heck reaction with ethyl acrylate afforded **15** as summarized in Scheme 4.[20]

Oligothiophenes and polythiophenes are found in a variety of organic materials such as organic TFTs, liquid crystalline compounds, conductive materials, and dye-sensitized solar cells.[22] Development of synthetic methodologies to form a

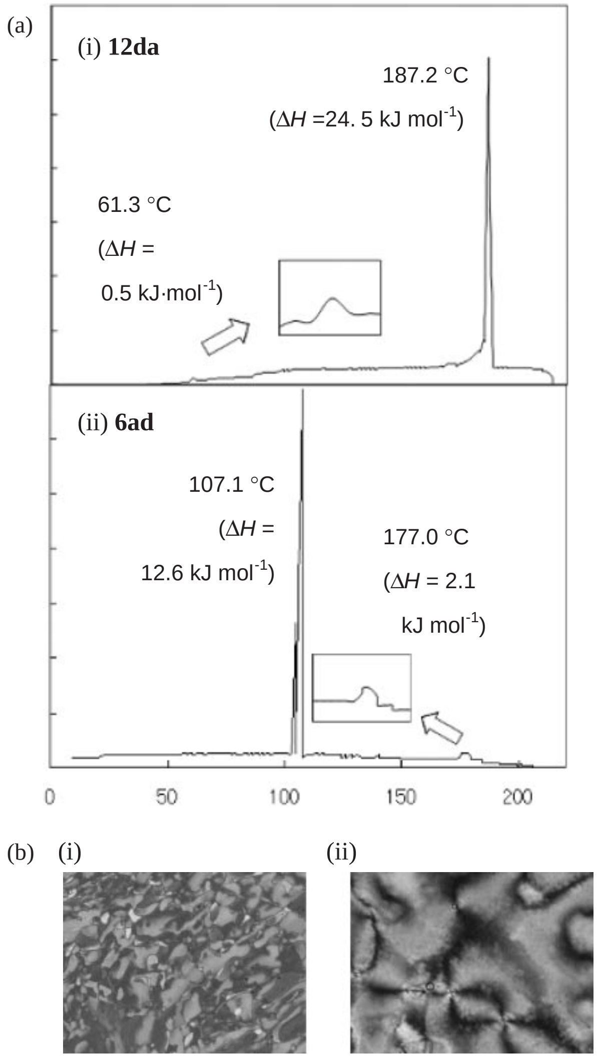
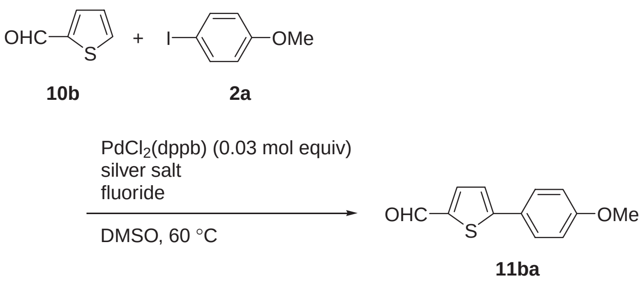


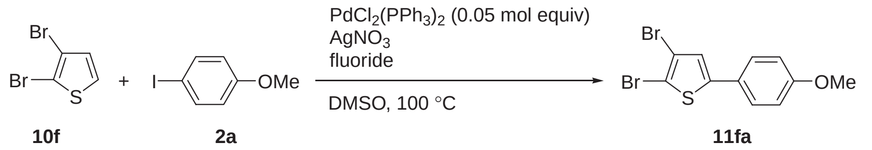
Figure 4. (a) DSC thermogram of **12da** (i) and **6ad** (ii) on the second cooling, (b) liquid crystalline texture of **12da** at 184 °C (i) and **6ad** at 177 °C (ii) at polarizing microscope.

Table 11. CH Bond Substitution Reaction Using Silver Salt and Fluorine Source



Silver salt	Fluoride	Time/h	Yield/%
$AgNO_3$	KF	23	45
		5	36
	CsF	26	55
	NaF	24	0
	TBAF	24	36
$AgBF_4$	KF	24	39
AgOTf		24	42
$AgOCOCF_3$		24	38

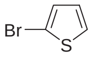
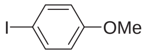
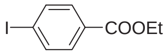
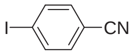
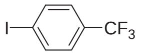
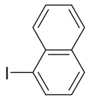
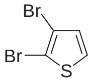
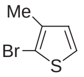
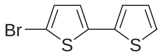
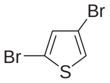
Table 12. Reaction of 2,3-Dibromothiophene (**10f**) with 4-Iodo(methoxy)benzene



$AgNO_3$/mol equiv	Fluoride	Time	Yield/%
1.0	KF (2 mol equiv)	24 h	41
0.5 × 4		2 h × 4	83
0.25 × 5	KF (1.25 mol equiv)	1 h × 5	87
1.0	TBAF (1.5 mol equiv)[a]	5 h	79

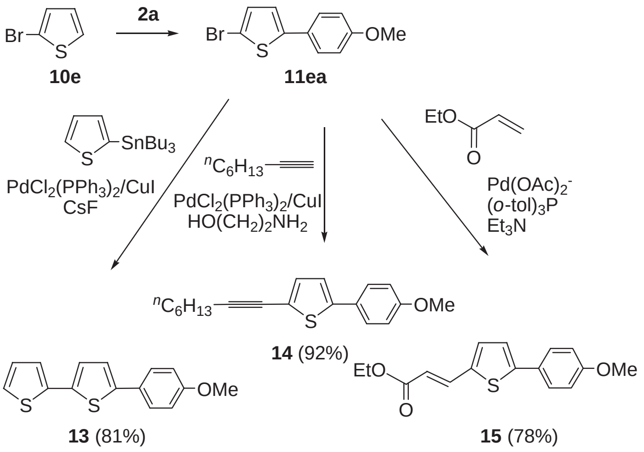
a) TBAF (1.5 mol equiv) was added dropwise to the reaction mixture as a DMSO solution.

Table 13. Reaction of Bromothiophene Derivatives with Various Aryl Iodides

Thiophene	Aryl–I	Method[a)]	Yield[b)]/%
 **10e**	 **2a**	B	60
	 **2d**	B	93
	 **2s**	B	64
	 **2k**	B	(75)
	 **2t**	B	(79)
 **10f**	**2a**	A	87
	2d	A	72
	2s	A	68
	2k	A	(67)
	2t	A	(86)
 **10g**	**2a**	B	61
	2d	A	51
	2s	A	53
 **10h**	**2a**	B	48
 **10i**	**2a**	B	65

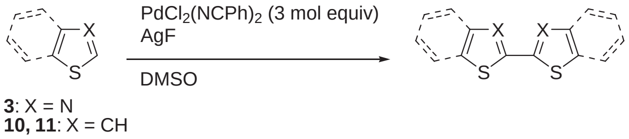
a) Method A: $AgNO_3$ (0.25 mol equiv, 1 h × 5); Method B: $AgNO_3$ (0.5 mol equiv, 2 h × 4). b) Isolated yield. The yield based on NMR is shown in parentheses.

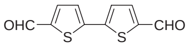
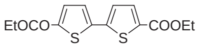
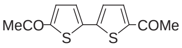
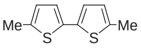
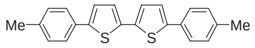
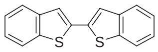
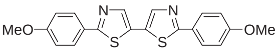
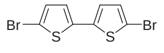
thiophene–thiophene bond is therefore an attractive issue in organic synthesis.[23] If the coupling of thiophene derivatives can be performed at the CH bond, the method is highly efficient from the view point of atom economy. We found that homocoupling of thiophenes took place at the CH bond adjacent to the sulfur atom by treatment of a catalytic amount of palladium and silver(I) fluoride.[24] Several thiophene derivatives bearing a substituent such as formyl, ethoxycarbonyl, acetyl, methyl, and aryl groups underwent the reaction. Benzothiophene and a thiazole derivative (5-position) also homocoupled smoothly as summarized in Table 14. Similar to the case of palladium-catalyzed CH arylation, homocoupling of 2-bromothiophene and related compounds was also found to occur at the CH bond leaving the carbon–bromine bond completely intact.



Scheme 4.

Table 14. Palladium-Catalyzed Homocoupling of Heteroaromatic Compounds

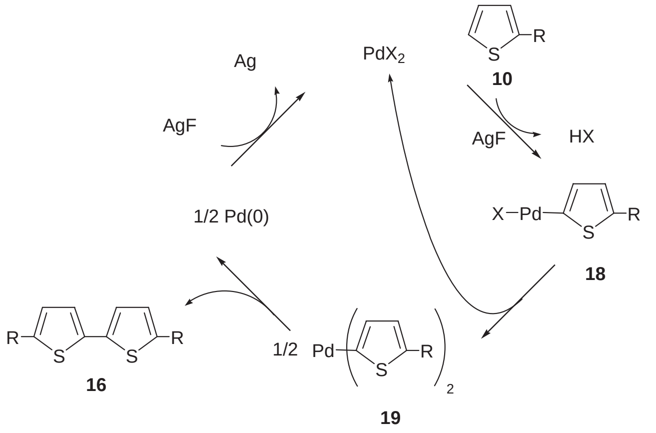


Product	Temp/°C	Time/h	Yield/%
 **16b**	60	5	69
 **16j**	60	5	85
 **16k**	60	5	69
 **16c**	60	5	43
 **16l**	60	5	58
 **16d**	60	5	41
 **17a**	60	5	63
	60	24	83[a)]
 **16e**	rt	5	77

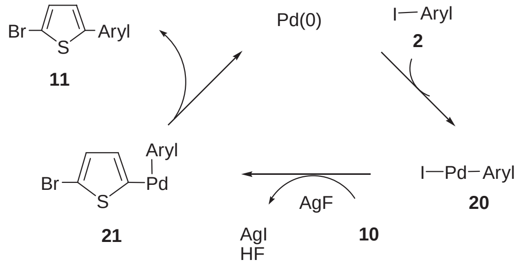
a) $AgOCOCH_3$ and $PdCl_2(dppb)$ were employed instead of AgF and $PdCl_2(NCPh)_2$.

The mechanism of the CH homocoupling reaction is explained as illustrated in Scheme 5. The reaction of a palladium(II) complex with thiophene **10** induces electrophilic substitution leading to formation of (thienyl)–Pd^{II}–X complex **18**. Further substitution follows to give $(thienyl)_2Pd^{II}$ complex **19** or alternatively disproportionation of **18** is a pathway to the intermediate **19** and PdX_2. Reductive elimination gives bithiophene along with the formation of Pd^0. The obtained palladium(0) complex is oxidized by AgF to form $Pd^{II}F_2$. Formation of silver(0) was confirmed by XRD analysis of the silver residue in the reaction mixture.

For the purpose of further understanding the catalytic reaction, stoichiometric reaction of a palladium complex,



Scheme 5. Plausible reaction mechanism of homocoupling.



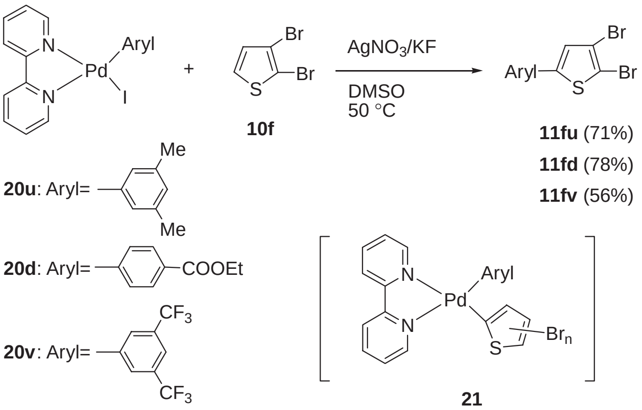
Scheme 6. Plausible reaction mechanism of CH arylation of bromothiophene.

$Pd(OAc)_2$ with a thiophene derivative **10b** was carried out. However, the reaction did not proceed in the absence of the silver reagent. These results suggest that AgF serves as an activator of the electrophilic substitution reaction as well as the oxidant of Pd^0.[19]

On the other hand, AgF was found to be transformed to AgI when the palladium-catalyzed CH arylation of thiazole or thiophene was performed with an aryl iodide. The formation of AgI was also confirmed by XRD analysis. The mechanism of the CH arylation reaction by the catalysis of a palladium complex is considered as shown in Scheme 6. Oxidative addition of Pd^0 to aryl iodide gives aryl–Pd^{II}–I complex **20**, to which electrophilic substitution to a thiophene or thiazole derivative leads to the formation of the (aryl)–Pd^{II}–(thienyl) complex **21**. Reductive elimination of **21** furnishes the arylation product **11** accompanied by Pd^0.[15]

A stoichiometric reaction of aryl–Pd^{II}–X complex **20** with thiophene derivatives **10** in the presence of AgF ($AgNO_3$/KF) was also carried out and formation of the arylated thiophene **11** was also confirmed.[25] The attempted formation of the (aryl)–Pd^{II}–(thienyl) complex **21** by employing an electron-deficient aryl group bearing a 4-ethoxycarbonyl or 3,5-bis(trifluoromethyl) group as a substituent has been unsuccessful so far (Scheme 7).

Since the synthetic protocol for several dibromobithiophene derivatives was in hand, we envisaged the synthesis of further oligothiophenes with palladium-catalyzed homocoupling and several cross-coupling methodologies.[26] Figure 5 illustrates the structures of well-defined oligothiophene, where head-to-head and/or tail-to-tail relationship is controlled.



Scheme 7. The reaction of aryl(iodo)palladium(II)(bpy) complex **20** with 2,3-dibromothiophene **10f**.

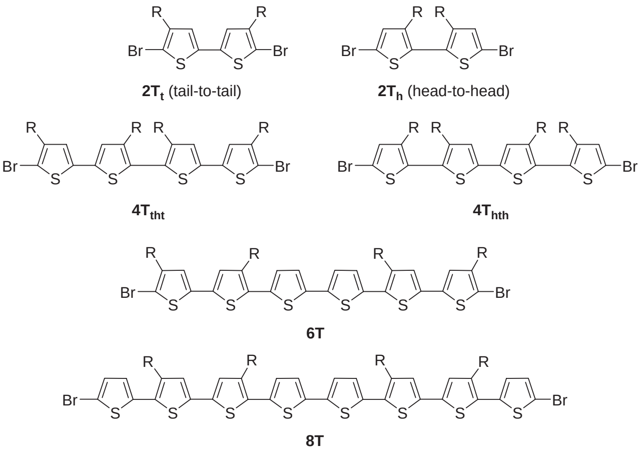


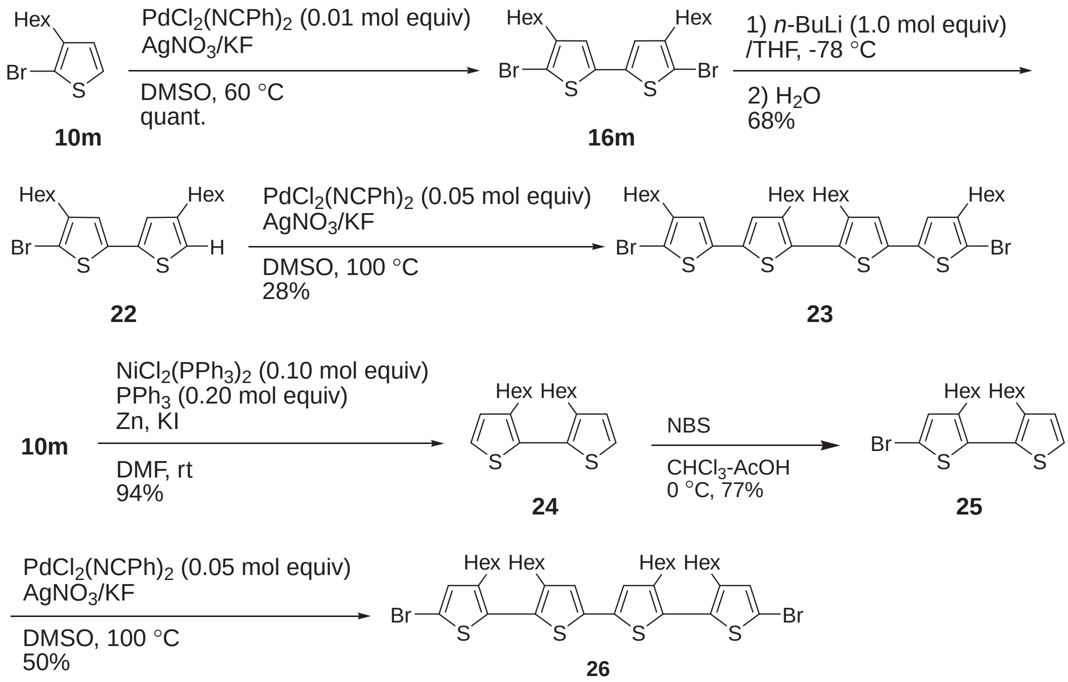
Figure 5. The structures of well-defined oligothiophene.

The reaction of 2-bromo-3-hexylthiophene afforded the corresponding bithiophene **16m** (tail-to-tail) in excellent yield. Treatment of dibromobithiophene **16m** with 1 molar equiv of butyllithium followed by protonation resulted in selective monodebromination to give **22**. Homocoupling of **22** under similar conditions afforded the tetramer **23** (t–t, h–h, t–t). On the other hand, another tetramer **26** (h–h, t–t, h–h) was synthesized by the homocoupling of bithiophene **25**, which was prepared by nickel-catalyzed debrominative homocoupling[27] of **10m** and following monobromination with 1 molar equiv of NBS (Scheme 8).

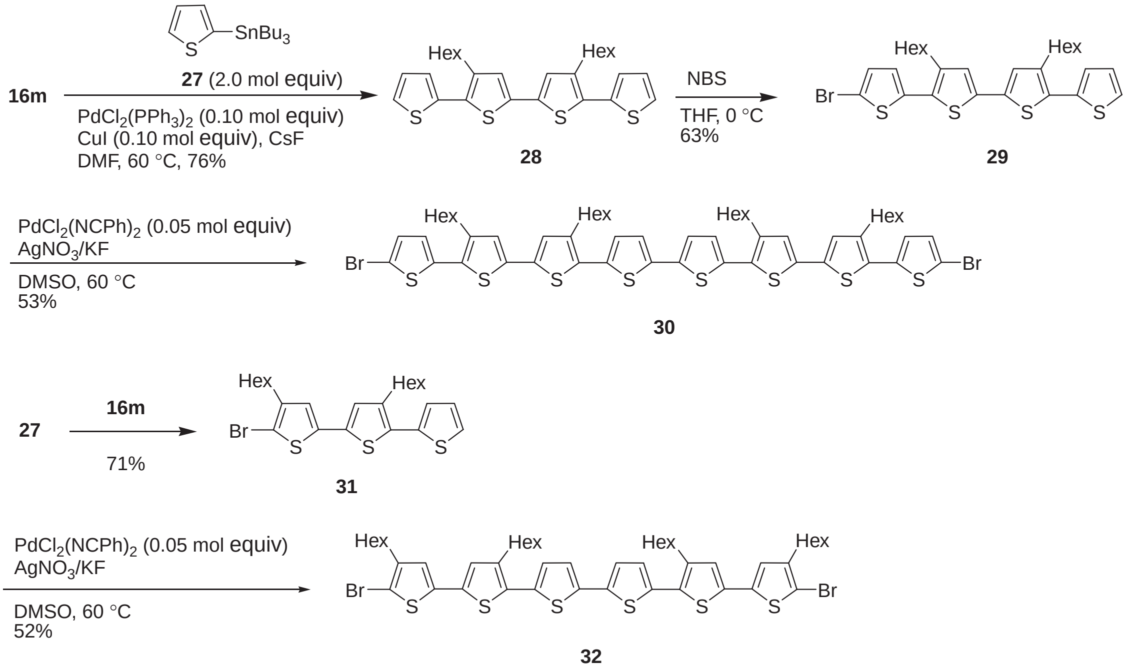
Synthesis of further oligomers was carried out as outlined in Scheme 9. Cross coupling of the dibromobithiophene **16m** with unsubstituted thienyl tin reagent **27** in the presence of a palladium catalyst afforded **28** when 2 molar equiv of **27** was employed, while the reaction with the ratio of **16m**/**27** = 3/1 furnished the trimer **31**. Monobromination of **28** and following homocoupling afforded the octamer **30** and the homocoupling reaction of trimer **31** yielded the hexamer **32**.

Conclusion

In summary, we have shown cross-coupling and homocoupling reactions of five-membered heteroaromatic compounds, thiophene and thiazole derivatives. Although further



Scheme 8.



Scheme 9.

improvement would be necessary to develop a highly practical synthetic methodology, these reactions are powerful tools for the construction of π-conjugated heteroaromatic systems, which are potentially available as advanced organic materials. Transition-metal-catalyzed carbon–carbon bond-forming reactions at the CH bond of heteroaromatic compounds are therefore an alternative choice to the use of organometallic reagents to prepare π-conjugated molecules in a facile manner.

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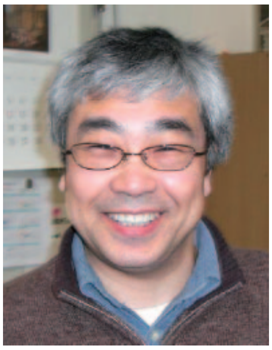

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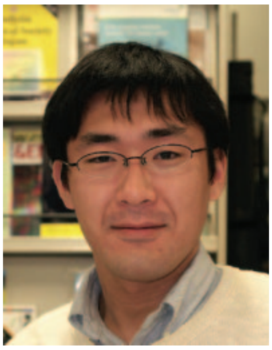

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