

## Palladium-Catalyzed C–H Homocoupling of Bromothiophene Derivatives and Synthetic Application to Well-Defined Oligothiophenes

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**Abstract:** Synthesis of oligothiophenes of well-defined structures that possess 2–8 thiophene units is performed with a new synthetic strategy involving C–H homocoupling of bromothiophenes and cross-coupling with organostannanes. Tolerance of the carbon–bromine bond to the palladium-catalyzed C–H homocoupling results in oligothiophenes bearing C–Br bonds at the terminal thiophene rings, which allow further transformation by the catalysis of a transition-metal complex.

### Introduction

Oligothiophenes have recently attracted remarkable attention as materials showing conductive, semiconductive, nonlinear optical, and liquid crystalline characteristics. Hence, it becomes important to synthesize oligothiophene derivatives with well-defined structures in high efficiency.<sup>1</sup> Homocoupling of thiophene is one of the most simple and practical pathways for bithiophenes; thus, repeating homocoupling of thiophene derivatives leads to further oligomers. Several homocoupling reactions of thiophene derivatives have been shown to proceed with a transition-metal catalyst. Dehalogenative coupling of halothiophenes<sup>2</sup> and oxidative coupling of metalated thiophenes<sup>3</sup> afford the corresponding bithiophenes. On the other hand, the coupling of thiophene at the carbon–hydrogen bond, which is much more straightforward, would be intriguing. We have preliminarily shown that palladium-catalyzed homocoupling of several thiophene derivatives takes place at the C–H bond adjacent to the sulfur atom

in the presence of silver(I) fluoride to afford the corresponding bithiophenes highly efficiently.<sup>4,5</sup> Worthy of note is that the homocoupling reaction of 2-bromothiophene also occurs at the C–H bond and the C–Br bond is completely intact. Accordingly, the obtained bithiophene possesses two C–Br bonds, which are readily available for a variety of transition-metal-catalyzed coupling and other reactions forming carbon–carbon bonds or carbon–heteroatom bonds.<sup>6</sup> Herein, we describe further studies on the homocoupling of several bromothiophene derivatives, and the synthesis of oligothiophenes bearing 2–8 thiophene units of well-defined structure is performed with the palladium-catalyzed C–H homocoupling of bromothiophene derivatives.

### Results and Discussion

When 2-bromothiophene (**1a**) was treated with silver(I) fluoride in the presence of 3 mol % of PdCl<sub>2</sub>(PhCN)<sub>2</sub> in DMSO, 5,5'-dibromo-2,2'-bithiophene (**2a**) was obtained in 77% yield as shown in eq 1. The reaction was shown to occur at room temperature, albeit the related homocoupling reaction of other thiophene derivatives must be carried out at elevated temperatures (60 °C or higher). Despite the use of the palladium complex as a catalyst, the C–Br bond of **1a** was found to be completely intact to afford the dibrominated bithiophene **2a**.



Further studies revealed that the reaction was found to take place with silver(I) nitrate/potassium fluoride system, which is



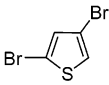
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**Table 1.** Palladium-Catalyzed C–H Homocoupling of Bromothiophene Derivatives<sup>a</sup>

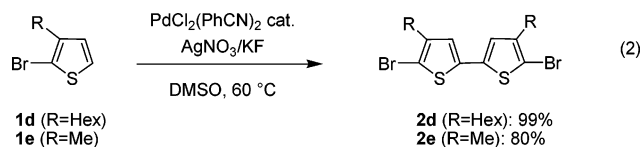
bromothiophene	method <sup>b</sup>	time, h	yield, % <sup>c</sup>
 <b>1a</b>	A	5	77
	B	24	52
	C	12+12	81
 <b>1b</b>	A	5	70 <sup>d</sup>
	C	12+12	90
 <b>1c</b>	A	5	59 <sup>d</sup>
	C	12+12	75 <sup>d</sup>

<sup>a</sup> The reaction was carried out with PdCl<sub>2</sub>(PhCN)<sub>2</sub> (3 mol %), AgF or AgNO<sub>3</sub>/KF in DMSO at room temperature. <sup>b</sup> Method A: The reaction with AgF (2 equiv). Method B: The reaction with AgNO<sub>3</sub>/KF (2 equiv/2 equiv, addition in one portion). Method C: The reaction with AgNO<sub>3</sub>/KF (2 equiv/2 equiv, addition in two portions). <sup>c</sup> Unless noted, isolated yield was shown. <sup>d</sup> The yield was estimated by <sup>1</sup>H NMR, using trichloroethene as an internal standard.

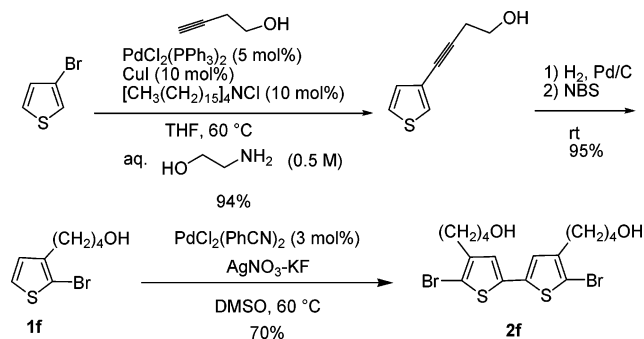
much less expensive than AgF, to afford **2a** in 52% yield under similar conditions. Table 1 summarizes the reaction of several bromothiophene derivatives. It was also found that the addition of AgF or AgNO<sub>3</sub>/KF in several portions improved the yield of homocoupling. When the addition of AgNO<sub>3</sub>/KF in two portions with stirring each 12 h was conducted at room temperature, **2a** was obtained in 81% yield. The homocoupling reaction of 2,3-dibromothiophene (**1b**) and 2,4-dibromothiophene (**1c**) was shown to take place under conditions similar to those of the reaction of **1a**. The reaction proceeded to afford the corresponding tetrabromobithiophenes **2b** and **2c** in 70% and 59% yields, respectively. Bromine atoms at the 3- and 4-positions were also intact under the palladium-catalyzed reaction conditions. It was also found that the addition of AgNO<sub>3</sub>/KF improved the yield of **2b** and **2c** to 90% and 75%, respectively. A similar effect with the use of the AgNO<sub>3</sub>/KF system instead of AgF was also observed in the related palladium-catalyzed C–H substitution reaction of thiophene and thiazole derivatives<sup>5b,7</sup> although the role of the silver reagent is completely different in that AgF was transformed into AgI in the C–H substitution, while homocoupling afforded Ag(0).

We then performed the reactions of thiophene bearing an alkyl substituent at the 3-position. Bromination of 3-hexylthiophene and 3-methylthiophene with NBS afforded 2-bromo-3-hexylthiophene (**1d**) and 2-bromo-3-methylthiophene (**1e**) regioselectively.<sup>8</sup> Treatment of **1d** with 1 mol % of PdCl<sub>2</sub>(PhCN)<sub>2</sub> in the presence of silver(I) nitrate and potassium fluoride at 60 °C for 6 h underwent homocoupling to give 5,5'-dibromo-4,4'-dihexyl-2,2'-bithiophene (**2d**) in 99% yield. The bithiophene derived from **1e** was also obtained in a similar manner. The reaction with AgF at room temperature for 5 h resulted in giving **2e** in 72% yield. The addition of AgNO<sub>3</sub>/KF (2 equiv) in two portions and stirring at 60 °C for 3 h × 2 improved the yield (80%).

Homocoupling of a bromothiophene derivative that possessed a hydroxy group in the alkyl chain at the 3-position was then



examined. Synthesis of 2-bromo-3-(4-hydroxybutyl)thiophene **1f** was carried out as outlined in Scheme 1. Sonogashira coupling of 3-bromothiophene with 2-ethanolamine as an activator at 60 °C followed by hydrogenation of the triple bond and bromination with NBS afforded **1f**.<sup>9</sup> Treatment of **1f** with AgNO<sub>3</sub>/KF (2 equiv) in two portions in the presence of 3 mol % of PdCl<sub>2</sub>(PhCN)<sub>2</sub> afforded **2f** in 70% yield. It should be pointed out that the homocoupling reaction of a bromothiophene derivative bearing a hydroxy group took place without protection of the hydroxy group.

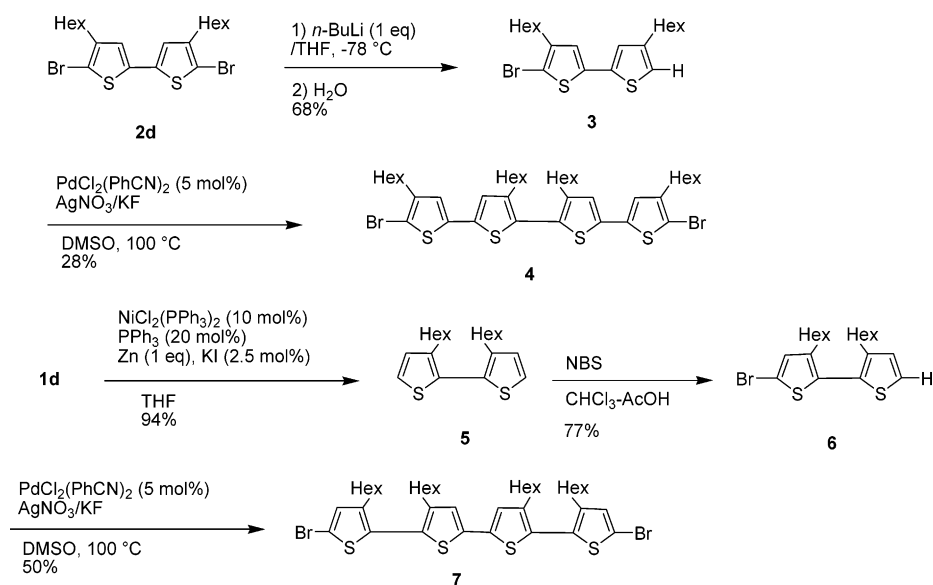
**Scheme 1**

Since the synthetic protocol for several dibromobithiophene derivatives was in hand, we envisaged the synthesis of further oligomers with the palladium-catalyzed homocoupling method. Selective monobromination of **2d** was performed with 1 equiv of *n*-butyllithium at –78 °C to afford **3**, which was again subjected to the palladium-catalyzed C–H homocoupling with AgNO<sub>3</sub>/KF at 100 °C. Quaterthiophene **4** was obtained in 28% yield after stirring at 100 °C for 24 h in DMSO. The low yield of **4** in the homocoupling would be due to the steric congestion of the head-to-head unit of the hexyl groups.

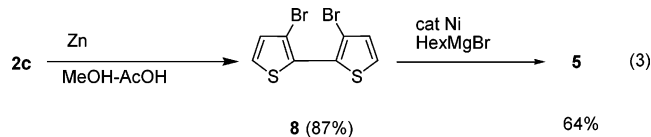
On the other hand, quaterthiophene with opposite head–tail regularity was synthesized by the combination of sequential nickel-catalyzed dehalogenative homocoupling<sup>2a,c</sup> and the palladium-catalyzed C–H homocoupling. Treatment of **1d** with zinc powder in the presence of a nickel catalyst underwent debrominative homocoupling to afford **5** in a good yield. The obtained **5** was then subjected to the selective monobromination under mild conditions with NBS. The palladium-catalyzed C–H homocoupling reaction of the monobrominated bithiophene **6** in the presence of AgNO<sub>3</sub>/KF furnished **7** in 50% yield (Scheme 2).

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## Scheme 2



Alternatively, the intermediate bithiophene **5** was obtained from tetrabromobithiophene **2c** as shown in eq 3. Selective debromination took place at the 5,5'-positions in the presence of Zn in AcOH to give **8**,<sup>10a</sup> followed by a nickel-catalyzed cross-coupling to introduce the hexyl group with Grignard reagent that also led to **5**.<sup>10a,11</sup>



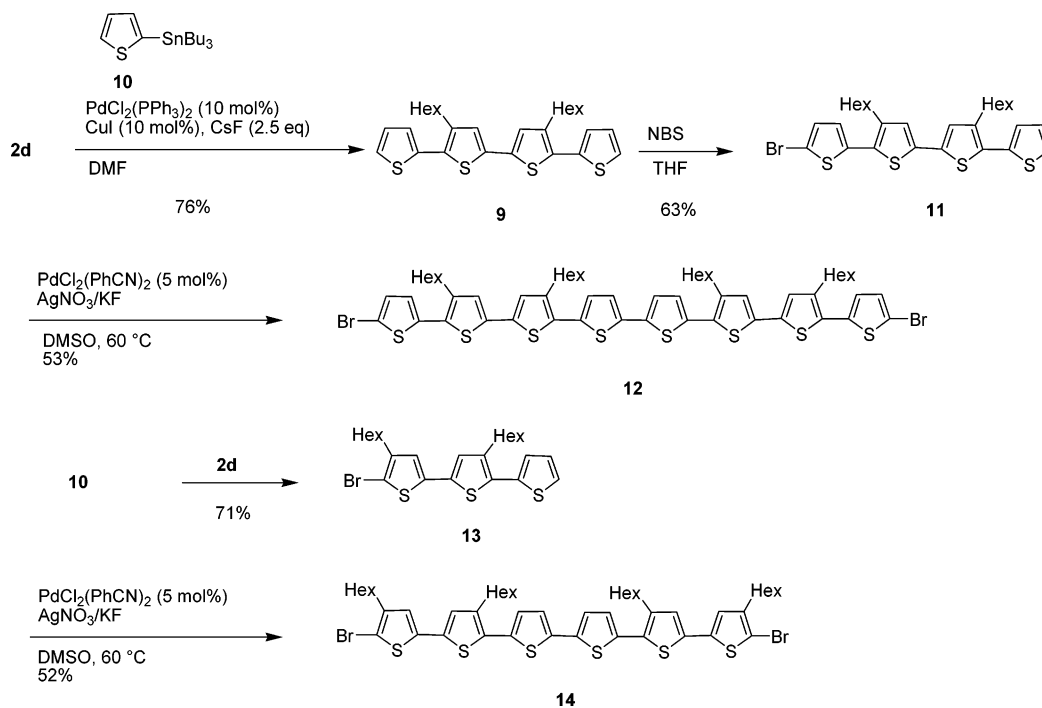
Synthesis of further oligomers was carried out as outlined in Scheme 3 with bithiophene **2d**. To avoid the head-to-head structure that may cause steric congestion, introduction of the

unsubstituted thieryl group by cross-coupling with 2-thienylstannanes was envisaged.<sup>12,13</sup> Quaterthiophene **9** was obtained in 76% yield when the Pd/Cu-catalyzed cross-coupling of **2d** was carried out with 2 equiv of thienyl(tributyl)stannane (**10**) at 60 °C for 21 h. Monobromination of **9** with NBS followed by C–H homocoupling led to the octamer **12**.

On the other hand, treatment of the thienyl tin reagent with excess **2d** afforded terthiophene **13** in 71% yield (based on **10**). The palladium-catalyzed C–H homocoupling reaction of **13** gave the corresponding hexamer **14**.

Properties of oligothiophenes **4**, **7**, **9'**, **12**, and **14** were compared. The tetramer **7** was prepared by bromination of **9** with 2 equiv of NBS. Table 2 shows the results of UV–vis absorption and photoluminescent spectra of the oligothiophenes. Among tetramers, **9'** exhibited the highest  $\lambda_{\text{max}}$  values of UV–

## Scheme 3



**Table 2.** Properties of Oligothiophene **4**, **7**, **9'**, **12**, and **14**<sup>a</sup>

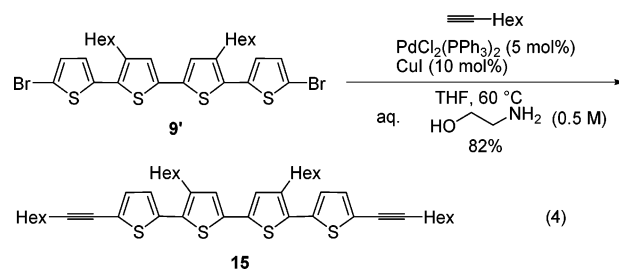
cmpd	UV-vis		emission	
	$\lambda_{\max}$ , nm	$\epsilon$ , M <sup>-1</sup> ·cm <sup>-1</sup>	$\lambda_{\max}$ , nm <sup>b</sup>	$\Phi$ <sup>c</sup>
<b>4</b> (4 mer)	355	47900	469	0.05
<b>7</b> (4 mer)	351	27900	460	0.01
<b>9'</b> (4 mer)	384	31600	471 (498)	0.04
<b>12</b> (8 mer)	437	75500	542 (578)	0.08
<b>14</b> (6 mer)	422	43600	521 (547, 574)	0.13

<sup>a</sup> UV-vis spectra were measured as 10<sup>-5</sup> M chloroform solution. Emission spectra were measured as 10<sup>-6</sup> M chloroform solution. <sup>b</sup> In the parentheses, shoulder peaks of emission are shown. <sup>c</sup> Quantum yield,  $\Phi$  was estimated by comparison of standard aqueous 1.0 M quinine sulfate solution ( $\Phi = 0.546$ ).

vis and emission spectra, while **4** and **7**, which bear head-to-head structures of two hexyl groups, showed  $\lambda_{\max}$  values of shorter wavelength due to the steric repulsion. The  $\lambda_{\max}$  values of UV-vis and emission spectra in further oligomers **12** and **14** red-shifted to 40–70 nm.

Since oligothiophenes **9'**, **12**, and **14** possess bromo groups, it would be possible to introduce several functional groups at the end with transition-metal-catalyzed reactions. Oligothiophenes bearing alkynyl moieties have recently been revealed to show conductivities with novel electron transport behaviors as well as liquid crystalline characteristics.<sup>1h</sup> Indeed, the reaction of dibromoquaterthiophene **9'** with 1-octyne was carried out with a Pd/Cu catalyst system in the presence of 2-ethanolamine as an activator to afford **15** in 82% yield as shown in eq 4.<sup>9a</sup>

Measurement of UV-vis and photoluminescent spectra of **15** revealed  $\lambda_{\max}$  of 405 nm and emission peak of 492 nm ( $\Phi = 0.15$ ), respectively. Further studies on liquid crystalline characteristics and electron mobility of **15** and several related compounds will be described in due course.



## Conclusion

In summary, C–H homocoupling of bromothiophene derivatives was found to take place under mild conditions. The use of the new activator system, AgNO<sub>3</sub>/KF, was shown to be similarly effective as AgF. Several oligothiophenes were synthesized efficiently with repeating palladium-catalyzed C–H homocoupling in the presence of the silver reagent system as an activator. In addition, cross-coupling of thienyl tin reagent with bromothiophene would also be remarkable for the homologation of thiophene unit for the synthesis of oligothiophenes. With these methodologies, further oligomers of well-defined structure would be prepared in a similar manner.

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**Supporting Information Available:** Experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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