1. Introduction

π-Conjugated aromatic and heteroaromatic compounds have been utilized as a wide variety of advanced organic materials. In particular, oligothiophenes and polythiophenes, which are composed of multiple linkage of sulfur-containing five-membered heteroaromatic compounds, involve potential utilization for conductive,\(^1\) organic-semiconductive,\(^2\) and liquid crystalline materials.\(^3\)

Cross coupling, which is a carbon-carbon bond-forming reaction with organometallic compounds and organic electrophiles in the presence of a transition metal catalyst, is a highly effective method for the synthesis of such π-conjugated organic materials,\(^4\) however, the major drawback of cross coupling strategy is the preparation of the organometallic reagent prior to the transition metal-catalyzed reaction as well as the formation of metal salt waste accompanied by the desired cross-coupling product. If the related coupling product is formed by the direct reaction at the C-H bond of an organic compound,\(^5\) the process is remarkably simplified. In recent years, extensive studies to synthesize π-conjugated organic compounds with C-H coupling are carried out.\(^6\) We herein describe our recent studies on the synthesis of oligo- and polythiophenes using C-H coupling reactions.

2. Oligothiophenes

Oligothiophenes have recently attracted considerable attention in materials science as advanced organic materials with electronic and optoelectronic characteristics. These are employed as various materials such as thin-film organic transistors,\(^7\) liquid crystalline compounds,\(^8\) and dye-sensitized organic photovoltaic cells\(^9\) as representative in Figure 1.

Oligothiophenes composed of a thiophene unit bearing a substituent at the 3-position form three type of possible regioisomers, head-to-head (HH), tail-to-tail (TT), and head-to-tail (HT) as shown in Figure 2. Among these, the HT isomer generally shows a superior performance as materials due to the least steric congestion and thus occurring extended π-conjugation.\(^{2c, 7d, 9d}\) Development of a concise preparative method of HT-type oligothiophenes is therefore an important issue in organic synthesis.

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**Figure 1.** Oligothiophene derivatives as advanced materials.
2-1. Previous synthetic methodologies of HT type oligothiophenes

Transition metal catalyzed cross coupling reaction of thiophene and thiophene to form bithiophene would be an effective synthetic method for HT type oligothiophenes. Suzuki-Miyaura coupling with organoboranes and Migita-Kosugi-Stille coupling with organostannanes have actually been employed for the oligothiophene synthesis.10,11) When halogenation of the bithiophene, which is formed by the thiophene-thiophene cross coupling, is conducted, the halogenated thiophene, again, can be a substrate for the reaction of further metallated thiophene thus allowing stepwise extension of the thiophene unit. Hence, oligothiophene with a certain number of thiophene unit would be formed by repeating the cross coupling and halogenation sequence as shown in Scheme 1.12-14) We have also reported iterative extension of thiophene unit leading to HT-oligothiophenes using palladium catalyzed C–H coupling.15) We have previously shown that C–H arylation of thiophenes with AgNO3/KF as an activator only takes place with aryl iodide whereas no reaction occurs with the corresponding bromides.16) Stepwise extension of a thiophene unit would be possible by combining C–H arylation of thiophene bearing carbon–bromine bond with iodothiophene affording the bithiophene and a halogen exchange reaction of thus formed bithiophene bromide to give the bithiophene iodide (Scheme 2).

Figure 2. Regioregularity of oligothiophenes.

Scheme 1. Synthetic strategy for the stepwise preparation of HT-oligothiophene.

Scheme 2. Iterative synthesis of oligothiophene by C-H functionalization and halogen exchange.
2-2. Synthetic method of HT type oligothiophenes with regioselective C–H coupling reaction 17)

A simpler synthesis of HT-type oligothiophenes is available by employing the regioselective C–H coupling of 3-hexylthiophene. We envisaged developing regioselective metalation of 3-substituted thiophene by hydrogen abstraction to generate a coupling precursor for the reaction of 2-bromo-3-hexylthiophene leading to the corresponding HT connected bithiophene. The bithiophene thus formed would be employed directly as a substrate for further extension without any transformation. Hence, this synthetic strategy would require only a single step per extension of the thiophene unit, which contrasts with the previous stepwise oligothiophene syntheses performed in the two steps sequence for extension of one thiophene unit.

Such strategy was achieved by the use of TMPMgCl·LiCl (Knochel-Hauser base)18,19) and a nickel-catalyzed cross-coupling. The single step extension of a thiophene unit leading to well-defined HT-oligothiophene was shown to take place highly efficiently. TMPMgCl·LiCl was indeed found to extract the C–H bond of 5-position of 3-hexylthiophene regioselectively. Treatment of 3-hexylthiophene with TMPMgCl·LiCl was carried out at room temperature for 3 h in THF, probably forming 5-metalated thiophene, which was confirmed by treatment of N,N-dimethylformamide (DMF) to afford the corresponding aldehyde, exclusively, in 93% yield. We also found that regioselective metalation of 3-hexylthiophene took place by using ethyl magnesium chloride (EtMgCl) and a catalytic amount of 2,2,6,6-tetramethylpiperidine (TMPH) instead of stoichiometric TMPMgCl·LiCl. (Scheme 4)

Asselin reports that treatment of 3-methylthiophene with 10 mol% of TMPH and EtMgCl and following addition of an aldehydes result in giving the corresponding secondary alcohol.20) We also confirmed the regioselective metalation of 3-hexylthiophene by the reaction of 10 mol% of TMPH and the

![Scheme 3. Oligothiophene synthesis by regioselective metalation.](image)

![Scheme 4. Regiochemical study on the metalation of 3-hexylthiophene with TMPMgCl·LiCl or cat.TMPH/EtMgCl.](image)

![Scheme 5. Mechanism of metalation of thiophene with cat.TMPH/EtMgCl.](image)
ethyl Grignard reagent, whereas the use of dicyclohexylamine instead of TMPH induced inferior regioselectivity.

Scheme 5 shows the reaction mechanism of the metation at the C−H bond of thiophene. The reaction of TMPH with EtMgCl forms magnesium amide TMPMgCl. The formed TMPMgCl abstracts the 5-position of 3-hexylthiophene accompanied by TMPH, thus, allowing the metation with catalytic use of secondary amine.

Scheme 6 summarizes the synthesis of HT-type oligomers of 3-hexylthiophene using TMPMgCl·LiCl or a combination of EtMgCl and 10 mol% of TMPH. The regioselective coupling of 3-hexylthiophene was found to proceed with 2-bromo-3-hexylthiophene (Th-Br) in the presence of 2.0 mol% of nickel catalyst bearing a N-heterocyclic carbene (NHC) ligand SIPr, 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidine, to afford HT-2-mer in >99% yield at 60 °C, whereas HH isomer was not observed at all. The obtained HT-2-mer was subjected to the further reaction with Th-Br with 10 mol% of TMPH and 1.5 equiv of EtMgCl in a similar manner furnishing terthiophene in 90% yield. Treatment of HT-3-mer with TMPH (10 mol%) and EtMgCl (1.8 equiv) and the reaction with Th-Br lead to quaterthiophene (HT-4-mer) in 72% yield. (a) It was also found that formation of HT-4-mer was also performed by the reaction of HT-2-mer with mono-brominated bithiophene to afford HT-4-mer in 69% yield. In addition, HT-3-mer reacted with brominated terthiophene to give the corresponding sexithiophene. The results are represented in Scheme 6. (b)

We also found that the reaction with 2-chloro-3-
hexylthiophene (Th-Cl) instead of Th-Br took place successfully by using 2.0 mol% of NiCl2(PPh3)IPr as a nickel catalyst to give HT-2-mer and HT-3-mer in excellent yield, respectively (Scheme 7).

This simple iterative extension of the thiophene ring is applied to the short formal synthesis of MK-1 and MK-2, which are organic dye molecules for the dye-sensitized organic photovoltaic cell showing excellent energy-conversion efficiency.9b,9d) As shown in Scheme 8, the reaction of terthiophene (HT-3-mer) and quaterthiophene (HT-4-mer) with TMPMgCl·LiCl and following addition of 3-iodo-9-ethylcarbazole in the presence of palladium catalyst PEPPSI-SiPr21-23) (2.0 mol%) led to incorporation of the carbazole moiety. The obtained products are identical with the reported intermediates and following sequential Vilsmeier formylation and Knoevenagel reaction to introduce the cyanoacrylic acid moiety into the terminal thiophene ring would be performed by the literature method leading to MK-1 and MK-2.9)

It was also found to be possible to undergo cross coupling between different 3-substituted thiophenes. The reaction proceeded in a similar manner to afford bithiophenes bearing various substituent in good yields as summarized in Scheme 9. Bithiophene obtained in this way was transformed into terthiophene bearing three different substitutents.

3. Polythiophene synthesis with bromothiophene derivatives as a monomer

Synthesis of HT-type-poly(3-hexylthiophene)s (P3HT) has been carried out with 2,5-dibromo-3-substituted-thiophene by the reaction of zinc or a Grignard reagent to induce metalation at the 5-position of thiophene ring in a regioselective manner and thus occurring cross coupling polycondensation with the remaining C-Br bond by Kumada-Tamao coupling (Mg) or Negishi coupling (Zn). In 1992, Rieke reported synthesis of HT-type P3HT by the reaction of 2,5-dibromo-3-hexylthiophene with Rieke zinc, which is the activated zinc, at low temperature leading to the corresponding organozinc and the following addition of palladium or nickel catalyst induced the cross-coupling polymerization.24) McCullough also showed that formation of the corresponding thiophene-magnesium species was achieved by the reaction of an alkyl Grignard reagent to undergo magnesium-halogen exchange and the nickel-catalyzed polymerization.23) Yokozawa improved the selective metalation by switching the exchanging bromine to iodine and discussed the possibility of living polymerization.26).

Concerning polythiophene synthesis utilizing the metalation at the C-H bond of thiophene, McCullough employed lithium amide to undergo proton abstraction at the 5-position
of thiophene, the following metal exchange by the addition of ZnCl₂ to afford the similar organometallic species, and nickel or palladium-catalyzed polymerization. The method had to be carried out with low-temperature process (−78 °C) and complicated procedures. We envisaged to develop much simpler and practical C-H coupling polymerization and the use of Knochel-Hauser base (TMPMgCl·LiCl), which was highly effective for oligothiophene synthesis, was examined. The reaction of 2-bromo-3-hexylthiophene with TMPMgCl·LiCl was found to proceed at room temperature within 30 min to afford the corresponding organometallic species. (Table 1)

When the polymerization of bromothiophene was carried out with TMPMgCl·LiCl, polymerization took place highly efficiently with NiCl₂dppe or NiCl₂dppp as a catalyst to afford P3HT in good yield with high HT selectivity as shown in Scheme 10. The reaction proceeded in a quantitative yield and the molecular weight showed good correspondence with the ratio of monomer/nickel catalyst. Polythiophene with molecular weight of higher than 40000 was obtained in the presence of 0.5 mol% of the catalyst with relatively narrow molecular weight distribution and high HT selectivity (>98%).

It is also an interesting issue as a facile synthetic protocol to achieve ‘one-shot’ polymerization, which is the addition of substrate, reagent, and catalyst in one portion. In terms of the GRIM method, debrumination polymerization of 2,5-dibromo-3-thiophene, complete conversion of the dibromothiophene with a Grignard reagent to the corresponding metalated thiophene and the following nickel-catalyzed cross-coupling polymerization is a requisite, otherwise, no polymer would be obtained because of the termination reaction of Thienyl‒Ni‒Br, which is the reactive propagation end, with a remaining alkyl Grignard reagent. On the other hand, Knochel-Hauser base, sterically congested

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**Table 1. Generation of metalated thiophenes as polythiophene precursors.**

<table>
<thead>
<tr>
<th>Method</th>
<th>X</th>
<th>Y</th>
<th>Step 1</th>
<th>ratio A:B (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rieke</td>
<td>Br</td>
<td>Br</td>
<td>Zn⁺, −78 °C to rt, 4 h</td>
<td>97:3 (ZnBr)</td>
</tr>
<tr>
<td>GRIM</td>
<td>Br</td>
<td>Br</td>
<td>RMgX, rt, 30 min</td>
<td>~85:~15 (MgX)</td>
</tr>
<tr>
<td>Yokozawa</td>
<td>Br</td>
<td>I</td>
<td>PrMgCl, 0 °C, 30 min</td>
<td>~99:~1 (MgCl)</td>
</tr>
<tr>
<td>McCullough</td>
<td>Br</td>
<td>H</td>
<td>1) LDA, −40 °C, 40 min</td>
<td>~98:~2 (ZnCl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) ZnCl₂, −60 to −40 °C, 40 min</td>
<td></td>
</tr>
<tr>
<td><strong>Our group</strong></td>
<td>Br</td>
<td>H</td>
<td>TMPMgCl·LiCl, rt, 30 min</td>
<td>~99:~1 (MgCl·LiCl)</td>
</tr>
</tbody>
</table>

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**Scheme 10. Synthesis of HT-P3HT with 2-bromo-3-hexylthiophene and Knochel-Hauser base.**
magnesium amide, would not cause any undesired side reactions such as termination of polymerization, thus one-shot addition would be plausible for the dehydrobrominative polymerization with 2-bromo-3-hexylthiophene with TMPMgCl. (Scheme 11)

When NiCl₂dppp was employed as a nickel catalyst for one-shot polymerization of 2-bromo-3-hexylthiophene, the corresponding P3HT was obtained in excellent yield and high HT-regioregularity. Although the molecular weight distribution of the polymer was relatively broad, this value was improved when a nickel complex bearing 2-methylphenyl (o-tol) group NiCl(o-tol)dppp was employed. (Scheme 12) This simple protocol allows to avoid preparation of metalated species prior to the polymerization, thus, a remarkable advantage of C-H coupling polymerization compared with the GRIM method.

4. Polythiophene synthesis of extremely high molecular weight

A nickel catalyst bearing N-heterocyclic carbene (SIPr) and cyclopentadienyl (Cp) group as ligands, which was developed by Nolan, was found to give the corresponding P3HT with the molecular weight of higher than 100,000. When the reaction was carried out with 2.0 mol% of CpNiCl(SIPr) at room temperature for 24 h, HT-type P3HT with Mw of higher than 400,000 was obtained. (Scheme 13) It has not been shown to give HT-type polythiophene with the molecular weight of higher than 100,000 and the molecular weight of commercially available polythiophene is as high as 50,000, therefore, novel characteristics of thus obtained extremely high HT-polythiophene may be interesting.
5. Polymerization of chlorothiophene

It is an important issue to consider atom efficiency particularly when a larger scale preparation is conducted. In the GRIM method with 2,5-dihalothiophene, the obtained P3HT would be as high as 50 g by employing 100 g of the starting material. On the other hand, 100 g of monobromothiophene can afford ca. 70 g of P3HT. Accordingly, we envisaged the P3HT synthesis with 2-chloro-3-hexylthiophene for the purpose of further improvement of the atom efficiency, which brings about the mass loss of only 17%. (Scheme 14) However, it is well known that the reactivity of cross coupling with aryl chloride is much lower than that of the corresponding iodide or bromide.

Indeed, when the polymerization of 2-chloro-3-hexylthiophene was conducted with TMPMgCl·LiCl and 0.5 mol% of NiCl₂dppe at 25 °C for 24 h, which is the conditions to undergo the polymerization of bromothiophene highly efficiently, only afforded P3HT in 18% with the molecular weight of 4200. (Scheme 15)

Although the yield and the molecular weight was improved by the use of NiCl₂dppp, it is still unsatisfactory, it was found that a commercially available nickel(II) chloride complex bearing triphenylphosphine and N-heterocyclic carbene (NHC) ligands NiCl₂(PPh₃)IPr dramatically improved the polymerization efficiency to afford P3HT with the molecular weight of 29200 with relatively narrow molecular weight distribution (Mw/Mn = 1.29). (Scheme 16)

Figure 3(a) shows the relationship of the ratio of the consumed monomer/nickel catalyst with the molecular weight (Mn) of the obtained polymer indicating linear increasing of


Scheme 15. Effect of halogen atom in the Ni-catalyzed P3HT synthesis.

Scheme 16. Polymerization of 2-chloro-3-hexylthiophene using NiCl₂(PPh₃)IPr.
$M_n$ by decreasing the catalyst loading. It was also found that the molecular weight showed linear increase corresponding to the monomer conversion and the molecular weight distribution was constantly narrow as shown in Figure 3(b). These results suggest that the polymerization of 2-chloro-3-hexylthiophene with NiCl$_2$(PPh$_3$)$_2$IPr as a catalyst proceeds in a living manner.

6. Polymerization with Grignard reagent and catalytic amine

As shown in the oligothiophene synthesis, metalation of 2-chloro-3-hexylthiophene was also examined with a Grignard reagent and a catalytic amount of secondary amine. Treatment of 2-chloro-3-hexylthiophene with EtMgCl (1.0 eq) and 10 mol% of TMPH at 60 °C for 10 h induced metalation at the 5-position, which was confirmed by treatment with iodine to

![Figure 3.](image_url)

Figure 3. (a) Relationship of the monomer/catalyst feed ratio toward $M_n$ and $M_w/M_n$. (b) Relationship of monomer conversion vs $M_n$.

![Scheme 17.](image_url)

Scheme 17. Metalation of 2-halothiophene with Grignard reagent and a catalytic amount of amine.

![Table 2.](image_url)

Table 2. Generation of thienyl magnesium species with a Grignard reagent and a catalytic amount of amine.
result in giving 5-iodinated product in 88% yield. By contrast, metalation at the 5-position was not observed in the similar reaction of 2-bromo-3-hexylthiophene but to afford bromine-iodine exchange at the 2-position. (Scheme 17) We then examined several combination of Grignard reagent and amine. Since regiochemical control was not necessary in this case, less bulky amines was found to be available in the deprotonation of 2-chloro-3-hexylthiophene. It should be pointed out that the reaction with EtMgCl and dicyclohexylamine (Cy₂NH) was found to complete the metalation within 1 h at 60 °C as shown in Table 2.

Several 3-substituted chlorothiophenes were subjected to the polymerization with the above optimized metalation protocol and following nickel-catalyzed cross coupling. Substituents bearing n-octyl group and ether functionality were successfully applied to the polymerization to afford the corresponding poly(3-substituted thiophene)s in excellent yield, high HT-selectivity, and narrow molecular weight distribution as shown in Table 3.³³

### Table 3. Polycondensation of chlorothiophene using Grignard reagent and catalytic amine.

<table>
<thead>
<tr>
<th>Chlorothiophene</th>
<th>$M_n$</th>
<th>$M_w/M_n$</th>
<th>%HT</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{HC}=$ Hex ⊠ Cl</td>
<td>14900</td>
<td>1.21</td>
<td>98</td>
<td>82</td>
</tr>
<tr>
<td>$\text{HC}=$ n-C₈H₁₇ ⊠ Cl</td>
<td>23100</td>
<td>1.29</td>
<td>99</td>
<td>76</td>
</tr>
<tr>
<td>$\text{HC}=$ CH₂OC₆H₁₃ ⊠ Cl</td>
<td>17000</td>
<td>1.31</td>
<td>99</td>
<td>84</td>
</tr>
</tbody>
</table>

7. **Practical head-to-tail-type polythiophene synthesis**

The following scheme represents comparison of our C-H coupling polymerization and the GRIM method. In addition to the difference of the starting monomer precursor, there is a difference in only the use of a catalytic amount of secondary amine. In considering the atom efficiency, the process with chlorothiophene by C-H coupling polymerization involves potentially practical advantage after further scale-up studies have been subjected. (Scheme 18)
8. Conclusion

We have described that thiophene-thiophene bond formation is successfully performed by the formation of thiophene organometallic species by the reaction of thiophene C-H bond with magnesium amide or the combined use of Grignard reagent and catalytic amine. The method efficiently leads to the formation of head-to-tail-type thiophene-thiophene bond to afford well-defined oligothiophenes and polythiophenes. The method can be applied to the synthesis of a variety of thiophene derivatives as advanced materials.

References


21) PEPPSI™: Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation.


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Shunsuke Tamba received his B.S. in 2009, M.S. in 2011, and Ph.D. in 2013 from Department of Chemical Science and Engineering, Kobe University. He had been a JSPS graduate research fellow in 2012-2014. In 2013-2014, he joined Professor Carlos Saa's group of Universidad de Santiago Compostela. He is now a JSPS postdoctoral fellow of Osaka University with Professors Yoshio Aso and Yutaka Ie since 2014.

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**TCI Related Products**

### Nickel Catalyst

![NiCl₂(Ph₃P)IPr](image)

NiCl₂(Ph₃P)IPr

200mg, 1g [B3235]

### 3-Alkylthiophene

- **3-Hexylthiophene**
  1g, 5g, 25g [H0756]

- **2-Bromo-3-hexylthiophene**
  5g, 25g [B3507]

- **2-Chloro-3-hexylthiophene**
  5g [C2613]

- **2-Bromo-3-hexyl-5-iodothiophene**
  (stabilized with Copper chip)
  1g, 5g [B3865]

- **3-Methoxythiophene**
  1g, 5g [M1093]

- **3-Methylthiophene**
  25g, 500g [M0440]

### Bithiophene

- **2,2'-Bithiophene**
  1g, 10g, 25g [B1276]

- **2,4'-Dihexyl-2,2'-bithiophene**
  1g, 5g [D3928]

- **P3HT (regioregular)**
  200mg, 1g [P2018]

### Others

- **B3691** 2-Bromo-3-dodecylthiophene
  5g

- **D4053** 2,5-Dibromo-3-octylthiophene
  5g

- **D4031** 2,5-Dibromo-3-dodecylthiophene
  5g

- **E0378** 3-Ethylthiophene
  5mL, 25mL

- **P1128** 3-Propylthiophene
  1g, 5g

- **B1458** 3-Butylthiophene
  1g, 5g

- **P1127** 3-Pentylthiophene
  1g, 5g

- **H0722** 3-Heptylthiophene
  1g, 5g

- **O0213** 3-Octylthiophene
  1g, 5g, 25g

- **E0973** 3-(2-Ethylhexyl)thiophene
  200mg, 1g

- **N0533** 3-Nonylthiophene
  1g, 5g

- **D2098** 3-Decyliothiophene
  1g, 5g

- **U0056** 3-Undecylthiophene
  1g, 5g

- **D2016** 3-Dodecylthiophene
  1g, 5g, 25g

- **O0245** 3-Octadecylthiophene
  1g, 5g