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Concise Synthesis of Well-Defined Linear and Branched Oligothiophenes with Nickel-Catalyzed Regiocontrolled Cross Coupling of 3-Substituted Thiophenes by Catalytically-Generated Magnesium Amide

Shota Tanaka, Daiki Tanaka, Go Tatsuta, Kohei Murakami, Shunsuke Tamba, Atsushi Sugie, and Atsunori Mori*[a]

Abstract: Synthesis of linear and branched oligothiophenes of well-defined structures is performed with regioselective deprotonation of 3-substituted thiophene and nickel-catalyzed cross coupling of the thus formed metalated species with bromothiophene. The reaction of 3-hexylthiophene with EtMgCl and 10 mol% of TMP-H induces the metalation at the 5-position selectively by catalytically-generated hindered magnesium amide (TMPMgCl) and the subsequent reaction of 2-halo-3-hexylthiophene (bromide or chloride) in the presence of a nickel catalyst affords head-to-tail (HT) type dimer. By repeating the same sequence the linear oligothiophene up to 4-mer is synthesized in good yield. The reaction of 3-hexylthiophene with 2,3-dibromothiophene also takes place to afford branched oligothiophene 3-mer in a quantitative yield. The obtained 3-mer is also metalated at the sterically less-hindered position in a regioselective manner furnishing 7-mer in >99% yield after the coupling reaction with 2,3-dibromothiophene again. These dendrimers react with several multi-functionalized organic electrophiles leading to a variety of branched oligothiophenes.

Keywords: oligothiophene • dendrimers • regioselective cross coupling • nickel catalyst• NHC ligand

Introduction

Oligothiophenes and polythiophenes have recently attracted remarkable attention as materials showing conductive, semiconductive, nonlinear optical, and liquid crystalline characteristics, etc. These are employed as thin-film organic transistors,[1] liquid-crystalline compounds,[2] and dye-sensitized organic photovoltaic cells.[3] Oligothiophenes composed of a thiophene unit bearing a substituent at the 3-position form three types of possible regioisomers, head-to-head (HH), tail-to-tail (TT), and head-to-tail (HT). Among these, the HT isomer generally shows a superior performance as materials due to the least steric congestion and thus occurring extended π-conjugation.[1d, 3b-d, 4] Development of a concise preparative method of HT-type oligothiophenes is therefore an important issue in organic synthesis.[5, 6]

Branched oligothiophene dendrimers have also been studied as represented by pioneering works of Advincula and Bäuerle as potentially applicable light-harvesting,[7] self-assembly,[8] and optoelectronic materials.[9, 10] These oligothiophene dendrimers have been synthesized employing cross-coupling reactions of organoboron[11] and organotin[12] reagents and the synthesis requires two-step sequence in each extension of the number of generation involving transition-metal-catalyzed coupling and further transformation of the thus coupled dendron again into the corresponding organometallic reagent.[13] Accordingly, a rather multi-step synthetic pathway has been repeated when oligothiophene dendrimers of higher order generations are designed to prepare. Development of a more concise preparative method of thiophene dendrimers is therefore intriguing.

On the other hand, we have been engaged in the coupling reaction at the C–H bond of heteroaromatic compounds with various organic electrophiles.[14, 15] The method allows remarkable step efficiency by the direct activation of the C–H bond or in situ formation of metallic species by deprotonative metalation prior to the coupling compared with existing cross coupling with the isolated organometallic compounds such as boron, silicon, and tin reagents.

We have recently reported HT-type oligothiophene[16, 17] and polythiophene[18] syntheses with nickel-catalyzed cross coupling at the C–H bond of thiophene, in which a stoichiometric amount of magnesium amide TMPMgCl·LiCl recognized as Knochel-Hauser base[19] served as an efficient deprotonating agent for in-situ

[a] S. Tanaka, D. Tanaka, G. Tatsuta, K. Murakami, S. Tamba, Dr. A. Sugie, Prof. Dr. A. Mori
Department of Chemical Science and Engineering
Kobe University
1-1 Rokkodai, Nada, Kobe 657-8501 (Japan)
Fax: (+81) 78-803-6181
E-mail: amori@kobe-u.ac.jp

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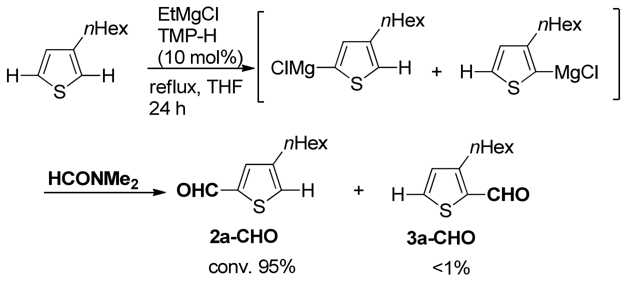
formation of the metalated species. A series of linear oligothiphenes can be synthesized by repeating the coupling reaction, in which a single one-pot reaction has extended a thiophene unit in a facile manner in contrast with multi-step conventional cross-coupling pathway. Although we have also shown that the combination of a Grignard reagent and catalytic secondary amine[20, 21] is equally effective for the metalation to the use of a stoichiometric amount of the Knochel-Hauser base, the reaction condition of such a catalytic metalation process has little been optimized and the scope and limitation have not been clear yet. Herein, we describe further studies of such a catalytic system of deprotonation for the synthesis and the application to the concise stepwise synthesis of well-defined linear HT-type oligothiophenes.

Furthermore, we envisaged that such regioselective deprotonation of thiophene and the subsequent coupling reaction with 2,3-dibromothiophene in the presence of a nickel catalyst afford a branched thiophene 3-mer and repeating of the similar reaction extends the generation leading to the oligothiophene dendron, which would be much simpler and step-economic synthesis of oligothiophene dendrimers. We also disclose that a variety of well-defined branched oligothiophenes are synthesized by the stepwise regioselective metalation and the following cross-coupling reaction of multifunctionalized organic electrophiles.

Results and Discussion

When 3-hexylthiophene (**1a**) was treated with ethyl magnesium chloride (EtMgCl) and 10 mol% of 2,2,6,6-tetramethylpiperidine (TMP-H) for 24 h in THF under reflux, the reaction proceeded to give metalothiophene at the C–H bond of the 5-position selectively, which was confirmed by treatment of *N*,*N*-dimethylformamide (DMF) to afford the corresponding 2-formyl-4-hexylthiophene (**2a-CHO**), exclusively (Scheme 1).



Scheme 1. Regioselective deprotonation of 3-hexylthiophene with EtMgCl and TMP-H

We examined the regioselectivity in the metalation of **1a** with ethylmagnesium chloride (EtMgCl) and a catalytic amount of several secondary amines to form the corresponding thienylmagnesium. Table 1 summarizes the results. The progress of the reaction was confirmed by quenching the mixture with DMF to afford 2-formyl-4-hexylthiophene (**2a-CHO**) and 2-formyl-3-hexylthiophene (**3a-CHO**). The reaction with 10 mol% of TMP-H under reflux in THF for 24 h completely proceeded to afforded **2a-CHO**, exclusively, while shorter reaction periods (10 h) resulted in inferior conversion. Although the reaction with 10 mol% of TMP-H at room temperature for 24 h selectively afforded **2a-CHO**, the conversion was decreased to 28%. The reaction with diisopropylamine (^{i}Pr$_2$NH) resulted in inferior regioselectivity and reactivity. The use of dicyclohexylamine (Cy$_2$NH) was also found to induce slightly inferior regioselectivity although the reaction proceeded smoothly. We have recently shown that metalation of 2-chloro-3-hexylthiophene with EtMgCl and 10 mol% of Cy$_2$NH proceeded completely within 1 h.[18a] However, the reaction of 3-hexylthiophene, whose C–H bond at the 5-position was less acidic, for 1 h underwent the metalation in insufficient conversion (26%).

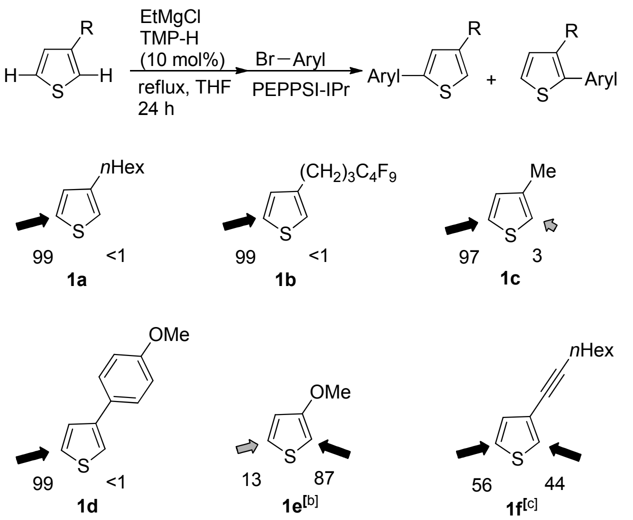
Table 1. Regioselectivity in the metalation of **1a** with several amine (10 mol%) and EtMgCl.[a]

Amine	Temp. (°C)	Time (h)	Conv. (%)[b] (**2a-CHO/3a-CHO**)
TMP-H	rt	24	28 (>99/1)
	reflux	10	56 (>99/1)
	reflux	24	95 (>99/1)
^{i}Pr$_2$NH	reflux	24	86 (93/7)
Cy$_2$NH	reflux	24	80 (91/9)
	reflux	1	26 (96/4)

[a] The reaction was performed with **1a** (0.5 mmol), EtMgCl (0.6 mmol), amine (0.05 mmol) in 0.6 mL of THF. [b] Conversion and the ratio of **2a-CHO**/**3a-CHO** were estimated by ^{1}H NMR analysis.

The transition metal-catalyzed cross-coupling reaction of 4-bromotoluene in the presence of a palladium catalyst (PEPPSI-IPr)[22] was carried out with the above optimized metalation conditions of **1a** at the 5-position using EtMgCl and 10 mol% of TMP-H for 24 h to afford 5-arylated product exclusively in 81% yield. The arylation reactions with several 3-substituted thiophenes were then examined to study the selectivity of the C–H bond as summarized in Table 2. The reaction of 3-fluoroalkylated thiophene (**1b**) and 3-arylated thiophene (**1d**) with 4-bromotoluene also occurred regioselectively at the 5-position. The reaction of 3-metylthiophene (**1c**) resulted in slightly inferior regioselectivity (97/3). By contrast, the reaction of 3-methoxythiophene (**1e**) resulted to afford 2-arylated product predominantly probably due to the directing effect of the methoxy group in the reaction of magnesium amide. Less selective metalation was found to occur with an alkynyl group-substituted thiophene (**1f**).

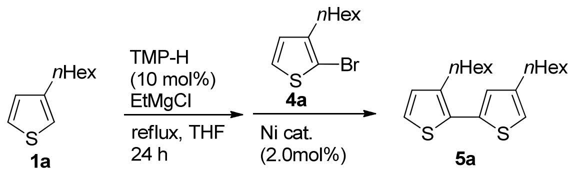
Table 2. Regiochemistry of 3-substituted thiophene.[a]



[a] Unless otherwise noted, the reaction was carried out with 3-substituted thiophene (0.50 mmol), 4-bromotoluene (0.75 mmol), EtMgCl (0.60 mmol), TMP-H (0.05 mmol) and PEPPSI-IPr (0.01 mmol) in 2.0 mL of THF. The ratio of 2-arylated and 5-arylated products was estimated by ^{1}H NMR analysis. [b] The ratio of 2-arylated and 5-arylated products was determined by GC analysis. [c] The reaction was performed with 4-bromoanisole (0.75 mmol).

With regioselective metalation at the 5-position of 3-substituted thiophene, we focused on the application to the formation of HT-type-thiophene–thiophene bond. The reaction of **1a** with 2-bromo-3-hexylthiophene (**4a**) was examined with several transition metal catalysts. As shown in Table 3, the reaction with nickel catalyst bearing bidentate diphosphine $NiCl_2$(dppp) at 60 °C for 24 h proceeded to afford the HT-type dimer (**5a**) in an excellent yield (90%). The reaction of $NiCl_2$(dppe) also resulted in a good yield. The use of a combination of Ni(cod)$_2$ and an *N*-heterocyclic carbene (NHC) ligand[23] SIPr, which showed excellent performance in the reaction of **1a** with **4a** using Knochel-Hauser base, resulted in 77% yield. Higher catalytic activity was achieved with nickel catalyst $NiCl_2(PPh_3)$IPr[24] bearing PPh_3 and NHC ligand IPr to afford **5a** in a quantitative yield at 60 °C for 24 h. The reaction with $NiCl_2(PPh_3)$IPr afforded **5a** in 89% yield within 2 h.

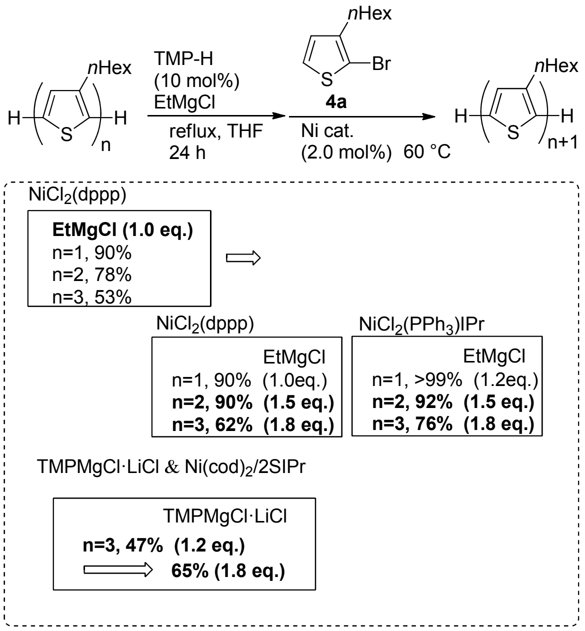
Table 3. The reaction of **1a** with 2-bromo-3-hexylthiophene (**4a**) with transition metal catalyst.[a]



Catalyst	EtMgCl (eq.), **4a** (eq.)	Temp. (°C), Time (h)	Yield (%)[c]
$NiCl_2$(dppp)	1.0, 1.0	60, 24	90
$NiCl_2$(dppe)	1.0[b], 1.0	60, 24	77
Ni(cod)$_2$/2SIPr	1.0, 1.0	60, 20	77
$NiCl_2(PPh_3)$IPr	1.2, 1.2	60, 2	89
$NiCl_2(PPh_3)$IPr	1.2[b], 1.2	60, 20	>99

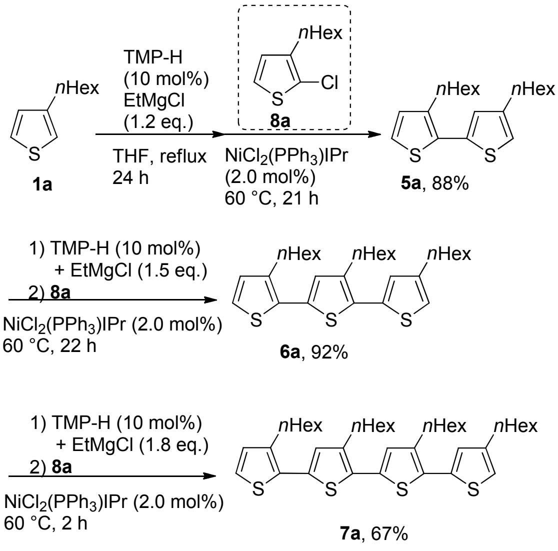
[a] Unless otherwise noted, The reaction was performed with **1a** (0.50 mmol) in 2.0 mL of THF. [b] The reaction was carried out with 1.0 mmol of **1a** in 3.0 mL of THF. [c] Isolated yield.

The synthesis of HT-type oligomers of 3-hexylthiophene using a combination of EtMgCl and 10 mol% of TMP-H was carried out as summarized in Scheme 2. The obtained HT-bithiophene (**5a**) was subjected to the further reaction with **4a** in the presence of $NiCl_2$(dppp) to afford the HT-type terthiophene (**6a**) in 78% yield. The obtained **6a** reacted with **4a** to give HT-type tetramer (**7a**) in a similar manner furnishing terthiophene in 53% yield. It was observed that the yield decreased as expansion of the number of the thiophene unit. When the deprotonation was performed with a stoichiometric amount of EtMgCl along with 10 mol% of TMP-H in the reaction of **5a**, it was found that only 83% of the dimer underwent the deprotonation, which was confirmed leading to the corresponding aldehyde by treatment with DMF. Increasing the amount of EtMgCl to 1.5 equiv. resulted in the formation of dianion, which suggested deprotonation also at the more hindered 2-position to afford mono-formylated and diformylated products in 69% and 31% yields, respectively. However, it was found that no coupling reaction at the hindered position took place in the reaction of **5a** with **4a** to afford the corresponding **6a** in 90% yield with $NiCl_2$(dppp) (2.0 mol%) or 92% yield with $NiCl_2(PPh_3)$IPr (2.0 mol%) as a sole product. The yield of the reaction of **6a** with 1.8 equiv. of EtMgCl improved to 76% with 2.0 mol% of $NiCl(PPh_3)$IPr. The similar trend was also observed in the reaction with a stoichiometric amount of TMPMgCl·LiCl to afford 65% of **7a**, while the yield was much lower (47%) by the deprotonation with 1.2 equiv. of the corresponding base.[16]



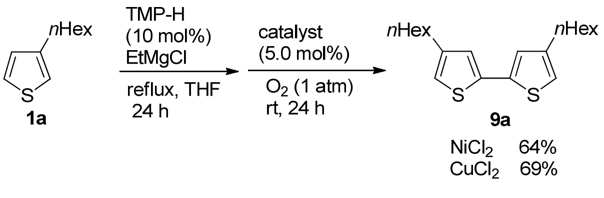
Scheme 2. HT-type oligothiophene synthesis with regioselective cross coupling.

We envisaged the HT-type oligothiophene synthesis with 2-chloro-3-hexylthiophene (**8a**) instead of bromide **4a** for the purpose of further improvement of the atom efficiency. The reaction of **1a** with 2-chloro-3-hexylthiophene (**8a**) in the presence of $NiCl_2$(dppp) as a nickel catalyst at 60 °C for 20 h only afforded **5a** in 19% yield. However, as shown in Scheme 3, the reaction with **8a** was found to take place successfully by 2.0 mol% of $NiCl_2(PPh_3)$IPr as a nickel catalyst to give **5a** in excellent yield. Noteworthy is that the effect of NHCs is markedly different from the one in the reaction with bromothiophene, which has reacted smoothly with bidentate phosphines as a ligand. The HT-trimer (**6a**) and tetramer (**7a**) were also obtained in good to excellent yields, in a similar manner.



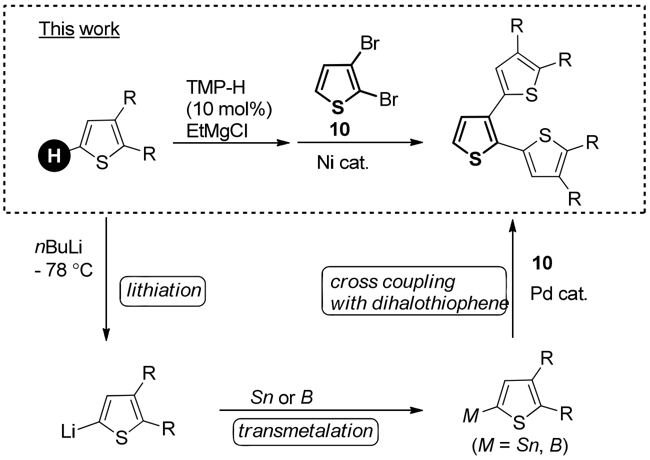
Scheme 3. HT-type oligothiophene synthesis with 2-chloro-3-hexylthiophene (**8a**).

Oxidative homocoupling through the regioselective deprotonation of **1a** was also examined.[25] The reaction of **1a** with a transition metal salt under an oxygen atmosphere proceeded to afford tail-to-tail (TT) type bithiophene (**9a**). The reaction with 5.0 mol% of nickel chloride at room temperature for 24 h took place to give **9a** exclusively in 64% yield. The use of copper chloride resulted in 69% yield (Scheme 4). It is remarkable that the TT-type bithiophene is synthesized in a single step, while conventional synthesis has been performed with two steps or more involving a much less atom and step economic bromination/debrominative homocoupling sequence.



Scheme 4. Synthesis of TT-type bithiophene by oxidative homocoupling of **1a**

Our further interest is then turned to the synthesis of dendritic oligothiophenes with the regioselective cross-coupling reaction of 3-substituted thiophenes. We envisaged that the regioselective deprotonation of thiophene and the subsequent reaction with 2,3-dibromothiophene (**10**) in the presence of a nickel catalyst afford thiophene dendron 3-mer and repeating the similar reaction extends the generation of thiophene dendron. The process would be much simpler and step-economic synthesis of oligothiophene dendrimers compared with conventional protocols involving the formation of thienyl boron or tin reagents and the following cross coupling as depicted in Scheme 5.[13]

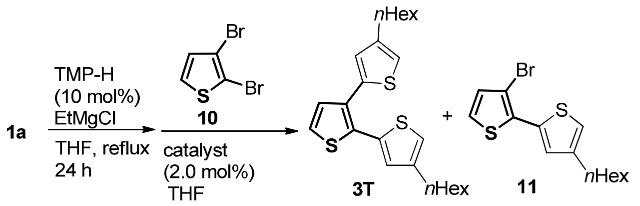


Scheme 5. Synthetic strategy of thiophene dendrimers

The reaction of 3-hexylthiophene (**1a**) with 2,3-dibromothiophene (**10**) was first carried out in a similar manner to the case of linear oligothiophenes. As shown in Table 4, the reaction of **1a** with EtMgCl and 10 mol% of TMP-H under reflux in THF for 24 h induced the metalation at the 5-position selectively. Following addition of 2,3-dibromothiophene (**10**) in the presence of 2.0 mol% of $NiCl_2(PPh_3)$IPr at room temperature for 24 h afforded thiophene dendron 3-mer (**3T**) in a quantitative yield (Table 4, Entry 1). It is also remarkable that the reaction was found rather fast to proceed in 78% yield within 10 min, whereas mono coupling product **11** was not observed at all in spite that the carbon–bromine bond at the 3-position is much less reactive than that at the 2-position (Table 4, Entry 2).

We next performed the reaction of an equimolar amount of 3-hexylthiophene (**1a**) to 2,3-dibromothiophene (**10**) in the presence of $NiCl_2(PPh_3)$IPr (Table 4, Entry 3). Even when the reaction was carried out with 1:1 of **1a** and **10** with 2.0 mol% of the catalyst, complete consumption of **1a** was confirmed at room temperature for 10 min to afford **3T** in 41% yield with recovery of 2,3-dibromothiophene (54%) and the mono coupling product **11** was not observed at all. The similar effect was shown to be observed with a palladium catalyst PEPPSI-IPr in the reaction of several multi-halogenated organic electrophiles with a variety of organometallic reagents,[26, 27] however, the reaction of thiophene catalyzed by $NiCl_2(PPh_3)$IPr indicated the improved performance to undergo the multiple coupling reaction. Indeed, the reaction of **1a** and **10** with 2.0 mol% of PEPPSI-IPr as a catalyst at 60 °C for 23 h resulted in a mixture of **3T** and **11** in 17% and 32% yield, respectively (Table 4, Entry 4). We also carried out the reaction with other nickel and palladium catalysts (Table 4, Entry 5-8). The reaction with $NiCl_2$(dppe) at 60 °C for 24 h gave **3T** in 33% yield, while the mono coupling product **11** was not observed at all. The reaction with nickel catalyst of bidentate diphosphine $NiCl_2$(dppp) at 60 °C for 24 h occurred to give the mixture of **3T** and **11** (6% and 14% respectively). The reaction with $NiCl_2$(dppf) proceeded to afford **11** in a poor yield. Although the reaction with palladium catalyst of bulky phosphine ligand $Pd(P^tBu_3)_2$ proceeded, the yield was found to be much inferior.

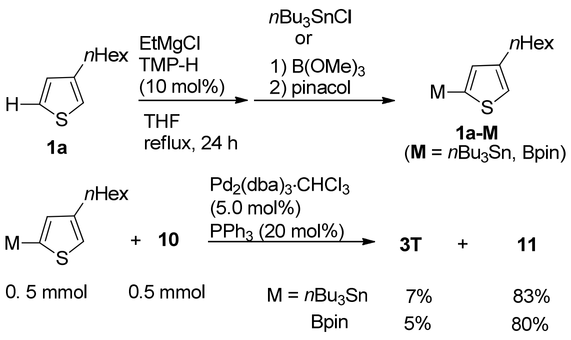
Table 4. The reaction of **1a** with **10** in the presence of nickel catalyst.[a]



Entry	1a/10	Catalyst	Temp. (°C), Time	Yield (%)	
				3T	11
1[b]	2.5/1	$NiCl_2(PPh_3)IPr$	rt, 24 h	>99[c]	0
2	2.5/1	$NiCl_2(PPh_3)IPr$	rt, 10 min	78[c]	0
3	1/1	$NiCl_2(PPh_3)IPr$	rt, 10 min	41[c]	0
4	1/1	PEPPSI-IPr	60, 23 h	17[c]	32
5	1/1	$NiCl_2(dppe)$	60, 24 h	33[d]	0
6	1/1	$NiCl_2(dppp)$	60, 24 h	6[d]	14
7	1/1	$NiCl_2(dppf)$	60, 24 h	<1[d]	21
8	1/1	$Pd(P^tBu_3)_2$	60, 24 h	<1[d]	26

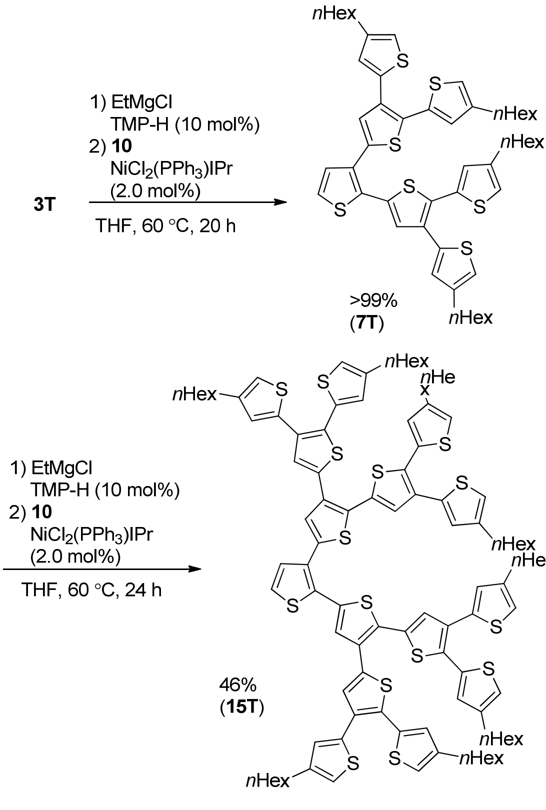
[a] Unless noted, the reaction was carried out with **1a** (0.50 mmol), TMP-H (0.05 mmol), EtMgCl (0.50 mmol) and nickel catalyst (0.01 mmol) in 2.0 mL of THF. [b] The reaction was performed with 3.0 mmol of **1a**. [c] Isolated yield. [d] The yield of **3T** and **11** was estimated by ^{1}H NMR analysis.

The observed multiple coupling seems to be the specific case in the reaction of a thienyl magnesium reagent with a nickel NHC catalyst, while such a drastic effect has not been found in the preceding synthesis of thiophene dendrimer with thienyl boron and tin reagents. Indeed, the related reaction of 4-hexyl-2-tributylstannylthiophene (**1a-*n*Bu$_3$Sn**) with **10** preferentially afforded the mono coupling product **11** in 83% yield and **3T** in a poor yield (7%) when the reaction was carried out employing an equimolar amount of the organometallic reagent and dibromothiophene **10** (Scheme 6). A similar trend was also observed in the reaction of thienylboronate pinacol ester (**1a-Bpin**) to afford 80% of **11** along with 5% of **3T**. Accordingly, it has been necessary to accomplish complete conversion with Suzuki-Miyaura or Migita-Kosugi-Stille's protocol,[28] thus, longer reaction period and excess use of the organometallic reagent have been conducted in the conventional reactions. In addition, separation of the once formed mono-coupled byproduct and the desired dendrimer must be performed. By contrast, the reaction of **1a** with the nickel catalyst does not require such troublesome separation of the undesired byproducts.



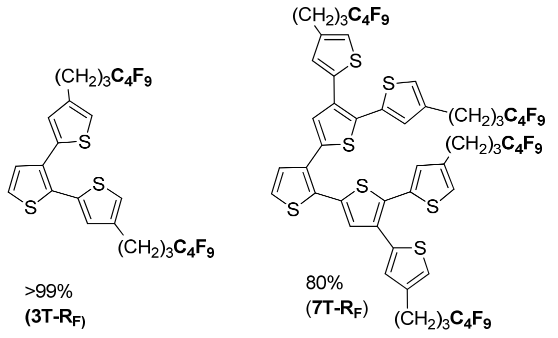
Scheme 6. The reaction of **10** with thienyl boronic acid ester and thienylstanannes.

We next performed further extension of thiophene dendrimer up to 15-mer in a similar manner (Scheme 7). The obtained **3T** was also metalated selectively at the sterically less-hindered position by TMP-H/EtMgCl and the reaction with **10** at 60 °C for 20 h led to thiophene dendron 7-mer (**7T**) in a quantitative yield. Treatment of **7T** with TMP-H (10 mol%) and EtMgCl and the reaction with **10** at 60 °C for 24 h led to the 15-mer **15T** in 46% yield.



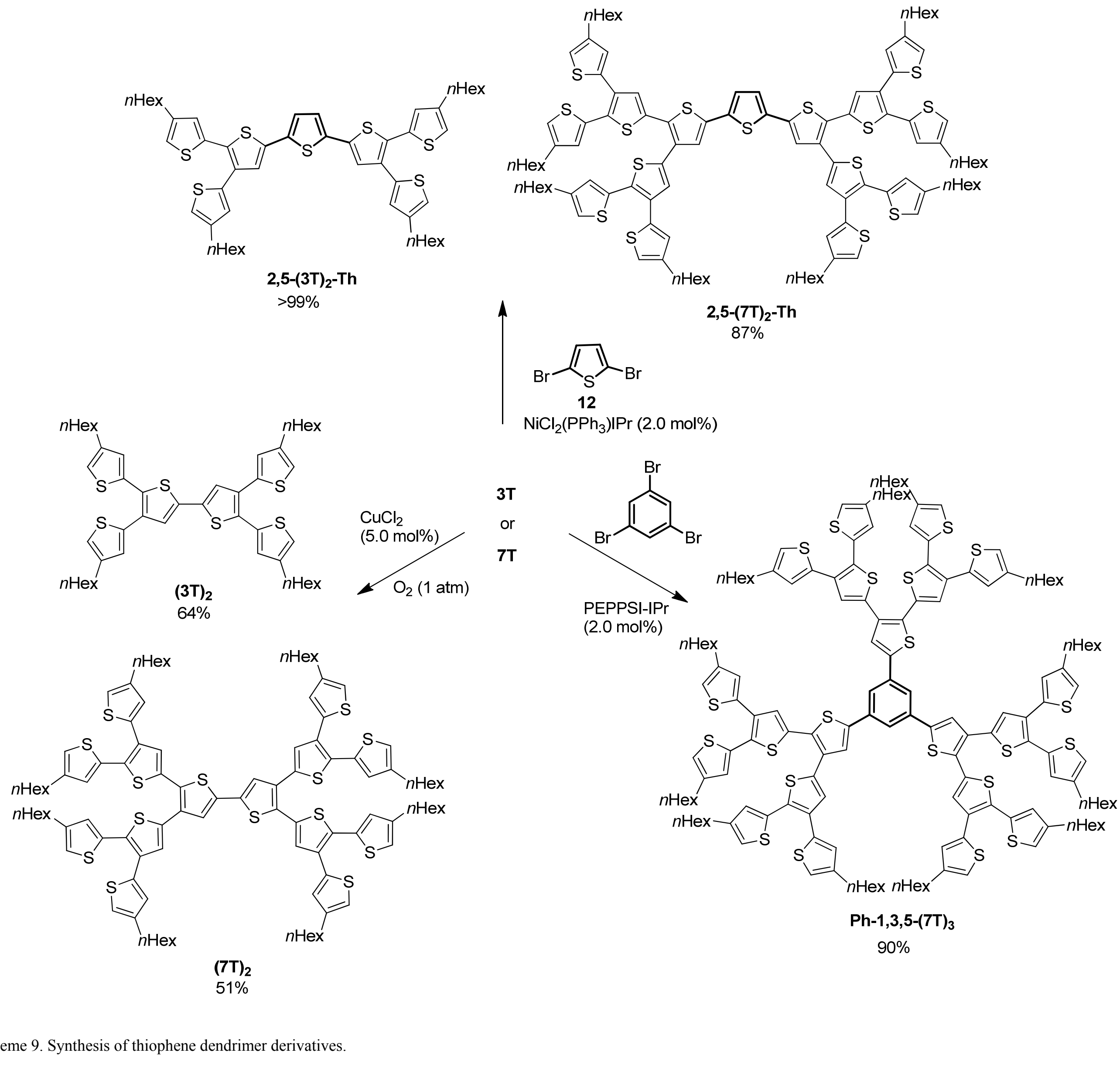
Scheme 7. Thiophene dendrimer synthesis up to 15-mer.

The synthesis of thiophene dendrimer bearing fluoroalkyl group,[29, 15b] $-(CH_2)_3C_4F_9$ was also achieved successfully in a similar manner as shown in Scheme 8. The deprotonation reaction of 3-fluoroalkylated thiophene **1b** with EtMgCl/TMP-H (10 mol%) also took place at the 5-position selectively and the subsequent reaction with **10** in the presence of 2.0 mol% of $NiCl_2(PPh_3)IPr$ at 60 °C for 27 h afforded **3T-R$_F$** in a quantitative yield. In addition, **7T-R$_F$** was also obtained by the cross-coupling reaction of **3T-R$_F$** with **10** in 80% yield.



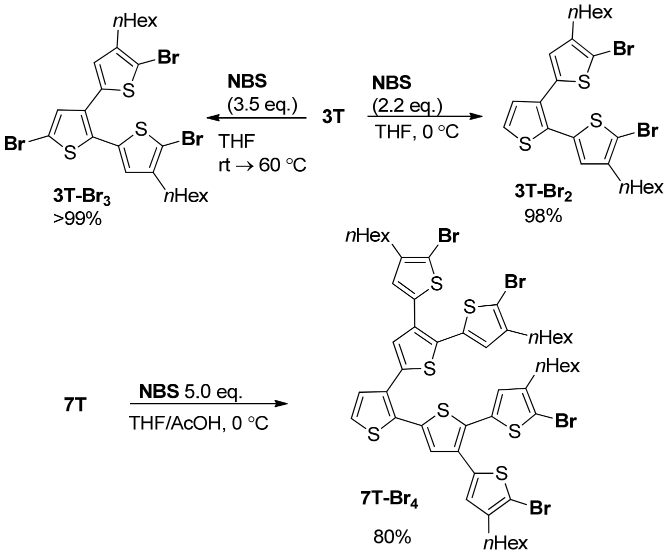
Scheme 8. Synthesis of 3-fluoroalkylated thiophene dendrimer.

Our further concern is the regioselective coupling of thiophene dendrimer with several bromothiophenes and aryl halides. These results are summarized in Scheme 9. The reaction of **3T** with 2,5-dibromothiophene (**12**) at 60 °C for 23 h smoothly took place to give **2,5-(3T)$_2$Th** in >99% yield. The reaction of **7T** with **12** also occurred to afford **2,5-(7T)$_2$-Th** in 87% yield. A benzene-ring-cored thiophen dendrimer was obtained by the reaction of **7T** with 1,3,5-tribromobenzene in the presence of palladium catalyst PEPPSI-IPr to give **Ph-1,3,5-(7T)$_3$** in 90% yield. The reaction of **3T** in the presence of 5.0 mol% of CuCl$_2$ under an oxygen atmosphere at 60 °C for 26 h proceeded to afford homo coupling product **(3T)$_2$** in 64% yield. The homo coupling reaction of **7T** also afforded **(7T)$_2$** in 51% yield.



Scheme 9. Synthesis of thiophene dendrimer derivatives.

Further transformations of the obtained dendrimers **3T** and **7T** are plausible when the synthesis is performed with regioselective deprotonative coupling reaction with 3-hexylthiophene (**1a**), in contrast that conventional thiophene dendrimers bearing hexyl groups adjacent to the sulfur atom would limit the related transformation. As shown in Scheme 10, the reaction of **3T** with N-bromosuccinimide (2.2 eq.) at 0 °C proceeded at the C–H bond adjacent to the hexyl group selectively to afford dibrominated product **3T-Br$_2$** in an excellent yield (98%), while the similar reaction with 3.5 equiv. of NBS at 60 °C led to the tribrominated product **3T-Br$_3$** in a quantitative yield. These results suggest allowing further transformation of the thus prepared bromides. The similar reaction of **7T** with 5.0 equiv. of NBS in THF and acetic acid at 0 °C afforded the tetrabrominated **7T-Br$_4$** in 80% yields.



Scheme 10. Regioselective bromination of thiophene dendrimers with NBS.

Conclusion

In conclusion, we have shown that regioselective deprotonation of 3-substituted thiophenes with a combination of a catalytic amount of TMP-H and EtMgCl as a selective metalating agent allows them to undergo the reaction with bromothiophenes and chlorothiophenes to form the thiophene–thiophene bond. Linear oligothiophenes were synthesized efficiently by repeating the similar reaction. It was also found that several oligothiophene dendrimers were synthesized by the sequential regioselective metalation of thiophene and the cross coupling with 2,3-dibromothiophene, whose reaction would also be remarkable as an unexpected rate acceleration in the coupling at the second carbon–bromine bond of dibromothiophene. With these methods, a wide variety of well-defined linear and branched oligothiophene derivatives can be synthesized in an extremely facile manner compared with conventional oligothiophene syntheses.

Experimental Section

General procedure for the reaction of 3-hexylthiophene (1a) with EtMgCl/TMP-H (10 mol%) and 2-bromo-3-hexylthiophene (4a) : To a 20 mL Schlenk tube equipped with a magnetic stirring bar was added a THF solution of EtMgCl (1.21 mL, 1.2 mmol) and TMP-H (0.017 mL, 0.1 mmol). To the solution was added 3-hexylthiophene (**1a**, 0.180 mL, 1.0 mmol) and stirring was continued under reflux for 24 h. Then, 1.8 mL of THF, 2-bromo3-hexylthiophene (**4a**, 0.239 mL, 1.2 mmol) and NiCl$_2$(PPh$_3$)IPr (15.6 mg, 0.02 mmol) were added successively. The mixture was allowed to stir at 60 ºC for 20 h. After cooling to room temperature the mixture was quenched by saturated aqueous solution of ammonium chloride (1.0 mL). The solution was poured into the mixture of diethyl ether/water and two phases were separated. Aqueous was extracted with diethyl ether twice and the combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel using hexanes as an eluent to afford 335.2 mg of 5-(3-hexylthiophen-2-yl)-3-hexylthiophene[4] (**5a**, light yellow oil, >99%).

General procedure for the reaction of 3-hexylthiophene (1a) and 2,3-dibromothiophene (10) with EtMgCl/TMP-H (10 mol%): To a 50 mL Schlenk tube equipped with a magnetic stirring bar were added 0.99 M EtMgCl (7.5 mL, 7.5 mmol) in THF and TMP-H (0.01 mL, 0.75 mmol). To the solution was added 3-hexylthiophene (**1a**, 0.048 mL, 7.5 mmol) and stirring was continued under reflux for 24 h. *The reaction mixture was cooled to 0 °C* (CAUTION: Otherwise, exotherm by the reaction causes boiling of the solvent.) and then 1.5 mL of THF, 2,3-dibromothiophene (**10**, 0.074 mL, 3.0 mmol) and NiCl$_2$(PPh$_3$)IPr (7.8 mg, 0.01 mmol) were added successively. The mixture was allowed to stir at room temperature for 24 h. The mixture was quenched by saturated aqueous solution of ammonium chloride (1.0 mL). The solution was poured into the mixture of diethyl ether/water and two phases were separated. Aqueous was extracted with diethyl ether twice and the combined organic layer was dried over anhydrous sodium sulfate. Concentration of the solvent under reduced pressure left a crude oil, which was purified by column chromatography on silica gel using hexanes as an eluent to afford 1.25 g of **3T** (yellow oil, >99%).

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[1] a) A. R. Murphy, J. M. J. Frèchet, *Chem. Rev.* **2007**, *107*, 1066-1096; b) I. Osaka, R. D. McCullough, *Acc. Chem. Res.* **2008**, *41*, 1202-1214; c) A. Facchetti, M.-H. Yoon, T. J. Marks, *Adv. Mater.* **2005**, *17*, 1705-1725; d) S. Allard, M. Forster, B. Souharce, H. Thiem, U. Scherf, *Angew. Chem., Int. Ed.* **2008**, *47*, 4070-4098.

[2] a) T. Yasuda, H. Ooi, J. Morita, Y. Akama, K. Minoura, M. Funahashi, T. Shimomura, T. Kato, *Adv. Funct. Mater.* **2009**, *19*, 411-419; b) M. Prehm, G. Götz, P. Bäuerle, F. Liu, X. Zeng, G. Ungar, C. Tschierske, *Angew. Chem. Int. Ed.* **2007**, *46*, 7856-7859; c) H. Zhang, S. Shiino, A. Shishido, A. Kanazawa, O. Tsutsumi, T. Shiono, T. Ikeda, *Adv. Mater.* **2000**, *12*, 1336-1339; d) I. McCulloch, M. Heeney, C. Bailey, K. Genevicius, I. MacDonald, M. Shkunov, D. Sparrowe, S. Tierney, R. Wagner, W. Zhang, M. L. Chabinyc, R. J. Kline, M. D. McGehee, M. F. Toney, *Nat. Mater.* **2006**, *5*, 328-333.

[3] a) A. Mishra, M. K. R. Fischer, P. Bäuerle, *Angew. Chem., Int. Ed.* **2009**, *48*, 2474-2499; b) N. Koumura, Z.-S. Wang, S. Mori, M. Miyashita, E. Suzuki, K. Hara, *J. Am. Chem. Soc.* **2006**, *128*, 14256-14257; c) M. Miyashita, K. Sunahara, T. Nishikawa, Y. Uemura, N. Koumura, K. Hara, A. Mori, T. Abe, E. Suzuki, S. Mori, *J. Am. Chem. Soc.* **2008**, *130*, 17874-17881; d) Z.-S. Wang, N. Koumura, Y. Cui, M. Takahashi, H. Sekiguchi, A. Mori, T. Kubo, A. Furube, K. Hara, *Chem. Mater.* **2008**, *20*, 3993-4003.

[4] See also: a) M.-K. Ng, L. Yu, *Angew. Chem., Int. Ed.* **2002**, *41*, 3598-3601; b) Y. Liu, X. Wan, F. Wang, J. Zhou, G. Long, J. Tian, Y. Chen, *Adv. Mater.* **2011**, *23*, 5387-5391; c) P. van Rijn, D. Janeliunas, A. M. A. Brizard, M. C. A. Stuart, R. Eelkema, J. H. van Esch, *Chem. Eur. J.* **2010**, *16*, 13417-13428; d) D. Bong, I. Tam, R. Breslow, *J. Am. Chem. Soc.* **2004**, *126*, 11796-11797.

[5] Conventional synthetic methodologies of HT-type oligothiophene, see: a) R. S. Loewe, P. C. Ewbank, J. Liu, L. Zhai, R. D. McCullough, *Macromolecules* **2001**, *34*, 4324-4333; b) T. Kirschbaum, C. A. Briehn, P. Bäuerle, *J. Chem. Soc., Perkin Trans.1* **2000**, 1211-1216; c) A. C. Spivey, D. J. Turner, M. L. Turner, S. Yeates, *Org. Lett.* **2002**, *4*, 1899-1902; d) J. Cremer, C. A. Briehn, *Chem. Mater.* **2007**, *19*, 4155-4165; e) J. M. Tour, R. Wu, J. S. Schumm, *J. Am. Chem. Soc.* **1991**, *113*, 7064-7066.

[6] See also: Y. Nakao, J. Chen, M. Tanaka, T. Hiyama, *J. Am. Chem. Soc.* **2007**, *129*, 11694-11695.

[7] a) S. Deng, T. M. Fulghum, G. Krueger, D. Patton, J.-Y. Park, R. C. Advincula, *Chem. Eur. J.* **2011**, *17*, 8929-8940; b) J. Locklin, D. Patton, S. Deng, A. Baba, M. Millan, R. C. Advincula, *Chem. Mater.* **2004**, *16*, 5187-5193; c) S. Deng, G. Krueger, P. Taranekar, S. Sriwichai, R. Zong, R. P. Thummel, R. C. Advincula, *Chem. Mater.* **2011**, *23*, 3302-3311.

[8] a) C. Xia, X. Fan, J. Locklin, R. C. Advincula, A. Gies, W. Nonidez, *J. Am. Chem. Soc.* **2004**, *126*, 8735-8743; b) C.-Q. Ma, W. Pisula, C. Weber, X.-L. Feng, K. Müllen, P. Bäuerle, *Chem. Eur. J.* **2011**, *17*, 1507-1518; c) M. Kimura, A. Kitao, T. Fukawa, H. Shirai, *Chem. Eur. J.* **2011**, *17*, 6821-6829.

[9] a) A. Mishra, P. Bäuerle, *Angew. Chem. Int. Ed.* **2012**, *51*, 2020-2067; b) N. Kopidakis, W. J. Mitchell, J. Van de Lagemaat, D. S. Ginley, G. Rumbles, S. E. Shaheen, W. L. Rance, *Appl. Phys. Lett.* **2006**, *89*, 103524; c) M. E. Köse, W. J. Mitchell, N. Kopidakis, C. H. Chang, S. E. Shaheen, K. Kim, G. Rumbles, *J. Am. Chem. Soc.* **2007**, *129*, 14257-14270; d) W. W. H. Wong, C. Q. Ma, W. Pisula, C. Yan, X. Feng, D. J. Jones, K. Müllen, R. A. J. Janssen, P. Bäuerle, A. B. Holmes, *Chem. Mater.* **2010**, *22*, 457-466.

[10] See also: a) J. S. Moore, *Acc. Chem. Res.* **1997**, *30*, 402-413; b) A. J. Berresheim, M. Müller, K. Müllen, *Chem. Rev.* **1999**, *99*, 1747-1786; c) K. Itami, K. Tonogaki, T. Nokami, Y. Ohashi, J. Yoshida, *Angew. Chem. Int. Ed.* **2006**, *45*, 2404-2409.

[11] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483.

[12] J. K. Stille, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524.

[13] a) A. Mishra, C.-Q. Ma, P. Bäuerle, *Chem. Rev.* **2009**, *109*, 1141-1276; b) C.-Q. Ma, E. Mena-Osteritz, T. Debaerdemaeker, M. M. Wienk, R. A. J. Janssen, P. Bäuerle, *Angew. Chem., Int. Ed.* **2007**, *46*, 1679-1683; c) C. Xia, X. Fan, J. Locklin, R. C. Advincula, *Org. Lett.* **2002**, *4*, 2067-2070.

[14] a) A. Sugie, A. Mori, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548-561; b) A. Mori, *J. Synth. Org. Chem. Jpn.* **2011**, *69*, 1202-1211; c) A. Mori, A, Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto, T. Ikeda, *J. Am. Chem. Soc.* **2003**, *125*, 1700-1701; d) K. Masui, H. Ikegami, A. Mori, *J. Am. Chem. Soc.* **2004**, *126*, 5074-5075; e) M. Takahashi, K. Masui, H. Sekiguchi, N. Kobayashi, A. Mori, M. Funahashi, N. Tamaoki, *J. Am. Chem. Soc.* **2006**, *128*, 10930-10933; f) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui, A. Mori, *Org. Lett.* **2005**, *7*, 5083-5085; g) D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Org. Lett.* **2009**, *11*, 1607-1610; h) S. Mitsuda, T. Fujiwara, K. Kimigafukuro, D. Monguchi, A. Mori, *Tetrahedron* **2012**, *68*, 3585-3590; i) S. Tamba, Y. Okubo, S. Tanaka, D. Monguchi, A. Mori, *J. Org. Chem.* **2010**, *75*, 6998-7001.

[15] HT-type oligothiophene synthesis with C−H functionalizaton, see: a) N. Masuda, S. Tanba, A. Sugie, D. Monguchi, N. Koumura, K. Hara, A. Mori, *Org. Lett.* **2009**, *11*, 2297-2300; b) S. Tanba, A. Sugie, N. Masuda, D. Monguchi, N. Koumura, K. Hara, A. Mori, *Heterocycles* **2010**, *82*, 505-529.

[16] S. Tanaka, S. Tamba, D. Tanaka, A. Sugie, A. Mori, *J. Am. Chem. Soc.* **2011**, *133*, 16734-16737.

[17] See also: S. Tanaka, S. Tamba, A. Sugie, A. Mori, *Heterocycles* **2012**, *86*, in press. doi: 10.3987/COM-12-S(N)6

[18] a) S. Tamba, K. Shono, A. Sugie, A. Mori, *J. Am. Chem. Soc.* **2011**, *133*, 9700-9703; b) S. Tamba, S. Tanaka, Y. Okubo, S. Okamoto, H. Meguro, A. Mori, *Chem. Lett.* **2011**, *40*, 398-399; c) S. Tamba, S. Mitsuda, F. Tanaka, A. Sugie, A. Mori, *Organometallics* **2012**, *31*, 2263-2267; d) S. Tamba, Y. Okubo, A. Sugie, A. Mori, *Polymer J.* **2012**, in press. doi:10.1038/pj.2012.89

[19] a) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.* **2011**, *50*, 9794-9824; b) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem.,Int. Ed.* **2006**, *45*, 2958-2961; c) C. R. Hauser, F. C. Frostick, *J. Am. Chem. Soc.* **1949**, *71*, 1350-1352.

[20] S. Tanaka, D. Tanaka, A. Sugie, A. Mori, *Tetrahedron Lett.* **2012**, *53*, 1173-1176.

[21] See also: S. M. Asselin, M. M. Bio, N. F. Langille, K. Y. Ngai, *Org. Process Res. Dev.* **2010**, *14*, 1427-1431.

[22] a) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743-4748; b) M. G. Organ, S. Calimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem., Int. Ed.* **2009**, *48*, 2383-2387.

[23] a) R. Dorta, E. D. Stevens, C. D. Hoff, S. P. Nolan, *J. Am. Chem. Soc.* **2003**, *125*, 10490-10491; b) B. R. Dible, M. S. Sigman, *J. Am. Chem. Soc.* **2003**, *125*, 872-873; c) W. A. Herrmann, G. Gerstberger, M. Spiegler, *Organometallics* **1997**, *16*, 2209-2212.

[24] K. Matsubara, K. Ueno, Y. Shibata, *Organometallics* **2006**, *25*, 3422-3427.

[25] H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2009**, *131*, 17052-17053.

[26] I. Larrosa, C. Somoza, A. Banquy, S. M. Goldup, *Org. Lett.* **2011**, *13*, 146-149.

[27] See also: a) T. Yokozawa, Y. Nanashima, Y. Ohta, *ACS Macro Lett.* **2012**, *1*, 862-866; b) E. E. Sheina, J. S. Liu, M. C. Iovu, D. W. Laird, R. D. McCullough, *Macromolecules* **2004**, *37*, 3526-3528; c) M. C. Iovu, E. E. Sheina, R. R. Gil, R. D. McCullough, *Macromolecules* **2005**, *38*, 8649-8656; d) R. Miyakoshi, A. Yokoyama, T. Yokozawa, *J. Am. Chem. Soc.* **2005**, *127*, 17542-17547.

[28] Only a few example of Suzuki-Miyaura and Migita-Kosugi-Stille coupling was shown to proceed with a nickel catalyst. See, for example: a) A. F. Indolese, *Tetrahedron Lett.* **1997**, *38*, 3513-3516; b) S. Saito, S. Oh-tani, N. Miyaura, *J. Org. Chem.* **1997**, *62*, 8024-8030.

[29] X. M. Hong, D. M. Collard, *Macromolecules* **2000**, *33*, 6916-6917.

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Entry for the Table of Contents (Please choose one layout only)

Layout 1:

Synthetic Methods

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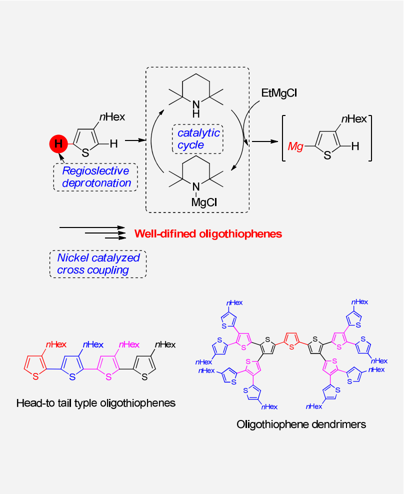
*Shota Tanaka, Daiki Tanaka, Go Tatsuta, Kohei Murakami, Shunsuke Tamba, Atsushi Sugie, Atsunori Mori** ……..…… Page – Page

Concise Synthesis of Well-Defined Linear and Branched Oligothiophenes with Nickel-Catalyzed Regiocontrolled Cross Coupling of 3-Substituted Thiophenes by Catalytically-Generated Magnesium Amide



Single step per extension protocol allows stepwise formation of the thiophene-thiophene bond, with which linear and branched oligothiophenes are synthesized in a remarkably concise manner. The method is based on regioselective deprotonation of 3-substituted thiophene with a combination of Grignard reagent and catalytic secondary amine. Nickel-catalyzed cross coupling of the thus formed metalated species with halothiophene leads to a variety of head-to-tail-type oligothiophenes and oligothiophene dendrimers.