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C−H ARYLATION OF 3-SUBSTITUTED THIOPHENE WITH REGIOSELECTIVE DEPROTONATION BY TMPMgCl·LiCl AND TRANSITION METAL CATALYZED CROSS COUPLING‡

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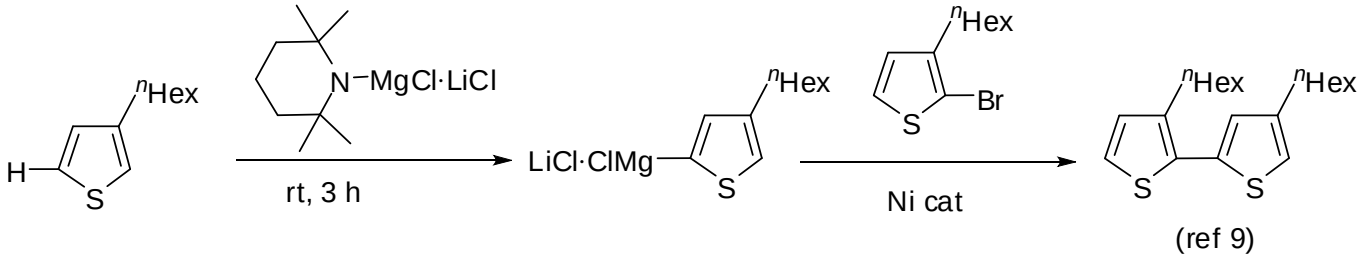
‡This paper is dedicated to Professor Ei-ichi Negishi on celebration of his 77th birthday.

Abstract – The reaction of 3-hexylthiophene with Knochel-Hauser base (TMPMgCl·LiCl) induced the metalation at the 5-position of the thiophene ring selectively. Following addition of several aryl halides in the presence of a nickel or palladium catalyst afforded regioselectively arylated thiophene in good to excellent yields.

INTRODUCTION

C–H functionalization of heteroaromatic compounds recently attracts much attention[1,2] since a variety of organic compounds bearing heteroaromatic moiety in the structure are found in a wide range of advanced organic materials[3] as well as biologically active molecules.[4] Therefore, development of a practical synthetic strategy for such molecules is an important issue in organic synthesis. We have been engaged in the development of synthetic methodologies to afford functionalized heteroaromotics via transition metal catalyzed C–H functionalization.[5] Several functionalization reactions, which take place at a carbon atom of an electron-deficient[6] and enriched[7] C–H bond have been achieved. Accordingly, the selective functionalization based on the electronic characteristics of the C–H bond of heteroaromatic compounds becomes indeed plausible. By contrast, selection of an electronically similar C–H bond based on stereochemical differentiation has not been extensively studied so far and thus controlled functionalization of such C–H bond is intriguing. We have recently found the reaction of 3-hexylthiophene in the presence of Knochel-Hauser base TMPMgCl·LiCl[8] (TMP =

2,2,6,6-tetramethylpiperidine) induces the metalation at room temperature for 3 h at the 5-position selectively. And we have shown novel synthetic methodology leading to head-to-tail-type oligothiophene with regioselective metalation of 3-substituted thiophene and nickel-catalyzed cross coupling of halothiophenes[9] (Scheme 1). We envisaged that such a regioselective metalating system of 3-substituted thiophenes is also effective not only for the coupling to form thiophene–thiophene bond but also for the reaction with various aryl halides. Herein, we describe regiocontrolled C–H arylation of several 3-substituted thiophene derivatives that occurs at the less hindered position selectively with TMPMgCl·LiCl.



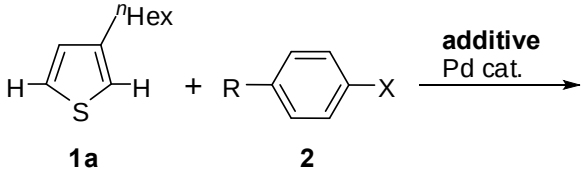
Scheme 1. Regioselective metalation of 3-hexylthiophene with TMPMgCl·LiCl and following coupling with a bromothiophene

RESULTS AND DISCUSSION

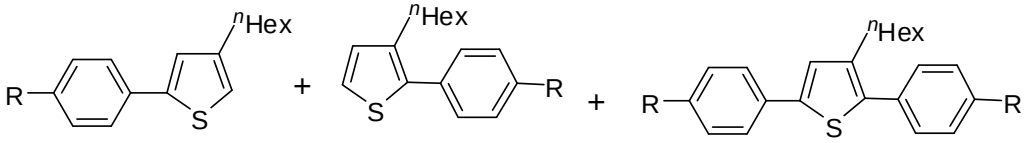
We first studied the reaction of 3-hexylthiophene (**1a**) that possessed two possible C–H bonds at the 2- and 5- positions with aryl halides under several conditions. The reaction with ^{t}BuOLi as a base[10] in the presence of 4-methyl-1-bromobenzene (**2a**) and 2.0 mol% of a palladium catalyst resulted to afford a mixture of **5-Aryl** (27%), **2-Aryl** (9%) and **2,5-diaryl** (20%) suggesting that uncontrollable metalation occurred at both 2- and 5-positions. The use of a catalytic amount of $PdCl_2(PPh_3)_2$ (2.0 mol%) and $AgNO_3$/KF[7c] resulted in giving a mixture of **5-Aryl** (21%), **2-Aryl** (8%) and 2,5-diarylated product (24%). The similar trend was observed in the arylation with K_2CO_3/^{t}BuCOONa.[4d] By contrast, the perfect selectivity was achieved when TMPMgCl·LiCl was employed as a base, to afford 5-arylated product in 91% yield. The use of diisopropyl amide ($^{i}Pr_2NMgCl$·LiCl) instead of TMPMgCl·LiCl decreased the selectivity and the reactivity. These results are summarized in Table 1.

The arylation reaction with several 3-substituted thiophenes is then examined to study the selectivity of the C–H bond as summarized in Table 2. The reaction of 4-methoxy-1-bromobenzene (**2b**) with 3-methylthiophene (**1b**), and 3-fluoroalkylated thiophene **1c,** 3-arylated thiophene **1d** also occurred

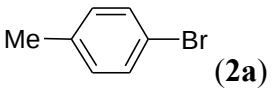
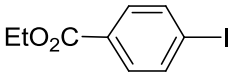
Table 1. Regiochemistry of the reaction of 3-hexylthiophene with C–H coupling[a]



1a **2**



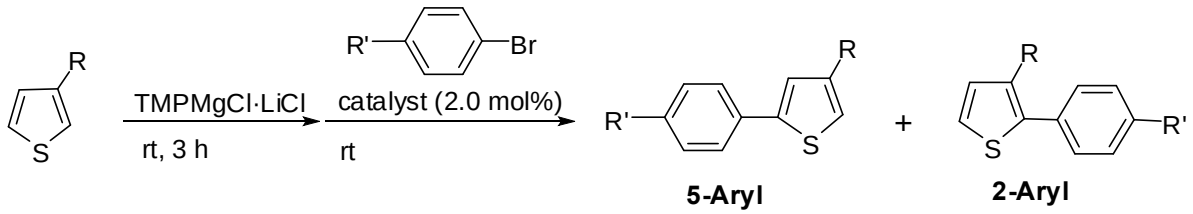
5-Aryl **2-Aryl** **2,5-Aryl**

Entry	Additive Pd cat. (2.0 mol%)	Aryl halide	Yield/%[b]		
			5-Aryl	**2-Aryl**	**2,5-Aryl**
1[c]	^{t}BuOLi Pd($P^t Bu_3$)$_2$	 (**2a**)	27	9	20
2[d]	$AgNO_3$/KF $PdCl_2(PPh_3)_2$		21	8	24
3[e]	K_2CO_3/^{t}BuCOONa Pd(OAc)$_2$/2PCy$_3$	**2a**	13	29	42
4	TMPMgCl·LiCl PEPPSI-IPr	**2a**	91	0	0
5	$^i Pr_2$NMgCl·LiCl PEPPSI-IPr	**2a**	28	2	0

[a] The reaction was carried out with **1a** (0.50 mmol) and aryl halide (0.6 mmol) according to literature procedure. [b] The ratio of **5-Aryl**/**2-Aryl** was determined by ^{1}H NMR analysis. [c] In 1.0 mL of DMF at 100 ºC for 20 h. [d] In 1.0 mL of DMSO at 100 ºC for 23 h. [e] In 1.6 mL of DMA at 100 ºC for 20 h.

regioselectively at the 5-position. By contrast, the reaction of 3-methoxythiophene (**1f**) resulted to afford 2-arylated product predominantly probably due to the directing effect of the methoxy group in the reaction of magnesium amide.[11] Less selective metalation was found to occur with an alkynyl group-substituted thiophene **1e**. Although the metalation reaction of 3-bromothiophene (**1g**) and *N,N*-diethyl-3-thiophenecarboxamide (**1h**) with TMPMgCl·LiCl proceeded smoothly in non-selective (40:60) and 2-selective (0/100) manners, respectively, following coupling with aryl halide in the presence of a palladium catalyst resulted in no arylation.

Table 2. Regiochemical preference of 3-substituted thiophenes in the reaction with TMPMgCl·LiCl[a]



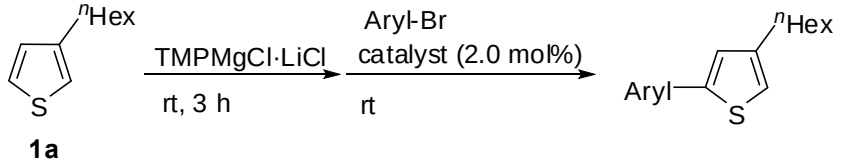
R	R'	Catalyst	Time/h	Yield/%[b] (**5-Aryl**/**2-Aryl**)[c]
^{n}Hex (**1a**)	Me	PEPPSI-IPr	20	91 (>99/1) (**3aa**)
Me (**1b**)	OMe	PEPPSI-IPr	2	87 (>99/1) (**3bb**)
-$(CH_2)_3{}^{n}C_4F_9$ (**1c**)	OMe	PEPPSI-IPr	20	64 (>99/1) (**3cb**)
-4-(OMe)C_6H_4 (**1d**)	Me	$NiCl_2$(dppf)	21	56 (>99/1) (**3da**)
-CC^{n}Hex (**1e**)	OMe	PEPPSI-IPr	20	62 (65/35)
-OMe (**1f**)	OMe	PEPPSI-IPr	21	46 (3/97)[d] (**3fb**)
-Br (**1g**)	OMe[e]	PEPPSI-IPr	16	0 (40/60)[f]
-$CONEt_2$ (**1h**)	OMe	PEPPSI-IPr	24	0 (0/100)[f]

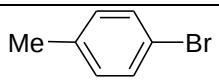
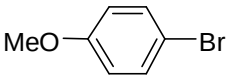
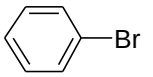
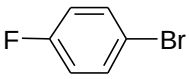
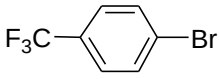
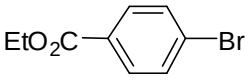
[a] Unless noted, the reaction was carried out with thiophene (0.5 mmol), TMPMgCl·LiCl (0.6 mmol), aryl bromide (0.6 mmol) and catalyst (0.01 mmol) in 2.0 mL of THF. [b] Isolated yield. [c] Unless otherwise specified, the ratio of **5-Aryl**/**2-Aryl** was determined by ^{1}H NMR analysis. [d] The ratio of **5-Aryl**/**2-Aryl** was determined by GC analysis. [e] The reaction was performed with 0.50 mmol of 1-iodo-4-methoxybenzene. [f] In the parenthesis, the metalation ratio, which was confirmed by formylation with DMF, was given.

Our further concern is the scope of the regioselective C–H arylation of 3-hexylthiophene (**1a**) with several aryl bromides. Results are summarized in Table 3. The reaction of **1a** with 4-methyl-1-bromobenzene (**2a**) was found to take place at room temperature to afford **3aa** in excellent yield when a palladium catalyst with NHC ligand PEPPSI-IPr[12] was employed. On the other hand, the use of a palladium catalyst with bulky phosphine ligand Pd(P^tBu_3)$_2$ resulted in poor yield (20%). The reaction with 2.0 mol% of nickel catalyst of bidentate diphosphine $NiCl_2$(dppf) at room temperature for 20 h proceeded smoothly to give **3aa** in 81% yield. The reaction with $NiCl_2$(dppe) also gave **3aa** in a reasonable yield (63%), whereas other nickel catalyst, $NiCl_2(PCy_3)_2$ and $NiCl_2$(dppb) was found to be ineffective. The use of Ni(cod)$_2$/2SIPr, which showed excellent performance in the reaction of **1a** with 2-bromo-3-hexylthiophene,[8] resulted in poor yield (7%). Various aryl bromides bearing an

electron-withdrawing or donating substituent (**2b**-**2e**) reacted with **1a** to afford the coupling products in good to excellent yields. Although the reaction with ethyl 4-bromobenzoate (**2f**) proceeded, the yield was slightly inferior (35%).

Table 3. Regioselective C–H coupling reaction of 3-hexylthiophene (**2a**) with aryl bromides[a]

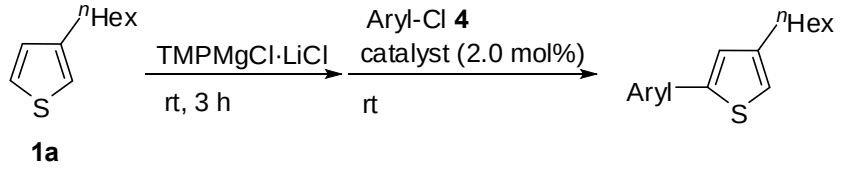


Aryl bromide	Catalyst	Time/h	Yield/%[b]
 (**2a**)	PEPPSI-IPr	20	91 (**3aa**)
	$Pd(P^tBu_3)_2$	20	20[c]
	$NiCl_2$(dppf)	20	81
	$NiCl_2$(dppe)	20	63
	$NiCl_2$(dppb)	20	9
	$NiCl_2(PCy_3)_2$	20	0
	$Ni(cod)_2$/2SIPr	20	7
 (**2b**)	$NiCl_2$(dppf)	25	77[d] (**3ab**)
 (**2c**)	$NiCl_2$(dppf)	20	82 (**3ac**)
 (**2d**)	PEPPSI-IPr	20	85 (**3ad**)
 (**2e**)	PEPPSI-IPr	5	88[d, e] (**3ae**)
 (**2f**)	PEPPSI-IPr	20	35 (**3af**)

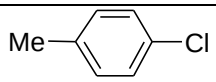
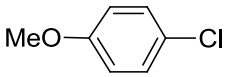
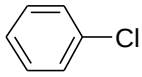
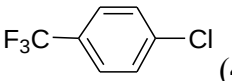
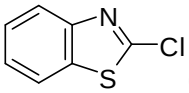
[a] Unless otherwise specified, the reaction was carried out with 0.5 mmol of **1a**, 0.6 mmol of TMPMgCl·LiCl and 0.6 mmol of aryl bromides in THF. [b] Isolated yield. [c] **1a**: 0.55 mmol, TMPMgCl·LiCl: 0.50 mmol, **2a**: 0.6 mmol. [d] The reaction was carried out with 0.5 mmol of aryl bromide. [e] Accompanied by **3ae**, 2,5-diarylated product was also obtained in 5% yield.

It is also remarkable that the reaction with aryl chlorides proceeded under similar conditions. The reaction of **1a** with 4-methyl-1-chlorobenzene (**4a**) took place at room temperature for 20 h with $NiCl_2$(dppf) to afford **3aa** in 82% yield. As shown in Table 4, several aryl chlorides such as **4b**, **4c** and **4e** reacted smoothly with **1a** to afford the corresponding coupling products in good to excellent yields. The reaction of **1a** with 2-chlorobenzothiazole (**4g**) in the presence of PEPPSI-IPr proceeded to give **3ag** in 83%.

Table 4. Regioselective C–H coupling reaction of 3-hexylthiophene (**1a**) with aryl chlorides[a]

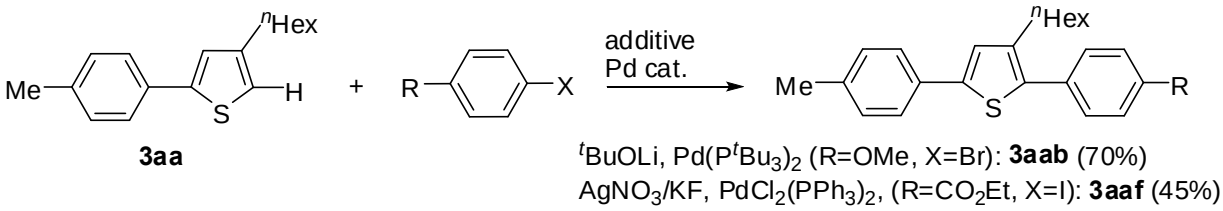


1a

Aryl chloride	Catalyst	Time/h	Yield/%
 (**4a**)	$NiCl_2$(dppf)	20	82 (**3aa**)
 (**4b**)	$NiCl_2$(dppf)	20	90 (**3ab**)
 (**4c**)	$NiCl_2$(dppf)	25	92[b] (**3ac**)
 (**4e**)	PEPPSI-IPr	5	92[b, c] (**3ae**)
 (**4g**)	PEPPSI-IPr	31	83 (**3ag**)

[a] Unless noted, the reaction was performed with **1a** (0.5 mmol), TMPMgCl·LiCl (0.6 mmol), aryl chloride (0.60 mmol) and a catalyst (2.0 mol %) in 2.0 mL of THF. [b] The reaction was carried out with 0.5 mmol of aryl chloride. [c] Accompanied by **3ae**, 2,5-diarylated product was also obtained in 7% yield.

By employing the selective 5-arylation method of thiophene it is possible to undergo concise synthesis of differently-substituted 2,5-diarylthiophene derivatives as illustrated in Scheme 2. The reaction at the sterically-hindered position was found to be operative when ^{t}BuOLi was used as an additive in the presence of a palladium catalyst, Pd(P^tBu_3)$_2$.[10a] The reaction of **3aa** with 4-methoxy-1-bromobenzene (**2b**) also afforded the corresponding 2,5-diarylated thiophene **3aab** in 70% yield. When $AgNO_3$/KF was employed as additives,[7c] the reaction of **3aa** with ethyl 4-iodobenzoate in the presence of 2.0 mol% of $PdCl_2(PPh_3)_2$ also proceeded at the 2-position to afford **3aaf** in 45% yield.



Scheme 2. Concise synthesis of differently-substituted 2,5-diarylthiophene

CONCLUSION

In summary, we have shown that regioselective C–H arylation of 3-substituted thiophene derivatives is achieved with TMPMgCl·LiCl, in which selective reaction takes place at the less hindered C–H bond. Accordingly, it was revealed that the regiocontrolled C–H functionalization with TMPMgCl·LiCl is not only effective for the formation of thiophene–thiophene bond but also for the arylation reaction of 3-substituted thiophene with aryl bromides and chlorides. Since the reaction proceeds under mild conditions, the method is potentially practical for syntheses of regioselectively arylated thiophenes.

EXPERIMENTAL

General. All the reactions were carried out under nitrogen atmosphere. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Varian Gemini 300 as a $CDCl_3$ solution unless noted. The chemical shifts were expressed in ppm with $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77.0 ppm for ^{13}C) as internal standards. IR spectra were recorded on Bruker Alpha with an ATR attachment (Ge). High resolution mass spectra (HRMS) were measured by JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment or JEOL JMS-700 MStation (EI) at the Graduate School of Material Science, Nara Institute of Science and Technology. For thin layer chromatoraphy (TLC) analyses throughout this work, Merck precoated TLC plates (silica gel 60 F254) were used. Purification by HPLC with preparative SEC column (JAI-GEL-2H) was performed by JAI LC-9201. Gas chromatography analyses were carried out with SHIMADZU GCMS-QP2010 Plus. TMPMgCl·LiCl was prepared by following the literature procedure[13] and stored in the freezer as 1.0 M THF solution. Nickel catalysts, $NiCl_2$(dppe), $NiCl_2$(dppp), $NiCl_2$(dppb), $NiCl_2$(dppf), and $NiCl_2(PCy_3)_2$ were prepared according to the literature procedures.[14] Other chemicals were purchased and used without further purification.

General procedure for the reaction of 3-hexylthiophene (1a) with aryl bromide in the presence of Knochel-Hauser base: To 25 mL Schlenk tube equipped with a magnetic stirring bar was added TMPMgCl·LiCl (0.60 mmol, 1.0 M in THF) at room temperature. To the resulting mixture 3-hexylthiophene (**1a**, 0.099 mL, 0.50 mmol) was added and stirring was continued for 3 h. Then, THF

(1.4 mL), 4-methyl-1-bromobenzene (0.074 mL, 0.60 mmol) and PEPPSI-IPr (6.79 mg, 0.01 mmol) were added successively. The mixture was stirred at room temperature for 20 h and quenched by hydrochloric acid (1.0 M, 1.0 mL). The solution was poured into the mixture of Et_2O/water and two phases were separated. The aqueous phase was extracted with Et_2O twice and the combined organic phase was dried over anhydrous sodium sulfate. Removal of the solvent left a crude oil, which was purified by chromatography on silica gel using hexanes as an eluent to afford 117.2 mg of 5-(4-methyphenyl)-3-hexylthiophene (**3aa**, colorless oil, 91%): ^{1}H NMR δ 0.90 (t, J = 6.6 Hz, 3H), 1.23-1.44 (m, 6H), 1.58-1.73 (m, 2H), 2.36 (s, 3H), 2.61 (t, J = 7.7 Hz, 2H) , 6.83 (d, J = 1.3 Hz, 1H), 7.11 (d, J = 1.3 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 14.1, 21.1, 22.6, 29.0, 30.4, 30.6, 31.7, 118.9, 124.0, 125.6 (×2), 129.4 (×2), 131.9, 137.1, 144.1, 144.2; IR (ATR) 2955, 2926, 2856, 1511, 1465, 1458, 812, 729, 649, 639 cm^{-1}; HRMS (EI+) Calcd for $C_{17}H_{22}S$ $[M]^+$: 258.1442; found: m/z 258.1439.

5-(4-Methoxyphenyl)-3-methylthiophene (**3bb**, colorless solid, 87%): ^{1}H NMR δ 2.28 (s, 3H), 3.83 (s, 3H), 6.80 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.02 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 15.8, 55.3, 114.2 (×2), 119.1, 124.5, 127.0 (×2), 127.5, 138.5, 144.0, 159.1; IR (ATR) 3004, 2960, 2934, 2836, 1606, 1510, 1289, 1248, 1184, 1031, 826, 810, 746, 734, 707 cm^{-1}; HRMS (EI+) Calcd for $C_{12}H_{12}OS$ $[M]^+$: 204.0609; found: m/z 204.0609.

5-(4-Methoxyphenyl)-3-(4,4,5,5,6,6,7,7,7-nonafluoroheptan-1-yl)thiophene (**3cb**, colorless oil, 64%): ^{1}H NMR δ 1.89-2.06 (m, 2H), 2.07-2.23 (m, 2H), 2.72 (t, J = 7.3 Hz, 2H), 3.84 (s, 3H), 6.84 (d, J = 1.1 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 1.1 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 20.9 (t, $J_{C\text{-}F}$ = 3.7 Hz), 29.7, 30.2 (t, $J_{C\text{-}F}$ = 22 Hz), 55.2, 114.2 (×2), 119.2, 122.8, 127.0 (×2), 127.2, 141.7, 144.7, 159.2; IR (ATR) 1513, 1357, 1295, 1274, 1253, 1216, 1181, 1170, 1132, 1091, 1031, 1009, 878, 867, 851, 824, 741, 723, 709, 649, 604 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{18}H_{16}F_9OS$ $[M+H]^+$: 451.0778; found: m/z 451.0781.

3-(4-Methoxyphenyl)-5-(4-methylphenyl)thiophene (3da): 56% yield. ^{1}H NMR δ 2.38 (s, 3H), 3.85 (s, 3H), 6.95 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 1.4 Hz, 1H), 7.50 (d, J = 1.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 21.2, 55.3, 114.2 (×2), 117.9, 121.8, 125.7 (×2), 127.4 (×2), 128.8, 129.6 (×2), 131.6, 137.5, 142.7, 145.0, 158.9; IR (ATR) 1500, 1295, 1254, 1183, 1029, 830, 812, 751 cm^{-1}; HRMS (EI+) Calcd for $C_{18}H_{16}OS$ $[M]^+$: 280.0922; found: m/z 280.0922.

3-Methoxy-2-(4-methoxyphenyl)thiophene (**3fb**, brown oil, 51 mg, 45%). ^{1}H NMR δ 3.83 (s, 3H), 3.90

(s, 3H), 6.92 (d, *J* = 5.5 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 5.5 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 55.3, 58.7, 114.0 (×2), 117.5, 121.1, 126.1, 126.7, 128.2 (×2), 152.8, 158.2; IR (ATR) 2956, 2936, 2847, 2836, 1609, 1549, 1510, 1462, 1378, 1291, 1266, 1246, 1180, 1098, 1070, 1035, 926, 830, 795, 707, 643 cm^{-1}; HRMS (EI+) Calcd for $C_{12}H_{12}O_2S$ $[M]^+$: 220.0558; found: m/z 220.0561.

The reaction of 3-(1-octyn-1-yl)thiophene (1e) with aryl bromide in the presence of Knochel-Hauser base: The reaction was carried out in a similar manner to that of **1a** with aryl bromide in the presence of Knochel-Hauser base with 3-(1-octyn-1-yl)thiophene (**1e**, 96.2 mg, 0.50 mmol), TMPMgCl·LiCl (0.60 mmol, 1.0 M in THF), 4-bromoanisole (**2b**, 0.075 mL, 0.60 mmol) and PEPPSI-IPr (6.79 mg, 0.01 mmol) at room temperature for 21 h to afford the mixture of 2-arylated and 5-arylated products. The ratio of 2-Ar/5-Ar was determined to be 35:65 by ^{1}H NMR analysis.

5-(4-Methoxyphenyl)-3-hexylthiophene (3ab): ^{1}H NMR δ 0.90 (t, *J* = 6.6 Hz, 3H), 1.24-1.43 (m, 6H), 1.57-1.71 (m, 2H), 1.86-2.20 (4H, m), 2.60 (t, *J* = 7.7 Hz, 2H), 3.83 (s, 3H), 6.80 (d, *J* = 1.1 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 1.4 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 14.1, 22.6, 29.0, 30.4, 30.6, 31.7, 55.3, 114.2 (×2), 118.4, 123.5, 127.0 (×2), 127.6, 143.8, 144.2, 159.0; IR (ATR) 2956, 2926, 2851, 1608, 1511, 1296, 1255, 1181, 1032, 824, 712, 649 cm^{-1}; HRMS (EI+) Calcd for $C_{17}H_{22}OS$ $[M]^+$: 274.1391; found: m/z 274.1389.

5-Phenyl-3-hexylthiophene (3ac): ^{1}H NMR δ 0.79 (t, *J* = 6.9 Hz, 3H), 1.19-1.46 (m, 6H), 1.57-1.72 (m, 2H), 1.86-2.20 (4H, m), 2.61 (t, *J* = 7.7 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 6.86 (d, *J* = 1.1 Hz, 1H), 7.15 (d, *J* = 1.4 Hz, 1H), 7.26 (ddd, *J* = 8.0, 6.6, 1.4 Hz, 1H), 7.36 (td, *J* = 6.6, 1.4 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.4 Hz, 1H); ^{13}C NMR δ 14.1, 22.6, 29.0, 30.4, 30.6, 31.7, 119.4, 124.5, 125.7 (×2), 127.2, 128.8 (×2), 134.7, 143.9, 144.2; IR (ATR) 2955, 2926, 2854, 1496, 1453, 837, 758, 715, 690 cm^{-1}; HRMS (EI+) Calcd for $C_{16}H_{20}S$ $[M]^+$: 244.1286; found: m/z 244.1283.

5-(4-Fluorophenyl)-3-hexylthiophene (3ad): ^{1}H NMR δ 0.93 (t, *J* = 6.6 Hz, 3H), 1.23-1.49 (m, 6H), 1.59-1.75 (m, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 1.1 Hz, 1H), 7.07 (dd, *J* = 8.8 Hz, J_{H-F} = 8.8 Hz, 2H), 7.10 (s, 1H), 7.56 (dd, *J* = 8.8 Hz, J_{H-F} = 5.2 Hz, 2H); 13C NMR δ 14.1, 22.6, 29.0, 30.4, 30.6, 31.7, 115.7 (×2, d, J_{C-F} = 21.8 Hz), 119.4, 127.2 (×2, d, J_{C-F} = 8.0 Hz), 130.9 (d, J_{C-F} = 3.4 Hz), 142.8, 144.3, 162.2 (d, J_{C-F} = 247 Hz); IR (ATR) 2955, 2927, 2856, 1509, 1465, 1232, 1159, 1095, 826, 810, 734 cm^{-1}; HRMS (EI+) Calcd for $C_{16}H_{19}FS$ $[M]^+$: 262.1191; found: m/z 262.1193.

5-(4-Trifluoromethylphenyl)-3-hexylthiophene (3ae): ^{1}H NMR δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.21-1.45 (m, 6H), 1.58-1.72 (m, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), 6.95 (d, *J* = 1.1 Hz, 1H), 7.23 (d, *J* = 1.1 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 14.1, 22.6, 29.0, 30.4, 30.6, 31.7, 120.9, 125.7, 125.8, 129.0 (q, $J_{C\text{-}F}$ = 33 Hz), 129.4, 138.0, 142.1, 144.6; IR (ATR) 2956, 2927, 2857, 1615, 1324, 1166, 1124, 1068, 1017, 831 cm^{-1}; HRMS (EI+) Calcd for $C_{17}H_{19}F_3S$ $[M]^+$: 312.1160; found: m/z 312.1160.

Ethyl 4-(3-hexylthiophen-2-yl)benzoate (3af): ^{1}H NMR δ 0.90 (t, *J* = 6.6 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.24-1.38 (m, 6H), 1.54-1.71 (m, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 6.94 (s, 1H), 7.26 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 14.0, 14.3, 22.5, 28.9, 30.4, 30.5, 31.6, 60.9, 120.9, 125.2 (×2), 125.8, 128.9, 130.1 (×2), 138.8, 142.6, 144.6, 166.3; IR (ATR) 2953, 2925, 2856, 1707, 1606, 1274, 1181, 1107, 770, 695 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{19}H_{25}O_2S$ $[M+H]^+$: 317.1575; found: m/z 317.1575.

5-(Benzothiazole-2-yl)-3-hexylthiophene (3ag): ^{1}H NMR δ 0.90 (t, *J* = 6.7 Hz, 3H), 1.20-1.47 (m, 6H), 1.59-1.77 (m, 2H), 2.64 (t, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 1.3 Hz, 1H), 7.32-7.40 (m, 1H), 7.43-7.50 (m, 1H), 7.50 (d, *J* = 1.3 Hz, 1H), 7.81-7.89 (m, 1H), 7.98-8.05 (m, 1H); ^{13}C NMR δ 14.0, 22.5, 28.9, 30.28, 30.33, 31.6, 121.3, 122.8, 124.1, 125.0, 126.3, 129.7, 134.6, 136.7, 144.3, 153.7, 161.6; IR (ATR) 2956, 2923, 2856, 1502, 1466, 1456, 1437, 1429, 1312, 1256, 1217, 1192, 1131, 1016, 901, 865, 832, 823, 793, 754, 727, 705, 672 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{17}H_{20}NS_2$ $[M+H]^+$: 302.1037; found: m/z 302.1038.

2-(4-Methoxyphenyl)-5-(4-methylphenyl)-3-hexylthiophene (3aab)[10a]: The reaction was carried out in a manner described previously with 5-(4-methyphenyl)-3-hexylthiophene (**3aa**, 129.2 mg, 0.50 mmol), 4-methoxy-l-bromobenzene (0.075 mL, 0.60 mmol), LiO^{t}Bu (1.5 mmol) in 1.0 mL of DMF at 100 ºC for 20 h to afford 128.5 mg of **3aab** as a colorless oil (70%). ^{1}H NMR δ 0.87 (t, *J* = 6.7 Hz, 3H), 1.17-1.41 (m, 6H), 1.56-1.73 (m, 2H), 2.36 (s, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 3.85 (s, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.14 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 14.1, 21.1, 22.6, 28.8, 29.2, 30.9, 31.6, 55.2, 113.9 (×2), 125.0, 125.4 (×2), 127.2, 129.5 (×2), 130.4 (×2), 131.8, 136.7, 137.0, 139.0, 141.6, 158.9; IR (ATR) 2955, 2927, 2857, 1608, 1504, 1462, 1441, 1289, 1248, 1177, 1037, 1111, 908, 830, 812, 793, 757, 735, 669, 622 cm^{-1}; HRMS (ESI+) Calcd for $C_{24}H_{29}OS$ $[M+H]^+$: 365.1939; found: m/z 365.1939.

2-(4-Ethoxycarbonylphenyl)-5-(4-methylphenyl)-3-hexylthiophene (3aaf)[7c]**:** The reaction was carried

out in a manner described previously with 5-(4-methyphenyl)-3-hexylthiophene (**3aa**, 129.2 mg, 0.50 mmol), 4-iodobenzoate (0.100 mL, 0.60 mmol), $AgNO_3$ (212.5 mg, 1.25 mmol), KF (72.6 mg, 1.25 mmol) in 3.0 mL of DMSO at 100 ºC for 27 h to afford 3aaf as a colorless oil (45%). ^{1}H NMR δ 0.86 (t, *J* = 6.7 Hz, 3H), 1.15-1.37 (m, 6H), 1.41 (t, *J* = 7.1 Hz, 3H), 1.59-1.73 (m, 2H), 2.37 (s, 3H), 2.68 (t, *J* = 7.9 Hz, 2H), 3.85 (q, *J* = 7.1 Hz, 2H), 7.18 (s, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 8.09 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR δ 14.0, 14.4, 21.2, 22.6, 29.1, 29.2, 30.9, 31.6, 61.0, 125.49, 125.52 (×2), 128.8 (×2), 128.9, 129.6 (×2), 129.8 (×2), 131.4, 135.5, 137.5, 139.4, 140.7, 143.4, 166.4; IR (ATR) 2954, 2925, 2856, 1716, 1605, 1503, 1457, 1405, 1366, 1308, 1271, 1178, 1104, 1021, 854, 812, 771, 721, 701 cm^{-1}; HRMS (DART-ESI+) Calcd for $C_{24}H_{31}O_2S$ $[M+H]^+$: 407.2045; found: m/z 407.2040.

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