Deprotonative Metalation of Chlorothiophene with Grignard Reagents and Catalytic *cis*-2,6-Dimethylpiperidine under Mild Conditions

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Abstract: Deprotonative metalation of chlorothiophene takes place with a catalytic amount of *cis*-2,6-dimethylpiperidine (DMP) and an alkyl Grignard reagent at room temperature for three hours to give the corresponding thienyl Grignard reagent. Polymerization leading to head-to-tail-type poly(3-substituted thiophene) with the thus metalated chlorothiophene proceeds in the presence of a nickel catalyst bearing an *N*-heterocyclic carbene (NHC) ligand. Palladium-catalyzed cross-coupling reaction with aryl bromides also gives arylated thiophenes in good to excellent yields while the C–Cl bond remains intact.

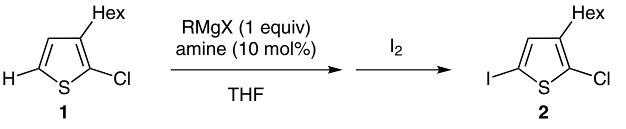
Key words: chlorothiophene, palladium, nickel, cross-coupling, Grignard reagent

Thiophene is an important chemical structure in many biologically important compounds[1] as well as advanced organic materials.[2] Transition-metal-catalyzed cross-coupling reaction of organometallic compounds and aryl halides is a powerful method for forming the arylated thiophene motif.[3] Thus, it is important to develop an efficient metalation method for use in cross-coupling reactions as well as for the generation of simple organometallic nucleophiles. Knochel and co-workers developed an efficient magnesium amide, the Knochel–Hauser base, chloromagnesium 2,2,6,6-tetramethylpiperidide lithium chloride salt (TMPMgCl·LiCl), and demonstrated deprotonative metalation of several heteroaromatic compounds and subsequent C–C bond formation with various electrophiles under mild conditions.[4] We have also reported recently that metalation of several heteroaromatic compounds occurs with the combined use of a catalytic amount of tetramethylpiperidine (TMP) and a Grignard reagent, and subsequent transition-metal-catalyzed reactions with the thus obtained thienyl magnesium species leads to the cross-coupled products and several π-conjugated polymers.[5] Although metalation using the combination of a catalytic amount of TMP and Grignard reagent is effective for several thiophene derivatives, the metalation required 60 °C and longer reaction periods (12–24 h).

Because chlorothiophene is an interesting building block for facile and efficient access to several biologically active compounds that incorporate a chlorothiophene moiety,[6] we were interested in developing a modified protocol for chlorothiophenes. We describe in this communication that efficient metalation of 2-chloro-3-substituted thiophene with a catalytic amount of *cis*-2,6-dimethylpiperidine and Grignard reagent takes place at room temperature and that the metalated species can be subjected to cross-coupling polymerization and arylation reactions in the presence of a transition-metal catalyst.

We first studied metalation of 2-chloro-3-hexylthiophene (**1**) in the presence of ethylmagnesium chloride and a catalytic amount of several amines. Table 1 summarizes the results of metalation, which was confirmed by quenching the generated thiophene-magnesium species with iodine, leading to 2-chloro-3-hexyl-5-iodothiophene (**2**). Although the use of dicyclohexylamine (Cy_2NH) as a catalyst showed superior catalytic activity to TMP at 60 °C for one hour, performing the reaction at room temperature for the same time resulted in only 44% yield of **2**. When 1,8-

Table 1 Deprotonative Metalation of Chlorothiophene **1**[a]



Entry	Amine	RMgX	Temp (°C)	Time (h)	Conv. (%)[b]
1	Cy_2NH	EtMgCl	60	1	90
2	Cy_2NH	EtMgCl	r.t.	1	44
3	Cy_2NH	EtMgCl	r.t.	3	77
4	DBU[c]	EtMgCl	60	1	0
5	Ph_2NH	EtMgCl	60	1	11
6	Cy(Me)NH	EtMgCl	60	1	69
7	DMP[d]	EtMgCl	60	0.5	93
8	DMP	EtMgCl	r.t.	1	60
9	DMP	*i*-PrMgBr	r.t.	1	42
10	DMP	EtMgCl	r.t.	3	94
11	DMP	EtMgCl + LiCl	r.t.	1	66

[a] Reaction conditions: 2-chloro-3-hexylthiophene (0.5 mmol), Grignard reagent (0.5 mmol), amine (0.05 mmol), THF (0.5 mL).
[b] The conversion was estimated by ^1H NMR analysis after quenching the reaction mixture with iodine.
[c] DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.
[d] DMP: *cis*-2,6-dimethylpiperidine.

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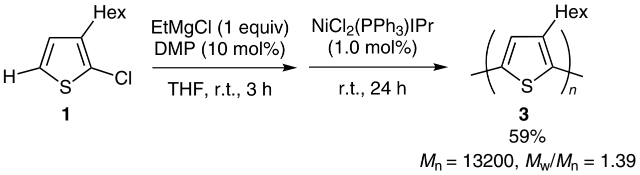
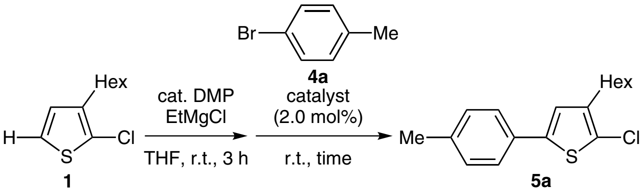
diazabicyclo[5.4.0]undec-7-ene (DBU) was used in the reaction instead of Cy_2NH, no iodinated product was obtained. The reaction with aromatic secondary amine diphenylamine (Ph_2NH) hardly took place at 60 °C for one hour. Compared with Cy_2NH, less hindered cyclohexylmethylamine was also ineffective. On the other hand, metalation with *cis*-2,6-dimethylpiperidine (DMP) showed superior catalytic activity to afford the iodinated product in 93% conversion, and the reaction at room temperature also improved the yield of **2** to 60% after stirring for one hour. Thus, we surveyed the effect of Grignard reagent at room temperature. The reaction with more sterically hindered *i*-PrMgBr afforded **2** in inferior yield (42%) to that with EtMgCl. The addition of LiCl to EtMgCl appeared to slightly improve the yield of **2** to 66%. When the reaction was carried out with 10 mol% Cy_2NH and EtMgCl at room temperature, the conversion of **1** was found to be 77% after stirring for three hours (entry 3). By contrast, the use of DMP instead of Cy_2NH induced the metalation much faster (94% conversion after 3 h) suggesting that subsequent transition-metal-catalyzed reactions after the metalation with DMP can be carried out under such conditions.



Scheme 1 Nickel-catalyzed polycondensation of chlorothiophene

Table 2 Optimization of Catalyst for the Coupling of **1** with Bromoarene **4a**[a]



Entry	Catalyst	Time (h)	Yield (%)[b]
1	$NiCl_2(PPh_3)_2$	19	trace
2	$PdCl_2(PPh_3)_2$	17	0
3	$PdCl_2dppf$	15	52
4	$PdCl_2$(d*t*-bpf)	20	25
5	Pd-PEPPSI-SIPr	23	49
6[c]	$PdCl_2dppf$	15.5	69

[a] Reaction conditions (unless noted otherwise): (i) **1** (0.5 mmol), DMP (10 mol%), EtMgCl (1.0 equiv), THF; (ii) catalyst (2.0 mol%), 4-bromotoluene (**4a**; 1.5 equiv).

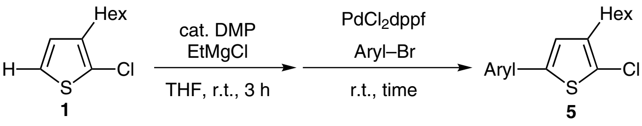
[b] Isolated yield.

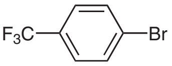
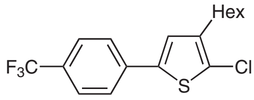
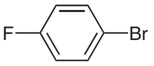
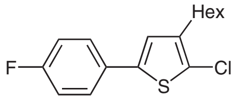
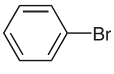
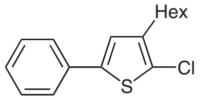
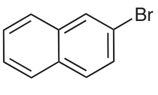
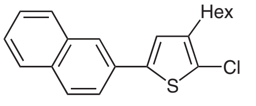
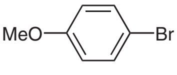
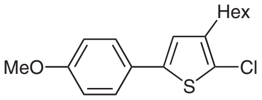
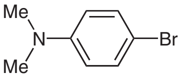
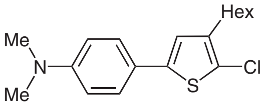
[c] The reaction was carried out with EtMgCl (1.5 equiv) and **4a** (1.8 equiv).

Catalytic generation of 2-chloro-3-hexyl-5-chloromagnesiothiophene was performed with 10 mol% DMP and EtMgCl at room temperature for three hours. Polymerization of the resulting solution was examined with 1.0 mol% $NiCl_2(PPh_3)$IPr at room temperature for 24 hours, which was the standard polymerization conditions employed previously, to afford poly(3-hexylthiophene) (P3HT; **3**) in 59% isolated yield with M_n of 13200 (M_w/M_n = 1.39) as shown in Scheme 1.[7] Considering that the deprotonation of **1** with catalytic Et_2NH required a higher reaction temperature and a longer period, the use of DMP allowed the total metalation-polymerization procedures to be conducted at room temperature within a shorter deprotonation period.

We then examined the coupling reaction of **1** with 4-bromotoluene (**4a**) leading to 2-chloro-3-hexyl-5-(4-methylphenyl)thiophene (**5a**); Table 2 summarizes the results.

Table 3 Pd-Catalyzed Coupling Reaction of **1** with Aryl Bromides[a]



Aryl-Br	Product	Time (h)	Yield (%)[b]
 **4b**	 **5b**	10	51
 **4c**	 **5c**	18	68
 **4d**	 **5d**	14	76
 **4e**	 **5e**	14	83
 **4f**	 **5f**	22	86
 **4g**	 **5g**	20	25

[a] Reaction conditions: (i) **1** (0.5 mmol), DMP (10 mol%), EtMgCl (1.5 equiv), THF; (ii) $PdCl_2dppf$ (2.0 mol%), aryl bromide (1.8 equiv).

When the coupling reaction of **1** was carried out with 10 mol% DMP and an equimolar amount of EtMgCl for deprotonation and with 2.0 mol% $NiCl_2(PPh_3)_2$ at room temperature for 24 hours, only a trace amount of coupling product **5a** was obtained. The coupling reaction was then performed with several palladium catalysts. When the coupling reaction was examined in the presence of $PdCl_2(PPh_3)_2$ as catalyst, no coupling product **5a** was obtained because of the insufficient activity of the palladium catalyst bearing PPh_3 ligands. Drastic improvement was observed when the reaction was carried out in the presence of 2.0 mol% $PdCl_2$dppf {dppf: 1,1′-bis(diphenylphosphino)ferrocene} to afford the corresponding coupling product in 52% yield. Similar reaction with $PdCl_2$(d*t*-bpf) {d*t*-bpf: 1,1′-bis[di(*tert*-butylphosphino)]ferrocene} gave **5a** in only 25% yield. When the catalyst was switched to Pd-PEPPSI-SIPr,[8] which showed excellent catalytic activity in the coupling reaction of 3-hexylthiophene,[9] **5a** was obtained in 49% yield. The metalation with EtMgCl (1.5 equiv) and the coupling reaction with 4-bromotoluene (1.8 equiv) in the presence of $PdCl_2$dppf (2.0 mol%) improved the yield to 69%.

The reaction conditions detailed in Table 2 were applied to the reaction of **1** and several aryl bromides, as summarized in Table 3. The reaction with aryl bromides bearing an electron-withdrawing substituent proceeded within a relatively short reaction period in good to excellent yield. The use of bromobenzene (**4d**) and 2-bromonaphthalene (**4e**) as aryl bromide afforded the corresponding products **5d** and **5e** in 76 and 83% yields, respectively. On the other hand, the reaction with an aryl bromide bearing a more electron-donating group was less effective. The reaction with 4-bromoanisole (**4f**) required relatively long reaction period and the reaction with 4-bromo-*N*,*N*-dimethylaniline (**4g**) gave only 25% yield.[10]

Thus, selective arylation at the 5-position of chlorothiophene leads to facile synthesis of regioregular head-to-tail-type oligothiophene by one-pot iterative Pd-catalyzed C–H coupling reaction at the 5-position and sequential Ni-catalyzed coupling reaction through C–Cl bond cleavage. Chlorothiophene **1** was first subjected to the reaction with iodocarbazole **6** in THF with DMP (10 mol%) and EtMgCl (1.0 equiv) at room temperature for 22 hours to undergo the coupling reaction (Scheme 2). Following addition of 1.2 equiv of 3-hexyl-5-chloromagnesiothiophehene, which was generated by selective metalation of 3-hexylthiophene and TMPMgCl·LiCl, and 2.0 mol% $NiCl_2(PPh_3)$IPr afforded 2,5-diarylated thiophene **7** in 44% overall yield. The obtained head-to-tail-type bithiophene, bearing a carbazole moiety, is a partial structure of MK-2 dye, which has been employed as dye-sensitized solar cells showing excellent power conversion efficiency.[11] Considering that the synthesis of such structures required three or four steps in our previous report,[5d,12] the present method improved the synthetic efficiency of linear head-to-tail-type oligothiophene-bearing carbazole moieties.[13]

In conclusion, the combination of a catalytic amount of *cis*-2,6-dimethylpiperidine and Grignard reagent is an efficient metalating system for chlorothiophene at the C–H bond. Polycondensation of metalated thiophene took place in the presence of a nickel catalyst to afford the corresponding P3HT in good yield. Head-to-tail-type bithiophene, bearing a carbazole moiety, was also synthesized by one-pot iterative Pd-catalyzed C–H arylation reaction and Ni-catalyzed coupling reaction through C–Cl bond cleavage.

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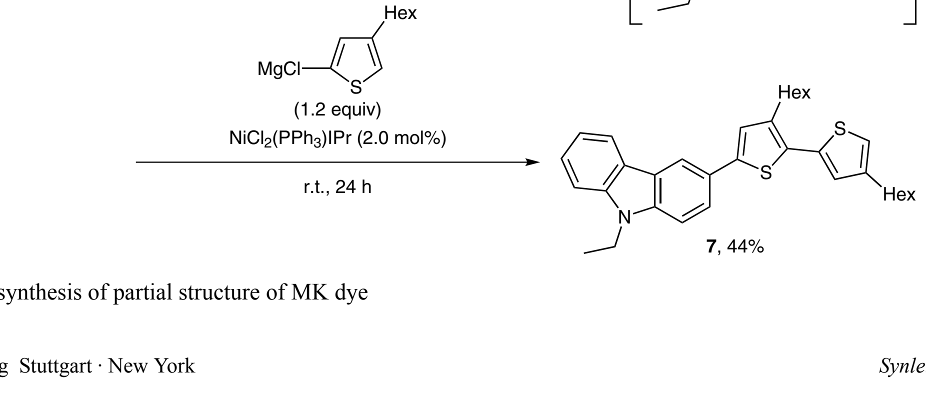

Scheme 2 One-pot synthesis of partial structure of MK dye

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(7) **General procedure for polymerization of chlorothiophene 1:** To a solution of 1.02 M EtMgCl (0.50 mL, 0.5 mmol) in THF were added 2-chloro-3-hexylthiophene (**1**; 0.5 mmol, 101 mg) and *cis*-2,6-dimethylpiperidine (0.05 mmol 6.7 μL) dropwise, and the resulting mixture was stirred at room temperature for 3 h. THF (4.5 mL) and NiCl$_2$(PPh$_3$)IPr (3.9 mg, 0.005 mmol) were successively added and stirring was continued at 25 °C for 24 h. Hydrochloric acid (1.0 M, 20 mL) and methanol (50 mL) were added to form a precipitate. The mixture was filtered and the residue was washed with methanol repeatedly to leave a dark-purple solid, which was dried under reduced pressure to afford poly(3-hexylthiophene) (**3**; 50 mg, 59% yield; $M_n = 13200$, $M_w/M_n = 1.39$).

(8) PEPPSI™: Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation. SIPr: 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene. See: (a) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J.* **2006**, *12*, 4743. (b) Organ, M. G.; Calimsiz, S.; Sayah, M.; Hoi, K. H.; Lough, A. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 2383.

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(10) **General procedure for arylation of chlorothiophene**: To a solution of 1.02 M EtMgCl (0.75 mL, 0.75 mmol) in THF were added 2-chloro-3-hexylthiophene (**1**; 0.5 mmol, 101 mg) and *cis*-2,6-dimethylpiperidine (0.05 mmol 6.7 μL) dropwise at room temperature and the resulting mixture was stirred at room temperature for 3 h. THF (2 mL), 4-bromotoluene (**4a**; 0.9 mmol, 0.11 mL), and PdCl$_2$(dppf) (8.2 mg, 0.01 mmol) were successively added and stirring was continued at room temperature for 15.5 h. The reaction mixture was poured into water and the organic materials were extracted with diethyl ether. The organic layer was washed with water twice and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel using hexane as an eluent to afford 2-chloro-3-hexyl-5-(4′-methylphenyl)thiophene (**5a**; 101 mg). ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.89$ (t, $J = 6.9$ Hz, 3 H), 1.25–1.43 (m, 6 H), 1.50–1.68 (m, 2 H), 2.35 (s, 3 H), 2.56 (t, $J = 7.7$ Hz, 2 H), 6.96 (s, 1 H), 7.16 (d, $J = 8.1$ Hz, 2 H), 7.39 (d, $J = 8.2$ Hz, 2 H); ^{13}C NMR (75 MHz, CDCl$_3$): $\delta = 14.07$, 21.13, 22.59, 28.15, 28.93, 29.59, 31.63, 123.02, 123.07, 125.24, 129.56, 131.08, 137.51, 140.21, 140.62; IR (neat): 809, 1041, 1453, 1513, 2856, 2925, 2954; HRMS (DART-ESI+): m/z [M + H]$^+$ calcd for C$_{17}$H$_{22}$^{35}ClS: 293.1131; found: 293.1131.

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