CHEMISTRY
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To be cited as: Chem. Eur. J. 10.1002/chem.201604293

Link to VoR: http://dx.doi.org/10.1002/chem.201604293

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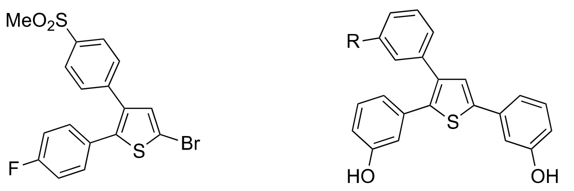
One-Pot Halogen Dance/Negishi Coupling of Dibromothiophenes for Regiocontrolled Synthesis of Multiply Arylated Thiophenes

Kentaro Okano,* Kazuhiro Sunahara, Yoshiki Yamane, Yuki Hayashi, and Atsunori Mori

Abstract: One-pot halogen dance/Negishi cross coupling of readily available 2,5-dibromothiophenes is described. An LDA-mediated halogen dance reaction resulted in the formation of thermodynamically stable α-lithiodibromothiophenes, which were transmetalated with $ZnCl_2$ and subjected to Negishi cross coupling to provide the corresponding arylated dibromothiophenes in one pot. The resultant β-bromo group was much less reactive than the remaining α-bromo group, which was used in a one-pot double Suzuki–Miyaura cross coupling, enabling facile synthesis of multiply arylated thiophenes.

Arylated thiophenes are structural constituents of drug candidates and pharmaceuticals,[1] biologically active natural products,[2] and functional organic materials[3] (Figure 1). Despite their potential utilities, general and practical synthetic methods for multiply arylated thiophenes have not yet been fully established. Unlike the cases of mono-/di-arylated thiophenes, regiochemical problems often arise in the synthesis of tri-/tetra-arylated thiophenes. Achieving sufficient regioselectivity using conventional cross coupling of brominated thiophenes is therefore challenging.[1f,4] Stepwise introduction of aryl groups requires a number of reaction steps; for example, Itami and co-workers reported the stepwise synthesis of multiply arylated thiophenes using palladium-catalyzed C–H arylations[5] [Scheme 1, Eq. (1)]. Knochel and co-workers also reported the synthesis of tetra-substituted thiophenes by deprotonation/functionalization with Mg(TMP)Cl·LiCl as a base.[6] The generated thienyl magnesium species can be used for cross-coupling reactions [Scheme 1, Eq. (2)]. Halogen dance of 2,5-dibromothiophene,[7] which is a halogen migration reaction, also holds the potential for pot-economical transformations because the α- and β-bromine atoms in the product have different reactivities in further transition metal-catalyzed reactions.[8] However, the scope of the electrophiles that have been trapped by the lithiated thiophenes is limited, although numerous halogen dance reactions of thiophenes have been performed.[7] To the best of our knowledge, the transient thienyl lithium species generated by the halogen dance reaction has not been used for cross-coupling reactions. Here, we report a one-pot halogen dance/Negishi coupling of bromothiophenes [Scheme 1, Eq. (3)] for regiocontrolled synthesis of multiply arylated thiophenes.



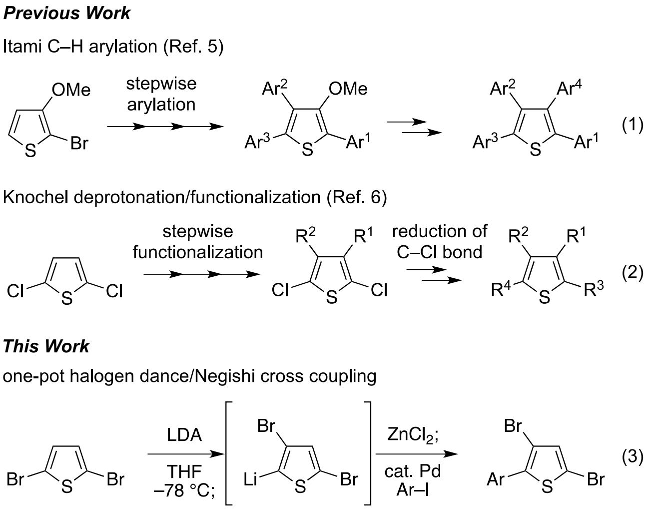
DuP697

COX-2 inhibitor (Ref. 1b)

Human 17β-HSD1 inhibitor (Ref. 1f)

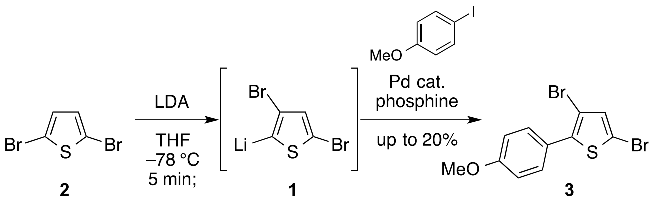
R = OH : IC_{50} = 119 nM
R = H : IC_{50} = 493 nM

Figure 1. Multiply arylated thiophenes.



Scheme 1. Examples of functional group introduction into thiophene ring.

First we attempted Murahashi coupling[9] to introduce a 4-anisyl group directly into lithiated dibromothiophene **1**, which was generated by treatment of 2,5-dibromothiophene (**2**) with LDA[10] at –78 °C using previously reported conditions[7] (Scheme 2). The halogen dance was completed at –78 °C within 5 min, and the resultant lithiothiophene **1** was immediately treated with *p*-iodoanisole in the presence of various palladium catalysts to provide the desired arylated compound **3** in up to 20% yield with concomitant generation of unidentified byproducts, probably through undesired iodine–lithium exchange.[11] We also attempted slow or inverse addition of lithiothiophene **1** using Feringa's method,[12] but the yields were low.



Scheme 2. Initial attempts to introduce anisyl group by Murahashi coupling.

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[a] Prof. Dr. K. Okano,* K. Sunahara, Y. Yamane, Y. Hayashi, and Prof. Dr. A. Mori
Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501 (Japan)
E-mail: okano@harbor.kobe-u.ac.jp
Supporting information for this article is given via a link at the end of the document.

To prevent undesired scrambling of the halogen atoms by halogen–lithium exchange and improve the operational processes, we next examined transmetalation of the transient lithiated dibromothiophene **1** and found that transmetalation with $ZnCl_2 \cdot TMEDA$[13] facilitated Negishi cross coupling[14] to give the desired arylated dibromothiophene (Table 1). The transient lithiated dibromothiophene **1** from 2,5-dibromothiophene (**2**) was treated with $ZnCl_2 \cdot TMEDA$ followed by *p*-iodoanisole, $Pd_2(dba)_3 \cdot CHCl_3$, and a phosphorus ligand. Among the bidentate ligands tested, DPEPhos provided the desired compound **3** in 44% yield with 20% recovery of **5** (Table 1, entries 1–3). Monodentate PPh_3 also gave a comparable yield; however, the desired product **3** was not generated with P(*o*-tolyl)$_3$ or JohnPhos (Table 1, entries 4–6).

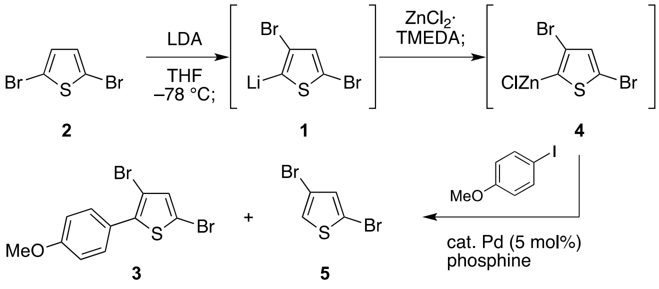


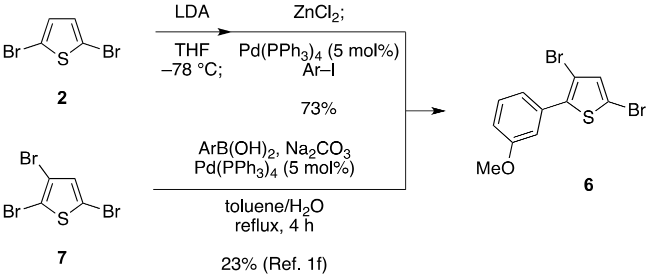
Table 1. Optimization of palladium catalyst for Negishi coupling[a]

Entry	Catalyst	**3** [%]	**5** [%]
1	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), DPPP (10 mol%)	6[b]	70[b]
2	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), DPPF (10 mol%)	33[b]	23[b]
3	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), DPEPhos (10 mol%)	44[b]	20[b]
4	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), PPh_3 (20 mol%)	45[b]	15[b]
5	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), P(*o*-tolyl)$_3$ (20 mol%)	–[c]	57[b]
6	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), JohnPhos (20 mol%)	–[c]	63[b]
7	$Pd(PPh_3)_4$ (5.0 mol%)	77[b]	11[b]
8	Pd(*t*Bu$_3$P)$_2$ (5.0 mol%)	18[b]	39[b]
9	Pd-PEPPSI-IPr (5.0 mol%)	–[c]	12[b]
10	Pd-PEPPSI-SIPr (5.0 mol%)	–[c]	8[b]
11	$Pd(PPh_3)_4$ (2.0 mol%)	42[b]	22[b]
12	$Pd(PPh_3)_4$ (1.0 mol%)	29[b]	42[b]

[a] Reaction conditions: 2,5-dibromothiophene (**2**) (1 equiv, 0.30 mmol), LDA (1.1 equiv, 0.33 mmol), THF, –78 to 0 °C, 5 min; $ZnCl_2 \cdot TMEDA$ (1.2 equiv, 0.36 mmol), RT, 15 min; catalyst, *p*-iodoanisole (1.2 equiv, 0.36 mmol), 60 °C, 24 h. [b] The yield was determined from the ^1H NMR spectrum of the crude material using 1,1,2,2-tetrachloroethane as an internal standard. [c] Not detected in the crude ^1H NMR spectrum. LDA = lithium diisopropylamide. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine. DBA = dibenzylidene acetone. DPPP = 1,3-bis(di phenylphosphino)propane. DPPF = 1,1′-bis(diphenylphosphino)ferrocene. DPEPhos = bis[(2-diphenylphosphino)phenyl] ether. JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl. PEPPSI-IPr = [1,3-bis(2,6-diisopropylphenyl)imidazolylidene](3-chloropyridyl)palladium(II) dichloride. PEPPSI-SIPr = [1,3-bis(2,6-diisopropylphenyl)imidazolidene](3-chloropyridyl)palladium(II) dichloride.

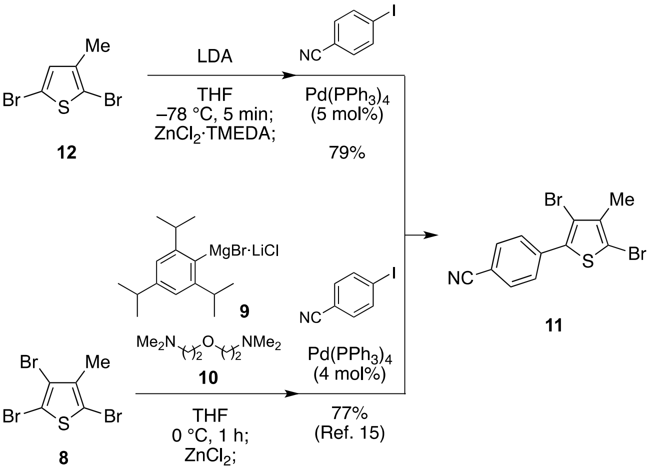
The use of $Pd(PPh_3)_4$ significantly improved the product yield, but Pd(*t*Bu$_3$P)$_2$ gave unsatisfactory results (Table 1, entries 7 and 8). The recently reported Pd-PEPPSI-IPr and Pd-PEPPSI-SIPr[15] provided no product, although recovery of **5** was low (Table 1, entries 9 and 10). A lower catalyst loading (2.0 mol%) still gave moderate yield (Table 1, entries 11 and 12).

The established halogen dance/Negishi cross coupling enabled efficient synthesis of an intermediate of a triarylated thiophene, human 17β-HSD1 inhibitor[1f] (Scheme 3). Hartmann and co-workers synthesized arylated dibromothiophene **6** from tribromothiophene **7** in 23% yield by Suzuki–Miyaura cross coupling, which indicates that it is difficult to control the regioselectivity of the three bromo groups in the cross coupling. The halogen dance/Negishi cross coupling of 2,5-dibromothiophene (**2**) provided **6** in 73% yield.



Scheme 3. Regiocontrolled synthesis of aryldibromothiophene via one-pot halogen dance/Negishi coupling.

These results are complementary to those reported by Knochel (Scheme 4).[16] They achieved regioselective magnesiation of tribromothiophene **8** using a combination of hindered Grignard reagent **9** and diamino ether **10**. The resultant thienyl Grignard was subjected to Negishi cross coupling to give arylated dibromothiophene **11**, which was also obtained from 2,5-dibromo-3-methylthiophene (**12**) using the halogen dance/Negishi coupling sequence, in 79% yield.



Scheme 4. Complementary results to those reported by Knochel.

Having identified the optimum reaction conditions, we investigated the scope of the coupling partner with 2,5-dibromothiophene (**2**) (Table 2).[17] In addition to the *p*-anisyl group, phenyl and 4-tolyl groups were successfully introduced to provide the corresponding products **13** and **14** in 59% and 62% yields, respectively. It is worth noting that the base-labile ester moiety survived under the reaction conditions to give the desired product **15** in excellent yield. In addition to *para*-substituted iodobenzenes, *meta*- and *ortho*-substituted substrates were investigated. Electron-donating/-withdrawing groups were both compatible and gave the desired products **6** and **16**–**18** in good to excellent yields. When *m*-bromoiodobenzene was used as the coupling partner, cross coupling took place selectively at the iodo group. The pyridine-conjugated thiophene **19** was obtained in 51% yield from 2-iodopyridine as the coupling partner.

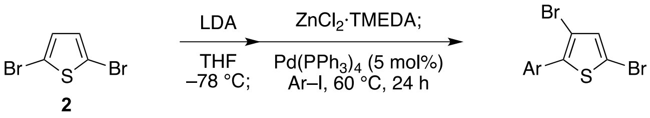
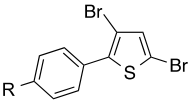
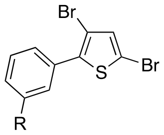
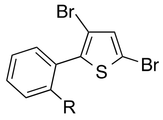
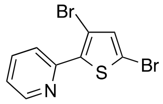


Table 2. Scope of aryl group in one-pot halogen dance/Negishi coupling[a]

Product	R	Yield [%][b]	
	OMe	68	**3**
	H	59	**13**
	Me	62	**14**
	CO_2Et	58	**15**
	OMe	51[c] 73[c,d]	**6**
	Br	68	**16**
	OMe	60	**17**
	NO_2	71	**18**
		51	**19**

[a] Reaction conditions: 2,5-dibromothiophene (**2**) (1.4 equiv, 0.42 mmol), LDA (1.3 equiv, 0.39 mmol), THF, –78 to 0 °C, 5 min; $ZnCl_2$·TMEDA (1.4 equiv, 0.42 mmol), RT, 15 min; $Pd(PPh_3)_4$ (5 mol%), aryl iodide (1.0 equiv, 0.30 mmol), 60 °C, 24 h. [b] Isolated yield. [c] Aryl iodide (2.0 mmol) was used. [d] $ZnCl_2$ (1 M in diethyl ether) was used instead of $ZnCl_2$·TMEDA.

We then investigated the scope of this one-pot reaction of readily available 3-aryl-2,5-dibromothiophenes[18] (Table 3). First, the scope of the coupling partner was examined using 3-(4-anisyl)-2,5-dibromothiophene (**20a**) as the substrate. Phenyl, α,α,α-trifluorotolyl, and ethoxycarbonylphenyl groups were introduced, providing the diarylated dibromothiophenes **21**–**23** in satisfactory yields. The same transformation of 3-(4-chloro)-2,5-dibromothiophene (**20b**) also took place smoothly to give the corresponding products **24**–**26**.

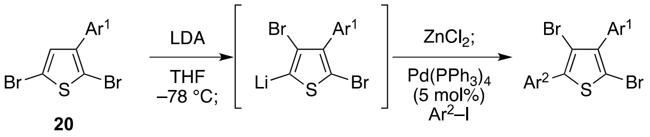
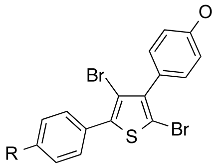
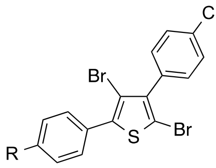
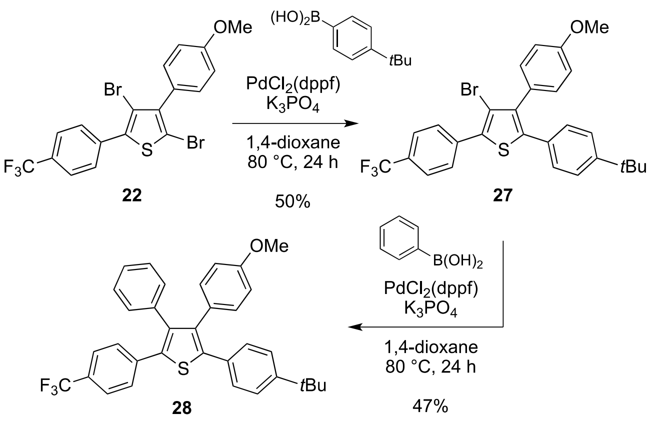


Table 3. Substrate scope for halogen dance–Negishi coupling

Product	R	Yield [%][a]	
	H	53	**21**
	CF_3	63	**22**
	CO_2Et	70	**23**
	H	53	**24**
	CF_3	57	**25**
	NO_2	67 83[c]	**26**

[a] Isolated yield. [b] Reaction conditions: 3-aryl-2,5-dibromothiophene (**20**) (1.4 equiv, 0.42 mmol), LDA (1.3 equiv, 0.39 mmol), THF, –78 to 0 °C, 5 min; $ZnCl_2$·TMEDA (1.4 equiv, 0.42 mmol), RT, 15 min; $Pd(PPh_3)_4$ (5 mol%), aryl iodide (1.0 equiv, 0.30 mmol), 60 °C, 24 h. [c] Aryl iodide (10 mmol) was used.

The resultant diarylated thiophenes had α- and β-bromo groups with distinct reactivities in transition metal-catalyzed transformations;[8] this enabled facile and regiocontrolled synthesis of tetraarylated thiophenes. We chose Suzuki–Miyaura cross coupling to perform mono-arylation at the α-position of the thiophene ring (Scheme 5). First, diaryldibromothiophene **22** was treated with a slight excess (1.1 equiv) of arylboronic acid in the presence of a palladium catalyst and base under the conventional conditions to give the triarylated thiophene **27** in 50% yield. The product was then subjected to a second cross-coupling reaction to provide the tetraarylated thiophene **28** in 47% yield; its ^1H and ^{13}C NMR spectra were identical to those previously reported.[5b]



Scheme 5. Regioselective stepwise Suzuki–Miyaura cross coupling.

The optimal conditions were used for one-pot double Suzuki–Miyaura cross coupling, which gave rapid access to a series of multiply arylated thiophenes (Table 4). Two different tetraarylated thiophenes **28** and **29** were synthesized simply by changing the order in which the boronic acids were added. The established protocol was also applied for gram-scale synthesis of tetraarylated thiophene **33**. Similarly, triarylated thiophenes **34** and **35** were synthesized from the corresponding dibromoarylthiophene.

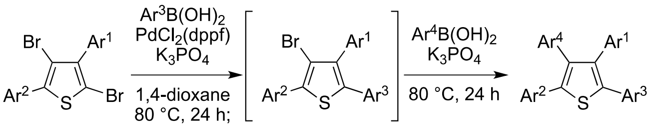
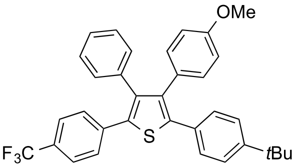
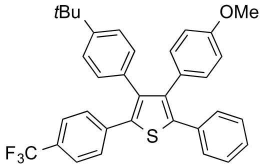


Table 4. One-pot double Suzuki–Miyaura cross coupling[a]

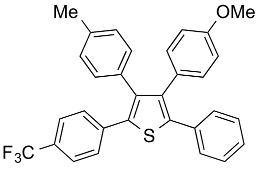
Product



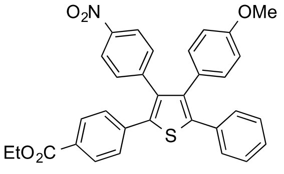
48%[b] **28** (Ref. 5b)



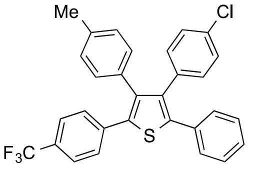
44%[b] **29**



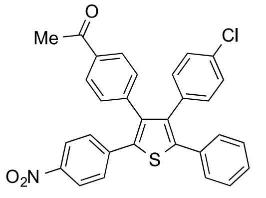
51%[b] **30** (Ref. 5a)



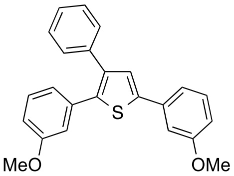
45%[b] **31**



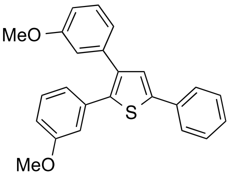
47%[b] **32** (Ref. 5a)



67%[b] (73%[b,c]) **33**



61%[b,d] **34** (Ref. 1f)



54%[b,d] **35**

[a] Reaction conditions: dibromothiophene (1 equiv, 0.15 mmol), $Ar^3B(OH)_2$ (1.1 equiv), $[PdCl_2(dppf)]\cdot CH_2Cl_2$ (5 mol%), K_3PO_4 (2.0 equiv), 1,4-dioxane, 80 °C, 24 h; $Ar^4B(OH)_2$ (1.1 equiv), K_3PO_4 (2.0 equiv), 80 °C, 24 h. [b] Isolated yield. [c] The one-pot double Suzuki–Miyaura reaction of dibromothiophene **26** (5.0 mmol) provided 1.86 g of tetraarylated thiophene **33**. The first Suzuki–Miyaura coupling was performed with 0.90 equiv (4.5 mmol) of $Ar^3B(OH)_2$. [d] Dibromothiophene **6** (0.30 mmol) was used. The first Suzuki–Miyaura coupling was performed with 1.0 equiv (0.30 mmol) of $Ar^3B(OH)_2$.

In conclusion, we have developed a one-pot LDA-mediated halogen dance/Negishi cross coupling of dibromothiophenes. This synthetic method provides a wide range of multiply arylated thiophenes based on one-pot migration of the bromo group and control of the reactivity of the transient anion species. The two bromo groups were regioselectively converted to aryl groups, enabling rapid access to multiply arylated thiophenes. The synthetic potential of this method was demonstrated by a concise and regioselective synthesis of tetraarylated thiophenes.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP26253001, JP16K05774, and JP16H01153 in the Middle Molecular Strategy, Creation of Innovation Centers for Advanced Interdisciplinary Research Areas (Innovative Bioproduction Kobe) by MEXT, and Kawanishi Memorial ShinMaywa Education Foundation.

Keywords: halogen dance • cross-coupling • one-pot reaction • thiophene • palladium

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[17] The heating conditions were necessary for satisfactory yields in the cross coupling reaction. When we performed the coupling reaction at room temperature with *p*-iodoanisole or *o*-iodoanisole as a coupling partner, the corresponding products **3** and **17** were obtained in 35% and 14% yields, respectively.

[18] For the preparation of 3-aryl-2,5-dibromothiophenes, see Supporting Information.

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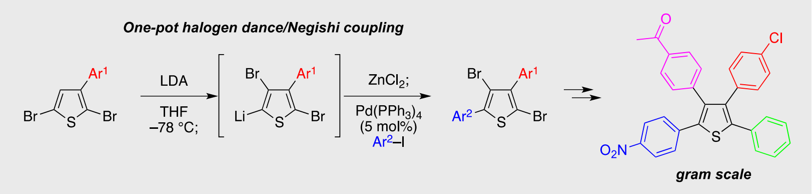
COMMUNICATION



A one-pot LDA-mediated halogen dance/Negishi cross coupling of readily prepared 2,5-dibromothiophenes is described. The one-pot reaction involves α-bromo group migration to the β position and then α-arylation. The resultant α- and β-bromo groups were regioselectively converted to aryl groups by one-pot Suzuki–Miyaura coupling. The synthetic potential of this method was shown by regiocontrolled gram-scale synthesis of tetraarylated thiophene.

Kentaro Okano, Kazuhiro Sunahara, Yoshiki Yamane, Yuki Hayashi, and Atsunori Mori*

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One-Pot Halogen Dance/Negishi Coupling of Dibromothiophenes for Regiocontrolled Synthesis of Multiply Arylated Thiophenes