HETEROCYCLES, Vol. 98, No. 10, 2019, pp. 1355 - 1374. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 12th July, 2019, Accepted, 18th October, 2019, Published online, 29th October, 2019
DOI: 10.3987/COM-19-14132

UNEXPECTED FORMATION OF 4,7-DIHALOBENZO[*b*]THIOPHENES USING OHIRA-BESTMANN REAGENT AND REACTIVITY OF THE HALOGEN-SUBSTITUTED BENZO[*b*]THIOPHENES IN SUZUKI-MIYAURA COUPLING WITH PHENYLBORONIC ACID

Kozo Toyota,* Hirotaka Mutoh, Hiroki Kishi, Shinichi Mikami, Hiroki Tanaka, Shuhei Yoshida, and Daisuke Naganuma

Department of Chemistry, Graduate School of Science, Tohoku University, Aoba, Sendai, Miyagi 980-8578, Japan. E-mail (new): toyota@tohoku.ac.jp
E-mail (previous): toyota@m.tohoku.ac.jp

Abstract – Reaction of 2-(1-adamantylsulfanyl)-3,6-dihalobenzaldehydes with Ohira-Bestmann reagent gave 4,7-dihalobenzo[*b*]thiophenes along with normal alkyne products. Nine types of 4,7-dihalobenzo[*b*]thiophenes bearing chlorine, bromine, or iodine atoms, were prepared by this method. Regioselectivity in Suzuki-Miyaura cross coupling reactions of the 4,7-dihalobenzo[*b*]thiophenes with $PhB(OH)_2$ was also studied.

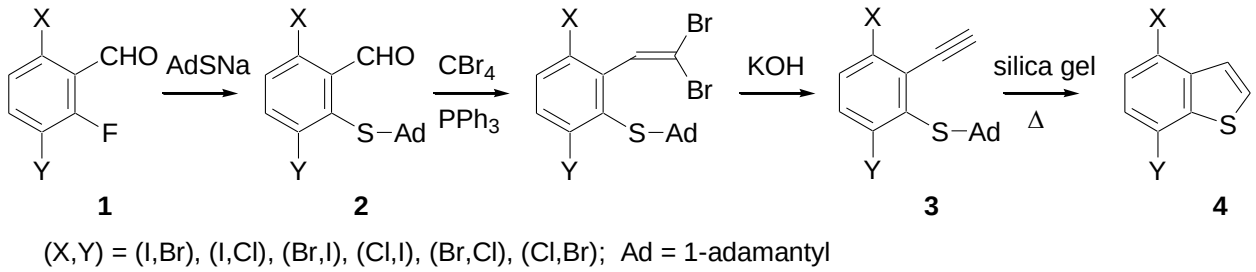
INTRODUCTION

Heterocyclic compounds have been very important, especially in pharmacology and materials science. Numerous reports have been published for preparation of heterocycles.[1] Nevertheless, new methods are continuously explored, in order to prepare compounds of more complicated and elaborated structure, which will be utilized in development of medicine, materials, and so on. For this purpose, reaction conditions as mild as compatible with various functional groups are favourable.

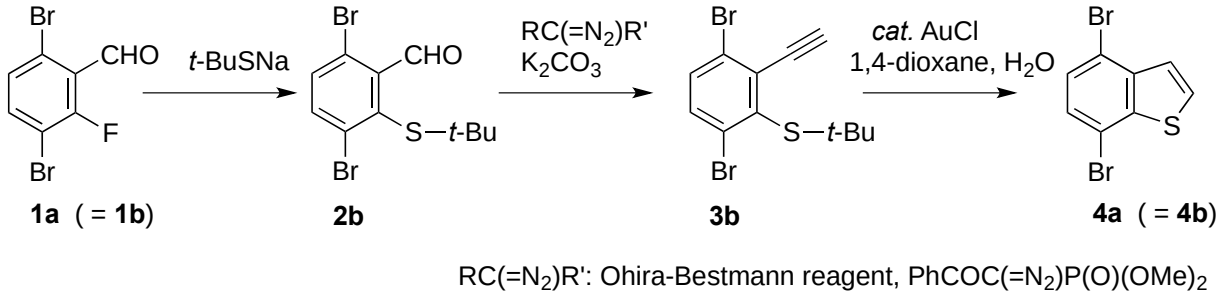
Recently, a considerable number of papers report preparations of heterocycles from *alkynes*[2,3] under mild conditions.[4] For example, azide-alkyne cycloadditions (AAC) have been widely applied in many research field, as one of typical 'click' reactions.[2,5] For other examples, various Lewis acidic transition metal catalysts were used in intramolecular cyclization of heteroatom compounds containing heteroatoms and proximate alkyne moiety.[6,7] Many ring-fused heterocycles were prepared by iodocyclization of analogous alkynes.[3,8–10] Moreover, reaction of arylalkynes with elemental sulfur[11] and electrochemical approach[12] leading to heterocycles have been reported.

As for the preparation of the alkyne precursors, Sonogashira coupling is often used for introduction of triple bonds.[13,14] Corey-Fuchs reaction using butyllithium is another well-known method of alkyne synthesis.[15] However, these reactions are not always suitable when both the substrate molecule and the target molecule contain reactive halogen atoms such as bromine and iodine: in typical Corey-Fuchs reaction and Sonogashira reaction, unfavourable reaction may occur on such reactive halogen atoms unselectively, affording undesired products.

A modified Corey-Fuchs reaction[16–18] using milder bases may be applicable to such sensitive targets. Another method of choice is Seyferth-Gilbert homologation (Ohira-Bestmann modification), in which Ohira-Bestmann reagent-derived species attack aldehydes under mild conditions to give alkynes.[19–22] Actually, we have prepared 4,7-dihalobenzo[*b*]thiophenes[18,23] and 2,4,7-trihalobenzo[*b*]thiophenes[18] via alkynes utilizing the modified Corey-Fuchs reaction (Scheme 1) or Ohira-Bestmann reagent (Scheme 2).



Scheme 1. Preparation of 4,7-dihalobenzo[*b*]thiophenes **4** from *o*-sulfanylbenzaldehydes **2** using a modified Corey-Fuchs reaction and silica gel-assisted cyclization.[18] Atoms X,Y are either Cl, Br, or I (X≠Y)



Scheme 2. Preparation of 4,7-dibromobenzo[*b*]thiophene from *o*-sulfanylbenzaldehyde using Ohira-Bestmann reagent and gold catalyst[23]

In the course of our investigation on synthesis of multi-halobenzo[*b*]thiophenes, we found unexpected product of Seyferth-Gilbert-Ohira-Bestmann reaction, and we report here unusual formation of

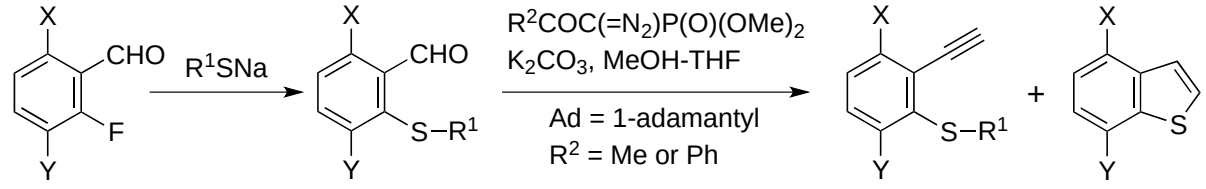
4,7-dihalobenzo[*b*]thiophenes by reaction of the corresponding 2-(1-adamantylsulfanyl)benzaldehydes with Ohira-Bestmann reagent.

RESULTS AND DISCUSSION

Unexpected formation of 4,7-dihalobenzo[*b*]thiophenes from *o*-sulfanylbenzaldehydes

The starting 2-(1-adamantylsulfanyl)benzaldehydes **2a**–**n** were prepared from the corresponding 2-fluorobenzaldehydes **1a**–**n** by a previously reported method[18] (Scheme 3). The dibromo derivative **2a** was reacted with dimethyl (1-diazo-2-oxopropyl)phosphonate in a THF (tetrahydrofuran)-MeOH mixed solvent. The reaction mixture was worked up with water and EtOAc. The organic layer was separated, dried with $MgSO_4$, and concentrated under reduced pressure. ^{1}H NMR spectrum of the residue showed formation of benzo[*b*]thiophene **4a**, besides the normal alkyne product **3a**. The ratio of the signals was 20:3 (**3a**:**4a**). The mixture was then treated with silica gel column chromatography at room temperature to give **3a** and **4a** in 74% and 8% isolated yields, respectively (Table 1, entry 1).

The preparative conditions were studied at room temperature or bellow (Table S1 in Supporting Information), taking into account the reaction conditions reported in Refs. 21 and 22: A safety data sheet of the reagent dimethyl (1-diazo-2-oxopropyl)phosphonate (Tokyo Chemical Industry Co., Ltd.) cautions that it may explosively decompose on heating, shock, and so on. The conditions shown in entry 1 of Table 1 gave a best sum of yields of the products **3a**+**4a**, among the conditions shown in Table S1 using **2a** and a commercially-available dimethyl (1-diazo-2-oxopropyl)phosphonate (see below).



1a-n **2a-n** **3a-n** **4a-n**

a: X = Y = Br, R^1 = Ad
b: X = Y = Br, R^1 = *t*-Bu
c: X = Y = I, R^1 = Ad
d: X = Y = Cl, R^1 = Ad
e: X = I, Y = Br, R^1 = Ad
f: X = I, Y = Cl, R^1 = Ad
g: X = Br, Y = I, R^1 = Ad
h: X = Cl, Y = I, R^1 = Ad
i: X = Br, Y = Cl, R^1 = Ad
j: X = Cl, Y = Br, R^1 = Ad
k: X = Cl, Y = H, R^1 = Ad
l: X = H, Y = Cl, R^1 = Ad
m: X = Y = H, R^1 = Ad
n: X = Y = H, R^1 = Me

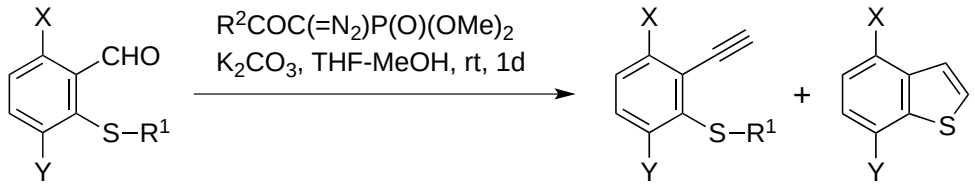
(**1a** = **1b**, **1m** = **1n**
4a = **4b**, **4m** = **4n**)

Scheme 3. Simultaneous preparation of compounds **3** and **4** by Ohira-Bestmann reagent

A similar tendency was shown in the case of dimethyl (1-diazo-2-oxo-2-*phenyl*ethyl)phosphonate instead of dimethyl (1-diazo-2-oxopropyl)phosphonate (Table 1, entries 2 and 3). Reinvestigation of reaction of **2b**[23] uncovered the formation of **4b** (= **4a**) along with the major product **3b** (entry 4).

4,7-Diiodobenzo[*b*]thiophene **4c** and dichlorobenzo[*b*]thiophene **4d**[24] were obtained from **2c**,**d** along with the corresponding alkynes **3c**,**d**, respectively (entries 5 and 6). *o*-Sulfanylbenzaldehydes **2e**–**j** containing two different halogen atoms X and Y were also subjected to reaction with Ohira-Bestmann reagent to give the corresponding alkynes and benzo[*b*]thiophenes (entries 7–12).

Table 1. Results of the reaction of Ohira-Bestmann reagent with the aldehydes **2**



2a-o **3a-o** **4a-o**

Entry	**2**	X	Y	R^1	R^2	Yield of **3** (%)	Yield of **4** (%)
1	**a**	Br	Br	Ad[a]	Me	74	8
2					Ph	70	20
3[b]					Ph	60	19
4	**b**	Br	Br	*t*-Bu	Ph	70	18 (**4a**)
5	**c**[c]	I	I	Ad	Me	72	9
6	**d**	Cl	Cl	Ad	Me	80	13
7	**e**	I	Br	Ad	Me	71	13
8	**f**	I	Cl	Ad	Me	72	13
9	**g**[d]	Br	I	Ad	Me	76	12
10	**h**	Cl	I	Ad	Me	80	9
11	**i**	Br	Cl	Ad	Me	76	18
12	**j**	Cl	Br	Ad	Me	72	11
13	**k**	Cl	H	Ad	Me	78	12
14	**l**	H	Cl	Ad	Me	89	0.8
15	**m**	H	H	Ad	Me	83	< 0.5
16	**n**	H	H	Me	Me	70	1 (**4m**)
17	**o**[e]	Ph	H	Ad	Me	29	9

[a]Ad = 1-adamantyl. [b]Two molar equivalents of Ohira-Bestmann reagent was used. [c]Compound **2c** (6%) was recovered. [d]Compound **2g** (7%) was recovered. [e]Compound **2o** (54%) was recovered.

For the purpose of seeing the effect of the substituent at the 3- and 6-positions of 2-(adamantylsulfanyl)benzaldehyde **2**, reactions of monochloro derivatives **2k**,**l** were studied (entries 13 and 14). The results show that absence of substituent at the 6-position (proximate to the CHO group) suppresses the formation of the by-product benzothiophene **4** almost completely (entry 14). In accordance with this structure-reactivity relationship, compounds **2m**,**n** without substituent on the 3- and 6-positions afforded only trace amount of parent benzo[*b*]thiophene **4m** (entries 15 and 16). Moreover, compound **2o** was prepared from **2k** and tested: The result exhibited decreased yield of **3o** (entry 17) and the total yield was low probably because of the increased steric congestion near the formyl group.

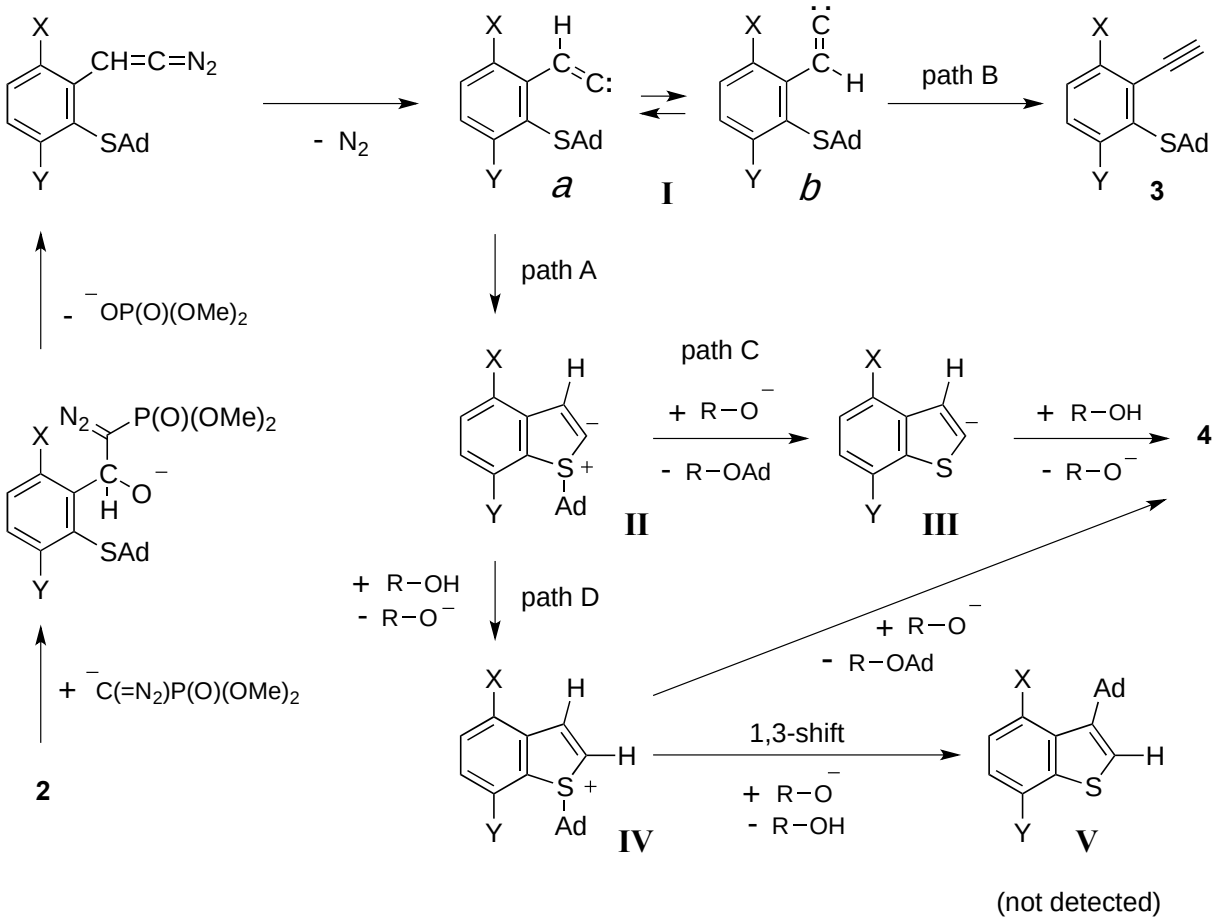
We also investigated several reaction conditions of **2a** in order to get some insight for reaction mechanism. Increased amount of Ohira-Bestmann reagent (1–2 equiv.) did not give a significant change in the yield of **4a** (Table 1, entry 3 vs entry 2). Reaction of the isolated alkyne **3a** with Ohira-Bestmann reagent under similar conditions did not form **4a**, indicating that **4a** is not an overreaction product. Reaction of **2a** at 0 °C or reaction in the presence of 18-crown-6 led to a slight decrease of **3a** (Table S1 in Supporting Information, entries 1–3).

Reaction of **2a** in MeOH (without THF) or EtOH also led to a slight decrease of **3a** (Table S1, entries 4–6). It should be mentioned here that 1-adamantyl ethyl ether was obtained in a yield similar to that of **4a** in the case of the reaction in EtOH (Table S1, entry 6). In the case of the reaction in MeOH, however, formation of 1-adamantyl methyl ether was unclear by ^{1}H NMR spectroscopy and attempted isolation of adamantyl-derived product by silica gel column chromatography has been unsuccessful. The reaction did not proceed in 1-PrOH nor in 2-PrOH (Table S1, entries 7 and 8). Reproducibility was not so good when MeONa was used instead of K_2CO_3 (Table S1, entry 9).

Based on the above results, we propose a plausible reaction mechanism as shown in Scheme 4: An *intramolecular* reaction of the intermediate **I** (possible conformations α and β in Scheme 4) to **4** and **3** seems to be appropriate, because the yields of **4** and **3** did not change so much in various conditions. In the case of X = H, conformation β is favourable leading to normal alkyne product **3** (path B).

On the other hand, in the case of X = halogen or phenyl, conformation β slightly suffers from steric congestion with increment of the ratio of conformation α, and an intramolecular attack of the sulfur atom to the electrophilic carbene generates ylide **II** (path A, probably under kinetic control, see Table S1, entry 2 vs entry 1), which loses the adamantyl moiety to give **4** via **III** (path C), releasing the steric congestion.

Formation of sulfonium intermediate **IV** (path D) may be possible, but not likely in this reaction: Neither 1,3-shift product **V** nor 1,2-shift product was detected in our hands, in contrast to many Lewis acid-catalyzed *o*-(alkylsulfanyl)(ethynyl)benzene cyclization reactions, which are supposed to proceed via sulfonium intermediates.[3,6,8–10]

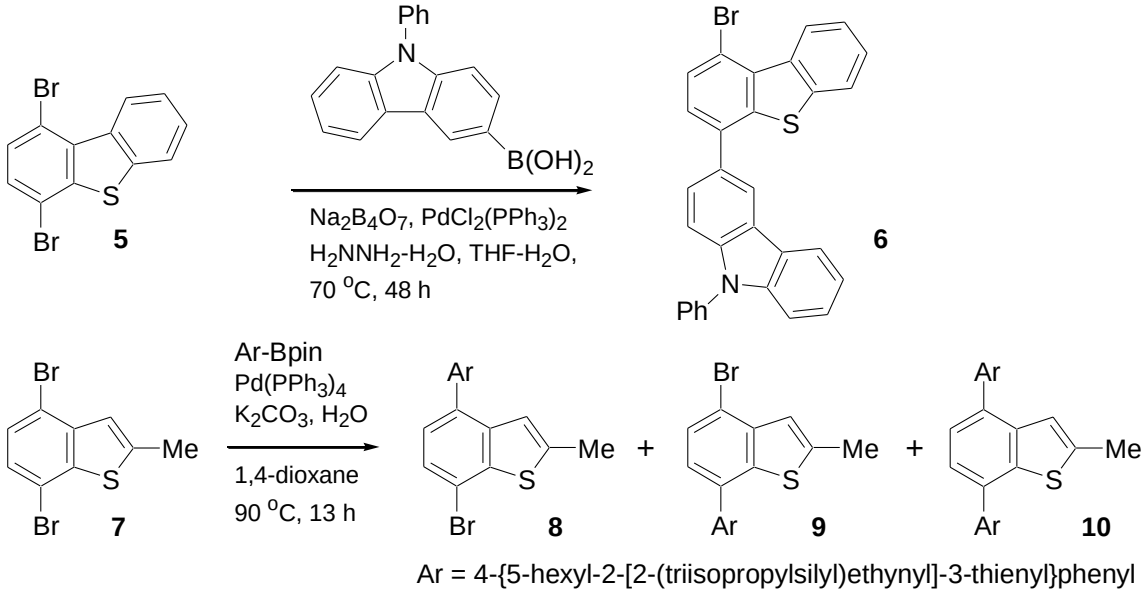


Scheme 4. Plausible reaction mechanism of **2** with Ohira-Bestmann reagent

Regioselectivity of 4,7-dihalobenzo[*b*]thiophenes in cross coupling reactions

In the next place, Suzuki-Miyaura cross coupling reactions of the dihalobenzo[*b*]thiophenes thus obtained were investigated. It is well known that relative reactivity of halogen atoms in palladium-catalyzed cross coupling is I>Br>Cl>>F. According to this order, we can easily predict the regioselectivity when the substrates contain different halogen atoms. However, regioselectivity in cross coupling becomes ambiguous when the substrates bear same halogen atoms at the 4- and 7-positions of benzo[*b*]thiophene (such as **4a**–**d**). In most of literary reported cases, *same* substituents were introduced to the 4- and 7-positions in a single operation to give a sole product, making the selectivity unclear.[25,26] Nevertheless, a few paper described mono-substituted product: Parham *et al*. described a preparation of mono-substituted product **6** (27% yield) by Suzuki-Miyaura cross coupling of **5** (Scheme 5).[27]

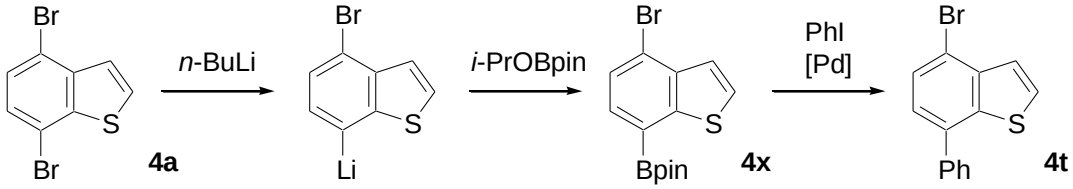
Buchwald-Hartwig amination of **5** with 2-chloroaniline is reported to react at the bromine atom near the sulfur in 79% yield.[28] We have reported formation of a mixture of **8**–**10** (*ca*. 2:1:1 ratio) by reaction of **7** with 1 equiv. of arylboronic acid pinacol ester (Ar-Bpin, where Ar = 4-{5-hexyl-2-[2-(triisopropylsilyl)ethynyl]-3-thienyl}phenyl).[23]



Scheme 5. Some reported cross coupling reactions of 4,7-dibromobenzo[*b*]thiophene derivatives[23,27]

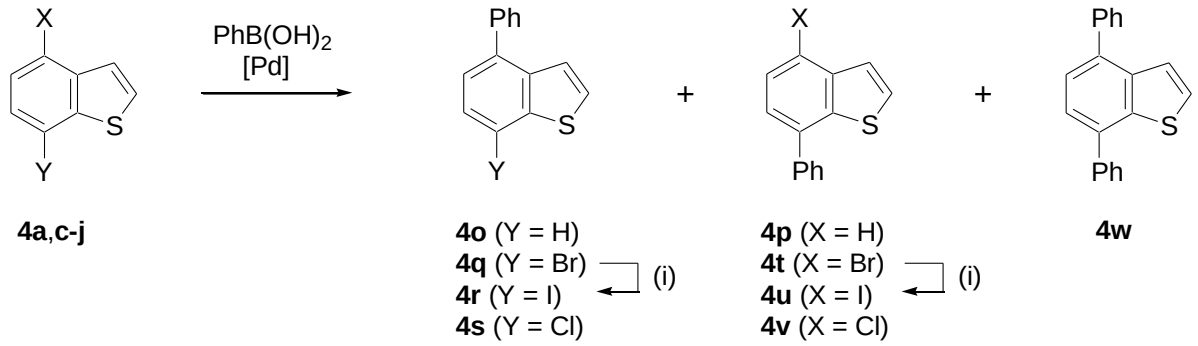
As we prepared 1,2-unsubstituted 4,7-dihalobenzo[*b*]thiophenes **4a**–**j**, we studied Suzuki-Miyaura cross coupling reactions of **4a**–**j** with phenylboronic acid, which will lead to phenyl-substituted benzo[*b*]thiophene derivatives **4o**–**w** (Table 2).

First, reactions of **4e**–**h** (X≠Y) were investigated. Compounds **4q**,**s** and **4t**,**v** were regioselectively obtained from **4e**–**h**, reflecting the different reactivity of halogen atoms (I>Br>Cl) in Suzuki-Miyaura cross coupling (Table 2, entries 7–12). For confirmation, compound **4t** was alternatively prepared from **4a** via **4x** as shown in Scheme 6, utilizing selective lithiation[23] of **4a** followed by borylation and cross coupling reaction. The structures of **4t** and some other products were analysed also by 2D-NMR.



Scheme 6. Alternative preparation of **4t** from **4a**

Table 2. Results of the cross coupling reaction of **4** with about 1 equiv. of $PhB(OH)_2$ [a]



(i) *n*-BuLi, Et_2O, –78 °C, then I-CH_2CH_2-I

Entry	**4**	X	Y	Method	Temp / °C	Time / h	4-Ph deriv. (%)[b]	7-Ph deriv. (%)[b]	**4w** / % [b,c]	Recov. **4** / % [b,c]
1	**a**	Br	Br	A	80	24	**4q** (33)[d]	**4t** (18)[d]	25	18
2				B	80	25	**4q** (25)[d]	**4t** (14)[d]	27	11
3				C	80	24	**4q** (13)[d]	**4t** (9)[d]	42	30
4	**c**	I	I	B	50	32	**4r** (4)[d]	**4u** (12)[d]	34	8
5[e]	**d**	Cl	Cl	C	90	18	**4s** (33)[d]	**4v** (18)[d]	26	14
6				D	90	27	**4o** (42)[f]	**4p** (24)[f]	15	0 [g]
7[e]	**e**	I	Br	B	50	48	**4q** (81)[c]			12
8	**f**	I	Cl	E	90	15	**4s** (86)[c]			
9[e]	**g**	Br	I	B	50	40		**4t** (93)[c]	5	
10	**h**	Cl	I	E	90	26		**4v** (97)[c]		
11	**i**	Br	Cl	B	80	16	**4s** (56)[c]			
12	**j**	Cl	Br	B	80	17		**4v** (96)[c]		

[a]The phenylboronic acid (containing anhydride) was purchased from Tokyo Chemical Industry Co., Ltd. and used as it was. Method A, $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O; Method B, $PhB(OH)_2$, $PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3, 1,4-dioxane, Method C, $PhB(OH)_2$, XPhosPdG3, K_2CO_3, 1,4-dioxane, H_2O; Method D, $PhB(OH)_2$, XPhosPdG3, K_2CO_3, toluene-EtOH, H_2O; Method E, $PhB(OH)_2$, $PdCl_2(PPh_3)_2$, K_2CO_3, toluene-EtOH, H_2O. [b]Yield based on **4**. [c]Isolated yield. [d]Obtained as an inseparable mixture of the regio-isomers; the yield was estimated by ^1H NMR spectroscopy. [e]A slightly excess amount (1.1–1.3 equiv.) of $PhB(OH)_2$ was used. [f]Obtained as a partially separated mixture; the yield was estimated by ^1H NMR spectroscopy. [g]Compound **4d** was consumed. Unsubstituted benzo[*b*]thiophene **4m** (hydrolytic dehalogenation product) was formed and sublimed in the evaporation process.

Authentic iodide **4r** was then prepared from **4q** by halogen-lithium exchange using butyllithium followed by reaction with 1,2-diiodoethane. A similar reaction of **4t** resulted in a mixture of **4u** and **4t**. Authentic **4w** was prepared by reaction of **4a** with *ca*. 2 equiv. of $PhB(OH)_2$.

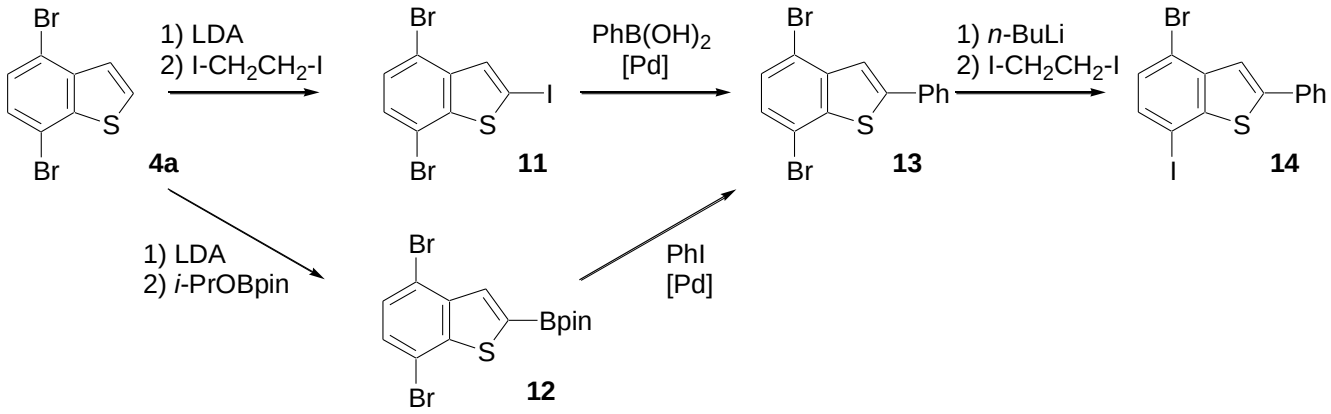
Then coupling reactions of **4a**,**c**,**d** (X=Y) with *ca*. 1 equiv. of $PhB(OH)_2$ were investigated. The reactions resulted in mixtures of **4q**–**w** and unreacted **4a**,**c**,**d** (Table 2, entries 1–5). Separation of the products by column chromatography was generally difficult, thus analyses of the isomeric mixture were performed by comparison of the ^1H and ^{13}C NMR spectra with those of the authentic samples obtained above. As for the effect of the catalyst, the yield of the doubly-substituted product **4w** (from **4a**) increased according to the well-known order of activity $Pd(PPh_3)_4$ < $PdCl_2$(dppf) < XPhosPdG3, while the reverse order was observed in the yield of the mono-phenyl product **4q**,**t**, in compensation (entries 1–3). When the reaction of **4d** was performed in toluene-EtOH-H_2O, products **4o**[29] and **4p**[30] were obtained probably via Pd-catalyzed hydrolytic dehalogenation of **4s** and **4v**, respectively (entry 6).

These results show the reactions are apparently not regioselective in the case of the reaction of **4a**,**c**,**d** (X=Y) with $PhB(OH)_2$, while compounds **4e**–**h** (X≠Y, either X or Y is iodine) afforded products in *good selectivity* with the reactivity of I > Br > Cl. As expected, difference of halogen atoms effectively controls the reaction site in **4e**–**h**, making these compounds valuable in organic synthesis as molecular scaffolds. Especially, the (chloro)(iodo)compounds **4f**,**h** exhibited good selectivity even at 90 °C.

(Bromo)(iodo)benzo[*b*]thiophenes **4e**,**g** are also promising building blocks for stepwise introduction of substituents, because both halogen atoms (iodine and bromine) are reported to have sufficient reactivity in many cross coupling reactions in addition to the advantage of excellent selectivity (iodine vs bromine) as is exhibited in Table 2 and Ref. 23.

It should be mentioned here again that some halogen atoms of **4** can be regioselectively converted to other halogens by using halogen-metal exchange, which is enhanced by the proximate lone pair of the sulfur atom. For example, **4a** was converted to **4g** by reactions with butyllithium followed by 1,2-diiodoethane in good yield[23] (see also, Scheme 7; compound **13** to **14**).

It is also noteworthy that phenyl group could be regioselectively introduced to the 2-position of the dibromo derivative **4a**, as follows (Scheme 7). Reaction of **4a** with lithium *N*,*N*-diisopropylamide (LDA) followed by treatment with 1,2-diiodoethane formed compound **11**, which was then converted to **13** by Suzuki-Miyaura cross coupling with $PhB(OH)_2$. Compound **13** was also obtained by reaction of **12** with iodobenzene. The bromine atom at the 7-position of **13** could be converted to iodine to give the corresponding (bromo)(iodo) derivative **14**, with which regioselective cross coupling reaction can be expected as is the case of compound **4g** (Table 2).



Scheme 7. Introduction of phenyl group to the 2-position of benzo[*b*]thiophene

In summary, we found unexpected formation of 4,7-dihalobenzo[*b*]thiophene derivatives from *o*-sulfanylbenzaldehydes and Ohira-Bestmann reagent in one synthetic operation. All possible 4,7-dihalobenzo[*b*]thiophenes, bearing chlorine, bromine, or iodine atoms at the 4- and 7-positions (total 9 types), were prepared by this method, although the yields were poor (8–20%) and the major products were normal product alkynes. We also demonstrated selective Suzuki-Miyaura cross coupling reactions of the 4,7-dihalobenzo[*b*]thiophenes bearing different halogen atoms. Since Suzuki-Miyaura cross coupling as well as Sonogashira cross coupling are compatible with various functional groups,[31] the present compounds are promising as versatile building blocks. This method, combined with our silica gel-assisted conversion method of **3** to **4** (Scheme 1)[18] and the halogen-metal exchange reaction of **4**, will contribute to the chemistry of benzo[*b*]thiophenes.

EXPERIMENTAL

Melting points were measured on a Yanagimoto MP-J3 micro melting point apparatus and are not corrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded either on a Bruker Avance III-400 or a Bruker Avance 400 spectrometer. ^{1}H (700 MHz) and ^{13}C (176 MHz) NMR spectra were measured on a Bruker Biospin Avance III-700 or a JEOL ECA 700 spectrometer. Mass spectra were taken on a Bruker solariX spectrometer or a JEOL JMS-T spectrometer. Compounds **1** except for **1c** have been known and were prepared by a method reported in the literature.[32,33] Compounds **2b**, **2m**, and **3n** are reported in the literature.[23,34,35] Dimethyl (1-diazo-2-oxopropyl)phosphonate, phenylboronic acid, and $PdCl_2(dppf)\cdot CH_2Cl_2$ were purchased from Tokyo Chemical Industry Co., Ltd. and used without further purification. $Pd(PPh_3)_4$ and XPhosPdG3 were purchased from Sigma-Aldrich Co. LLC. and used without further purification.

Preparation of 2-fluoro-3,6-diiodobenzaldehyde (1c). 2-Fluoro-1,4-diiodobenzene (3.0054 g, 8.639 mmol) in THF (14 mL) was cooled to –63 °C with a dry ice-$CHCl_3$ bath under nitrogen atmosphere. Lithium *N*,*N*-diisopropylamide (LDA, 10.37 mmol; 1.08 M solution in hexane-THF, 9.6 mL) was slowly added to the solution and the reaction mixture was stirred at –63 °C for 1 h. DMF (1.0 mL, 13.00 mmol) was slowly added to the reaction mixture and the mixture was stirred at –63 °C for 1.5 h, warmed to 0 °C, and stirred for 40 min. The mixture was slowly poured into *ca*. 20 mL of 4 M hydrochloric acid at 0 °C with stirring. Water and EtOAc were added to the resulting mixture and extracted with EtOAc. The organic phase was separated, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with a silica gel column chromatography (hexane-$CHCl_3$, 1:1) to give 2.7528 g of **1c** (7.323 mmol) and 226.5 mg of the starting 2-fluoro-1,4-diiodobenzene (0.651 mmol, 8% recovery). **1c**; a pale yellow solid; 72% yield; mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, dd, $^4J_{FH}$ = 11.6 Hz, ^3J = 8.4 Hz, arom.), 7.60 (1H, d, ^3J = 8.4 Hz, arom.), 10.05 (1H, d, $^4J_{FH}$ = 1.2 Hz, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 83.3 (d, $^3J_{FC}$ = 25.9 Hz, C-I), 96.5 (s, C-I), 124.7 (d, $^2J_{FC}$ = 11.1 Hz, *C*-CHO), 138.5 (d, J_{FC} = 3.8 Hz, CH), 144.6 (d, J_{FC} = 3.7 Hz, CH), 162.1 (d, $^1J_{FC}$ = 262.1 Hz, C-F), 189.6 (CHO). Found: *m*/*z* 375.8252. Calcd for $C_7H_3FI_2O$: M^+, 375.8252.

Typical procedure for the preparation of compounds 2. To a suspension of NaH (592 mg, *ca*. 60% in mineral oil, washed with hexane, *ca*. 15 mmol) in *N*,*N*-dimethylformamide (DMF, 13 mL) was added 1-adamantanethiol (2.17 g, 12.9 mmol) in DMF (20 mL) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 1.5 h, and a solution of **1a** (2.97 g, 10.5 mmol) in DMF (20 mL) was added at –40 °C. The reaction mixture was stirred at –40 °C for 2 h. The reaction mixture was poured into water, and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure, and purified by silica gel column chromatography (hexane-EtOAc, 4:1) to give 4.27 g (9.93 mmol) of **2a**.

2-(1-Adamantylsulfanyl)-3,6-dibromobenzaldehyde (2a): 95% yield; a pale yellow solid; mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (6H, s, Ad), 1.87 (6H, s, Ad), 2.02 (3H, s, Ad), 7.54 (1H, dd, ^3J = 8.6 Hz, J = 0.8 Hz, arom.), 7.70 (1H, d, ^3J = 8.6 Hz, arom.), 10.4 (1H, d, J = 0.8 Hz, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.3 (Ad), 35.8 (Ad), 44.1 (Ad), 55.2 (Ad), 119.6 (C-Br), 134.7 (C-Br), 135.9 (C-S), 136.0 (CH), 136.5 (CH), 143.3 (*C*-CHO), 192.3 (CHO). Found: *m*/*z* 452.9317 Calcd for $C_{17}H_{18}{}^{79}Br^{81}BrNaOS$: $(M+Na)^+$, 452.9317. Compound **2a** likely include DMF molecule in the solid.

2-(1-Adamantylsulfanyl)-3,6-diiodobenzaldehyde (2c): 84% yield; a yellow solid; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.65 (6H, m, Ad), 1.86 (6H, s, Ad), 2.02 (3H, s, Ad), 7.71 (1H, dd, ^3J = 8.4 Hz, J = 0.8 Hz, arom.), 7.79 (1H, d, ^3J = 8.4 Hz, arom.), 10.22 (1H, d, J = 0.8 Hz, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.5 (Ad), 36.0 (Ad), 44.3 (Ad), 55.8 (Ad), 93.2 (C-I), 116.8 (C-I), 140.5,

143.4 (CH), 143.5 (CH), 144.4, 194.0 (CHO). Found: *m*/*z* 546.9060. Calcd for $C_{17}H_{18}I_2NaOS$: $(M+Na)^+$, 546.9060.

2-(1-Adamantylsulfanyl)-3,6-dichlorobenzaldehyde (2d): 64% yield; a yellow solid; mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.66 (6H, m, Ad), 1.86–1.87 (6H, m, Ad), 2.02 (3H, m, Ad), 7.43 (1H, dd, ^3J = 8.4 Hz, J = 0.8 Hz, arom.), 7.60 (1H, d, ^3J = 8.4 Hz, arom.), 10.56 (1H, d, J = 0.8 Hz, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.4 (Ad), 36.0 (Ad), 44.2 (Ad), 54.9 (Ad), 131.4, 132.8 (CH), 133.2 (CH), 133.9, 141.6, 142.0, 191.8 (CHO). Found: *m*/*z* 363.0348. Calcd for $C_{17}H_{18}{}^{35}Cl_2NaOS$: $(M+Na)^+$, 363.0348.

2-(1-Adamantylsulfanyl)-6-chlorobenzaldehyde (2k): 87% yield; a yellow solid; mp 121.5–123.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–1.67 (6H, m, Ad), 1.80–1.81 (6H, m, Ad), 2.03 (3H, br s, Ad), 7.41 (1H, dd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, arom.), 7.48–7.51 (2H, m, arom.), 10.70 (1H, s, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.2 (Ad), 36.0 (Ad), 43.8 (Ad), 51.0 (Ad), 132.0 (CH), 132.1 (CH), 133.7, 135.4, 138.4 (CH), 138.5 (C-Cl), 192.7 (CHO). Found: *m*/*z* 329.0737. Calc. for $C_{17}H_{19}{}^{35}ClNaOS$: $(M+Na)^+$, 329.0737.

2-(1-Adamantylsulfanyl)-3-chlorobenzaldehyde (2l): 91% yield; a pale yellow solid; mp 105.5–106.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–1.66 (6H, m, Ad), 1.86–1.87 (6H, m, Ad), 2.02 (3H, br s, Ad), 7.44 (1H, ddd, ^3J = 8.4 Hz, ^3J = 8.4 Hz, ^3J = 0.8 Hz, arom.), 7.76 (1H, dd, ^3J = 8.4 Hz, J = 1.2 Hz, arom.), 7.89 (1H, dd, ^3J = 8.4 Hz, J = 1.6 Hz, arom.), 10.79 (1H, d, J = 0.8 Hz, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.4 (Ad), 36.1 (Ad), 44.0 (Ad), 53.2 (Ad), 126.6 (CH), 130.2 (CH), 134.0, 135.0 (CH), 142.5, 143.7, 193.6 (CHO). Found: *m*/*z* 329.0737. Calc. for $C_{17}H_{19}{}^{35}ClNaOS$: $(M+Na)^+$, 329.0737.

Preparation of 2-(1-adamantylsulfanyl)-6-phenylbenzaldehyde (2o). A mixture of **2k** (304.1 mg, 0.991 mmol), $PhB(OH)_2$ (131.6 mg, 1.079 mmol), XPhosPd G3 (Aldrich, 35.4 mg, 0.0397 mmol as 95% purity), K_2CO_3 (689.1 mg, 4.99 mmol), 1,4-dioxane (50 mL), and water (5.0 mL) was stirred under nitrogen atmosphere at 90 °C for 18.5 h, then the reaction mixture was cooled to room temperature. To the mixture were added EtOAc and H_2O. The organic phase was separated, washed with brine, and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane-CH_2Cl_2, 1:1) to give a crude product. The crude product was purified by repeating silica gel column chromatography (hexane-CH_2Cl_2, 7:3) to give 263.2 mg (0.755 mmol) of **2o**; 76% yield; a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (6H, m, Ad), 1.85 (6H, br d, J = 2.8 Hz, Ad), 2.02 (3H, br s, Ad), 7.25 (2H, m, arom.), 7.31-7.40 (4H, m, arom.), 7.47 (1H, dd, ^3J = 8.0 Hz, ^3J = 8.0 Hz, arom.), 7.57 (1H, dd, ^3J = 8.0 Hz, J = 1.2 Hz, arom.), 10.67 (1H, s, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.1 (Ad), 36.0 (Ad), 43.8 (Ad), 50.3 (Ad), 127.4 (CH),

128.1 (CH), 129.3 (CH), 130.9 (CH), 132.0 (CH), 132.9, 138.6 (CH), 140.0, 140.1, 143.5, 195.1 (CHO). Found: *m*/*z* 371.1440. Calc. for $C_{23}H_{24}{}^{35}ClNaOS$: $(M+Na)^+$, 371.1440.

Typical procedure for the preparation of compounds 3 and 4. To a mixture of **2a** (500.0 mg, 1.162 mmol), K_2CO_3 (321.9 mg, 2.329 mmol), THF (3.5 mL) in MeOH (5 mL) was added a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (276.6 mg, 1.439 mmol) in MeOH (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min then at room temperature for 19 h. The reaction mixture was poured into brine and extracted with EtOAc. The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane-$CHCl_3$, 4:1) to give 367.6 mg of **3a** (0.8625 mmol) and 26.5 mg of **4a** (0.09076 mmol).

2-(1-Adamantylsulfanyl)-1,4-dibromo-3-ethynylbenzene (3a): 74% yield; a colorless solid; mp 129–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (6H, m, Ad), 2.03 (9H, m, Ad), 3.66 (1H, s, C≡CH), 7.43 (1H, d, ^3J = 8.4 Hz, arom.), 7.53 (1H, d, ^3J = 8.4 Hz, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.2 (Ad), 35.9 (Ad), 44.2 (Ad), 55.3 (Ad), 82.6 (C≡C), 87.2 (C≡C), 125.7 (C-S), 133.4, 133.5 (CH), 133.5 (CH), 133.6, 137.1. Found: *m*/*z* 426.9548. Calcd for $C_{18}H_{19}{}^{79}Br^{81}BrS$: $(M+H)^+$, 426.9548.

2-(1-Adamantylsulfanyl)-3-ethynyl-1,4-diiodobenzene (3c): 72% yield; a pale yellow solid; mp 193–195 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (6H, m, Ad), 2.06 (9H, m, Ad), 3.62 (1H, s, C≡CH), 7.47 (1H, d, ^3J = 8.4 Hz, arom.), 7.62 (1H, d, ^3J = 8.4 Hz, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.6 (Ad), 36.2 (Ad), 44.7 (Ad), 56.3 (Ad), 85.9 (C≡C), 87.1 (C≡C), 102.2 (C-I), 114.4 (C-I), 136.5, 140.3 (CH), 140.6 (CH), 140.7 (C-Br). Found: *m*/*z* 542.9111. Calcd for $C_{18}H_{18}I_2NaS$: $(M+Na)^+$, 542.9111.

2-(1-Adamantylsulfanyl)-1,4-dichloro-3-ethynylbenzene (3d): 80% yield; a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (6H, m, Ad), 2.01 (9H, m, Ad), 3.70 (1H, s, C≡CH), 7.35 (1H, d, ^3J = 8.4 Hz, arom.), 7.41 (1H, d, ^3J = 8.4 Hz, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.4 (Ad), 36.1 (Ad), 44.3 (Ad), 55.1 (Ad), 80.5 (C≡C), 88.1 (C≡C), 130.2 (CH), 130.5 (CH), 132.0, 135.0, 135.9, 141.3. Found: *m*/*z* 359.0398. Calc. for $C_{18}H_{18}{}^{35}Cl_2NaS$: $(M+Na)^+$, 359.0398.

1-(1-Adamantylsulfanyl)-3-chloro-2-ethynylbenzene (3k): 78% yield; a pale yellow solid; mp 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.67 (6H, m, Ad), 1.90 (6H, m, Ad), 2.02 (3H, br s, Ad), 3.64 (1H, s, C≡CH), 7.20 (1H, dd, ^3J = 8.0 Hz, ^3J = 7.6 Hz, arom.), 7.42 (1H, dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, arom.), 7.47 (1H, dd, ^3J = 7.6 Hz, ^4J = 1.2 Hz, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.2 (Ad), 36.2 (Ad), 43.9 (Ad), 51.2 (Ad), 80.2 (C≡C), 87.2 (C≡C), 128.3 (CH), 129.3, 129.7 (CH), 135.9, 137.0 (CH), 137.5. Found: *m*/*z* 325.0788. Calc. for $C_{18}H_{19}{}^{35}ClNaS$: $(M+Na)^+$, 325.0788.

2-(1-Adamantylsulfanyl)-1-chloro-3-ethynylbenzene (3l): 89% yield; a pale yellow solid; mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (6H, br s, Ad), 2.01 (9H, br s, Ad), 3.33 (1H, s, C≡CH), 7.22 (1H, dd, ^3J = 8.0 Hz,^3J = 8.0 Hz, arom.), 7.48 (1H, dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, arom.), 7.50 (1H, dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.4 (Ad), 36.2 (Ad), 44.3 (Ad), 54.3 (Ad), 82.1 (C≡C), 83.6 (C≡C), 129.5 (CH), 130.4 (CH), 132.3 (CH), 132.8, 133.1, 143.0. Found: *m*/*z* 325.0788. Calc. for $C_{18}H_{19}{}^{35}ClNaS$: $(M+Na)^+$, 325.0788.

1-(1-Adamantylsulfanyl)-2-ethynylbenzene (3m): 83% yield; a pale yellow solid; mp 58–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.67 (6H, m, Ad), 1.90 (6H, m, Ad), 2.02 (3H, br s, Ad), 3.31 (1H, s, C≡CH), 7.27–7.34 (2H, m, arom.), 7.53–7.61 (2H, m, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.1 (Ad), 36.1 (Ad), 43.7 (Ad), 50.3 (Ad), 81.4 (C≡C), 83.5 (*C*≡C), 128.2 (CH), 128.5 (CH), 129.8, 133.2, 133.7 (CH), 138.8 (CH). Found: *m*/*z* 291.11778. Calcd for $C_{18}H_{20}NaS$: $(M+Na)^+$, 291.11779.

1-(1-Adamantylsulfanyl)-2-ethynyl-3-phenylbenzene (3o): 29% yield; a colorless solid; mp 112.5–114.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61–1.68 (6H, m, Ad), 1.94 (6H, br d, J = 2.8 Hz, Ad), 2.03 (3H, br s, Ad), 3.24 (1H, s, C≡CH), 7.30–7.43 (5H, m, arom.), 7.53–7.58 (3H, m, arom.); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.3 (Ad), 36.3 (Ad), 44.0 (Ad), 50.7 (Ad), 82.6 (C≡C), 85.5 (C≡C), 127.7 (CH), 127.8 (CH), 127.96 (Ph), 127.99, 129.5 (Ph), 130.2 (CH), 134.7, 137.7 (CH), 140.8, 146.4. Found: *m*/*z* 367.1491. Calcd for $C_{24}H_{24}NaS$: $(M+Na)^+$, 367.1491.

4,7-Diiodobenzo[*b*]thiophene (4c): 9% yield; a colorless solid; mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, d, ^3J = 8.0 Hz), 7.48 (1H, d, ^3J = 8.0 Hz), 7.57 (1H, d, ^3J = 5.6 Hz), 7.64 (1H, d, ^3J = 5.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 87.5 (C-I), 90.4 (C-I), 127.3 (CH), 129.6 (CH), 134.8 (CH), 135.4 (CH), 142.2, 145.8; Found: *m*/*z* 385.8117. Calcd for $C_8H_4I_2S$: M^+, 385.8118.

4-Phenylbenzo[*b*]thiophene (4o): 9% yield; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, dd, ^3J = 7.2 Hz, ^4J = 1.2 Hz), 7.38–7.50 (6H, m), 7.56–7.59 (2H, m), 7.88 (1H, dm, ^3J = 8.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 121.7 (CH), 123.5 (CH), 124.5 (CH), 124.8 (CH), 126.4 (CH), 127.5 (CH), 128.6 (Ph), 129.2 (Ph), 138.0, 138.0, 140.6, 141.2; Found: *m*/*z* 210.0498. Calcd for $C_{14}H_{10}S$: M^+, 210.0498. ^{1}H NMR data reported in Ref. 29b seem to be deviated from the correct chemical shift, probably due to miss-assignment of Me_4Si standard signal.

Typical procedure for the preparation of compounds 4q,s and 4t,v. A mixture of **4e** (66.9 mg, 0.197 mmol), $PhB(OH)_2$ (26.6 mg, 0.218 mmmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (4.6 mg, 0.00563 mmol), and K_2CO_3 (82.7 mg, 0.598 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was stirred under nitrogen atmosphere at 50 °C for 48 h. To the reaction mixture was added $CHCl_3$ (*ca*. 10 mL) at room temperature, stirred for a few minitues, and the resulting solution was dried over Na_2SO_4. The solvent was removed under

reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 46.4 mg of **4q** (0.160 mmol) and 7.7 mg of the starting **4e** (0.023 mmol, 12% recovery).

7-Bromo-4-phenylbenzo[*b*]thiophene (4q): 81% yield from **4e**; a pale yellow solid; mp 74–75 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.23 (1H, d, ^3J = 7.7 Hz), 7.40 (1H, tt, ^3J = 7.7 Hz, ^4J = 1.4 Hz, *p*-Ph), 7.47 (2H, dd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, *m*-Ph), 7.48 (1H, d, ^3J = 5.6 Hz), 7.52–7.53 (2H, m, *o*-Ph), 7.53 (1H, d, ^3J = 5.6 Hz), 7.55 (1H, d, ^3J = 7.7 Hz); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 114.9 (C-Br), 124.4 (CH), 126.0 (CH), 127.20 (CH), 127.22 (CH), 127.6 (*p*-Ph), 128.6 (*m*-Ph), 129.0 (*o*-Ph), 137.1, 138.7, 140.1 (*ipso*-Ph), 142.0; Found: *m*/*z* 287.9603. Calcd for $C_{14}H_9{}^{79}BrS$: M^+, 287.9603.

7-Chloro-4-phenylbenzo[*b*]thiophene (4s): 86% yield from **4f**; a colorless solid; mp 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, d, ^3J = 8.4 Hz), 7.40 (1H, tt, ^3J = 7.2 Hz, ^4J = 0.8 Hz, *p*-Ph), 7.40 (1H, d, ^3J = 8.4 Hz), 7.45–7.49 (4H, m), 7.51–7.54 (2H, m, *o*-Ph); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 124.1 (CH), 124.4 (CH), 126.1 (CH), 127.1, 127.5 (CH), 127.8 (CH), 128.8 (Ph), 129.2 (Ph), 136.7, 139.3, 139.7, 140.3. Found: *m*/*z* 244.01077. Calcd for $C_{14}H_9{}^{35}ClS$: M^+, 244.01080.

4-Bromo-7-phenylbenzo[*b*]thiophene (4t): 93% yield from **4g**; a pale yellow solid; mp 45–47 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24 (1H, d, ^3J = 7.7 Hz), 7.46 (1H, tt, ^3J = 7.0 Hz, ^4J = 1.4 Hz, *p*-Ph), 7.52 (2H, dd, ^3J = 8.4 Hz, ^3J = 7.0 Hz, *m*-Ph), 7.55 (1H, d, ^3J = 5.6 Hz), 7.59 (1H, d, ^3J = 5.6 Hz), 7.65 (1H, d, ^3J = 7.7 Hz), 7.70 (2H, dd, ^3J = 8.4 Hz, ^3J = 1.4 Hz, *o*-Ph); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 116.5 (C-Br), 124.7 (CH), 125.1 (CH), 127.7 (CH), 128.1 (CH), 128.1 (*o*-Ph), 128.2 (*p*-Ph), 128.8 (*m*-Ph), 136.1, 139.6, 139.8, 139.8 (*ipso*-Ph); Found: *m*/*z* 287.9602. Calcd for $C_{14}H_9{}^{79}BrS$: M^+, 287.9603.

4-Chloro-7-phenylbenzo[*b*]thiophene (4v): 97% yield from **4h**; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (1H, d, ^3J = 8.4 Hz), 7.35–7.46 (5H, m), 7.52 (1H, d, ^3J = 5.2 Hz), 7.61–7.64 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 122.7 (CH), 124.8 (CH), 124.9 (CH), 127.7 (CH) 127.8, 128.1 (Ph+Ph), 128.8 (Ph), 135.5, 138.2, 139.7, 140.0; Found: *m*/*z* 244.01077. Calcd for $C_{14}H_9{}^{35}ClS$: M^+, 244.01080.

Alternative preparation of 4t via 4x. To a solution of **4a** (100.3 mg, 0.344 mmol) in Et_2O (3.0 mL) was added 0.402 mmol of *n*-BuLi (1.61 M solution in hexane, 0.25 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 30 min. To this solution was added a solution of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (107.6 mg, 0.578 mmol) in Et_2O (3.0 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 10 min, allowed to warm to room temperature, and stirred for 1 h. The reaction was poured into *ca*. 50 mL of chilled water and the resulting mixture was extracted with EtOAc. The organic phase was separated, washed with brine, dried over Na_2SO_4, and filtered. The solvent of the filtrate was removed under reduced pressure to give 109.3 mg of crude boronate **4x**. The crude product was used in the following reaction without further purification: A

mixture of the crude **4x**, iodobenzene (80.8 mg, 0.396 mmol), $PdCl_2(dppf)CH_2Cl_2$ (8.7 mg, 0.011 mmol), and K_2CO_3 (143.6 mg, 1.034 mmol), 1,4-dioxane (5 mL), and water (0.5 mL) was stirred under nitrogen atmosphere at 50 °C for 24 h. The reaction mixture was extracted with EtOAc. The organic phase was separated, dried over Na_2SO_4, and filtrated. The solvent of the filtrate was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 55.8 mg of **4t** (0.192 mmol, 56% overall yield based on **4a**) and 22.8 mg (0.107 mmol) of 4-bromobenzo[*b*]thiophene[23,36] in 31% yield (based on **4a**).

Typical procedure for the preparation of compounds 4r and 4u. To a solution of 7-bromo-4-phenylbenzo[*b*]thiophene (**4q**, 38.8 mg, 0.134 mmol) in Et_2O (1.0 mL) was added 0.161 mmol of butyllithium (1.61 M solution in hexane, 0.10 mL) at –78 °C under nitrogen atmosphere. The resulting solution was stirred for 30 min, then a solution of 1,2-diiodoethane (42.1 mg, 0.149 mmol) in Et_2O (1.0 mL) was added. The reaction mixture was stirred at –78 °C for 10 min, allowed to warm to room temperature, and stirred for 2.5 h. The mixture was poured into *ca*. 20 mL of aqueous saturated Na_2SO_3 solution at 0 °C, and extracted with EtOAc. The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 23.7 mg of 7-iodo-4-phenylbenzo[*b*]thiophene (**4r**, 0.070 mmol). Compound **4u** was obtained by a similar method, as a mixture with the starting **4t**. **4t**:**4u** = 11:10.

7-Iodo-4-phenylbenzo[*b*]thiophene (4r): 53% yield from **4q**; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, d, ^3J = 7.6 Hz), 7.41 (1H, tt, ^3J = 6.8 Hz, ^4J = 1.2 Hz), 7.46–7.55 (5H, m), 7.70 (1H, ^3J = 5.2 Hz), 7.77 (1H, d, ^3J = 7.6 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 86.4 (C-I), 125.0 (CH), 126.2 (CH), 126.8 (CH), 127.8 (CH), 128.8 (Ph, CH), 129.2 (Ph, CH), 134.0 (CH), 137.6, 138.1, 140.3, 147.0. Found: *m*/*z* 335.9464. Calcd for $C_{14}H_9IS$: M^+, 335.9464.

4-Iodo-7-phenylbenzo[*b*]thiophene (4u), as a mixture with 4t: 44% calculated yield from **4t**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (1H, d, ^3J = 7.6 Hz), 7.43 (1H, tt, ^3J = 7.2 Hz, ^4J = 1.2 Hz, *p*-Ph), 7.49–7.55 (4H, m, *o*- and *m*-Ph), 7.67–7.69 (2H, m), 7.88 (1H, d, ^3J = 7.6 Hz).

Preparation of 4,7-diphenylbenzo[*b*]thiophene (4w). A mixture of 4,7-dibromobenzo[*b*]thiophene (**4a**, 309 mg, 1.06 mmol), $PhB(OH)_2$ (286 mg, 2.35 mmol), $Pd(PPh_3)_4$ (92.6 mg, 0.131 mmol), K_2CO_3 (657 mg, 4.75 mmol), 1,4-dioxane (13 mL), and water (2.6 mL) was stirred under nitrogen atmosphere at 80 °C for 1 d, then the reaction mixture was cooled to room temperature. To the mixture were added $CHCl_3$ and H_2O. The organic phase was separated, washed with brine, and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane) to give 250 mg (0.873 mmol) of **4w**; 82% yield; colorless fine

needles; mp 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.55 (10H, m), 7.59–7.64 (2H, m), 7.75–7.80 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 123.9 (CH), 124.7 (CH), 125.7 (CH), 126.9 (CH), 127.5 (CH), 128.1 (CH), 128.5 (Ph), 128.7 (Ph), 128.9 (Ph), 129.3 (Ph), 136.0, 137.1, 138.6, 139.7, 140.8, 141.1; Found: *m*/*z* 286.0808. Calcd for $C_{20}H_{14}S$: M^+, 286.0811.

Typical procedure of the cross coupling of 4a,c,d with PhB(OH)$_2$. A mixture of 4,7-dibromobenzo[*b*]thiophene (**4a**, 197.9 mg, 0.678 mmol), $PhB(OH)_2$ (83.8 mg, 0.687 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (17.0 mg, 0.0208 mmol), K_2CO_3 (284.4 mg, 2.06 mmol), 1,4-dioxane (25 mL), and water (2.5 mL) was stirred under nitrogen atmosphere at 80 °C for 25 h, then the reaction mixture was cooled to room temperature. To the mixture was added $CHCl_3$ (*ca*. 25 mL) at room temperature. The reaction mixture was stirred for a few minutes and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 51.9 mg of 4,7-diphenylbenzo[*b*]thiophene **4w** (0.181 mmol, 27% yield), 21.0 mg of the starting **4a** (11% recovery), and 77.2 mg of a mixture of **4q** and **4t** (^{1}H NMR signal ratio was 17:10 in CD_2Cl_2). Calculated yields of **4q** and **4t** were 25% and 14%, respectively.

Preparation of 4,7-dibromo-2-iodobenzo[*b*]thiophene (11). To a solution of **4a** (224.6 mg, 0.769 mmol) in THF (5 mL) was added 0.940 mmol of LDA (0.627 M solution in THF, 1.5 mL) at –78 °C. The reaction mixture was stirred at 0 °C for 30 min and a solution of 1,2-diiodoethane (254 mg, 0.900 mmol) in THF (4.5 mL) was added at –78 °C. The resulting mixture was allowed to warm to room temperature and stirred for 3 h. EtOAc and water were added to the reaction mixture. The organic phase was separated, washed with brine, separated, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was treated with a silica-gel column chromatography (hexane) to give 246 mg (0.630 mmol) of **11**; 82% yield; a colorless solid; mp 158–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, ^3J = 8.0 Hz), 7.36 (1H, d, ^3J = 8.0 Hz), 7.77 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, THF-d_8) δ 83.0 (C-I), 113.8 (C-Br), 115.1 (C-Br), 128.9 (CH), 130.1 (CH), 135.6 (CH), 142.1, 147.3. Found: *m*/*z* 417.7341. Calcd for $C_8H_3{}^{79}Br^{81}BrIS$: M^+, 417.7341. This compound was not so stable at room temperature in air and partially turned red in a day.

Preparation of 4,7-dibromo-2-phenylbenzo[*b*]thiophene (13). Method I. A mixture of **11** (105.0 mg, 0.2513 mmol), $PhB(OH)_2$ (36.6 mg, 0.300 mmmol), PEPPSI-IPr (5.6 mg, 0.0082 mmol), and K_2CO_3 (173.8 mg, 1.258 mmol), toluene (2 mL), THF (2.5 mL), and water (0.5 mL) was stirred under nitrogen atmosphere at 50 °C for 3 d. To the reaction mixture was poured into brine and extracted with EtOAc. The organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give **13** (57.1 mg, 0.155 mmol) in 62% yield.

Method II. To a solution of **4a** (211.5 mg, 0.724 mmol) in THF (5.3 mL) was added 0.818 mmol of LDA (1.09 M solution in hexane-THF, 0.75 mL) at –78 °C. The resulting mixture was stirred at –78 °C for 5 min and then at 0 °C for 1 h. To this solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.969 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 5 min, allowed to warm to room temperature, and stirred for 18 h. The reaction was quenched with *ca*. 10 mL of water and the resulting mixture was extracted with EtOAc. The organic phase was separated, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 280.5 mg of crude boronate **12**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (12H, s, Me), 7.37 (1H, d, ^3J = 8.0 Hz), 7.41 (1H, d, ^3J = 8.0 Hz), 8.08 (1H, s). Found: *m*/*z* 415.9251. Calcd for $C_{14}H_{15}B^{79}Br^{79}BrO_2S$: M^+, 415.9253. The product was used in the following reaction without further purification: A mixture of **12** (*ca*. 0.67 mmol), iodobenzene (168.7 mg, 0.802 mmol), $PdCl_2(dppf)CH_2Cl_2$ (17.4 mg, 0.021 mmol), and K_2CO_3 (300.5 mg, 2.163 mmol), 1,4-dioxane (10 mL), and water (1.0 mL) was stirred under nitrogen atmosphere at 50 °C for 40 h. The reaction mixture was extracted with EtOAc, the organic phase was separated, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 93.8 mg of **13** (0.254 mmol, 35% overall yield based on **4a**) and 78.9 mg (0.270 mmol) of the starting benzothiophene **4a** in 37% recovery. **13**; a colorless solid; mp 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, ^3J = 8.4 Hz), 7.37 (1H, d, ^3J = 8.4 Hz), 7.37 (1H, tt, ^3J = 7.2 Hz, ^4J = 1.2 Hz, *p*-Ph), 7.44 (2H, tt, ^3J = 7.2 Hz, ^4J = 1.2 Hz, *o*-Ph), 7.71–7.73 (2H, m, *m*-Ph), 7.72 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 114.6 (C-Br), 116.2 (C-Br), 120.6 (CH), 126.7 (CH), 127.9 (CH), 129.1 (CH), 129.2 (CH), 129.2 (CH), 133.5, 141.0, 141.7, 146.4. Found: *m*/*z* 367.8688. Calcd for $C_{14}H_8{}^{79}Br^{81}BrS$: M^+, 367.8688.

Preparation of 4-bromo-7-iodo-2-phenylbenzo[*b*]thiophene (14). To a solution of **13** (93.8 mg, 0.255 mmol) in Et_2O (15 mL) was added 0.314 mmol of butyllithium (1.57 M solution in hexane, 0.20 mL) at –78 °C under nitrogen atmosphere. The resulting solution was stirred at –78 °C for 40 min, then 1,2-diiodoethane (104.7 mg, 0.371 mmol) was added. The reaction mixture was stirred at –78 °C for 10 min, then at room temperature for 18 h. The mixture was poured into a chilled aqueous Na_2SO_3 solution and extracted with EtOAc. The organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 23.8 mg of pure **14** (0.057 mmol, 22% yield) and a mixture (65.5 mg) containing **14** as a major component. **14**; a colorless solid; mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, ^3J = 8.0 Hz), 7.39 (1H, tt, ^3J = 7.6 Hz, ^4J = 1.2 Hz, *p*-Ph), 7.43–7.48 (2H, m, *o*-Ph), 7.48 (1H, d, ^3J = 8.0 Hz), 7.73–7.76 (2H, m, *m*-Ph), 7.90 (1H, s); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 85.6 (C-I), 117.6 (C-Br),

121.0 (C-H), 126.7 (Ph), 129.1 (C-H), 129.1 (C-H), 129.2 (Ph), 133.6, 134.3 (C-H), 139.9, 145.8, 146.5. HRMS (FD) Found *m*/*z* 413.8574. Calcd for $C_{14}H_8{}^{79}BrIS$: M^+, 413.8575.

ACKNOWLEDGEMENTS

The authors thank Prof. Takeaki Iwamoto, Tohoku University, for discussion at the early stage of this research. This work was supported in part by Grants-in-Aid for Scientific Research (No. 23655026) from the Ministry of Education, Culture, Supports, Science and Technology, Japanese Government.

REFERENCES

1. M. Sainsbury, *Heterocyclic Chemistry*, Wiley, New York, 2002.
2. S. Schoffelen and M. Meldal, 'Alkyne-azide reactions,' in 'Modern Alkyne Chemistry,' Chapter 5, ed. by B. M. Trost and C.-J. Li, Wiley-VCH, Weinheim, 2015.
3. R. C. Larock, 'Synthesis of Heterocycles and Carbocycles by Electrophilic Cyclization of Alkynes,' in 'Acetylene Chemistry,' Chapter 2, ed. by F. Diederich, P. J. Stang, and R. R. Tykwinski, Wiley-VCH, Weinheim, 2005.
4. T. A. Nizami and R. Hua, *Molecules*, 2014, **19**, 13788.
5. T. M. A. Barlow, D. Tourwé, and S. Ballet, *Eur. J. Org. Chem*., 2017, 4678.
6. (a) Y. Yamamoto, I. D. Gridnev, N. T. Patil, and T. Jin, *Chem. Commun*., 2009, 5075; (b) I. Nakamura, T. Sato, and Y. Yamamoto, *Angew. Chem. Int. Ed*., 2006, **45**, 4473.
7. S. R. Pathipati, A. van der Werf, and N. Selander, *Synthesis*, 2017, **49**, 4931.
8. B. Godoi, R. F. Schumacher, and G. Zeni, *Chem. Rev*., 2011, **111**, 2937.
9. R. C. Larock and D. Yue, *Tetrahedron Lett*., 2001, **42**, 6011.
10. B. L. Flynn, P. Verdier-Pinard, and E. Hamel, *Org. Lett*., 2001, **3**, 651.
11. L. Meng, T. Fujikawa, M. Kuwayama, Y. Segawa, and K. Itami, *J. Am. Chem. Soc*., 2016, **138**, 10351.
12. A. Arcadi, G. Bianchi, A. Inesi, F. Marinelli, and L. Rossi, *Eur. J. Org. Chem.*, 2008, 783.
13. L. Brandsma, 'Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques,' Elsevier Ltd., Oxford, 2004.
14. K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett*., 1975, **16**, 4467.
15. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett*., 1972, **13**, 3769.
16. M. Zhao, C. Kuang, Q. Yang, and X. Cheng, *Tetrahedron Lett*., 2011, **52**, 992.
17. A. K. Morri, Y. Thummala, and V. R. Doddi, *Org. Lett*., 2015, **17**, 4640.
18. S. Mikami, H. Tanaka, H. Kishi, S. Yoshida, and K. Toyota, *Heterocycles*, 2018, **96**, 1529.
19. E. W. Colvin and B. J. Hamill, *J. Chem. Soc., Chem. Commun*., 1973, 151.

20. J. C. Gilbert and U. Weerasooriya, *J. Org. Chem.*, 1979, **44**, 4997.
21. S. Ohira, *Synth. Commun.*, 1989, **19**, 561.
22. S. Müller, B. Liepold, G. J. Roth, and H. J. Bestmann, *Synlett*, 1996, 521.
23. T. Yamamoto, H. Katsuta, K. Toyota, T. Iwamoto, and N. Morita, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 613.
24. J. M. Besterman, D. Delorme, and J. Rahil, PCT Int. Appl. Patent 2001, WO 2001002411 (*Chem. Abstr.*, 2001, **134**, 95480).
25. Y. Ni, K. Nakajima, K. Kanno, and T. Takahashi, *Org. Lett.*, 2009, **11**, 3702.
26. Q. Tao, T. Liu, L. Duan, Y. Cai, W. Xiong, P. Wang, H. Tan, G. Lei, Y. Pei, W. Zhu, R. Yang, and Y. Sun, *J. Mater. Chem. A.*, 2016, **4**, 18792.
27. A. H. Parham, A. Jatsch, T. Eberle, T. Grossmann, J. V. Kroeber, and L. Dobelmann, PCT Int. Appl. Patent 2015, WO 2015169412 (*Chem. Abstr.*, 2015, **163**, 713325).
28. J. Park, J. Park, H. Jung, M. Kang, J.-J. Ha, W. Kim, S.-G. Kim, and M. Lee, PCT Int. Appl. Patent 2016, WO 2016140497 (*Chem. Abstr.*, 2016, **165**, 392739).
29. (a) M. C. Kloetzel, J. E. Little, Jr., and D. M. Frisch, *J. Org. Chem.*, 1953, **18**, 1511; (b) E. Zhang, J. Tang, S. Li, P. Wu, J. E. Moses, and K. B. Sharpless, *Chem. Eur. J.*, 2016, **22**, 5692.
30. D. W. H. MacDowell and T. D. Greenwood, *J. Heterocycl. Chem.*, 1965, **2**, 44.
31. L. Kürti and B. Czakó, 'Strategic Applications of Named Reactions in Organic Synthesis,' Elsevier, Oxford, 2005.
32. S. Yoshimura, N. Kawano, T. Kawano, D. Sasuga, T. Koike, H. Watanabe, H. Fukudome, N. Shiraishi, R. Munakata, H. Hoshii, and K. Mihara, PCT Int. Appl. Patent 2010, WO 2010001946 (*Chem. Abstr.*, 2010, **152**, 144681).
33. P. Y. S. Lam, C. G. Clark, J. R. Corte, W. R. Ewing, P. J. Gilligan, Y. Jeon, W. Yang, L. M. Smith, and Y. Wang, PCT Int. Appl. Patent 2013, WO 2013022814 (*Chem. Abstr.*, 2013, **158**, 331259).
34. R. Patchett, I. Magpantay, L. Saudan, C. Schotes, A. Mezzetti, and F. Santoro, *Angew. Chem. Int. Ed.*, 2013, **52**, 10352.
35. K. N. Lehane, E. J. A. Moynihan, N. Brondel, S. E. Lawrence, and A. R. Maguire, *CrystEngComm*, 2007, **9**, 1041.
36. S. Akay, W. Yang, J. Wang, L. Lin, and B. Wang, *Chem. Biol. Drug Des.*, 2007, **70**, 279.