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SYNTHESIS OF 4,7-DIBROMOBENZO[*b*]THIOPHENE DERIVATIVES VIA 2-(1-ADAMANTYLSULFANYL)-1,4-DIBROMO-3-(ETHYNYL)-BENZENES AND THEIR REACTIONS

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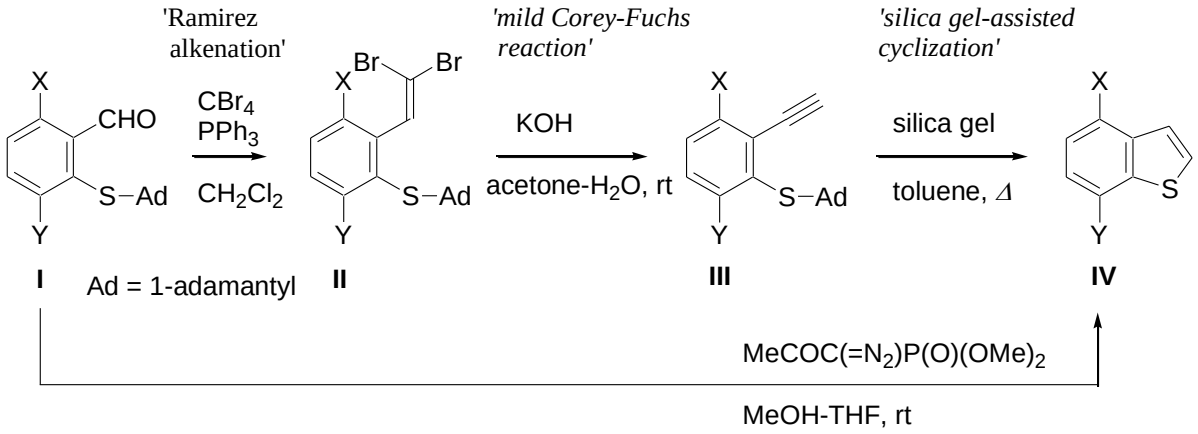
Abstract – Mild Corey-Fuchs reaction conditions using dimethyl sulfoxide - aqueous KOH solution at room temperature were applied to preparation of 2-(1-adamantylsulfanyl)-1,4-dibromo-3-(ethynyl)benzene. Various substituents were introduced to the terminal alkyne moiety of the (ethynyl)(sulfanyl)benzene, either by substitution reaction or by Sonogashira cross coupling. The alkynes thus obtained were converted to the corresponding 4,7-dibromobenzo[*b*]thiophene derivatives by the 'silica gel-assisted cyclization' method. Reactions of 4,7-dibromobenzo[*b*]thiophene and 2,4,7-tribromobenzo[*b*]thiophene were also investigated.

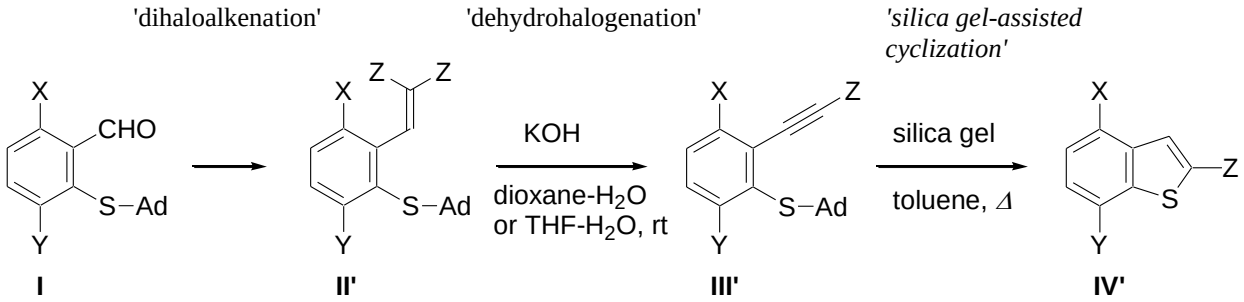
INTRODUCTION

Recently, ring-fused aromatic sulfur-heterocycles such as thienothiophenes and benzothiophenes have attracted interest in materials science, because of their unique properties of the heterocyclic π systems.[1] Benzo[*b*]thiophenes play important roles also in medicinal chemistry.[2] From viewpoint of synthetic chemistry, halogen-substituted aromatic heterocycles are important because they can be regarded as versatile building blocks for larger molecular systems. In this context, 4,7-dihalobenzo[*b*]thiophenes with various substituent are of interest as promising building blocks for larger molecular systems such as peptide-inspired or alpha helix-inspired artificial systems.[3] In the course of our continuous investigation for such heterocyclic building blocks, we found silica gel-assisted cyclization of 2-(1-adamantylsulfanyl)-3-ethynyl-1,4-dihalobenezenes, which afforded the corresponding

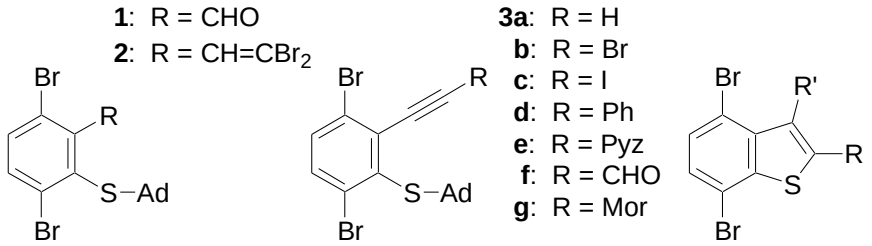
benzo[*b*]thiophenes (Scheme 1).[4] Utilization of the adamantyl group relieved us from tedious operations and bad smell, because the starting 1-adamantanethiol is a solid at room temperature and almost odorless.



Scheme 1. Preparation of 4,7-dihalobenzo[*b*]thiophenes; X, Y = Cl, Br, or I[4,5]



Scheme 2. Preparation of 2,4,7-trihalobenzo[*b*]thiophenes; X, Y, Z = Cl, Br, or I (X ≠ Y ≠ Z)[4]



1: R = CHO
2: R = CH=CBr$_2$

3a: R = H
b: R = Br
c: R = I
d: R = Ph
e: R = Pyz
f: R = CHO
g: R = Mor

Pyz = 4-pyrazolyl
Mor = morpholino

4a: R = H, R' = H
b: R = Br, R' = H
c: R = I, R' = H
d: R = Ph, R' = H
e: R = Pyz, R' = H
f: R = CHO, R' = H
g: R = Mor, R' = H
h: R = H, R' = I
i: R = Cl, R' = H
j: R = CCSi*i*-Pr$_3$, R' = H
k: R = CCH, R' = H
l: R = Bpin, R' = H
m: R = Me, R' = H

Chart 1

We also found that the terminal alkynes **III** could be prepared from the corresponding dibromoalkenes, under mild Corey-Fuchs reaction conditions using KOH in acetone-H_2O mixed solvent at room temperature (Scheme 1).[4] Furthermore, we have reported single-step preparation of 4,7-dihalobenzo[*b*]thiophenes **IV** (as a minor product) from the aldehyde **I** by using Ohira-Bestmann reagent, $MeCO(C{=}N_2)P(O)(OMe)_2$ (Scheme 1).[5] For the purpose of evaluation of efficiency of Corey-Fuchs reaction[6–11] as well as the silica gel-assisted cyclization method (Schemes 1,2), we have studied preparation of the terminal alkyne **3a** (Chart 1) and its conversion to some internal alkynes and benzo[*b*]thiophenes: We report here preparation and diverse reactions of alkynes **3a**,**b**, benzo[*b*]thiophenes **4a**–**k**, and some other related compounds.

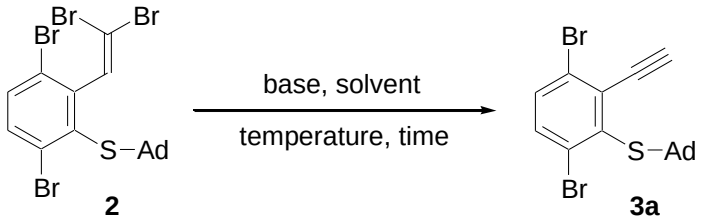
RESULTS AND DISCUSSION

Preparation of 2-(1-adamantylsulfanyl)-1,4-dibromo-3-(ethynyl)benzene (3a)

The starting dibromoalkene **2** was prepared from aldehyde **1** by standard Ramirez alkenation (Scheme 3).[6] Then conversion of **2** to the alkyne **3a** was studied: In the first place, typical Corey-Fuchs reaction[7] of **2** with butyllithium was tried but resulted in a complex mixture of products. Thus, reaction conditions similar to those reported by Kuang *et al*.[8] using Cs_2CO_3 in dimethyl sulfoxide (DMSO) were examined. Under the reported conditions at 115 °C, the dibromoalkene **2** gave **3a** in 71% yield (Table 1, entry 1). Longer or shorter reaction time gave similar results (entries 2–4). Effect of moisture was studied using a DMSO-H_2O mixed solvent at 115 °C (oil bath temperature: an apparatus equipped with a reflux condenser was used; entries 5,6), which led to a slightly worse yield. The silica gel-assisted conversion of **3a** to **4a** occasionally occurred even at room temperature during the silica gel column chromatographic separation, especially when the relative amount of the silica gel became larger (for example, entry 4). When reaction of **2** with Cs_2CO_3 was performed at room temperature, the yield of **3a** was trace in accordance with the literature case (entries 7,8). In some cases, nearly quantitative formation of bromoalkyne **3b** was indicated by ^{1}H NMR spectroscopy (for example, entry 8). To our delight, when KOH was used as a base stronger than Cs_2CO_3, the terminal alkyne **3a** was obtained in better yield in a DMSO-H_2O mixed solvent (entry 9). A much better yields were recorded with 10 equiv. of KOH at room temperature (entries 10,11).

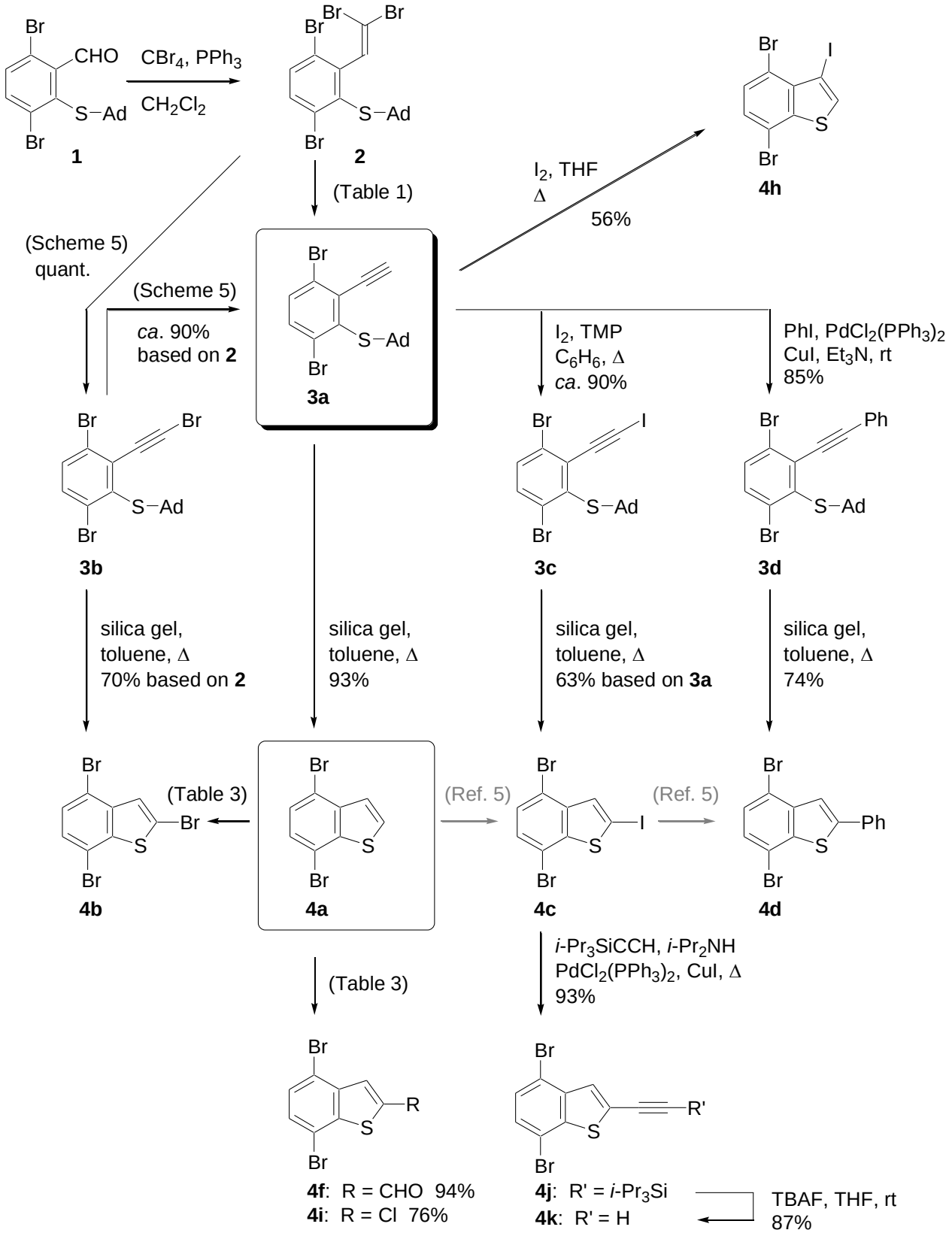
In 1994, Ratovelomanana *et al*. reported that dibromoalkenes reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMSO at 15 °C to give bromoalkynes in 80–95% yield.[9] Doddi *et al*. reported that dibromoalkenes reacted with DBU in MeCN to give terminal alkynes in *ca*. 60–90% yields.[10] Among the reaction conditions of Doddi *et al*, MeCN exhibited a remarkably and nearly crucially good effect, compared with other solvents tested.

Table 1. Preparation of the compound **3a** under mild Corey-Fuchs reaction conditions



Entry	Base	Equiv.	Solvent[a]	Temp. / °C	Time / h	Yield **3a** / %
1	Cs_2CO_3	2.5	DMSO	115	12	71
2	Cs_2CO_3	2.5	DMSO	115	4	72
3	Cs_2CO_3	2.5	DMSO	115	24	68
4	Cs_2CO_3	2.5	DMSO	115	24	56[b]
5	Cs_2CO_3	2.5	DMSO-H_2O (10:1)	115	24	54
6	Cs_2CO_3	2.5	DMSO-H_2O (1:1)	115	3.5	61
7	Cs_2CO_3	2.5	DMSO	rt	15	8[c]
8	Cs_2CO_3	2.5	DMSO-H_2O (10:1)	rt	15	0[d]
9	KOH	2.5	DMSO-H_2O (10:1)	rt	15	56
10	KOH	10	DMSO	rt	15	<85[e]
11	KOH	10	DMSO-H_2O (10:1)	rt	15	**85**
12	KOH	10	1,4-dioxane-H_2O (10:1)	rt	15	0[d]
13	DBU	4	DMSO	rt	29	34
14	DBU	4	THF	rt	48	---[f]
15	DBU	4	EtCN	rt	18	43
16	DBU	4	MeCN-EtCN (1:1)	rt	48	60
17	DBN	4	MeCN-EtCN (1:1)	rt	18	45
18	TBD	4	MeCN-EtCN (1:1)	rt	21	82

[a]Dehydrated THF was purchased from Kanto Chemical Co. Inc. DMSO was purchased from Wako Pure Chemical Industries Ltd. and used without further purification. [b]4,7-Dibromobenzo[*b*]thiophene **4a** was obtained in 7% yield after silica gel column chromatography. [c]The yield was estimated from ^{1}H NMR spectrum of the crude mixture of products: the ratio of the compounds (**2**:**3a**:**3b**) was 0:8:92. [d]Nearly quantitative formation of **3b** (determined by ^{1}H NMR spectroscopy). [e]A small amount of **3b** was included. [f]A complex mixture of products was obtained.

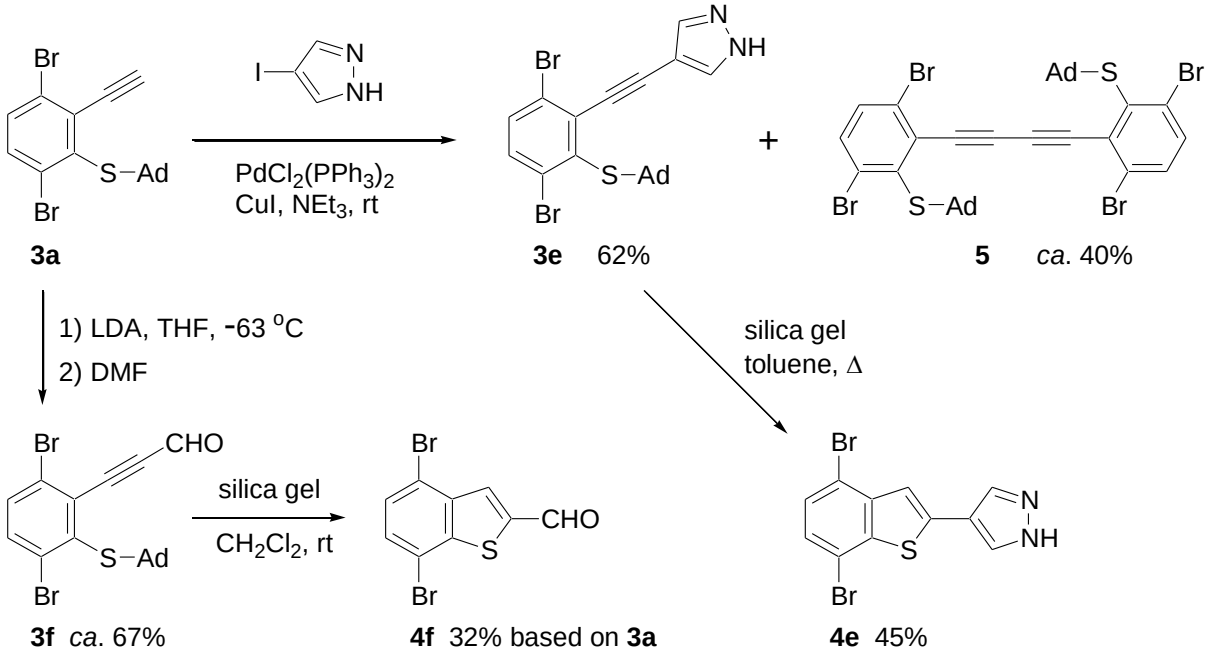


Scheme 3. Synthetic route to some 4,7-dibromobenzo[*b*]thiophene derivatives, using the silica gel-assisted cyclization. TMP = 2,2,6,6-tetramethylpiperidine; TBAF = tetrabutylammonium fluoride.

Thus, reactions of **2** with bicyclic amines such as DBU and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) were also investigated. Reactions in DMSO or tetrahydrofuran (THF) did not afford good results (entries 13,14). As **2** is nearly insoluble in MeCN, some analogous solvent systems were applied (entries 15–18). When the reaction was performed in MeCN-EtCN (1:1), **3a** was obtained in 60% yield (entry 16). Reaction with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in MeCN-EtCN (1:1) gave good result (entry 18), however, reproducibility was not good, especially in a larger scale reaction. Summarizing the results, the conditions shown in entry 11 seem to be efficient from viewpoints of yield and reagent cost.

Reactions of 2-(1-adamantylsulfanyl)-1,4-dibromo-3-(ethynyl)benzene (3a)

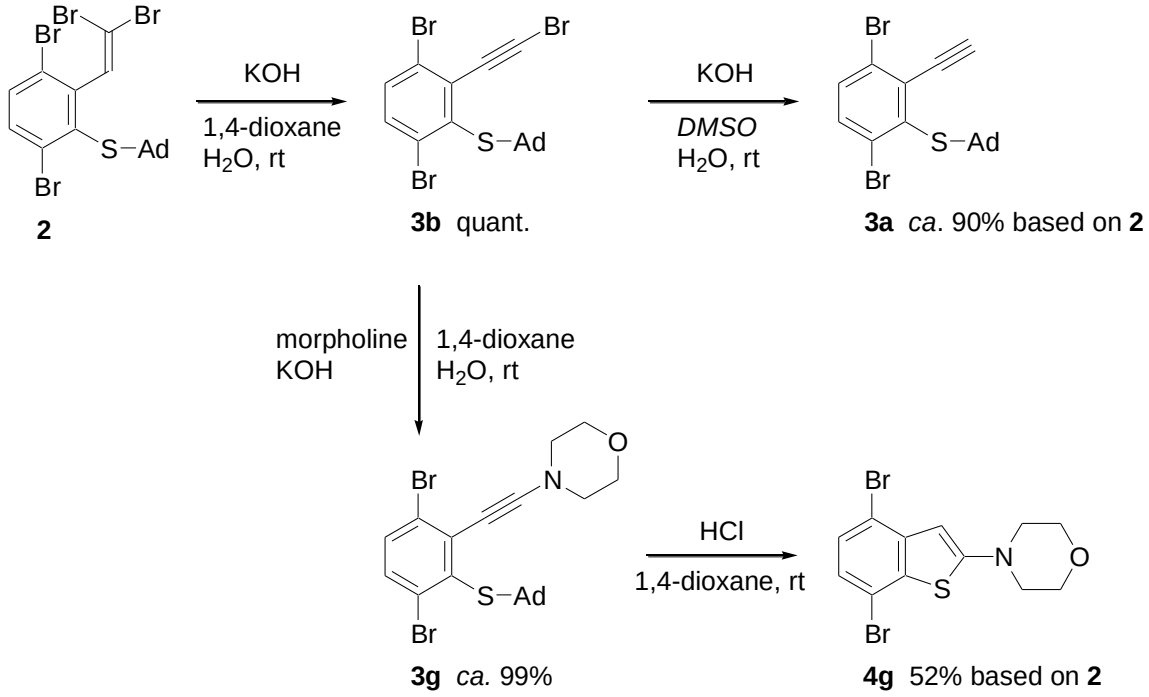
As we could obtain the terminal alkyne **3a** in good yield under mild conditions, we studied several reactions of **3a**: Reaction of **3a** with I_2 in the presence of 2,2,6,6-tetramethylpiperidine (TMP) afforded iodoalkyne **3c** in about 90% yield (Scheme 3), while Sonogashira cross coupling of **3a** with iodobenzene afforded (phenylethynyl)benzene **3d** (85% yield). Pyrazole moiety was introduced also by Sonogashira coupling to give **3e** in 62% yield (Scheme 4): In this reaction of **3a** with iodopyrazole, by-prodcut **5** was also formed. Abstraction of the alkyne proton of **3a** with lithium diisopropylamide (LDA) followed by reaction with *N*,*N*-dimethylformamide (DMF) afforded **3f** (*ca*. 67% yield). Compounds **3c**,**f** were not purified, because partial cyclization occurred during silica gel column chromatographic separation. It is also noteworthy that Sonogashira cross coupling of **3a** should be done with iodoarenes (not bromoarenes) at room temperature or slightly higher than room temperature, otherwise the bromine atoms of **3a** itself may react with the alkyne moiety to give polymeric products.



Scheme 4. Reactions of **3a**, see also Table 2

Reactions of 2-(1-adamantylsulfanyl)-1,4-dibromo-3-(bromoethynyl)benzene (3b)

In some reactions of **2** with Cs_2CO_3 under milder conditions (Table 1, entries 7 and 8, footnotes c and d), bromoalkyne **3b** instead of the terminal alkyne **3a** was obtained. Thus, compound **3b** seems to be an intermediate of **3a**. This speculation was supported as shown in Scheme 5: Reaction of **2** with KOH in 1,4-dioxane instead of DMSO exhibited nearly quantitative formation of **3b**, which was converted to **3a** in good yield by changing the solvent to DMSO-H_2O. When **3b** was generated in 1,4-dioxane-H_2O solution and quenched with morpholine, almost quantitative formation of ynamine **3g** was observed by NMR spectroscopy.

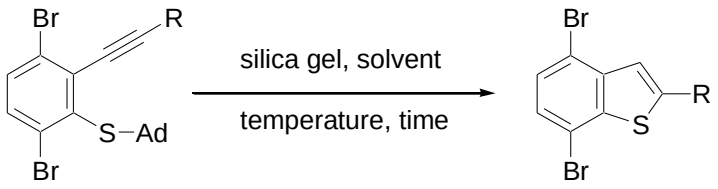


Scheme 5. Reactions of **3b**

Conversion of (ethynyl)(sulfanyl)benzenes 3a–g to the benzo[*b*]thiophenes 4a–g

Next, transformation of the (adamantylsulfanyl)(ethynyl)benzenes **3a**–**g** into benzo[*b*]thiophenes were studied. Results of the silica gel-assisted cyclization are shown in Schemes 3,4 and Table 2. Silica gel-assisted cyclization of the terminal alkyne **3a** gave **4a** in 93% yield (Table 2, entry 1). As mentioned above, alkynes **3b**,**c**,**f** were prepared and used without chromatographic isolation, because silica gel (or alumina) column chromatographic treatment of these compounds causes partial cyclization reaction even at room temperature: When crude **3b**,**c** were heated in toluene in the presence of silica gel, compounds **4b**,**c** were obtained in good 2-step yields (entries 2,3).

Table 2. Preparation of benzothiophenes **4** by 'silica gel-assisted cyclization' method



3a-f **4a-f**

Entry	Reactant	R	Solvent	Temp. / °C	Time / h	Product	Yield / %
1	**3a**	H	toluene	90	21	**4a**	93
2	**3b**	Br	toluene	90	22	**4b**	70[a]
3	**3c**	I	toluene	90	20	**4c**	63[b]
4	**3d**	Ph	toluene	110	64	**4d**	74
5	**3e**	Pyz	toluene	110	18	**4e**	45
6	**3f**	CHO	CH_2Cl_2	rt	18	**4f**	48[c]

[a]Yield based on the starting **2** (2 steps), see Scheme 3. [b]Approximate yield based on the starting **3a** (2 steps). [c]Approximate yield based on crude **3f**; yield based on the starting **3a** (2 steps) was 32%.

In entry 4 of Table 2, silica gel-assisted cyclization of **3d** afforded **4d** in 74% yield. As described in our previous paper,[5] compound **4d** was also obtained by Suzuki-Miyaura coupling of **4c** with benzeneboronic acid (Scheme 3), or by coupling of the boronic acid ester **4l** with iodobenzene vice versa. Thus the 2-step route (**3a** → **3d** → **4d**) including Sonogashira coupling is an efficient alternative to the 3-step route (**3a** → **4a**/**3c** → **4c** → **4d**) or (**3a** → **4a** → **4l** → **4d**) including Suzuki-Miyaura coupling.

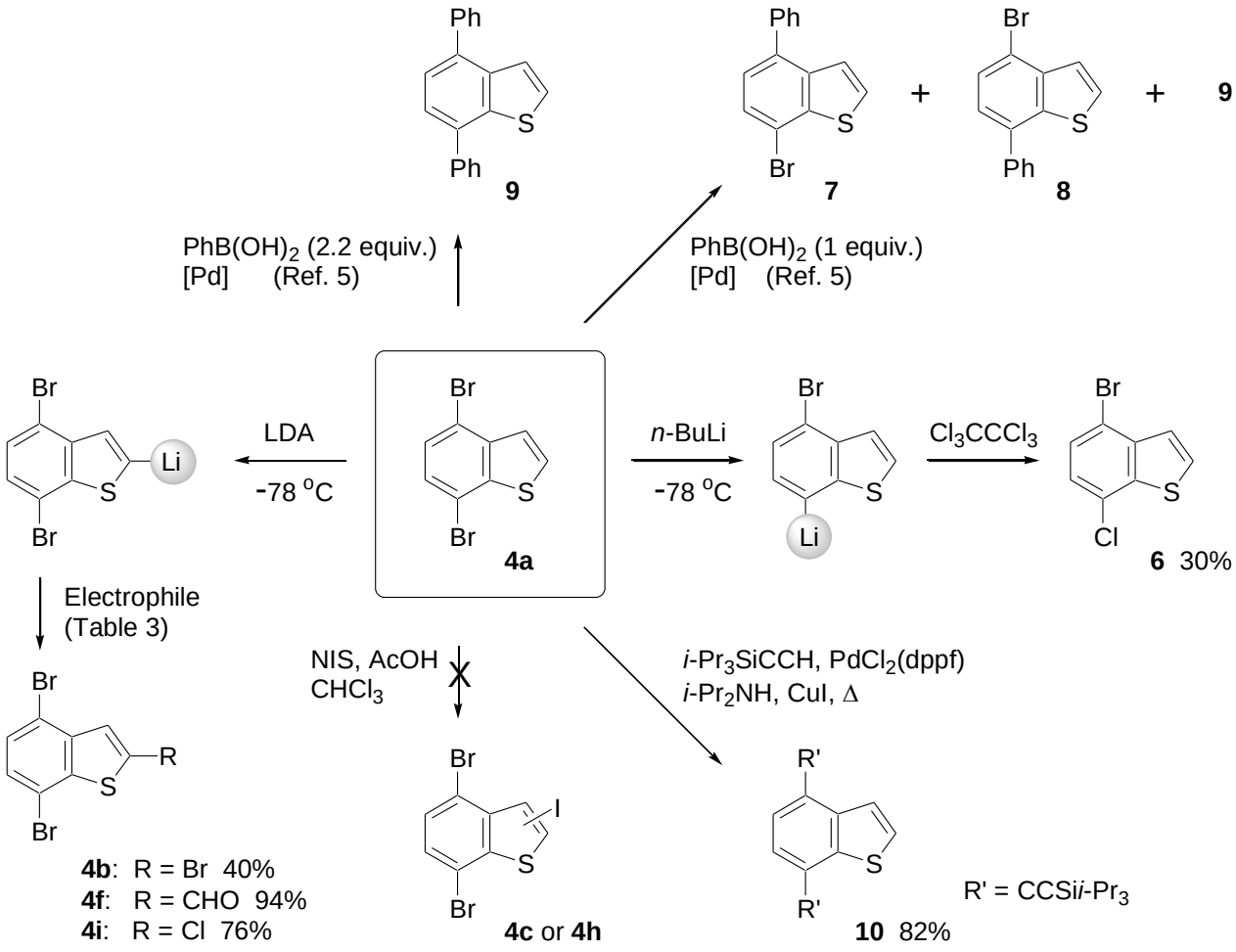
The internal alkynes **3e**,**f** were cyclized also in the presence of silica gel to give **4e** and **4f**, respectively, in medium yields (entries 5,6). Probably, adsorption of the polar moiety to the silica gel decreased yields. In the case of **3e**, intra- or intermolecular migration of the adamantyl group to the nitrogen atom seemed to proceed to some extent and decrease the yield of **4e**.

It is noteworthy that the well-known iodocyclization of **3a** using I_2 afforded 3-iodo product **4h** (56% yield, Scheme 3). In general, acid or transition metal-catalyzed cyclization as well as the iodocyclization of *o*-(alkylsulfanyl)(ethynyl)benzene leads to 3-substituted benzo[*b*]thiophenes. Thus, the present method using silica gel can be regarded as a unique, simple, and straightforward method to 3-*unsubstituted* benzo[*b*]thiophenes such as **4a**–**f**. In the case of ynamine **3g**, however, silica gel did not give good results. Alternatively, **4g** was obtained by treatment of **3g** with HCl / 1,4-dioxane solution (Scheme 5).

Reactions of 4,7-dibromobenzo[*b*]thiophene (4a)

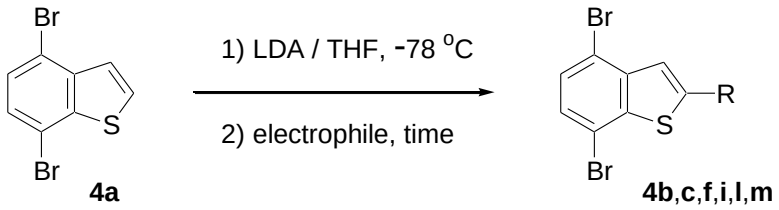
In our previous paper, reactivity of the 4,7-dibromobenzothiophene **4a** was studied: Bromine-lithium exchange of **4a** with butyllithium in THF occurred at the 7-position affording 4-bromobenzo[*b*]thiophene.[3] Probably, coordination with the lone pair of the sulfur atom favored lithiation of the proximate bromine atom. When the intermediate was quenched with hexachloroethane, 4-bromo-7-chloro derivative **6**[4] was obtained in 30% yield (Scheme 6) along with some by-products, see experimental part.

In contrast to the case of reaction with butyllithium, reaction of **4a** with LDA occurs at the 2-position: We previously reported that reaction of **4a** with LDA followed by treatment with iodomethane afforded 4,7-dibromo-2-methylbenzo[*b*]thiophene **4m** (Table 3, entry 6).[3] Other reactions of **4a** with LDA/electrophiles are also shown in Scheme 6 and Table 3 (products **4b**,**f**,**i**,**l**). In the case of **4l**, diisopropylamine-boron interaction may have lowered the yield (entry 5). An attempted reaction of **4a** with NIS in AcOH-$CHCl_3$ resulted in recovery of **4a** (*i.e.*, neither **4c** nor **4h**).



Scheme 6. Reactions of **4a**

Table 3. Reaction of **4a** with LDA / electrophile



4a **4b**,**c**,**f**,**i**,**l**,**m**

Entry	Electrophile	Time / h	R	Product	Yield / %
1	$(CH_2Br)_2$	1	Br	**4b**	65[a]
2	$(CH_2I)_2$	3	I	**4c**	82[b]
3	$(CCl_3)_2$	1	Cl	**4i**	76
4	DMF	2	CHO	**4f**	94
5	*i*-PrOBpin	47	Bpin	**4l**	38[c]
6	MeI	15	Me	**4m**	74[d]

[a]The starting compound **4a** was recovered in 30% recovery. [b]Data taken from Ref. 5. [c]After gel permeation column chromatographic separation (Bio-Beads® S-X3, $CHCl_3$ as an eluent). [d]Data taken from Ref. 3.

Suzuki-Miyaura cross coupling of **4a** with 2.2 equiv. of benzeneboronic acid afforded 4,7-diphenyl derivative **9** in 82% yield[5] (Scheme 6). Sonogashira cross coupling of **4a** with ethynyltriisopropylsilane (2.6 equiv.) gave **10** also in 82% yield. As reported in ref. 5, coupling reaction of **4a** with 1 equiv. of benzeneboronic acid was not regioselective to give a mixture of products **7**, **8**, and **9** (for analogous reaction of **4b**, see below).

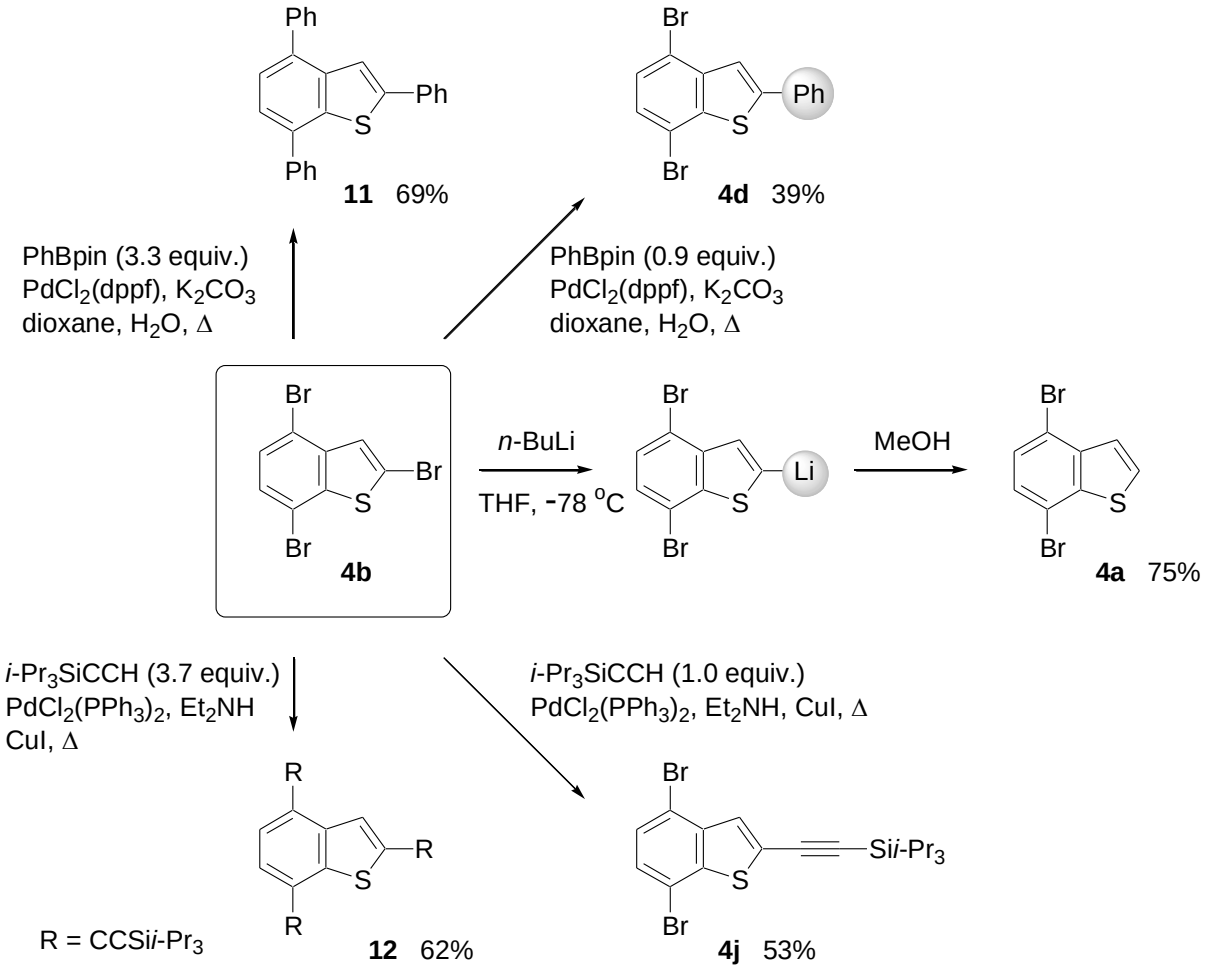
Reactions of 2,4,7-tribromobenzo[*b*]thiophene (4b)

In contrast to the case of **4a**, bromine-lithium exchange reaction of the tribromo derivative **4b** with butyllithium proceeded at the 2-position to give **4a** as a major product (75% yield, Scheme 7) after quenching with MeOH (13% recovery of the starting **4b**). An attempted halogen-dance reaction of **4b** with LDA in THF resulted in recovery of **4b**. Suzuki-Miyaura cross coupling of **4b** with 3.3 equiv. of PhBpin afforded 2,4,7-triphenyl derivative **11** in 69% yield, whereas reaction with *ca*. 1 equiv. of PhBpin formed 2-phenyl derivative **4d** as a major product in 39% yield (32% recovery of **4b**). In the latter case, prolonged heating or severer reaction conditions may cause multi-substitution.

Sonogashira coupling of **4b** with 3.7 equiv. of ethynyltriisopropylsilane gave compound **12** in 62% yield. Similarly to the case of Suzuki-Miyaura coupling, Sonogashira coupling of **4b** with 1 equiv. of

ethynyltriisopropylsilane proceeded mainly at the 2-position to give **4j** (53% yield, determined by ^{1}H NMR spectroscopy) along with **4a** (12% yield) and **4b** (24% recovery).

For better selectivity in cross coupling reactions, introduction of different halogen atoms such as iodine and chlorine is usually an effective strategy, and this was realized using the 2-iodo derivative **4c**. Sonogashira coupling of **4c** with 1.5 equiv. of ethynyltriisopropylsilane afforded compound **4j** (93% yield), which was desilylated to give **4k** in 87% yield (Scheme 3).



Scheme 7. Reactions of **4b**

In summary, preparations and reactions of 4,7-dibromobenzo[*b*]thiophene (**4a**) and 2,4,7-tribromobenzo[*b*]thiophene (**4b**) were investigated. Mild Corey-Fuchs reaction using KOH / DMSO-H_2O at room temperature and the silica gel-assisted cyclization were effectively utilized in these syntheses. Functional group-diversity in the preparation of 2-substituted 4,7-dibromobenzothiophenes were demonstrated in the cases of electrophilic substitution, nucleophilic substitution, and cross coupling

reactions of the intermediate alkynes **3a** and/or **3b**. Reactivity of the bromine atoms in **4a** and **4b** were also studied. Bromine-metal exchange reaction and cross coupling reactions of **4b** turned out to proceed mainly at the C-2 position. The fundamental information obtained in this paper will benefit the chemistry of benzo[*b*]thiophenes. Constructions of larger and more sophisticated molecules are currently in progress in our laboratory, using the benzothiophene building blocks.

EXPERIMENTAL

For silica gel column chromatography and the silica gel-assisted cyclization, silica gel PSQ 60B (Fuji Silysia Chemical Ltd.) was used as it was. 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. The internal standard for ^{1}H NMR chemical shifts is Me_4Si (δ 0.00). ^{13}C NMR chemical shifts are given relative to the appropriate internal standard such as Me_4Si (δ 0.00), $CDCl_3$ (δ 77.16), or THF-d_8 (δ 67.21). Mass spectra were taken on a Bruker solariX spectrometer or a JEOL JMS-T spectrometer.

Preparation of 2-(1-Adamantylsulfanyl)-1,4-dibromo-3-(2,2-dibromoethenyl)benzene (2). A solution of PPh_3 (7.34 g, 28.0 mmol) in CH_2Cl_2 (30 mL) was slowly added to a mixture of the aldehyde **1** (4.50 g, 10.5 mmol) and CBr_4 (4.64 g, 14.0 mmol) in CH_2Cl_2 (30 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at room temperature for 2.5 h and worked up with CH_2Cl_2 and water. The organic phase 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-$CHCl_3$ 4:1) to give 5.62 g (9.59 mmol) of **2**; 92% yield; a colorless solid; mp 119.5–122 °C; ^{1}H NMR (700 MHz, $CDCl_3$) δ 1.66 (6H, br s, Ad), 1.92–1.99 (6H, m, Ad), 2.04 (3H, br s, Ad), 7.45 (1H, d, ^{3}J = 8.4 Hz), 7.52 (1H, br s, CH=CBr_2), 7.57 (1H, dd, ^{3}J = 8.4 Hz, ^{5}J = 0.7 Hz); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 30.6 (Ad), 36.2 (Ad), 44.6 (Ad), 54.5 (Ad), 96.3 (CBr_2), 122.5 (CBr), 134.1 (CH), 134.5 (CBr), 134.6 (br s, C-S and *C*H=CBr_2), 138.5 (CH), 145.8 (*C*-CH=CBr_2). Found: *m*/*z* 608.7714. Calcd for $C_{18}H_{18}{}^{79}Br_2{}^{81}Br_2NaS$: $(M+Na)^+$, 608.7713.

Preparation of 2-(1-Adamantylsulfanyl)-1,4-dibromo-3-(ethynyl)benzene (3a). Method I. A solution of KOH (2.36 g, 35.7 mmol) in water (45 mL) was added to a solution of **2** (2.07 g, 3.57 mmol) in DMSO (450 mL). The resulting mixture was vigorously stirred at room temperature for 15 h. Hydrochloric acid (4 mol/L, 7.1 mL) was added to the reaction mixture and the mixture was extracted with hexane-EtOAc (4:1). The organic phase was dried over Na_2SO_4 and the solvent was removed

under reduced pressure. The residue was treated with silica gel column chromatography (hexane-CH_2Cl_2 4:1) to give 1.3002 g (3.05 mmol, 85% yield) of **3a**.[5]

Method II, via 3b. A solution of KOH (181.1 mg, 3.23 mmol) in water (1 mL) was added to a solution of **2** (205.0 mg, 0.350 mmol) in 1,4-dioxane (10 mL). The resulting mixture was vigorously stirred at room temperature overnight and worked up with hexane-EtOAc. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give 179.5 mg (*ca*. 0.35 mmol) of crude **3b**. The crude product was dissolved in DMSO (45 mL). To this solution was added a solution of KOH (230.2 mg, 4.1 mmol) in water (4.5 mL) and the resulting mixture was stirred at room temperature for 15 h. The mixture was worked up with hexane-EtOAc (4:1) and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give 136.3 mg of crude **3a** (*ca*. 90% yield based on **2**).

Preparation of 2-(1-Adamantylsulfanyl)-1,4-dibromo-3-(bromoethynyl)benzene (3b). A solution of KOH (128.1 mg, *ca*. 2 mmol) in water (2 mL) was added to a solution of **2** (98.0 mg, 0.167 mmol) in 1,4-dioxane (20 mL). The resulting mixture was stirred at room temperature for 17 h, quenched with 4 M HCl (0.4 mL), and worked up with EtOAc. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give **3b** quantitatively. A colorless solid; mp 94.5–97.5 °C (decomp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (6H, br s, Ad), 2.01+2.04 (9H, s+s, Ad), 7.40 (1H, d, ^3J = 8.4 Hz), 7.50 (1H, d, ^3J = 8.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.6 (Ad), 36.2 (Ad), 44.5 (Ad), 55.3 (Ad), 60.7 (C≡*C*Br), 80.1 (*C*≡CBr), 126.0 (CBr), 133.6 (CH), 133.7 (CBr), 133.8 (CH), 134.5, 137.7. Found: *m*/*z* 501.8601. Calcd for $C_{18}H_{17}{}^{79}Br_3S$: M^+, 501.8601.

Preparation of 2-(1-Adamantylsulfanyl)-1,4-dibromo-3-(2-phenylethynyl)benzene (3d). To a mixture of **3a** (142.7 mg, 0.335 mmol), $PdCl_2(PPh_3)_2$ (2.3 mg, 0.0033 mmol), and CuI (0.7 mg, 0.0037 mmol) was added a solution of iodobenzene (84.8 mg, 0.416 mmol) in triethylamine (9 mL). The reaction mixture was stirred at room temperature for 41 h. To the mixture were added EtOAc and water. The organic phase was separated, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane-CH_2Cl_2, 4:1) to give 143.8 mg (0.286 mmol) of **3d**; 85% yield; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.65 (6H, br s, Ad), 2.02 (3H, br s, Ad), 2.07–2.08 (6H, br s, Ad), 7.36-7.39 (3H, m, Ph), 7.43 (1H, d, ^3J = 8.8 Hz), 7.48 (1H, d, ^3J = 8.8 Hz), 7.60–7.62 (2H, m, Ph); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.6 (Ad), 36.3 (Ad), 44.7 (Ad), 55.1 (Ad), 90.0 (C≡C), 98.9 (C≡C), 123.1 (CBr), 125.6 (CBr), 128.6 (Ph, CH), 129.1 (CH), 132.0 (Ph, CH), 133.1 (CH), 133.7, 133.8 (CH), 135.2, 136.8. Found: *m*/*z* 499.9809. Calcd for $C_{24}H_{22}{}^{79}Br_2S$: M^+, 499.9809.

Preparation of 2-(1-Adamantylsulfanyl)-1,4-dibromo-3-[2-(1*H*-pyrazol-4-yl)ethynyl]benzene (3e). A mixture of **3a** (101.1 mg, 0.237 mmol), 4-iodo-1*H*-pyrazole (43.6 mg, 0.225 mmol), $PdCl_2(PPh_3)_2$ (1.7 mg, 0.0024 mmol), and CuI (0.5 mg, 0.0026 mmol) in triethylamine (6 mL) was stirred at room temperature for 18 h. EtOAc and water were added to the reaction mixture. The organic phase was separated, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane-EtOAc, 3:2) to give **3e** (71.8 mg, 0.146 mmol) and crude diyne **5** (44.2 mg, *ca*. 0.052 mmol).

3e: 62% yield (based on **3a**); a colorless solid; mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (6H, br s, Ad), 2.06 + 2.07 (9H, br s + br s, Ad), 7.43 (1H, d, ^3J = 8.0 Hz), 7.48 (1H, d, ^3J = 8.0 Hz), 7.85 (2H, br s, pyrazole), 10.68 (1H, br s, NH); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.6 (Ad), 36.3 (Ad), 44.7 (Ad), 55.1 (Ad), 91.1 (C≡C), 125.1 (CBr), 132.9 (CH), 133.7 (CBr), 133.8 (CH), 135.3, 136.5. Found: *m*/*z* 514.9585. Calcd for $C_{21}H_{20}{}^{79}Br^{81}BrN_2NaS$: $(M+Na)^+$, 514.9585. Some ^{13}C NMR signals were not observed probably because of tautomerization of the NH proton.

5: *ca*. 40% yield; a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (12H, m, Ad), 2.04–2.07 (18H, m, Ad), 7.43 (2H, d, ^3J = 8.4 Hz), 7.53 (2H, d, ^3J = 8.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.7 (Ad), 36.3 (Ad), 44.7 (Ad), 55.8 (Ad), 83.1 (C≡C), 83.8 (C≡C), 126.4 (CBr), 133.8 (CBr), 133.9 (CH), 134.0, 134.1 (CH), 138.4. Found: *m*/*z* 872.8685. Calcd for $C_{36}H_{34}Br_4NaS_2$: $(M+Na)^+$, 872.8685.

Preparation of 4,7-Dibromobenzo[*b*]thiophene (4a). A mixture of **3a** (511.1 mg, 1.199 mmol), silica gel (3.9583 g), and toluene (23 mL) was heated at 90 °C for 21 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature and the silica gel was removed by filtration. The silica gel was washed with CH_2Cl_2 until no further product **4a** was eluted out (monitored with silica gel TLC). The solvent of the filtrate was evaporated under reduced pressure. Silica gel column chromatographic treatment (hexane) of the residue afforded 325.4 mg (1.114 mmol, 93% yield) of **4a**.[3]

Preparation of 2,4,7-Tribromobenzo[*b*]thiophene (4b). Method I, via 3b. A solution of KOH (574.5 mg, 10.2 mmol) in water (1 mL) was added to a solution of **2** (595.7 mg, 1.02 mmol) in 1,4-dioxane (30 mL). The resulting mixture was stirred at room temperature for 20 h. The reaction mixture was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure to give crude **3b**. A mixture of the crude **3b**, silica gel (4.50 g), and toluene (20 mL) was heated at 90 °C for 22 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature and the silica gel was removed by filtration. The silica gel was washed with $CHCl_3$ until no further product **4b** was eluted out (monitored with silica gel TLC).

The solvent of the filtrate was evaporated under reduced pressure. The residue was recrystallized from hexane to give 265.3 mg of **4b** (0.715 mmol, 70% yield based on **2**).

Method II, via 4a. To a solution of **4a** (199.4 mg, 0.683 mmol) in THF (6.5 mL) was added 0.810 mmol of LDA (1.08 M solution in THF, 0.75 mL) at –78 °C. The reaction mixture was stirred at 0 °C for a few minutes and 1,2-dibromoethane (0.10 mL, 1.149 mmol) was added at –78 °C. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was poured into *ca*. 10 mL of brine. The mixture was extracted with EtOAc and the organic layer was washed with saturated aqueous Na_2SO_3 solution twice. The organic phase was separated, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was treated with a silica gel column chromatography (cyclohexane) to give 163.7 mg (0.441 mmol, 65% yield) of **4b** and 60.4 mg of the starting **4a** (30% recovery).

4b: Colorless needles; mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, d, ^3J = 8.2 Hz), 7.39 (1H, d, ^3J = 8.2 Hz), 7.58 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 113.7 (CBr), 115.2 (CBr), 117.9 (CBr), 128.2 (CH+CH), 129.3 (CH), 140.2, 143.3. Found: *m*/*z* 371.7459. Calcd for $C_8H_3{}^{79}Br^{81}Br_2S$: M^+, 371.7459.

Preparation of 4,7-Dibromo-2-iodobenzo[*b*]thiophene (4c) via 3c. To a solution of iodine (90.4 mg, 0.356 mmol) and 2,2,6,6-tetramethylpiperidine (53.5 mg, 0.379 mmol) in benzene (2.0 mL) was added a solution of **3a** (150.5 mg, 0.353 mmol) in benzene (2.0 mL) at room temperature. The resulting mixture was stirred at 50 °C for 1 h and aqueous Na_2SO_3 solution was added at room temperature and extracted with hexane. The organic phase was washed with aqueous Na_2SO_3 solution twice, washed with aqueous NH_4Cl solution twice, dried over $MgSO_4$, and the solvent was removed under reduced pressure to give crude **3c** (174.5 mg, *ca*. 0.32 mmol, *ca*. 90% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (6H, br, Ad), 2.01 (9H, br, Ad), 7.40 (1H, d, ^3J = 8.0 Hz), 7.48 (1H, d, ^3J = 8.0 Hz).

The crude **3c** thus obtained was used in the following reaction without further purification. A mixture of the crude **3c** (174.5 mg, *ca*. 0.32 mmol), silica gel (1.02 g), and toluene (5.0 mL) was heated at 90 °C for 20 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature and the silica gel was removed by filtration. The silica gel was washed with CH_2Cl_2 until no further product **4c** was eluted out. The solvent of the filtrate was evaporated under reduced pressure. Silica gel column chromatographic treatment (hexane) of the residue (119.4 mg) afforded 92.7 mg (0.222 mmol, 63% yield in 2 steps) of **4c**[5] containing a trace of impurity in ^{1}H NMR spectroscopy.

Preparation of 4,7-Dibromo-2-phenylbenzo[*b*]thiophene (4d). A mixture of **3d** (143.8 mg, 0.286 mmol), silica gel (0.9 g), and toluene (4.6 mL) was heated at 110 °C for 64 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature and the silica gel was removed by

filtration. The silica gel was washed with $CHCl_3$ until no further product **4d** was eluted out (*ca*. 100 mL, monitored with silica gel TLC). The solvent of the filtrate was evaporated under reduced pressure. Silica gel column chromatographic treatment (cyclohexane) of the residue afforded 77.8 mg (0.211 mmol, 74% yield) of **4d**.[5]

Preparation of 4,7-Dibromo-2-(1*H*-pyrazol-4-yl)benzo[*b*]thiophene (4e). A mixture of **3e** (57.2 mg, 0.116 mmol), silica gel (765.2 mg), and toluene (5 mL) was refluxed for 18 h under nitrogen atmosphere. The reaction mixture was allowed to cool down to room temperature and the silica gel was removed by filtration (eluent: $CHCl_3$-MeOH, 95:5). The silica gel was washed with the eluent until no further product **4e** was eluted out (monitored with silica gel TLC). The solvent of the filtrate was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane-EtOAc) to give 18.8 mg (0.0525 mmol) of **4e**; 45% yield; a colorless solid; mp 210–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1H, d, ^3J = 8.0 Hz), 7.40 (1H, d, ^3J = 8.0 Hz), 7.53 (1H, s), 7.93 (2H, s, pyrazole); ^{13}C{^{1}H} NMR (100 MHz, THF-d_8) δ 114.8, 115.7, 115.8, 119.1 (CH), 127.9 (CH), 129.8 (CH), 139.7, 141.1, 141.9. Found: *m*/*z* 358.8671. Calcd for $C_{11}H_7{}^{79}Br^{81}BrN_2S$: $(M+H)^+$, 358.8671. Some ^{13}C NMR signals were not observed probably because of tautomerization of the NH proton.

Preparation of 4,7-Dibromo-2-formylbenzo[*b*]thiophene (4f). Method I. via 3f. To a solution of **3a** (167.4 mg, 0.393 mmol) in THF (2.0 mL) was added 0.60 mmol of LDA (1.09 M solution in hexane-THF, 0.55 mL) at –63 °C under N_2. The resulting mixture was stirred at –63 °C for 15 min and DMF (0.3 mL, 3.90 mmol) was added. The reaction mixture was stirred for 1.5 h, allowed to warm to room temperature, and quenched with water. The mixture was extracted with EtOAc, the organic phase was washed with 4 M hydrochloric acid twice, dried over $MgSO_4$, and the solvent was removed under reduced pressure to give crude **3f** (119.0 mg, *ca*. 0.262 mmol, *ca*. 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (6H, br, Ad), 2.02 (9H, br, Ad), 7.47 (1H, d, ^3J = 8.4 Hz), 7.63 (1H, d, ^3J = 8.4 Hz), 9.53 (1H, s, CHO). The crude **3f** was not subjected to silica gel column chromatography at this stage because partial cyclization of **3f** to **4f** occurs even at room temperature in the presence of silica gel. Thus, a mixture of the crude **3f** and silica gel (1.229 g) in CH_2Cl_2 (4.0 mL) was stirred at room temperature for 18 h. The silica gel was removed by filtration and washed with CH_2Cl_2 until no further product **4f** was eluted out. The solvent of the combined filtrate was evaporated under reduced pressure. Silica gel column chromatographic treatment (hexane-CH_2Cl_2 4:1 to 1:1) of the residue afforded 40.1 mg (0.125 mmol) of **4f** (32% yield based on **3a**, 2 steps).

Method II. To a solution of **4a** (201.1 mg, 0.689 mmol) in THF (3 mL) was added 0.981 mmol of LDA (1.09 M solution in hexane-THF, 0.90 mL) at –78 °C under N_2. The resulting solution was stirred for 1 h and warmed to 0 °C. The reaction mixture was stirred for 5 min, cooled to –78 °C again, and DMF

(0.10 mL, 1.30 mmol) was added. The reaction mixture was stirred for 1.5 h, allowed to warm to 0 °C, stirred for 30 min, and poured into ice-cooled 4 M HCl (*ca*. 20 mL). The mixture was extracted with EtOAc, the organic phase was separated, washed with brine, and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane-CH_2Cl_2 1:1) to give 206.2 mg (0.644 mmol, 94% yield) of **4f**.

4f: A pale yellow solid; mp 175.5–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, s), 8.24 (1H, s), 10.12 (1H, s, CHO); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 115.8 (C-Br), 119.0 (CBr), 129.8 (CH), 131.5 (CH), 134.6 (CH), 139.3, 144.4, 145.1, 184.3 (CHO). Found: *m*/*z* 319.8323. Calcd for $C_9H_4{}^{79}Br^{81}BrOS$: M^+, 319.8324.

Preparation of 4,7-Dibromo-2-(morpholino)benzo[*b*]thiophene (4g) via 3g. A solution of KOH (330.9 mg, 5.90 mmol) in water (1.5 mL) was added to a solution of **2** (300.1 mg, 0.512 mmol) in 1,4-dioxane (15 mL). The resulting mixture was stirred at room temperature for 30 min and 3 mL (34.3 mmol) of morpholine was added to the mixture. The resulting solution was stirred at room temperature for 20 h and worked up with EtOAc and brine. The organic phase was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure to give 259.5 mg of crude **3g** (*ca*. 0.508 mmol, *ca*. 99% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (6H, m, Ad), 2.02 (9H, br s, Ad), 3.30 (4H, m, CH_2), 3.78 (4H, m, CH_2), 7.25 (1H, d, ^3J = 8.4 Hz), 7.32 (1H, d, ^3J = 8.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 30.3 (Ad), 36.1 (Ad, CH_2), 44.6 (Ad, CH_2), 51.3 (Mor, CH_2), 54.3 (Ad), 66.1 (Mor, CH_2), 67.0 (C≡C), 106.1 (C≡C), 121.9, 129.5 (CH), 132.4, 133.2 (CH), 133.3, 136.9.

A solution of the crude **3g** in THF (8 mL) was slowly added to HCl/1,4-dioxane (*ca*. 4 mol / L solution, 2 mL) at room temperature. The reaction mixture was stirred at room temperature for 30 min and quenched with aqueous KOH. The mixture was extracted with EtOAc and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane-CH_2Cl_2 1:1). The crude product was recrystallized from hexane to give 100.5 mg (0.2665 mmol) of **4g**; 52% yield (based on **2**); colorless fine needles; mp 117–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29–3.32 (4H, m, CH_2), 3.86–3.88 (4H, m, CH_2), 6.37 (1H, s), 7.07 (1H, d, ^3J = 8.4 Hz), 7.29 (1H, d, ^3J = 8.4 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 50.4 (CH_2), 66.2 (CH_2), 99.9 (CH), 113.0 (CBr), 113.9 (CBr), 124.7 (CH), 129.1 (CH), 134.1, 141.1, 158.7. Found: *m*/*z* 376.8903. Calcd for $C_{12}H_{11}{}^{79}Br^{81}BrNOS$: M^+, 376.8902.

Preparation of 4,7-Dibromo-3-iodobenzo[*b*]thiophene (4h). A mixture of **3a** (519.3 mg, 1.218 mmol), iodine (0.473 g, 1.864 mmol), and THF (125 mL) was stirred in the dark at 50 °C for 25 h under nitrogen atmosphere. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution and extracted with EtOAc. The organic phase was separated and dried over $MgSO_4$. The solvent was removed under

reduced pressure and the residue was separated with silica gel column chromatography (hexane). In order to remove the resulting 1-iodoadamantane, the crude product was recrystallized from hexane to give 286.2 mg (0.685 mmol) of **4h** in 56% yield. A colorless solid; mp 131.5–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (1H, d, ^3J = 8.4 Hz), 7.52 (1H, d, ^3J = 8.4 Hz), 7.86 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 75.0 (CI), 115.5 (CBr), 117.3 (CBr), 128.7 (CH), 132.3 (CH), 134.6, 134.7 (CH), 141.7. Found: *m*/*z* 417.7341. Calcd for $C_8H_3{}^{79}Br^{81}BrIS$: M^+, 417.7341.

Preparation of 4,7-Dibromo-2-chlorobenzo[*b*]thiophene (4i). To a solution of **4a** (91.9 mg, 0.315 mmol) in THF (12.6 mL) was added 0.38 mmol of LDA (1.09 M solution in hexane-THF, 0.35 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 30 min and a THF (*ca*. 1 mL) solution of hexachloroethane (74.8 mg, 0.316 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was worked up with EtOAc and brine. The organic phase was separated, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane) to give 78.0 mg (0.239 mmol) of **4i**; 76% yield; colorless fine needles; mp 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, d, ^3J = 8.2 Hz), 7.41 (1H, d, ^3J = 8.2 Hz), 7.42 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 114.0 (CBr), 115.4 (CBr), 124.5 (CH), 128.3 (CH), 129.4 (CH), 134.4, 139.3, 141.0. Found: *m*/*z* 323.8005. Calcd for $C_8H_3{}^{79}Br_2ClS$: M^+, 323.8005.

Preparation of 4,7-Dibromo-2-[2-(triisopropylsilyl)ethynyl]benzo[*b*]thiophene (4j). To a mixture of **4c** (35.9 mg, 0.0859 mmol), CuI (1.0 mg, 0.0053 mmol) and $PdCl_2(PPh_3)_2$ (2.0 mg, 0.0029 mmol) in THF (1 mL), toluene (0.5 mL), and diisopropylamine (0.5 mL) was added ethynyltriisopropylsilane (30 μL, 0.135 mmol). The reaction mixture was stirred at 40 °C for 23 h. To the mixture were added EtOAc and brine. The organic phase was separated, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane) to give 37.9 mg (0.0802 mmol) of **4j**; 93% yield; a colorless solid, mp 42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (21H, s, *i*-Pr), 7.35 (1H, d, ^3J = 8.1 Hz), 7.40 (1H, d, ^3J = 8.1 Hz), 7.64 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 11.4 (*C*HMe_2), 18.7 (Me), 98.6 (C≡C), 100.6 (C≡C), 114.2 (CBr), 116.3 (CBr), 125.7 (*C*-C≡C), 128.9 (CH), 129.2 (CH), 130.0 (CH), 139.5, 142.1. Found: *m*/*z* 469.9729 Calcd for $C_{19}H_{24}{}^{79}Br_2SSi$: M^+, 469.9729.

Preparation of 4,7-Dibromo-2-(ethynyl)benzo[*b*]thiophene (4k). A mixture of **4j** (204 mg, 0.432 mmol) and tetrabutylammonium fluoride (0.465 ml, 0.465 mmol) in THF (4.2 mL) was stirred at room temperature for 90 min. To the reaction mixture were added EtOAc and water. The organic phase was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane) and recrystallized from hexane

to give 119 mg (0.376 mmol) of **4k**; 87% yield; colorless needles; mp 125–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (1H, s, C≡CH), 7.38 (1H, d, ^3J = 8.1 Hz), 7.43 (1H, d, ^3J = 8.1 Hz), 7.72 (1H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 76.4 (C≡C), 85.0 (C≡C), 114.3 (CBr), 116.5 (CBr), 124.2 (*C*-C≡C), 129.2 (CH), 129.4 (CH), 131.1 (CH), 139.4, 142.3. Found: *m*/*z* 313.8395. Calcd for $C_{10}H_4{}^{79}Br_2S$: M^+, 313.8395.

Preparation of 4,7-Dibromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*b*]thiophene (4l). To a solution of **4a** (100.1 mg, 0.343 mmol) in THF (2.5 mL) was added 0.373 mmol of LDA (0.187 M solution in hexane-THF, 2 mL) at –78 °C under N_2. The resulting mixture was stirred at 0 °C for 30 min. To the solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.090 mL, 0.44 mmol) at –78 °C. The reaction mixture was allowed to warm to room temperature, and stirred for 47 h. EtOAc (*ca*. 50 mL) and water (*ca*. 50 mL) were added to the mixture. The organic phase was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was treated with gel permeation column chromatography ($CHCl_3$) to give 54.1 mg (0.129 mmol, 38% yield) of **4l**:[5] A pale yellow solid, ^{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); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 26.0 (Me), 85.4 (O*C*Me$_2$), 115.5 (CBr), 117.6 (CBr), 129.2 (CH), 129.3 (CH), 135.7 (CH), 141.3, 146.4. A signal due to the boron-bound carbon was not observed in the ^{13}C NMR spectra.

Preparation of 4-Bromo-7-chlorobenzo[*b*]thiophene (6). To a solution of **4a** (80.7 mg, 0.276 mmol) in THF (2 mL) was added 0.31 mmol of *n*-BuLi (1.64 M solution in hexane, 0.19 mL) at –78 °C under N_2. The resulting solution was stirred at –78 °C for 5 min and a THF (2 mL) solution of hexachloroethane (86.0 mg, 0.363 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was worked up with EtOAc and water. The organic phase was separated, and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (hexane) to give 20.2 mg (0.0816 mmol, 30% yield) of **6**,[4] 7.4 mg (0.0347 mmol, 13% yield) of 4-bromobenzo[*b*]thiophene, and 6.8 mg of an inseparable mixture containing 4-bromo-2,7-dichlorobenzo[*b*]thiophene (*ca*. 7% yield) and **4i** (*ca*. 2% yield).

Preparation of 4,7-Bis[2-(triisopropylsilyl)ethynyl]benzo[*b*]thiophene (10). A mixture of **4a** (121 mg, 0.414 mmol), ethynyltriisopropylsilane (0.24 mL, 1.08 mmol), $PdCl_2$(dppf)·CH_2Cl_2 (12.0 mg, 0.0147 mmol), CuI (5.6 mg, 0.029 mmol), and diisopropylamine (1.6 mL) in toluene (5 mL) was stirred at 80 °C for 12 h. To the resulting mixture were added EtOAc and water. The organic phase was separated, washed with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was treated with a silica gel column chromatography (hexane) to give 168 mg (0.340 mmol) of **10**; 82% yield; colorless scales; mp 135–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16–1.18 (42H, br, *i*-Pr$_3$Si), 7.40 (1H, d, ^3J = 7.7 Hz), 7.45 (1H, d, ^3J = 7.7 Hz), 7.53 (1H, d, ^3J = 5.5 Hz), 7.57 (1H, d, ^3J =

5.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*HMe$_2$), 11.5 (*C*HMe$_2$), 18.7 (Me), 18.7 (Me), 96.3 (C≡C), 97.8 (C≡C), 104.3 (C≡C), 105.1 (C≡C), 118.1 (CBr), 118.7 (CBr), 124.2 (CH), 127.4 (CH), 127.9 (CH), 128.4 (CH), 140.9, 143.0. Found: *m*/*z* 494.2860. Calcd for $C_{30}H_{46}SSi_2$: M^+, 494.2859.

Preparation of 2,4,7-Triphenylbenzo[*b*]thiophene (11). A mixture of **4b** (77.2 mg, 0.208 mmol), $PhB(OH)_2$ (83.8 mg, 0.687 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (8.5 mg, 0.0104 mmol), K_2CO_3 (143.8 mg, 1.04 mmol), 1,4-dioxane (10 mL), and water (1 mL) were stirred under nitrogen atmosphere at 80 °C for 40 h, then the reaction mixture was cooled to room temperature. The reaction mixture was added to 30 mL of $CHCl_3$ 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 51.8 mg (0.143 mmol) of **11**; 69% yield; a colorless solid; mp 154–155 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, tt, ^3J = 7.2 Hz, ^4J = 1.2 Hz, Ph), 7.34–7.46 (6H, m), 7.50–7.54 (4H, m), 7.62–7.67 (4H, m), 7.72 (1H, s), 7.77–7.80 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 119.4 (CH), 124.8 (CH), 126.1 (CH), 126.6 (CH x 2), 127.6 (CH), 128.2 (CH), 128.4 (CH), 128.5 (CH x 2), 128.8 (CH x 2), 128.9 (CH x 2), 129.0 (CH x 2), 129.3 (CH x 2), 134.4, 135.8, 137.0, 139.4, 139.7, 140.7, 141.1, 144.7. Found: *m*/*z* 362.1124. Calcd for $C_{26}H_{18}S$: M^+, 362.1124.

Preparation of 2,4,7-Tris[2-(triisopropylsilyl)ethynyl]benzo[*b*]thiophene (12). To a mixture of **4b** (88.1 mg, 0.238 mmol), and $PdCl_2(PPh_3)_2$ (3.3 mg, 0.00470 mmol), and CuI (0.5 mg, 0.0026 mmol) in diethyllamine (4 mL) was added ethynyltriisopropylsilane (0.2 mL, 0.892 mmol). The reaction mixture was stirred at 70 °C for 13 h. To the mixture were added hexane and water. The organic phase was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane) to give 99.5 mg (0.147 mmol) of **12**; 62% yield; a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14–1.18 (63H, br, *i*-Pr$_3$Si), 7.39 (1H, d, ^3J = 7.6 Hz), 7.42 (1H, d, ^3J = 7.6 Hz), 7.65 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 11.5 (*C*HMe$_2$), 11.6 (*C*HMe$_2$), 18.8 (Me), 18.9 (Me), 97.2 (C≡C), 98.4 (C≡C), 99.4 (C≡C), 99.8 (C≡C), 103.9 (C≡C), 104.7 (C≡C), 117.7(*C*-C≡C), 118.6 (*C*-C≡C), 125.1 (*C*-C≡C), 128.5 (CH), 128.7 (CH), 129.7 (CH), 140.3, 143.1. Found: *m*/*z* 697.4085. Calcd for $C_{41}H_{66}NaSSi_3$: $(M+Na)^+$, 697.4085.

Reaction of 4b with 1 Equivalent of *n*-BuLi. To a solution of **4b** (84.3 mg, 0.227 mmol) in THF (8 mL) was added 0.227 mmol of butyllithium (1.62 M solution in hexane, 0.14 mL) at –78 °C under N_2. The reaction mixture was stirred at –78 °C for 1 h and quenched with 0.1 mL of MeOH. The resulting solution was allowed to warm to room temperature and worked up with water and EtOAc. The organic phase was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (hexane) to give 49.9 mg (0.171 mmol, 75% yield) of **4a** and 10.9 mg (13% recovery) of the starting **4b**.

Suzuki-Miyaura Coupling of 4b with *ca.* 1 Equivalent of PhBpin. A mixture of **4b** (71.9 mg, 0.194 mmol), PhBpin (34.0 mg, 0.167 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (4.8 mg, 0.00588 mmol), K_2CO_3 (69.1 mg, 0.500 mmol), 1,4-dioxane (10 mL), and water (1 mL) were stirred under nitrogen atmosphere at 80 °C for 16 h, then the reaction mixture was cooled to room temperature. To the mixture was added $CHCl_3$ (*ca.* 30 mL) at room temperature. The reaction mixture was stirred for a few minutes and dried over Na_2SO_4. After filtration of Na_2SO_4, the solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (hexane) to give 27.6 mg (0.0750 mmol) of **4d** (45% yield based on PhBpin) and 23.3 mg of the starting **4b** (32% recovery).

Sonogashira Coupling of 4b with 1 Equivalent of Ethynyltriisopropylsilane. To a mixture of **4b** (78.2 mg, 0.211 mmol), $PdCl_2(PPh_3)_2$ (1.5 mg, 0.00214 mmol), and CuI (0.4 mg, 0.0021 mmol) in diethylamine (3.5 mL) was added ethynyltriisopropylsilane (47 μL, 0.210 mmol). The reaction mixture was stirred at 70 °C for 29 h. To the mixture were added hexane and water. The organic phase was separated, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane) to give **4j** as a major product (52.8 mg, 0.112 mmol, 53% yield) and 18.8 mg (24% recovery) of the starting **4b**.

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REFERENCES

1. (a) K. Takimiya, I. Osaka, T. Mori, and M. Nakano, *Acc. Chem. Res.*, 2014, **47**, 1493; (b) L. Ye, S. Zhang, L. Huo, M. Zhang, and J. Hou, *Acc. Chem. Res.*, 2014, **47**, 1595.
2. (a) Y. Kawamoto, M. Tomino, K. Hiramatsu, Y. Oyama, and Y. Hayashi, *Bioorg. Med. Chem. Lett.*, 2019, **29**, 1419; (b) R. S. Keri, K. Chand, S. Budagumpi, S. B. Somappa, S. A. Patil, and B. M. Nagaraja, *Eur. J. Med. Chem.*, 2017, **138**, 1002; (c) N. Fukuda and T. Ikemoto, *Synthesis*, 2015, **47**, 3467; (d) M. Setoh, N. Ishii, M. Kono, Y. Miyanohana, E. Shiraishi, T. Harasawa, H. Ota, T. Odani, N. Kanzaki, K. Aoyama, T. Hamada, and M. Kori, *J. Med. Chem.*, 2014, **57**, 5226.
3. T. Yamamoto, H. Katsuta, K. Toyota, T. Iwamoto, and N. Morita, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 613.
4. S. Mikami, H. Tanaka, H. Kishi, S. Yoshida, and K. Toyota, *Heterocycles*, 2018, **96**, 1529.
5. K. Toyota, H. Mutoh, H. Kishi, S. Mikami, H. Tanaka, S. Yoshida, and D. Naganuma, *Heterocycles*, 2019, **98**, 1355.

6. N. B. Desai, N. McKelvie, and F. Ramirez, *J. Am. Chem. Soc*., 1962, **84**, 1745.
7. (a) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett*., 1972, **13**, 3769; (b) D. Habrant, V. Rauhala, and A. M. P. Koskinen, *Chem. Soc. Rev*., 2010, **39**, 2007.
8. M. Zhao, C. Kuang, Q. Yang, and X. Cheng, *Tetrahedron Lett*., 2011, **52**, 992.
9. V. Ratovelomanana, Y. Rollin, C. Gébéhenne, C. Gosmini, and J. Périchon, *Tetrahedron Lett*., 1994, **35**, 4777.
10. (a) A. K. Morri, Y. Thummala, and V. R. Doddi, *Org. Lett*., 2015, **17**, 4640; (b) S. K. Moodapelly, G. V. M. Sharma, and V. R. Doddi, *Adv. Synth. Catal*., 2017, **359**, 1535.
11. P. Michel, D. Gennet, and A. Rassat, *Tetrahedron Lett*., 1999, **40**, 8575.