SILICA GEL-ASSISTED PREPARATION OF (BROMO)(CHLORO)(IODO)BENZO[b]THIOPHENES BEARING HALOGEN ATOMS AT THE 2-, 4-, AND 7-POSITIONS

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Abstract – Six types of (bromo)(chloro)(iodo)benzo[b]thiophenes bearing halogen atoms at the 2-, 4-, and 7-positions were prepared from the corresponding 2-(1-adamantylsulfanyl)-1,4-dihalo-3-(haloethynyl)benzene derivatives, by treatment with silica gel under thermal conditions. 4,7-Dihalobenzo[b]thiophenes, bearing two different halogen atoms (chlorine, bromine, or iodine), were also prepared from 2-(1-adamantylsulfanyl)-3-(ethynyl)-1,4-dihalobenzene derivatives.

INTRODUCTION

Benzo[b]thiophenes are currently of interest as useful building blocks. Utilization and functionalization of benzo[b]thiophene derivatives have been extensively explored in the fields of synthetic chemistry, medicinal chemistry, as well as materials science, because they provide many valuable compounds in these fields. Consequently, several synthetic methods have been developed as shown in Scheme 1.

Scheme 1. Some typical synthetic methods of benzo[b]thiophene derivatives
Various benzo[b]thiophene derivatives have been synthesized by cyclodehydration (Scheme 1, methods A–C)\(^{4a,b}\) as well as some specific methods.\(^{4c-g}\) More recently, many 3-substituted benzo[b]thiophenes have been prepared from 1-alkynyl-2-sulfanylbenzene derivatives (method D), by utilization of suitable reagents such as halogen reagents,\(^5\) Lewis acidic transition metal catalysts,\(^6\) or sulfur reagents.\(^{5a,7}\)

2-Substituted benzo[b]thiophenes have been prepared also from 1-alkynyl-2-sulfanylbenzene derivatives\(^8\) (method D) as well as from 1-alkenyl-2-sulfanylbenzene derivatives (method E).\(^9\)

In the course of our research in development of ring-fused thiophene building blocks,\(^10\) we have reported a preparation of 4,7-dihalobenzo[b]thiophenes from (ethynyl)(t-butylsulfanyl)benzene derivative (Scheme 2)\(^{10b}\) as follows: 3,6-Dibromo-2-fluorobenzaldehyde (1a) was converted to the corresponding t-butylsulfanylbenzaldehyde 2 by using t-butyl mercaptan (2-methyl-2-propanethiol) sodium salt. Compound 2 reacted with Ohira-Bestmann reagent \([\text{PhCOC(=N}2\text{)}\text{P(O)(OMe)}2\text{]}\) to give 3, which was cyclized by addition of AuCl catalyst to give 4,7-dibromobenzo[b]thiophene (4a). Lithiation of 4a with lithium \(N,N\)-diisopropylamide (LDA) followed by treatment with iodomethane gave 5a (Chart 1, \(X = Y = \text{Br}, Z = \text{Me}\)), while lithiation of 4a with butyllithium followed by treatment with 1,2-diiodoethane afforded 4c (\(X = \text{Br}, Y = \text{I}\)).

$$\text{RC(=N}2\text{)}\text{R'}: \text{Ohira-Bestmann reagent, PhCOC(=N}2\text{)}\text{P(O)(OMe)}2\text{]}$$

**Scheme 2.** Previously reported preparation of 4,7-dibromobenzo[b]thiophene

**Chart 1.** Structures of compounds 1, 4, and 5
The compound 4c bearing different halogen atoms is expected to possess several reaction site of different reactivity, which makes 4c a promising regioselective building block: Dihalo- or trihalo-aromatic compounds, whose halogen atoms are different each other, are potentially regioselective building blocks, taking the difference in reactivity in cross coupling reactions into account. During our continuing effort of preparation of various 4,7-dihalobenzothiophenes, we fortunately found efficient and practical preparative methods of 4,7-dihalobenzo[b]thiophenes and 2,4,7-trihalobenzo[b]thiophenes. We report here preparation of trihalobenzo[b]thiophenes 5b–g (Chart 1, where X ≠ Y ≠ Z) bearing different halogen atoms at the 2-, 4-, and 7-positions, which may work as ‘quasi T-shape’ scaffolds regarding to the directions of the carbon–halogen bonds. We also describe preparation of 4,7-dihalobenzo[b]thiophenes 4b–g (where X ≠ Y). In both cases, silica gel was effectively utilized for preparations under thermal conditions.

RESULTS AND DISCUSSION
Preparation of 2,4,7-trihalobenzo[b]thiophenes
In the present study, we sought some improvements in our preparation of multihalo-benzothiophenes. In the first place, we utilized 1-adamantanethiol instead of t-butyld mercaptan. 1-Adamantanethiol is a solid at room temperature and has only slight and gentle perfume. Thus, handling of 1-adamantanethiol is much easier, compared to a liquid and bad smelling t-butyld mercaptan: an introduction of adamantylsulfanyl group into 1b–g\textsuperscript{11} was performed with its sodium salt to give 6b–g in moderate to excellent yields (64–96%) (Scheme 3, Table 1).

![Scheme 3. Preparations of 4,7-dihalobenzo[b]thiophenes and 2,4,7-trihalobenzo[b]thiophenes](image-url)
Table 1. Summary of the yield (%) of the products 4–13

<table>
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<tr>
<th>compound</th>
<th>( (X \quad Y) )</th>
<th>6</th>
<th>7</th>
<th>8 (^{bc} )</th>
<th>9 (^{bc} )</th>
<th>4</th>
<th>( (X \quad Y \quad Z) )</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>5</th>
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<td>87</td>
<td>90</td>
<td>98(^d )</td>
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<td>89</td>
<td>Br Cl I</td>
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<td>–</td>
<td>71</td>
<td>95</td>
<td>75(^e )</td>
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<tr>
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<td>64</td>
<td>86</td>
<td>–</td>
<td>77</td>
<td>98</td>
<td>Br I Cl</td>
<td>((67)^{fg})</td>
<td>((90)^{g})</td>
<td>–</td>
<td>–</td>
<td>89(^h )</td>
</tr>
<tr>
<td>d</td>
<td>Cl Br</td>
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<td>93</td>
<td>–</td>
<td>87</td>
<td>97</td>
<td>Cl Br I</td>
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<tr>
<td>e</td>
<td>Cl I</td>
<td>89</td>
<td>86</td>
<td>91(^i )</td>
<td>96</td>
<td>66</td>
<td>Cl I Br</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>90(^b )</td>
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<td>84</td>
<td>92</td>
<td>93(^j )</td>
<td>79(^b )</td>
<td>I Cl Br</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>74(^b )</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>I Br</td>
<td>96</td>
<td>93</td>
<td>–</td>
<td>99</td>
<td>93</td>
<td>I Br Cl</td>
<td>((67)^{fg})</td>
<td>((99)^{g})</td>
<td>–</td>
<td>–</td>
<td>80(^h )</td>
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<td>–</td>
<td>Br Cl Br</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>69(^j )</td>
</tr>
</tbody>
</table>

\(^{a}\)Isolated yield, unless otherwise specified. \(^{b}\)Yield based on 7. \(^{c}\)Reaction in acetone-H₂O (intermediate 8 was not isolated). \(^{d}\)Reaction in THF-H₂O. \(^{e}\)Yield based on 13. \(^{f}\)Data obtained in Scheme 4, method B. \(^{g}\)Approximate yield due to difficulty in separation of 10 and 15; determined by \(^{1}\)H NMR. \(^{h}\)Yield based on 11. \(^{i}\)Reaction in 1,4-dioxane-H₂O. \(^{j}\)Yield based on 8b.

In the second place, we investigated a modified Corey-Fuchs alkynation of the aldehydes 6, instead of Ohira-Bestmann type alkynation. In our previous preparation of 4a,\(^{10b}\) the alkyne 3 was introduced by the reaction of the aldehyde 2 with Ohira-Bestmann reagent, which has a reactive diazo group in the molecule, demanding a careful handling in experiments. In the present study, we sought safe and easy-handling preparation of alkynes from aldehydes via the corresponding dibromoethenyl derivatives 7.

Thus, the aldehydes 6b–g were treated with carbon tetrabromide and triphenylphosphine to give the corresponding dibromoalkenes 7b–g (86–93%).

We then tried to prepare terminal alkynes by reaction of 7 with a base, by a method reported by Zhao et al.\(^{12}\) When 7b was treated with Cs₂CO₃ in DMSO at 115 °C for 20 min under N₂, we obtained a corresponding terminal alkyne 9b (31% yield), 2-bromobenzo[b]thiophene derivative 5h (34%), and a trace amount of bromoalkyne 8b (1%), after silica gel column chromatography (Kanto Chemical Co. Ltd., spherical silica gel 60N, neutral; eluent: hexane-CHCl₃ 95:5 to 83:17). At this stage, we recognized that 5h was formed during the silica gel column chromatographic treatment, because \(^{1}\)H NMR spectrum of the crude product before column chromatography showed signals only due to 8b and 9b (about 1:2 ratio); signals due to 5h were not detected before the column chromatography. We were interested in this easy formation of 5h losing the adamantyl group. In many reported synthetic methods of benzo[b]thiophenes, a metal catalyst or iodine is needed for this kind of cyclization of o-(alkynyl)(sulfanyl)benzene derivatives, to give 3-substituted benzo[b]thiophenes.\(^{5,6}\) In our case, formation of 3-adamantylbenzo[b]thiophene was not observed. Thus we examined the reaction conditions in detail.

For the purpose of investigation of the reaction conditions, we tried to prepare the alkynes 8 and 9 in better yields and this was done by tuning the bases, solvents, and reaction time as follows:\(^{13}\) When the dibromoalkene 7b was reacted with aqueous KOH solution in acetone at room temperature for 3 h in air,
the terminal alkyne 9b was obtained in 86% yield (Table 1). On the other hand, when 7b was reacted with aqueous KOH solution in THF at room temperature for 40 h, 8b was obtained nearly quantitatively. It should be mentioned that information of 1-(haloethynyl)-2-(sulfanyl)benzene derivatives has been limited until recently.5g,6f,9h,14

When 8b thus formed was stirred with silica gel in toluene at room temperature for 16 h, formation of 5h was confirmed by 1H NMR and 5h was obtained in 17% yield after basic alumina column chromatography (hexane-CHCl3 4:1). A significant acceleration occurred, when 8b was heated with silica gel in toluene at 90 °C for 16 h, to give 5h in 69% yield (Table 1). In the absence of silica gel in toluene at 90 °C for 16 h, most of 8b remained unchanged (checked by 1H NMR spectroscopy) and only a small amount of a complex mixture including 5h was obtained after column chromatography.

Probably, silica gel as an acid activates the triple bond under thermal conditions (Figure 1, A, B; hydrogen bondings among the Si-OH groups and incorporated H2O are omitted in the drawing) to form sulphonium ion intermediate (C), and then contact ion pair (D).6c At the same time, the proximate Si-OH or water acts as a trapping reagent of the adamantyl portion, preventing rearrangement of the substituents into the 2- or 3-positions. Actually, in some cases, a small amount of 1-adamantanol was obtained by eluting the silica gel with MeOH after reaction.

![Figure 1. Plausible reaction mechanism](image)

Analogous results were obtained with silica gel of other supplier (Merck 1.07734, silica gel 60; 76% yield, or Sigma-Aldrich 288594, silica gel 60 Å; 71% yield), and with alumina (Merck 1.01076, aluminium oxide 90 active basic; ca. 10% conversion by 1H NMR at room temperature for 16 h). When the silica gel was pre-washed with MeOH and dried to remove inorganic salts, 5h was obtained in 68% yield under similar conditions, suggesting that silica gel itself catalyzed the cyclization as an acid. However, we do not exclude the possibility that trace amount of salts or metals in silica gel causes the cyclization, because complete removal of salt or metal impurities from silica gel is generally very difficult.

We then tried to prepare benzo[h]thiophehnes 5b–g bearing three different halogen atoms at the 2-, 4,
and 7-positions, by this method (Chart 1, X ≠ Y ≠ Z). 2-Bromo-4,7-dihalobenzo[b]thiophenes 5e,f were obtained in good yields from the corresponding (2,2-dibromoethenyl)benzene derivatives 7e,f, by treatment of the intermediates 8e,f with silica gel under thermal conditions (Scheme 3): 5e, 90% yield based on 7e (2 steps); 5f, 74% based on 7f (2 steps).

2-Chloro-4,7-dihalobenzo[b]thiophene 5g was obtained as follows: Dichloroalkene 10g (Scheme 4) was prepared by reaction of 6g with CCl4 (or CBrCl3)15 and PPh3. In the reaction of 6g with CCl4 and PPh3, a small amount (ca. 5%) of (E)-(2-chloroethenyl)benzene 14g (Chart 2) was obtained as a by-product, which was not fully removed either by column chromatography or recrystallization.

In the case of reaction of 6g with CBrCl3 and PPh3, a significant amount of (2-bromo-2-chloroethenyl)benzene 15g was formed as a by-product (ca. 21% yield by 1H NMR, as (E)- and (Z)-mixture), besides the desired 10g (ca. 67% yield by 1H NMR).

Scheme 4. Reagents and conditions: i, method A, CCl4, PPh3, reflux, 43 h (Z = Cl), method B, CBrCl3, PPh3, MeCN, 50 °C, 20 h (Z = Cl), method C, (EtO)2P(O)CH2I, I2, (Me3Si)2NLi, THF, −78 °C, 0.5 h, then rt, 3 h (Z = I); ii, t-BuOK, THF, −78 °C, 0.5 h (Z = I) or 1.5 h (Z = Cl); iii, silica gel, toluene, 90 °C, 19 h (Z = I) or 20 h (Z = Cl)

However, to our delight, when the crude mixture of 10g, (E)-15g, and (Z)-15g were reacted with KOH, only (chloroethenyl)benzene derivative 11g was formed as a product and the corresponding (bromoethenyl)benzene derivative was not detected by 1H NMR. It should be mentioned that an attempted isolation of 11g by column chromatography failed, because partial isomerization to 5g occurred.
during the chromatographic treatment, even with alumina. This facile isomerization of \textit{11g} favors the preparation of \textit{5g}. By heating \textit{11g} (generated by the latter method) with silica gel in toluene at 90 °C for 20 h followed by silica gel column chromatography, \textit{5g} was obtained in pure form (80% yield based on \textit{11g}). Similar results were obtained in the preparation of \textit{5c} (89% yield based on \textit{11c}).

2-Iodo-4,7-dihalobenzo[\textit{b}]thiophenes \textit{5b,d} were obtained as follows: Diiodoalkenes \textit{12b,d} were prepared from \textit{6b,d} in pure form (71% and 70% yield, respectively) by using (EtO)\textsubscript{2}P(O)CH\textsubscript{2}I, Tms\textsubscript{2}NLi, and I\textsubscript{2}.\textsuperscript{16} Compounds \textit{5b,d} were then obtained by analogous method from \textit{12b,d} via \textit{13b,d} (Table 1). It should be noted that compounds \textit{5b,d} could also be obtained by lithiation of \textit{4b,d} followed by iodination (see below).

**Preparation of 4,7-dihalobenzo[\textit{b}]thiophenes**

Next, we studied a cyclization reaction of \textit{9b–g} for preparation of 4,7-dihalobenzo[\textit{b}]thiophenes \textit{4b–g}, bearing different halogen atoms at the 4- and 7-positions (Scheme 3, where \(X \neq Y\)). A preliminary examination suggested that cyclization of the terminal alkynes \textit{9b–g} did not proceed so smoothly at room temperature, as that of haloalkynes \textit{8, 11}, or \textit{13}. Thus, we sought suitable reaction conditions using \textit{9g} as a probe (Table 2). Highly polar solvents did not give good results (entries 1–4, 9). Chloroform as well as some hydrophobic solvents such as benzene and toluene gave better yield at 60 °C (entries 5–7). Hexane (60 °C) and toluene (90 °C) afforded \textit{4g} nearly quantitatively (entries 8, 10). The reaction is

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp./°C</th>
<th>Conv./%b</th>
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<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>n.d.</td>
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</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CHCl\textsubscript{3}</td>
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</tr>
<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>toluene</td>
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</tr>
<tr>
<td>8</td>
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</tr>
<tr>
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</tr>
<tr>
<td>10</td>
<td>toluene</td>
<td>&gt; 99</td>
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</tr>
<tr>
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<td>toluene</td>
<td>22</td>
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</tr>
<tr>
<td>12</td>
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<td>rt</td>
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</tr>
<tr>
<td>13\textsuperscript{d}</td>
<td>toluene</td>
<td>110</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\textsuperscript{a} \textit{9g} (0.021 mmol), silica gel (1 g), solv. (5 mL), 15 h in air. \textsuperscript{b} Determined by \textsuperscript{1}H NMR; n.d. = not detected. \textsuperscript{c} Silica gel (26 mg) was used. \textsuperscript{d} Without silica gel.
very slow at room temperature (entry 12). With less amount of silica gel, the reaction proceeds insufficiently (entry 11), while the reaction did not proceed without silica gel even at 110 °C (entry 13). Taking the above results into account, compounds 4b–f were also obtained in 66–98% isolated yields (Table 1) by analogous reaction conditions of 4g (Table 2, entry 10). It should be mentioned that preparations of 2,3-unsubstituted benzo[b]thiophenes from (alkynyl)(sulfanyl)benzenes are rarely reported except for those from trialkylsilyl-protected (ethynyl)(sulfanyl)benzenes followed by desilylation or desilylation-deiodination process.

As mentioned above, compounds 4 can be converted into the corresponding 2-substituted compounds 5 by alternative methods. For example, lithiation of 4b,d with LDA followed by treatment with 1,2-diiodoethane afforded 5b,d in 97% and 95% yields, respectively.

In summary, we have prepared all possible (bromo)(chloro)(iodo) benzo[b]thiophenes bearing halogen atoms at the 2-, 4-, and 7-positions, from the corresponding 1-(1-adamantylsulfanyl)-2-(haloethynyl)-benzene derivatives, by a practical and rather safe method using silica gel under thermal conditions. 4,7-Dihalobenzo[b]thiophene derivatives, whose halogen atoms are different each other (either chlorine, bromine, or iodine), were also prepared from 1-(1-adamantylsulfanyl)-2-(ethynyl)benzene derivatives. The trihalobenzo[b]thiophenes obtained in this paper are promising scaffolds for regioselective introduction of different substituents by cross coupling reaction. Further investigation concerning their reactivities and applications are currently in progress.

EXPERIMENTAL

Melting points were measured on a Yanagimoto MP-J3 micro melting point apparatus and are not corrected. 1H (400 MHz) and 13C (100 MHz) NMR spectra were recorded on a Bruker Avance III-400 spectrometer. MS spectra were taken on a Bruker solariX spectrometer or a JEOL JMS-T spectrometer. Elemental analyses were performed at Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University. Silica gel (either Kanto Chemical spherical silica gel 60N, Merck 1.07734, silica gel 60, or Sigma-Aldrich 288594, silica gel 60 Å) and alumina (Merck 1.01076; aluminium oxide 90 active basic) were purchased and used as it is, unless otherwise specified. Compounds 1b–d,g have been known and were prepared by a standard method.

Typical Procedure for the Preparation of Products 1e,f. 6-Chloro-2-fluoro-3-iodobenzaldehyde (1e). 4-Chloro-2-fluoro-1-iodobenzene (5.0127 g, 19.55 mmol) in THF (35 mL) was cooled to –63 °C with a dry ice-CHCl3 bath under nitrogen atmosphere. LDA (23.1 mmol; 1.10 M solution in hexane-THF) was slowly added to the solution and the reaction mixture was stirred at –63 °C for 1 h. DMF (2.3 mL, 29.89 mmol) was slowly added to the reaction mixture and the mixture was stirred at
−63 °C for 1.5 h, warmed to room temperature. The mixture was slowly poured into 50 mL of 4 M hydrochloric acid at 0 °C with stirring. The resulting mixture was extracted with hexane-EtOAc (1:1). The organic phase was separated, dried over MgSO₄, and the solvent was removed under reduced pressure. Recrystallization of the crude product from hexane followed by silica gel column chromatographic treatment (hexane-CHCl₃ 80:20 to 50:50) afforded 1e (4.5746 g, 16.08 mmol) in 82% yield; a pale yellow solid; mp 115–116 °C; ¹H NMR (CDCl₃) δ 7.08 (1H, dd, ¾J = 8.4 Hz, ¼J = 1.4 Hz), 7.87 (1H, dd, ¾J = 8.4 Hz, ¼JFH = 6.2 Hz), 10.4 (1H, d, J = 1.2 Hz, CHO); ¹³C{¹H} NMR (CDCl₃) δ 81.0 (d, ¾JFC = 26.0 Hz), 122.2 (d, ¾JFC = 12.4 Hz), 128.2 (d, ¾JFC = 4.9 Hz), 137.2 (d, ¾JFC = 2.5 Hz), 143.9 (d, ¾JFC = 3.7 Hz), 162.1 (d, ¾JFC = 260.9 Hz), 186.0 (s, CHO). Found: m/z 284.8974. Calcd for C₇H₄Cl₅FIO: (M+H)+, 284.8974.

3-Chloro-2-fluoro-6-iodobenzaldehyde (1f): 83% yield from 1-chloro-2-fluoro-4-iodobenzene; a colorless solid; mp 61–63 °C; ¹H NMR (CDCl₃) δ 7.30 (1H, dd, ¾J = 8.6 Hz, ¼JFH = 7.4 Hz), 7.75 (1H, dd, ¾J = 8.6 Hz, ¼JFH = 1.8 Hz), 10.1 (1H, d, ¾J = 0.4 Hz, CHO); ¹³C{¹H} NMR (CDCl₃) δ 94.0 (s, C-I), 123.4 (d, ¾JFC = 18.5 Hz), 125.3 (d, ¾JFC = 8.7 Hz), 135.9 (s), 137.2 (d, ¾JFC = 5.0 Hz), 158.7 (d, ¾JFC = 265.8 Hz), 189.7 (d, ¾JFC = 3.7 Hz, CHO). Found: m/z 284.8974. Calcd for C₇H₄Cl₅FIO: (M+H)+, 284.8974.

Typical Procedure for the Preparation of Products 6b–g. 2-(1-Adamantylsulfanyl)-6-bromo-3-chlorobenzaldehyde (6b). NaH (0.3687 g, ca. 60% in mineral oil, ca. 9.2 mmol) was washed with hexane under nitrogen atmosphere. 1-Adamantanethiol (1.5670 g, 9.218 mmol) in DMF (15 mL) was slowly added to the NaH at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. After cooling the mixture to −40 °C, 1b (1.9756 g, 8.320 mmol) in THF (8 mL) was added and the resulting mixture was stirred at −40 °C for 6 h then warmed to room temperature. The solution was poured into a saturated aqueous NaCl solution (brine), then worked up with a hexane-AcOEt (4:1) solution. The organic phase was separated, dried over Na₂SO₄, and the solvent was removed under reduced pressure. Silica gel column chromatographic treatment of the residue (hexane-CHCl₃ 7:3) afforded 6b (2.7929 g, 7.240 mmol, 87% yield); a pale yellow solid; mp 97–99 °C; ¹H NMR (CDCl₃) δ 1.25–1.66 (6H, m, Ad), 1.86–1.87 (6H, m, Ad), 2.02 (3H, s, Ad), 7.51 (1H, d, ¾J = 8.8 Hz), 7.63 (1H, d, ¾J = 8.8 Hz), 10.46 (1H, s, CHO); ¹³C{¹H} NMR (CDCl₃) δ 30.3 (Ad), 35.9 (Ad), 44.1 (Ad), 54.9 (Ad), 118.8 (C-Br), 133.2, 133.8, 135.9, 142.7, 143.2, 192.2 (CHO). Found: m/z 406.9842. Calcd for C₁₇H₁₈BrCl₃NaOS: (M+Na)+, 406.9843. Anal. Calcd for C₁₇H₁₈BrCl₃OS: C, 52.93; H, 4.70; Br, 20.71; Cl, 9.19; S, 8.31%. Found: C, 52.83; H, 4.73; Br, 20.78; Cl, 9.15; S, 8.23%.

2-(1-Adamantylsulfanyl)-6-bromo-3-iodobenzaldehyde (6c): Reaction with AdSnNa at −40 °C; 64% yield; a pale yellow solid; mp 148–150 °C; ¹H NMR (CDCl₃) δ 1.58–1.66 (6H, m, Ad), 1.88 (6H, br s, Ad), 2.02 (3H, s, Ad), 7.39 (1H, dd, ¾J = 8.4 Hz and ¾J = 0.8 Hz), 7.98 (1H, d, ¾J = 8.4 Hz), 10.32 (1H, d,
\( J = 0.8 \) Hz, (CHO); \(^{13}\)C\(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 30.6 (Ad), 36.0 (Ad), 44.4 (Ad), 55.9 (Ad), 115.1 (C-1), 121.3 (C-Br), 136.4, 140.3, 142.7, 143.2, 192.9 (CHO). Found: \( m/z \) 498.9199. Calcd for C\(_{17}\)H\(_{18}\)Br\(_{18}\)I\(_{18}\)Na\(_{18}\)OS: (M+Na\(^{+}\)), 498.9204. Anal. Calcd for C\(_{17}\)H\(_{18}\)Br\(_{18}\)I\(_{18}\)OS: C, 42.79; H, 3.80; Br, 16.74; I, 26.59; S, 6.72%. Found: C, 42.86; H, 3.76; Br, 16.93; I, 26.68; S, 6.66%.

2-(1-Adamantylsulfanyl)-3-bromo-6-chlorobenzaldehyde (6d): Reaction with AdSNa at –78 °C; 91% yield; a yellow-green solid; mp 108–109 °C; \(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 1.62 (6H, m, Ad), 1.88 (6H, m, Ad), 2.03 (3H, m, Ad), 7.35 (1H, m), 7.79 (1H, d, \( ^{3}J = 8.8 \) Hz), 10.5 (1H, s, CHO); \(^{13}\)C\(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 30.2 (Ad), 35.7 (Ad), 44.0 (Ad), 56.8 (Ad), 131.9, 132.8 (CH), 133.7, 135.8, 136.3 (CH), 141.5, 191.7 (CHO). Found: \( m/z \) 406.9842. Calcd for C\(_{17}\)H\(_{18}\)Br\(_{18}\)I\(_{18}\)Na\(_{18}\)OS: (M+Na\(^{+}\)), 406.9843.

2-(1-Adamantylsulfanyl)-6-chloro-3-iodobenzaldehyde (6e): Reaction with AdSNa at –63 °C; 89% yield; a colorless solid; mp 150–153 °C; \(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 1.62 (6H, m, Ad), 1.88 (6H, m, Ad), 2.02 (3H, s, Ad), 7.20 (1H, d, \( ^{3}J = 8.3 \) Hz, \( ^{5}J = 0.5 \) Hz), 8.07 (1H, d, \( ^{3}J = 8.3 \) Hz), 10.42 (1H, d, \( ^{5}J = 0.5 \) Hz, CHO); \(^{13}\)C\(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 30.6 (Ad), 36.0 (Ad), 44.4 (Ad), 56.8 (Ad), 114.0 (C-I), 133.2, 133.6, 140.3, 141.1, 143.1, 192.4 (CHO). Found: \( m/z \) 432.9884. Calcd for C\(_{17}\)H\(_{19}\)Br\(_{19}\)I\(_{19}\)OS: (M+H\(^{+}\)), 432.9884.

2-(1-Adamantylsulfanyl)-3-chloro-6-iodobenzaldehyde (6f): Reaction with AdSNa at –63 °C; 84% yield; a pale yellow solid; mp 124–126 °C; \(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 1.62 (6H, m, Ad), 1.85 (6H, m, Ad), 2.02 (3H, s, Ad), 7.35 (1H, d, \( ^{3}J = 8.6 \) Hz), 7.95 (1H, d, \( ^{3}J = 8.6 \) Hz, \( ^{5}J = 0.8 \) Hz), 10.36 (1H, d, \( ^{5}J = 0.6 \) Hz, CHO); \(^{13}\)C\(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 30.5 (Ad), 36.0 (Ad), 44.1 (Ad), 54.9 (Ad), 90.5 (C-I), 133.8, 134.2, 143.0, 144.1, 145.2, 193.4 (CHO). Found: \( m/z \) 432.9884. Calcd for C\(_{17}\)H\(_{19}\)Br\(_{19}\)I\(_{19}\)OS: (M+H\(^{+}\)), 432.9884.

2-(1-Adamantylsulfanyl)-3-bromo-6-iodobenzaldehyde (6g): Reaction with AdSNa at –15 °C; 96% yield; a pale yellow solid; mp 89–91 °C; \(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 1.62 (6H, m, Ad), 1.86 (6H, m, Ad), 2.02 (3H, s, Ad), 7.53 (1H, d, \( ^{3}J = 8.4 \) Hz), 7.86 (1H, dd, \( ^{3}J = 8.4 \) Hz and \( ^{5}J = 0.4 \) Hz), 10.31 (1H, d, \( ^{5}J = 0.4 \) Hz, CHO); \(^{13}\)C\(^{1}H\) NMR (CDCl\(_3\)) \( \delta \) 30.5 (Ad), 36.0 (Ad), 44.2 (Ad), 55.2 (Ad), 77.4 (C-I), 91.5 (C-Br), 136.4, 137.1, 143.2, 145.4, 193.5 (CHO). Found: \( m/z \) 498.9198. Calcd for C\(_{17}\)H\(_{18}\)Br\(_{18}\)I\(_{18}\)OS: (M+Na\(^{+}\)), 498.9204. Anal. Calcd for C\(_{17}\)H\(_{18}\)Br\(_{18}\)I\(_{18}\)OS: C, 42.79; H, 3.80; Br, 16.74; I, 26.59; S, 6.72%. Found: C, 42.87; H, 3.70; Br, 16.85; I, 26.34; S, 6.60%.

Typical Procedure for the Preparation of Products 7b–g. 2-(1-Adamantylsulfanyl)-4-bromo-1-chloro-3-(2,2-dibromoethenyl)benzene (7b). A solution of PPh\(_{3}\) (2.5328 g, 9.656 mmol) in CH\(_2\)Cl\(_2\) (11 mL) was slowly added to a mixture of 6b (1.5063 g, 3.905 mmol) and CBr\(_{4}\) (1.5610 g, 4.707 mmol) in CH\(_2\)Cl\(_2\) (9 mL) at 0 °C under nitrogen atmosphere. During stirring for 10 min at 0 °C, the color of the mixture changed yellow to brown. The mixture was stirred at room temperature for 2 h and 20 mL of water was added. The resulting mixture was extracted with CH\(_2\)Cl\(_2\), the organic phase was washed with brine, and dried over Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure, and the residue was
treated with silica gel column chromatography (hexane-CHCl₃ 4:1) to give 1.9056 g (3.519 mmol, 90% yield) of 7b; a colorless solid; mp 108–110 °C; ¹H NMR (CDCl₃) δ 1.65–1.66 (6H, m, Ad), 1.90–1.96 (6H, m, Ad), 2.03 (3H, s, Ad), 7.38 (1H, d, ³J = 8.4 Hz), 7.49 (1H, s, CH=CBr₂), 7.54 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.5 (Ad), 36.2 (Ad), 44.5 (Ad), 54.3 (Ad), 96.2 (CBr₂), 121.5 (C-Br), 130.8, 132.3, 134.4, 138.1, 142.6, 145.9; Found: m/z 560.8260. Calcd for C₁₈H₁₈Br₃ClNaS: (M+Na)⁺, 560.8260.

2-(1-Adamantylsulfanyl)-4-bromo-3-(2,2-dibromoethenyl)-1-iodobenzene (7c): 86% yield; a colorless solid; mp 137–138 °C; ¹H NMR (CDCl₃) δ = 1.66 (6H, s, Ad), 1.96–2.04 (9H, m, Ad), 7.26 (1H, dd, ³J = 8.8 Hz), 7.54 (1H, br s, CH=CBr₂), 7.83 (1H, d, ³J = 8.8 Hz); ¹³C{¹H} NMR (CDCl₃) 30.7 (Ad), 36.2 (Ad), 44.8 (Ad), 55.0 (Ad), 96.3, 114.3, 123.8, 134.8, 138.7, 139.1, 140.6, 144.5. Found: m/z 654.7596. Calcd for C₁₈H₁₈Br₂81BrINaS: (M+Na)⁺, 654.7595. Anal. Calcd for C₁₈H₁₈Br₃IS: C, 34.15; H, 2.87; Br, 38.11; I, 19.89; S, 5.05%.

2-(1-Adamantylsulfanyl)-1-bromo-4-chloro-3-(2,2-dibromoethenyl)benzene (7d): 93% yield; a colorless solid; mp 136–137 °C; ¹H NMR (CD₂Cl₂) δ 1.63–1.70 (6H, m, Ad), 1.96 (6H, m, Ad), 2.03 (3H, s, Ad), 7.30 (1H, d, ³J = 8.4 Hz), 7.58 (1H, s, CH=CBr₂), 7.68 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) 30.6 (Ad), 36.2 (Ad), 44.6 (Ad), 54.4 (Ad), 96.1 (C=CBr₂), 131.5, 132.9, 133.6, 133.8, 134.4, 136.5, 143.8. Found: m/z 560.8260. Calcd for C₁₈H₁₈Br₃ClNaS: (M+Na)⁺, 560.8260.

2-(1-Adamantylsulfanyl)-4-chloro-3-(2,2-dibromoethenyl)-1-iodobenzene (7e): 86% yield; a colorless solid; mp 152–153 °C; ¹H NMR (CDCl₃) δ 1.67 (6H, m, Ad), 1.99 (6H, m, Ad), 2.05 (3H, s, Ad), 7.10 (1H, d, ³J = 8.4 Hz), 7.58 (1H, s, CH=CBr₂), 7.92 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.7 (Ad), 36.2 (Ad), 44.8 (Ad), 54.9 (Ad), 96.2 (C-I), 113.3, 131.7, 134.2, 137.2, 138.6, 140.3, 142.6. Found: m/z 588.8280. Calcd for C₁₈H₁₉Br₈1Br₃5ClNaS: (M+H)⁺, 588.8280.

2-(1-Adamantylsulfanyl)-1-chloro-3-(2,2-dibromoethenyl)-4-iodobenzene (7f): 92% yield; a colorless solid; mp 130–132 °C; ¹H NMR (CDCl₃) δ 1.65 (6H, m, Ad), 1.92 (6H, m, Ad), 2.03 (3H, s, Ad), 7.22 (1H, d, ³J = 8.6 Hz), 7.48 (1H, s, CH=CBr₂), 7.78 (1H, d, ³J = 8.6 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.5 (Ad), 36.2 (Ad), 44.4 (Ad), 54.3 (Ad), 95.9, 96.7, 131.1, 131.6, 140.6, 141.7, 143.8, 149.7. Found: m/z 588.8280. Calcd for C₁₈H₁₉Br₈1Br₃5ClNaS: (M+H)⁺, 588.8280.

2-(1-Adamantylsulfanyl)-1-bromo-3-(2,2-dibromoethenyl)-4-iodobenzene (7g): 93% yield; a colorless solid; mp 142–144 °C; ¹H NMR (CDCl₃) δ 1.66 (6H, s, Ad), 1.90–2.03 (9H, m, Ad), 7.39 (1H, dd, ³J = 8.4 Hz, ⁵J = 0.4 Hz), 7.50 (1H, br s, CH=CBr₂), 7.68 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.5 (Ad), 36.1 (Ad), 44.5 (Ad), 54.4 (Ad), 96.7, 96.9, 133.6, 134.4, 135.8, 140.7, 141.9, 149.5. Found: m/z 654.7596. Calcd for C₁₈H₁₈Br₂81BrNaS: (M+Na)⁺, 654.7595. Anal. Calcd for C₁₉H₁₈Br₃IS:
Typical Procedure for the Preparation of Products 8b,e,f.  2-(1-Adamantylsulfanyl)-4-bromo-3-(2-bromoethynyl)-1-chlorobenzene (8b): A solution of KOH (1.3 g) in water (4.4 mL) was added to a solution of 7b (733.3 mg, 1.354 mmol) in THF (44 mL) and the resulting mixture was stirred at room temperature for 40 h in air. Brine was added to this mixture and the resulting mixture was extracted with AcOEt. The organic phase was separated, dried over Na₂SO₄, and the solvent was removed under reduced pressure. ¹H NMR spectroscopy of the residue (610.4 mg, 1.325 mmol) indicated nearly quantitative formation of 8b; 98% yield; a pale yellow solid; mp 100–103 °C; ¹H NMR (CDCl₃) δ 1.65–1.66 (6H, m, Ad), 1.98 (6H, m, Ad), 2.04 (3H, m, Ad), 7.32 (1H, d, ³J = 8.4 Hz), 7.50 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.5 (Ad), 36.2 (Ad), 44.4 (Ad), 54.9 (Ad), 60.7 (C≡C), 79.8 (C≡C), 125.0, 130.4, 133.7, 134.7, 135.5, 142.1. Found: m/z 480.89982. Calcd for C₁₈H₁₇Br₂ClNaS: (M+Na)+, 480.89985. Anal. Calcd for C₁₈H₁₇Br₂ClS: C, 46.93; H, 3.72; Br, 34.74; Cl, 7.70; S, 6.87%. Found: C, 47.07; H, 3.92; Br, 34.74; Cl, 7.51; S, 6.87%.

2-(1-Adamantylsulfanyl)-3-(2-bromoethynyl)-4-chloro-1-iodobenzene (8e): 91% yield after alumina column chromatography; a colorless solid; mp 145–148 °C; ¹H NMR (CDCl₃) δ 1.66 (6H, m, Ad), 2.04 (9H, m, Ad), 7.06 (1H, d, ³J = 8.8 Hz), 7.85 (1H, d, ³J = 8.8 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.7 (Ad), 36.2 (Ad), 44.7 (Ad), 55.8 (Ad), 61.0 (C=C), 78.7 (C≡C), 111.9 (C-I), 130.7, 130.8, 138.1, 139.7, 141.8. Found: m/z 508.9019. Calcd for C₁₈H₁₇Br₂ClI₅: (M+H)+, 508.9019.

2-(1-Adamantylsulfanyl)-3-(2-bromoethynyl)-1-chloro-4-iodobenzene (8f): 99% yield after alumina column chromatography; a colorless solid; mp 99–104 °C (decomp); ¹H NMR (CDCl₃) δ 1.65 (6H, m, Ad), 1.98 (6H, m, Ad), 2.03 (3H, s, Ad), 7.16 (1H, d, ³J = 8.4 Hz), 7.73 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.4 (Ad), 36.1 (Ad), 44.3 (Ad), 54.8 (Ad), 59.8 (C=C), 83.4 (C≡C), 99.3 (C-I), 130.6, 134.6, 138.8, 139.9, 143.1. Found: m/z 508.9019. Calcd for C₁₈H₁₇Br₂ClI₅: (M+H)+, 508.9019.

Typical Procedure for the Preparation of Products 9b–g. 2-(1-Adamantylsulfanyl)-4-bromo-1-chloro-3-(ethynyl)benzene (9b). A solution of KOH (7.7 g) in water (40 mL) was added to a solution of 7b (3.123 g, 5.767 mmol) in acetone (405 mL). The resulting mixture was vigorously stirred at room temperature for 3 h. Brine was added, and the reaction mixture was extracted with hexane-AcOEt (4:1). The organic phase was washed with brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was treated with silica gel column chromatography (hexane-CHCl₃ 4:1) to give 1.8917 g (4.955 mmol, 86% yield) of 9b; a pale yellow solid; mp 87–89 °C; ¹H NMR (CDCl₃) δ 1.64 (6H, s, Ad), 2.01 (9H, m, Ad), 3.67 (1H, s, C≡CH), 7.34 (1H, d, ³J = 8.4 Hz), 7.53 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.5 (Ad), 36.2 (Ad), 44.4 (Ad), 55.4 (Ad), 82.6 (C≡C), 87.5 (C=C), 125.1, 130.6, 133.8, 134.2, 135.3, 142.2. Found: m/z 402.9893. Calcd for
C_{18}H_{18}^{79}Br_{35}ClNaS: (M+Na)^{+}, 402.9893. Anal. Calcd for C_{18}H_{18}BrClS: C, 56.63; H, 4.75; Br, 20.93; Cl, 9.29; S, 8.40%. Found: C, 56.66; H, 4.75; Br, 21.01; Cl, 9.26; S, 8.40%.

2-(1-Adamantylsulfanyl)-4-bromo-3-(ethynyl)-1-iodobenzene (9c): 77% yield based on 7c; a pale yellow solid; mp 188–190 °C (decomp); ¹H NMR (CDCl₃) δ 1.65 (6H, s, Ad), 2.06 (9H, m, Ad), 3.63 (1H, s, C≡CH), 7.25 (1H, d, 3 J = 8.8 Hz), 7.80 (1H, d, 3 J = 8.8 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.6 (Ad), 56.3 (Ad), 83.5 (C≡CH), 87.0 (C≡CH), 113.0, 127.4, 132.4, 133.9, 140.2, 141.6. Found: m/z 494.9250. Calcd for C_{18}H_{18}^{79}BrINaS: (M+Na)^{+}, 494.9250. Anal. Calcd for C_{18}H_{18}BrIS: C, 45.69; H, 3.86; Br, 16.90; I, 140.1. Found: C, 45.65; H, 3.86; Br, 16.90; I, 140.1. Present: m/z 494.9249. Calcd for C_{18}H_{18}^{79}BrINaS: (M+Na)^{+}, 494.9250. Anal. Calcd for C_{18}H_{18}BrIS: C, 45.69; H, 3.86; Br, 16.90; I, 140.1. Found: C, 45.54; H, 3.78; Br, 16.87; I, 26.73; S, 6.53%.

Typical Procedure for the Preparation of Products 10c,g. 2-(1-Adamantylsulfanyl)-4-bromo-3-(2,2-dichloroethenyl)-1-iodobenzene (10c): A mixture of 6c (501.5 mg, 1.051 mmol) and PPh₃ (1.0831 g, 4.129 mmol) in CCl₄ (15 mL) was heated at 80 °C for 44 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue
was treated with silica gel column chromatography (hexane-CHCl₃ 4:1) to give 411.2 mg (ca. 72% yield) of crude 10c. Recrystallization from hot EtOH afforded 237.2 mg (ca. 41% yield, containing 3 mol% of (E)-14c, by ¹H NMR) of 10c as a colorless solid. 10c: ¹H NMR (CDCl₃) δ 1.66 (6H, s, Ad), 1.97 (6H, s, Ad), 2.04 (3H, s, CH=CCl₂), 7.27 (1H, d, ³J = 8.4 Hz), 7.82 (1H, dd, ³J = 8.4 Hz, ⁵J = 0.8 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.7 (Ad), 36.2 (Ad), 44.8 (Ad), 54.9 (Ad), 114.2, 124.4, 125.6, 130.8, 134.7, 139.2, 140.6, 142.3. Found: m/z 564.8626. Calcd for C₁₈H₁₈F₂Br₃Cl₂I: M⁺, 564.8626.

2-(1-Adamantylsulfanyl)-1-bromo-3-(2,2-dichloroethenyl)-4-iodobenzene (10g): A crude product (ca. 83% yield) was recrystallized from hot EtOH to give 10g (containing 5 mol% of (E)-14g) in ca. 46% yield. 10g: ¹H NMR (CDCl₃) δ 1.65 (6H, m, Ad), 1.93 (6H, m, Ad), 2.03 (3H, s, Ad), 6.95 (1H, br s, CH=CCl₂), 7.38 (1H, dd, ³J = 8.4 Hz, ⁵J = 0.8 Hz), 7.68 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃) δ 30.6 (Ad), 36.2 (Ad), 44.5 (Ad), 97.5, 125.8, 133.8 (CH=CCl₂), 134.2, 134.5, 135.7, 140.8, 147.4. Found: m/z 564.8627. Calcd for C₁₈H₁₈F₂Br₃Cl₂I: (M+Na)+, 564.8626.

Typical Procedure for the Preparation of Products 11c,g. 2-(1-Adamantylsulfanyl)-4-bromo-3-(chloroethynyl)-1-iodobenzene (11c): A mixture of 6c (955.3 mg, 2.002 mmol), CBrCl₃ (1.0095 g, 5.092 mmol), and PPh₃ (1.6541 g, 6.306 mmol) in MeCN (100 mL) was heated at 50 °C for 22 h. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. Hexane (hot)-soluble product was collected by decantation and the hexane was evaporated. The residue was treated with silica gel column chromatography (hexane-CHCl₃ 9:1) to give a mixture (922.8 mg) containing 10c (ca. 67% yield) and 15c (ca. 16% yield, E- and Z-forms). The crude mixture (50.8 mg) was dissolved in 2.0 mL of THF and the solution was added to a mixture of t-BuOK (50.1 mg, 0.446 mmol) in THF (1 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1.5 h and quenched with 10 mL of brine, then extracted with AcOEt. The organic phase was separated, dried with Na₂SO₄, and the solvent was removed in vacuo to give 41.8 mg of 11c (ca. 90% yield based on the starting mixture of 10c and 15c); a colorless oil; ¹H NMR (CDCl₃) δ 1.65–2.1 (15H, Ad), 6.41 (1H, d, ³J = 14.0 Hz), 7.00 (1H, d, ³J = 14.0 Hz), 7.31 (1H, d, ³J = 8.4 Hz), 7.69 (1H, d, ³J = 8.4 Hz).

2-(1-Adamantylsulfanyl)-1-bromo-3-(2,2-dichloroethenyl)-4-iodobenzene (11g): A mixture of 10g (ca. 67% yield) and 15g (ca. 21% yield, E- and Z-forms) was obtained from 6g. The mixture was converted to 11g in ca. 99% yield (based on 10g and 15g); a colorless oil; ¹H NMR (CDCl₃) δ 1.65–1.66 (6H, m, Ad), 2.00–2.04 (9H, m, Ad), 7.33 (1H, d, ³J = 8.4 Hz), 7.63 (1H, d, ³J = 8.4 Hz); ¹³C{¹H} NMR (CDCl₃)
δ 30.6 (Ad), 36.2 (Ad), 44.5 (Ad), 55.2 (Ad), 73.4 (C≡C), 76.9 (C≡C), 100.4, 134.0, 135.0, 134.9, 136.9, 138.2, 140.1. Found: m/z 528.8860. Calcd for C₁₈H₁₇₇₉BrClINaS: (M+Na)+, 528.8860.

Typical Procedure for the Preparation of Products 12b,d. 2-(1-Adamantylsulfanyl)-4-bromo-1-chloro-3-(2,2-diiodoethenyl)benzene (12b). A solution of lithium bis(trimethylsilyl)amide (23.8 mmol, 1.3 M solution in THF) was added to THF (90 mL). To the resulting solution was added a solution of I₂ (3.0122 g, 11.868 mmol) in THF (25 mL) at –78 °C. To this mixture was added a solution of diethyl iodomethylphosphonate (3.3203 g, 11.942 mmol) in THF (15 mL) and the resulting solution was stirred at –78 °C for 75 min. This solution was transferred into a THF (30 mL) solution of 6b (4.1817 g, 10.840 mmol) at –78 °C during a period of 35 min, and the resulting mixture was stirred at that temperature for 3 h. The mixture was then poured into brine and extracted with AcOEt. The organic phase was washed with brine, then with saturated aqueous Na₂SO₃ solution, and dried over MgSO₄. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-CHCl₃ 4:1) to give 4.9157 g (7.734 mmol, 71% yield) of 12b and 561.4 mg of the starting 6b (13% recovery). 12b: a pale yellow solid; mp 113–114 °C; ¹H NMR (CDCl₃) δ 1.66 (6H, m, Ad), 1.89–1.97 (6H, m, Ad), 2.04 (3H, s, Ad), 7.41 (1H, d, J = 8.8 Hz), 7.54 (1H, d, J = 8.8 Hz), 8.17 (1H, s, CH=Cl₂); ¹³C{¹H} NMR (CDCl₃) δ 21.9 (C=CI₂), 30.5 (Ad), 36.2 (Ad), 44.6 (Ad), 54.4 (Ad), 120.8, 130.7, 131.6, 134.5, 142.8, 150.2, 152.1. Found: m/z 656.7982. Calcd for C₁₈H₁₈₇₉Br₃ClI₂NaS: (M+Na)+, 656.7983.

Typical Procedure for the Preparation of Products 13b,d. 2-(1-Adamantylsulfanyl)-4-bromo-1-chloro-3-(2-iodoethynyl)benzene (13b). A solution of 12b (512.5 mg, 0.806 mmol) in THF (5 mL) was slowly added to a mixture of t-BuOK (450.0 mg, 4.010 mmol) in THF (3 mL) at –78 °C under nitrogen atmosphere and the resulting mixture was stirred for 30 min. Brine was added to this mixture and the resulting mixture was extracted with AcOEt. The organic layer was washed with brine, then with saturated aqueous Na₂SO₃ solution, separated, dried over Na₂SO₄, and the solvent was removed under reduced pressure to give 387.2 mg (0.763 mmol) of 13b in 95% yield; a colorless solid; mp 138–140 °C; ¹H NMR (CDCl₃) δ 1.65–1.66 (6H, m, Ad), 1.98–1.99 (6H, m, Ad), 2.04 (3H, m, Ad), 7.30
(1H, d, $^3J = 8.4$ Hz), 7.50 (1H, d, $^3J = 8.4$ Hz); $^{13}$C{¹H} NMR (CDCl₃) δ 19.0 (C≡Cl), 30.6 (Ad), 36.3 (Ad), 44.5 (Ad), 55.0 (Ad), 93.6 (C≡Cl), 125.5, 130.4, 133.6, 135.2, 135.9, 142.0. Found: $m/z$ 528.8860. Calcd for C₁₈H₁₇BrClINaS: (M+Na)$^+$, 528.8860. Anal. Calcd for C₁₈H₁₇Br₃ClIS: C, 42.59; H, 3.38; Br, 15.74; Cl, 6.98; I, 25.00; S, 6.32%. Found: C, 42.73; H, 3.37; Br, 15.79; Cl, 7.09; I, 25.02; S, 6.31%.

2-(1-Adamantylsulfanyl)-1-bromo-4-chloro-3-(iodoethynyl)benzene (13d): 95% yield; a colorless solid; mp 135–137 °C; $^1$H NMR (CDCl₃) δ 1.66 (6H, m, Ad), 2.02–2.04 (9H, m, Ad), 7.24 (1H, d, $^3J = 8.4$ Hz), 7.56 (1H, d, $^3J = 8.4$ Hz); $^{13}$C{¹H} NMR (CDCl₃) δ 19.5 (C≡CI), 30.6 (Ad), 36.3 (Ad), 44.6 (Ad), 55.3 (Ad), 91.9 (C≡CI), 130.6, 132.7, 132.9, 133.4, 137.2, 137.9. Found: $m/z$ 528.8860. Calcd for C₁₈H₁₇Br₃ClIS: (M+Na)$^+$, 528.8860.

Typical Procedure for the Preparation of Products 4b–g. 4-Bromo-7-chlorobenzo[b]thiophene (4b). A mixture of 9b (1.8864 g, 4.941 mmol), silica gel 60N (13.0842 g), and toluene (65 mL) was heated at 90 °C for 13 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 55 mL of CHCl₃ and a combined filtrate was evaporated under reduced pressure. Silica gel column chromatographic treatment (hexane) of the residue afforded 1.09 19 g (4.411 mmol) of 4b in 89% yield; a colorless solid; mp 77–79 °C; $^1$H NMR (CDCl₃) δ 7.22 (1H, d, $^3J = 8.4$ Hz), 7.50 (1H, d, $^3J = 8.4$ Hz), 7.51 (1H, d, $^3J = 5.6$ Hz), 7.58 (1H, d, $^3J = 5.6$ Hz); $^{13}$C{¹H} NMR (CDCl₃) δ 115.6 (C-Br), 124.8, 125.3, 127.3, 128.4, 128.6, 139.8, 140.5. Found: $m/z$ 245.8901. Calcd for C₈H₄BrClS: M+, 245.8900. Anal. Calcd for C₈H₄BrClS: C, 38.82; H, 1.63; Br, 32.39; Cl, 14.27; S, 12.94%.

4-Bromo-7-iodobenzo[b]thiophene (4c): 98% yield. 7-Bromo-4-chlorobenzo[b]thiophene (4d): 97% yield; a colorless solid; mp 57 °C (sublime); $^1$H NMR (CDCl₃) δ 7.26 (1H, d, $^3J = 8.0$ Hz), 7.42 (1H, d, $^3J = 8.0$ Hz), 7.57 (1H, d, $^3J = 5.6$ Hz), 7.58 (1H, d, $^3J = 5.6$ Hz); $^{13}$C{¹H} NMR (CDCl₃) δ 84.9 (C-I), 125.0, 129.4, 134.3, 134.3, 137.4, 147.5. Found: $m/z$ 293.8761. Calcd for C₈H₄Br₃ClS: 293.8761.

Typical Procedure for the Preparation of Products 4b–g. 4-Bromo-7-chlorobenzo[b]thiophene (4b). A mixture of 9b (1.8864 g, 4.941 mmol), silica gel 60N (13.0842 g), and toluene (65 mL) was heated at 90 °C for 13 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 55 mL of CHCl₃ and a combined filtrate was evaporated under reduced pressure. Silica gel column chromatographic treatment (hexane) of the residue afforded 1.09 19 g (4.411 mmol) of 4b in 89% yield; a colorless solid; mp 77–79 °C; $^1$H NMR (CDCl₃) δ 7.22 (1H, d, $^3J = 8.4$ Hz), 7.50 (1H, d, $^3J = 8.4$ Hz), 7.51 (1H, d, $^3J = 5.6$ Hz), 7.58 (1H, d, $^3J = 5.6$ Hz); $^{13}$C{¹H} NMR (CDCl₃) δ 115.6 (C-Br), 124.8, 125.3, 127.3, 128.4, 128.6, 139.8, 140.5. Found: $m/z$ 245.8901. Calcd for C₈H₄BrClS: M+, 245.8900. Anal. Calcd for C₈H₄BrClS: C, 38.82; H, 1.63; Br, 32.28; Cl, 14.32; S, 12.95%. Found: C, 38.88; H, 1.73; Br, 32.39; Cl, 14.27; S, 12.94%.

4-Bromo-7-iodobenzo[b]thiophene (4c): 98% yield. 7-Bromo-4-chlorobenzo[b]thiophene (4d): 97% yield; a colorless solid; mp 57 °C (sublime); $^1$H NMR (CDCl₃) δ 7.26 (1H, d, $^3J = 8.0$ Hz), 7.42 (1H, d, $^3J = 8.0$ Hz), 7.57 (1H, d, $^3J = 5.6$ Hz), 7.58 (1H, d, $^3J = 5.6$ Hz); $^{13}$C{¹H} NMR (CDCl₃) δ 84.9 (C-I), 125.0, 129.4, 134.3, 134.3, 137.4, 147.5. Found: $m/z$ 293.8761. Calcd for C₈H₄Br₃ClS: 293.8761.
7-Bromo-4-iodobenzo[b]thiophene (4g):  93% yield; a colorless solid; mp 78–79 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 7.22 \,(1\,H, \,d, \,^3J = 8.4\,\text{Hz})\), 7.50 (1\,H, \,d, \,^3J = 5.2\,\text{Hz})\), 7.58 (1\,H, \,d, \,^3J = 5.2\,\text{Hz})\), 7.65 (1\,H, \,d, \,^3J = 8.4\,\text{Hz})\); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta 88.6\,\text{(C-I)}\), 116.3, 127.8, 128.2, 129.0, 135.2, 140.9, 143.3. Found: \(m/z\) 337.8257. Calcd for C\(_8\)H\(_4\)BrI\(_5\): M\(^+\), 337.8256. Anal. Calcd for C\(_8\)H\(_4\)BrI\(_5\): C, 28.35; H, 1.19; Br, 23.57; I, 37.44; S, 9.46%. Found: C, 28.51; H, 1.26; Br, 23.31; I, 37.44; S, 9.42%.

Typical Procedure for the Preparation of Products 5b–h.  4-Bromo-7-chloro-2-iodobenzo[b]thiophene (5b).  A mixture of 13b (149.5 mg, 0.295 mmol), silica gel (1.1098 g), and toluene (5.5 mL) was heated at 90 °C for 19 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 20 mL of AcOEt and a combined filtrate was washed with saturated aqueous Na\(_2\)SO\(_3\) solution and dried over Na\(_2\)SO\(_4\). Silica gel column chromatographic treatment (hexane) of the residue afforded 82.3 mg (0.220 mmol) of 5b in 75% yield; a colorless solid; mp 136–137 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 7.15 \,(1\,H, \,d, \,^3J = 8.4\,\text{Hz})\), 7.43 (1\,H, \,d, \,^3J = 8.4\,\text{Hz})\), 7.70 (1H, s); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta 81.1\,\text{(C-I)}\), 113.8, 125.0, 125.8, 128.9, 135.0, 141.6, 144.2. Found: \(m/z\) 371.7867. Calcd for C\(_8\)H\(_3\)Br\(_3\)ClI\(_5\): M\(^+\), 371.7867. Anal. Calcd for C\(_8\)H\(_3\)BrClI\(_5\): C, 25.73; H, 0.81; Br, 21.40; Cl, 9.49; I, 33.98; S, 8.59%. Found: C, 29.19; H, 0.91; Br, 21.48; Cl, 9.47; I, 33.97; S, 8.67%.

4-Bromo-2-chloro-7-iodobenzo[b]thiophene (5c):  89% yield based on 11c; a colorless solid; mp 126–128 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 7.43 \,(1\,H, \,d, \,^3J = 8.4\,\text{Hz})\), 7.70 (1H, s); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta 84.7 \,(\text{C-I})\), 116.8, 124.8, 129.4, 135.0, 136.5, 138.2, 138.2. Found: \(m/z\) 371.7866. Calcd for C\(_8\)H\(_3\)BrI\(_3\)ClI\(_5\): M\(^+\), 371.7866. Anal. Calcd for C\(_8\)H\(_3\)BrClI\(_5\): C, 25.73; H, 0.81; Br, 21.40; Cl, 9.49; I, 33.98; S, 8.59%. Found: C, 25.85; H, 0.84; Br, 21.67; Cl, 9.42; I, 33.72; S, 8.57%.

7-Bromo-4-chloro-2-iodobenzo[b]thiophene (5d):  80% yield based on 13d; a colorless solid; mp 132–134 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 7.35 \,(1\,H, \,d, \,^3J = 8.0\,\text{Hz})\), 7.78 (1H, s); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta 83.1 \,(\text{C-I})\), 112.4 (C-Br), 125.9, 126.5, 127.8, 132.2, 139.6, 147.1. Found: \(m/z\) 371.7866. Calcd for C\(_8\)H\(_3\)BrI\(_3\)ClI\(_5\): M\(^+\), 371.7866. 2-Bromo-4-chloro-7-iodobenzo[b]thiophene (5e):  90% yield based on 7e (2 steps); a colorless solid; mp 123–124 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 7.08 \,(1\,H, \,d, \,^3J = 8.0\,\text{Hz})\), 7.54 (1H, s); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta 83.5 \,(\text{C-I})\), 117.3, 126.2, 126.6, 128.2, 134.3, 137.5, 148.5. Found: \(m/z\) 371.7866. Calcd for C\(_8\)H\(_3\)BrI\(_3\)ClI\(_5\): M\(^+\), 371.7866.

2-Bromo-7-chloro-4-iodobenzo[b]thiophene (5f):  74% yield based on 7f (2 steps); a colorless solid; mp 121–125 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta 7.03 \,(1\,H, \,d, \,^3J = 8.0\,\text{Hz})\), 7.66 (1H, s); \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\)) \(\delta 86.2 \,(\text{C-I})\), 117.7, 125.3, 127.4, 131.6, 135.7, 139.4, 143.8. Found: \(m/z\) 371.7866. Calcd for C\(_8\)H\(_3\)BrI\(_3\)ClI\(_5\): M\(^+\), 371.7866.
7-Bromo-2-chloro-4-iodobenzo[b]thiophene (5g): 80% yield based on 11g; a colorless solid; mp 132–133 °C; $^1$H NMR (CDCl$_3$) $\delta$ 7.18 (1H, d, $^3$J = 8.4 Hz), 7.37 (1H, s), 7.62 (1H, d, $^3$J = 8.4 Hz); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 87.4 (C-I), 115.3, 128.0, 128.5, 133.9, 135.9, 139.7, 142.5. Found: m/z 371.7867. Calcd for C$_8$H$_3$Br$_3$Cl$_5$S: M$^+$, 371.7867. Anal. Calcd for C$_8$H$_3$BrClIS: C, 25.73; H, 0.81%. Found: C, 25.74; H, 0.88%.

2,4-Dibromo-7-chlorobenzo[b]thiophene (5h): 69% yield based on 8b; a colorless solid; mp 135 °C; $^1$H NMR (CDCl$_3$) $\delta$ 7.18 (1H, d, $^3$J = 8.4 Hz), 7.46 (1H, d, $^3$J = 8.4 Hz), 7.51 (1H, s); $^{13}$C{$^1$H} NMR (CDCl$_3$) $\delta$ 114.3, 118.1, 125.1, 126.2, 128.0, 129.2, 140.5, 140.7. Found: m/z 323.80053. Calcd for C$_8$H$_3$Br$_2$Cl$_5$S: M$^+$, 323.80053. Anal. Calcd for C$_8$H$_3$Br$_2$ClS: C, 29.44; H, 0.93; Br, 48.96; Cl, 10.86; S, 9.82%. Found: C, 29.56; H, 1.02; Br, 49.24; Cl, 10.60; S, 9.80%.

Alternative Preparation of Products 5b,d. To a solution of 4b (302.0 mg, 1.220 mmol) in 3.5 mL of THF was added 1.452 mmol of LDA (1.10 M solution in hexane-THF, 1.32 mL) at −78 °C under nitrogen atmosphere. The reaction mixture was stirred at −78 °C for 15 min and then at −20 °C for 40 min. To this solution was added a solution of 1,2-diiodoethane (1.691 mmol) in THF (3.4 mL) at −78 °C and the resulting mixture was stirred at −78 °C for 30 min, then at room temperature for 90 min. Saturated aqueous Na$_2$SO$_3$ solution was added, and the mixture was extracted with AcOEt. The organic phase was separated and dried over MgSO$_4$. The solvent was removed under reduced pressure and the residue was treated with silica gel column chromatography (hexane) to give 442.1 mg (1.184 mmol, 97% yield) of 5b. Compound 5d was obtained from 4d by an analogous method in 95% yield.

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REFERENCES AND NOTES


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13. Details of the optimization of reaction conditions will be reported elsewhere.

