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IODINE-CONTAINING 4,7-DIHALOBENZO[*b*]THIOPHENE BUILDING BLOCKS AND RELATED IODOBENZO[*b*]THIOPHENES: PROMISING MOLECULAR SCAFFOLDS FOR BIO-INSPIRED MOLECULAR ARCHITECTURE

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Abstract – This review describes preparations and reactions of 4,7-dihalobenzo[*b*]thiophenes bearing iodine atom(s). A short survey of typical preparative methods for iodobenzo[*b*]thiophenes and relatively simple benzo[*b*]thiophenes is included. Reactions of the iodine-containing 4,7-dihalobenzo[*b*]thiophenes are shown and their application to α helix-inspired artificial molecular architecture is referred.

CONTENTS

1. Introduction
2. Short survey of preparative methods for iodobenzo[*b*]thiophenes
 - 2.1. Preparation of iodobenzo[*b*]thiophenes from iodine-free precursors
 - 2.1.1. By iodination of benzo[*b*]thiophene derivatives
 - 2.1.1.1. Direct iodination of the C-H bond
 - 2.1.1.1.1. Direct C-H bond iodination at the 2-position
 - 2.1.1.1.2. Direct C-H bond iodination at the 3-position
 - 2.1.1.1.3. Direct C-H bond iodination at the 4-position
 - 2.1.1.1.4. Direct C-H bond iodination at the 5-position
 - 2.1.1.1.5. Direct C-H bond iodination at the 6-position
 - 2.1.1.1.6. Direct C-H bond iodination at the 7-position
 - 2.1.1.2. Iodination via C-Li bond
 - 2.1.1.3. Iodination via C-B bond
 - 2.1.1.4. Iodination via C-N bond
 - 2.1.1.5. Iodination via C-Si bond

- 2.1.1.6. Iodination via other C-Metal bonds
- 2.1.2. By iodocyclization of (ethynyl)(sulfanyl)benzenes
- 2.2. Precursors for benzo[*b*]thiophene core; with or without iodine
 - 2.2.1. Benzene-based precursors for preparation of benzo[*b*]thiophenes
 - 2.2.2. Thiophene-based precursors for preparation of benzo[*b*]thiophenes
 - 2.2.3. Other precursors
3. Preparation and reactions of 4,7-dihalobenzo[*b*]thiophenes containing iodine
 - 3.1. Preparation of 4,7-dihalobenzo[*b*]thiophenes containing iodine
 - 3.1.1. Iodine at the 6-membered ring
 - 3.1.2. Iodine at the 5-membered ring
 - 3.2. Reactions of 4,7-dihalobenzo[*b*]thiophenes containing iodine
4. Conclusion

1. INTRODUCTION

Organic building block is an important concept in organic synthesis: In many cases, the building blocks correspond to synthetic intermediates and frequently called *molecular scaffolds*, focusing on their rolls in the synthetic strategy. Halogenated aromatic compounds are often used as such molecular scaffolds, because of the usefulness in many reactions as well as their relatively rigid and stable aromatic framework. From a synthetic point of view, multi-halo arenes containing different halogen atoms are especially valuable for molecular scaffolds, because good regioselectivity is expected in reactions such as halogen-metal exchange and transition metal-catalyzed cross couplings. Concerning the cross coupling reactions, it is well known that the reactivity is generally $I > OTf > Br \gg Cl$.¹ This order of reactivity makes iodine-containing arenes and heteroarenes particularly useful, and consequently, chemistry of such iodo-building blocks is worth studying.

Among aromatic heterocyclic compounds, benzo[*b*]thiophenes have attracted a great interest in materials chemistry,² medicinal chemistry,³ and synthetic chemistry,⁴ because of their unique and excellent properties. Thus, benzo[*b*]thiophenes containing several different halogen atoms are supposed to have a large potential for synthetic application. Furthermore, from a viewpoint of molecular scaffolds, 4,7-dihalobenzo[*b*]thiophenes bearing different halogen atoms (Figure 1, $X \neq Y$) are useful building blocks with featured molecular geometry: They have an axis $X \cdots Y$, where the C2-R bond locates nearly perpendicular to the $X \cdots Y$ axis, like *pillars and beams* which define floors of specific heights in architectural buildings. Preparation and utilization of benzo[*b*]thiophenes bearing iodine atoms at the benzene ring (*i.e.* C-4 to C-7 positions), however, seem to have been limited: This review shows a short survey of typical preparative methods for iodobenzo[*b*]thiophenes in Section 2, while Section 3 exhibits

preparations, reactions, and application of 4,7-dihalobenzo[*b*]thiophenes containing iodine. It should be mentioned here that reactivity of multi-ring-fused benzothiophenes such as benzodithiophenes containing more than two rings is much different from that of simple benzothiophenes. The reactions shown in this review are mainly those of simple benzo[*b*]thiophenes.

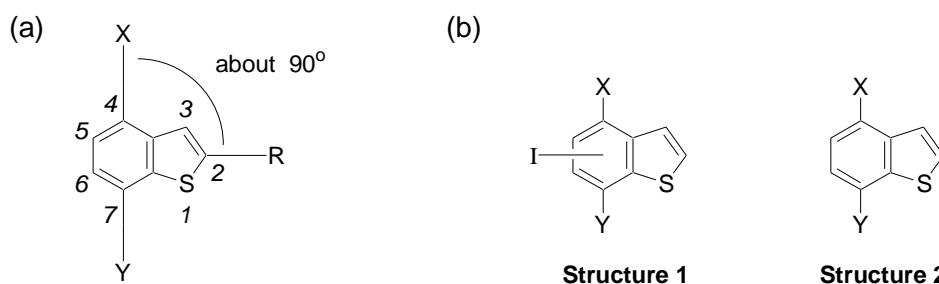


Figure 1. (a) Concept and numbering of a ‘quasi T-shape’ benzo[*b*]thiophene scaffold. (b) Structures of 4,7-dihalobenzo[*b*]thiophenes containing iodine. Atoms X and Y are halogen atoms. Structure 2 contains at least one iodine atom as X or Y.

2. SHORT SURVEY OF PREPARATIVE METHODS FOR IODOBENZO[*b*]THIOPHENES

First, we glance some typical preparative methods for iodobenzo[*b*]thiophenes, focusing on the derivatives having simple benzo[*b*]thiophene core. The synthetic methods can be divided into two categories, one is those from iodine-containing materials and the other is from iodine-free precursors.

2.1. Preparation of iodobenzo[*b*]thiophenes from iodine-free precursors

As the starting materials in this category do not contain iodine, (1) iodination of benzo[*b*]thiophene core or (2) simultaneous construction of benzo[*b*]thiophene framework and iodination (for example, iodocyclization) is needed. Various iodination methods have been applied for this purpose as listed below.

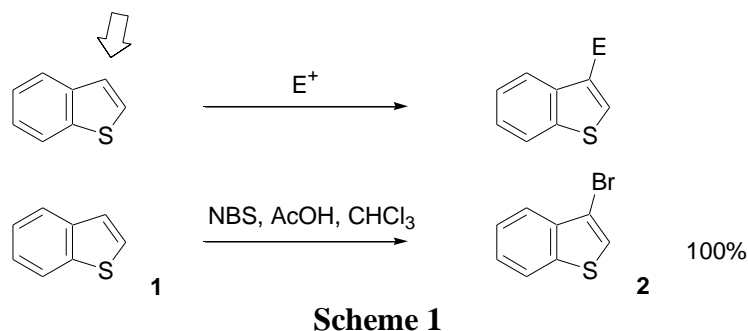
2.1.1. By iodination of benzo[*b*]thiophene derivatives

Several methods for direct or indirect iodination of C-H bond have been reported. Indirect iodination of C-H bond includes iodination of C-Li, C-B, or C-N bonds, for instance. Direct C-H iodination at each position is described in section 2.1.1.1., while indirect methods are noted in the sections from 2.1.1.2. to 2.1.1.6.

2.1.1.1. Direct iodination of the C-H bond

(As has been mentioned, reactivity of polyfused benzothiophenes, such as dibenzothiophenes and benzodithiophenes, differs from that of simple benzothiophenes. This review mainly treats simple two-ring benzo[*b*]thiophenes.)

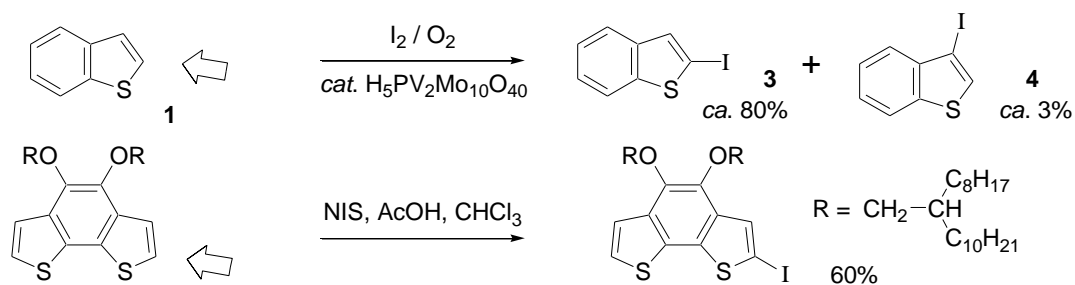
In general, electrophilic substitution of parent benzo[*b*]thiophene **1** takes place at C-3 position (Scheme 1, compound **1** to **2**).⁵



Iodination, however, often occurs at either 2- or 3-position, or both (see, Schemes 2,3).⁶ For selective iodination at C-2 position, deprotonation by organolithium reagent is generally used prior to reaction with iodine species such as I₂ or ICl (indirect C-H iodination), see section 2.1.1.2. Direct iodination at C-4 to C-7 positions become possible, when the reactive C-2 and/or C-3 positions are already substituted or an appropriate directing group (NR₂ or OR, for example) exists near or next to the desired position. It should be mentioned that introduction of the directing group itself may suffer from the relatively poor reactivity of the 6-membered ring moiety of benzo[*b*]thiophenes. Thus, synthetic plans should be made, taking these facts into account. In many reported cases, the directing groups were introduced before completion of benzothiophene skeleton, which was constructed often from single-ring derivatives (see section 2.2.). Also in many cases, the directing groups were not removed after iodination but utilized for further conversion. The following sections describe some typical iodination methods at each position.

2.1.1.1.1. Direct C-H bond iodination at the 2-position

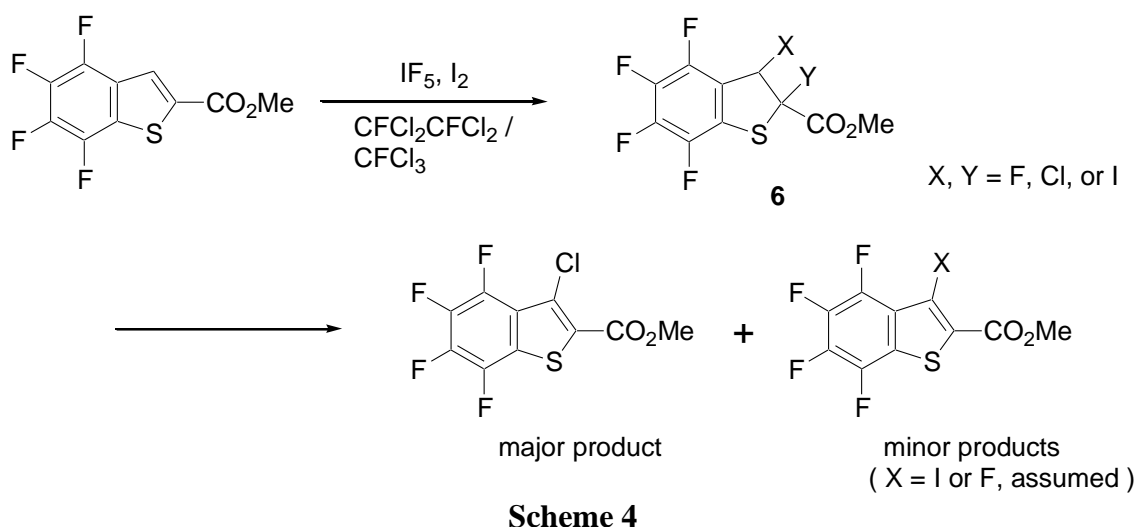
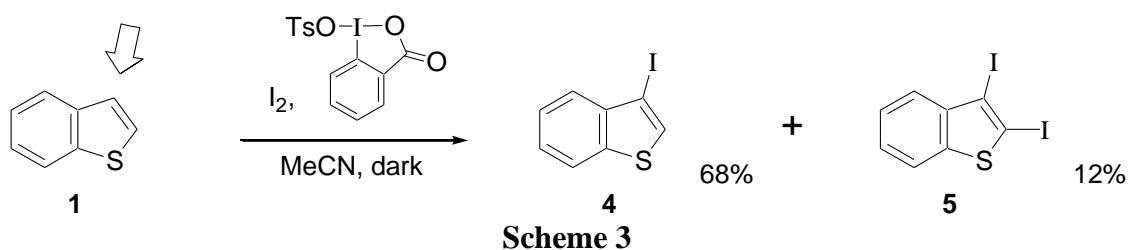
Probably, most popular method of iodination at this position is deprotonation-iodination (see section 2.1.1.2.). When the substrate is sensitive to bases, direct C-H iodination may become valuable. Simple iodination at C-2 position was performed with I₂ using Mo catalyst to give **3** as a major product (Scheme 2).⁷ (I₂ is also used for iodination of C-3 position under different conditions, see section 2.1.1.1.2.)



Iodination of C-2 position could also be performed using other iodination reagents such as NIS⁸ and $\text{PhI}(\text{OAc})_2 / \text{I}_2$.⁹

2.1.1.1.2. Direct C-H bond iodination at the 3-position

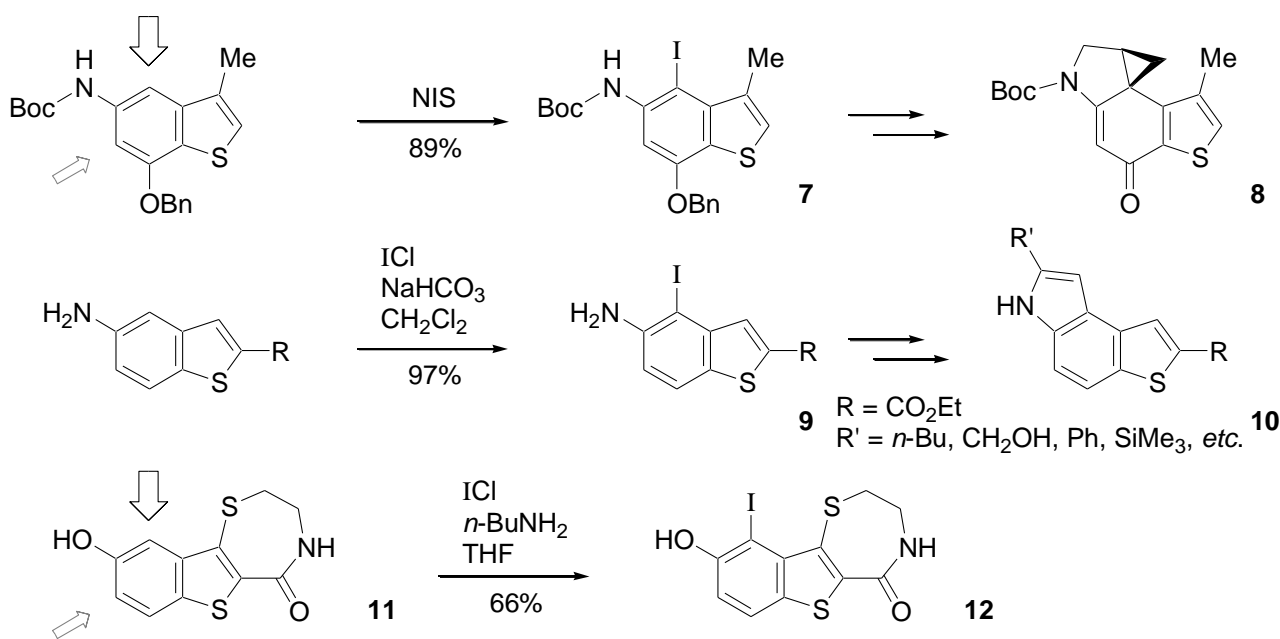
As electrophilic substitution tends to proceed at C-3 position, a variety of methods have been reported using I_2 as a common iodine source, usually with appropriate activating reagents, giving **4,5** (Scheme 3).^{10,11} In some cases, 1,2-dihalo-1,2-dihydrobenzo[*b*]thiophene derivatives are assumed to be formed as intermediates: In the following reaction, an intermediate **6** is proposed (Scheme 4).¹² Iodocyclization of *o*-(alkylsulfanyl)(ethynyl)benzene is an alternative method to 3-iodobenzo[*b*]thiophenes, see section 2.1.2.



2.1.1.1.3 Direct C-H bond iodination at the 4-position

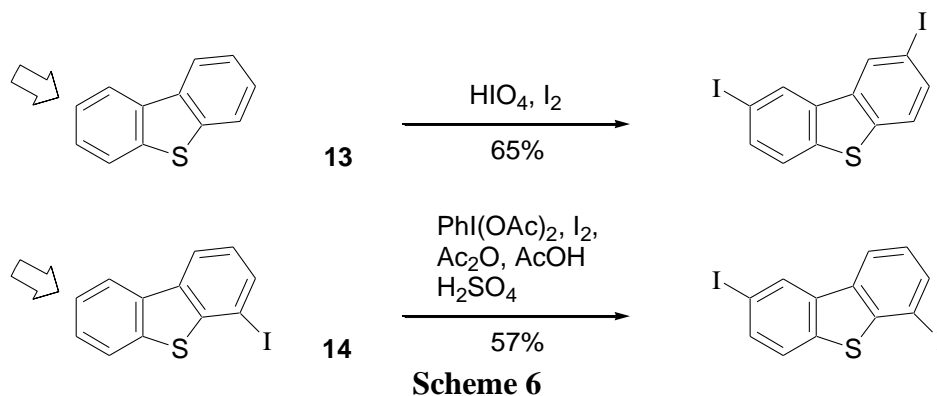
As mentioned above, direct iodination at the 4- to 7-positions can occur when C-2 and/or C-3 positions are blocked by substituents, or when directing groups such as protected amino,¹³ unprotected amino,¹⁴ or hydroxyl¹⁵ groups exist at appropriate positions. In the following reactions, one of the two *o*-positions of the directing group was predominantly iodinated to give products **7, 9, 12** in good yields (Scheme 5). Utilization of such directing groups becomes valuable when the target compounds contain the directing

group-derived substituents. In fact, the directing nitrogen atoms remained in the molecules **8** and **10**, while the iodine atoms in **7,9** were utilized and consumed during the process.



2.1.1.1.4. Direct C-H bond iodination at the 5-position

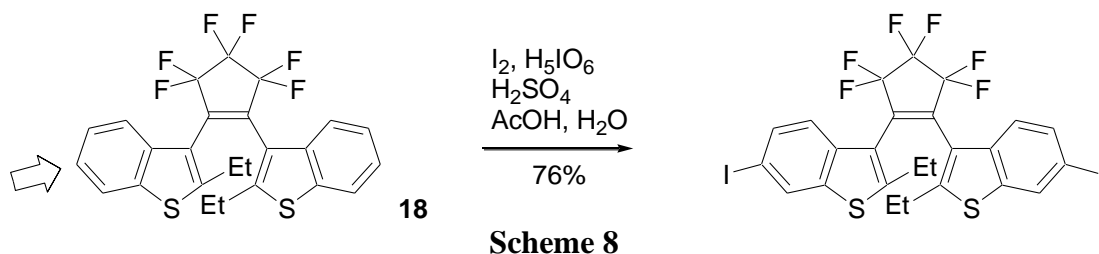
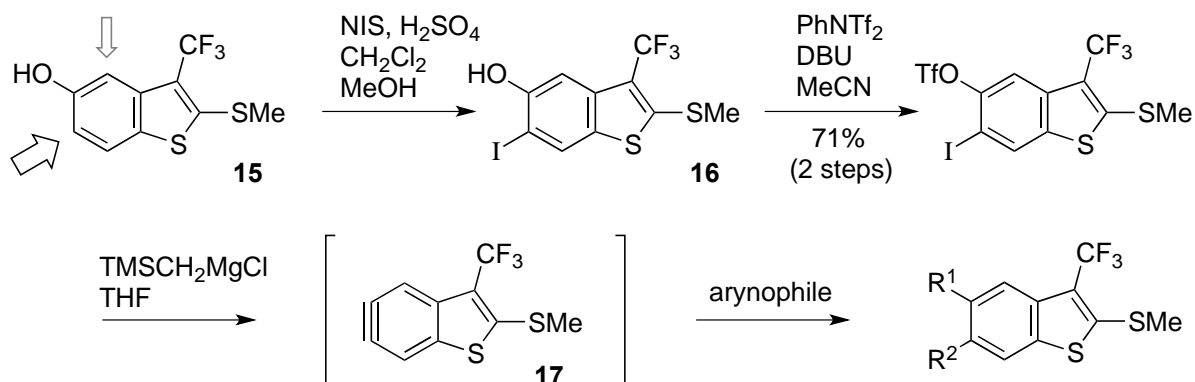
A specific position was iodinated in the π -system of dibenzothiophenes **13** and **14** (Scheme 6).^{16,17}



2.1.1.1.5. Direct C-H bond iodination at the 6-position

Again, a directing group caused iodination at one of the *o*-positions of **15** (Scheme 7), in which the 5-membered ring is fully substituted.¹⁸ The directing OH group in **15** was well-designed and utilized to induce benzyne **17**. In this case of 5-hydroxybenzo[*b*]thiophene **15**, 6-iodo product **16** was formed, in contrast to the case of the 5-hydroxy derivative **11** in section 2.1.1.1.3., which led to the 4-iodo product **12**. Thus, electronic effects of the substituents even in the distant 5-membered ring should be carefully evaluated, in a synthetic plan of iodination. 6-Iodobenzo[*b*]thiophenes were also obtained in some

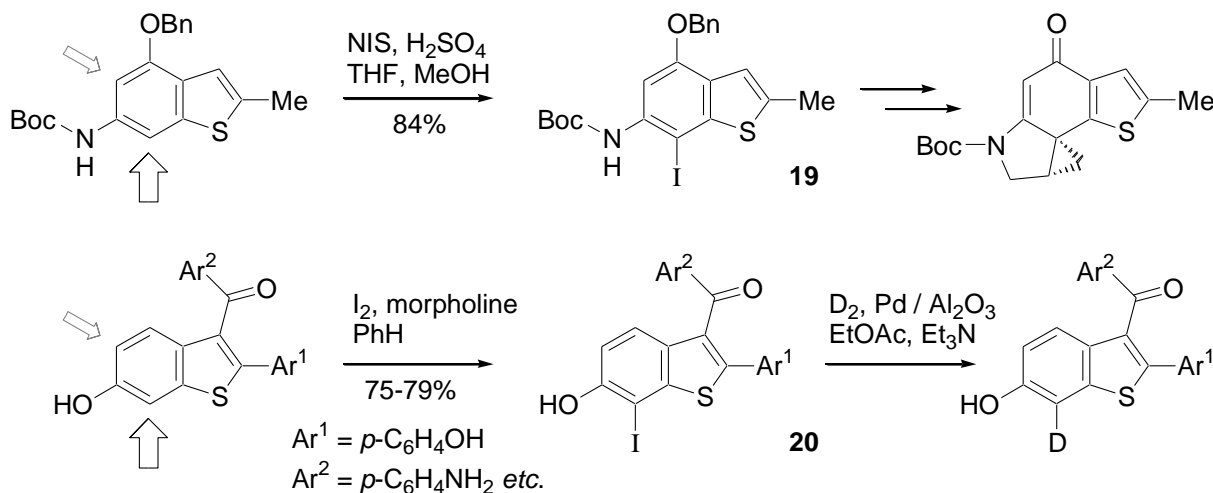
specific cases,^{19,20} although there is no directing group on the benzene ring of **18** (Scheme 8). Electron-withdrawing group at C-3 position may prefer the iodination at C-6 position.



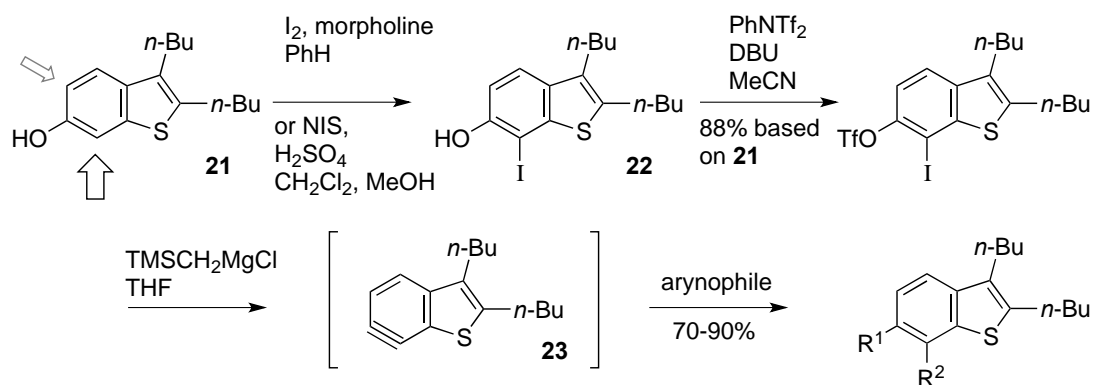
Furthermore, a particular 6-iodo derivative was prepared by indirect and formal C-H bond iodination via nitration-reduction-diazotization process, see section 2.1.1.4.

2.1.1.1.6. Direct C-H bond iodination at the 7-position

When a suitable amino¹³ or hydroxyl²¹ directing group exists at C-6 position, the *o*-position more proximate to the sulfur atom (*i.e.*, C-7 position) tends to be iodinated to give **19** and **20** (Scheme 9).



By analogous method shown in Scheme 7, aryne **23** was generated via the OH-directed iodination of **21** and triflation of **22** (Scheme 10).¹⁸



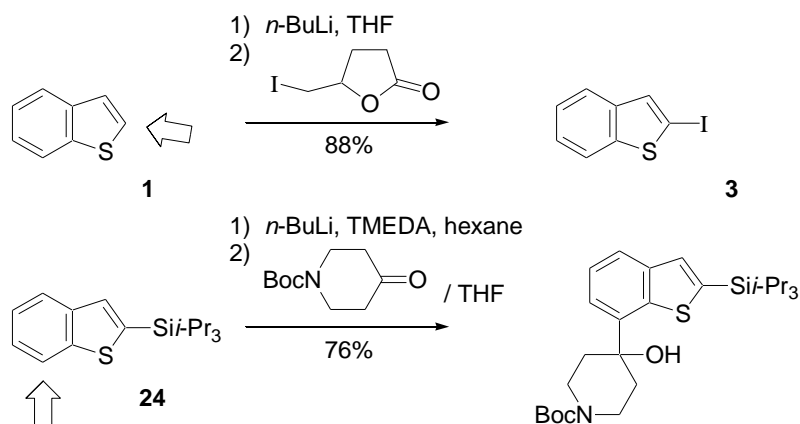
Scheme 10

2.1.1.2. Iodination via C-Li bond

As mentioned above (Scheme 3), direct C-H iodination of 2- or 3-position of benzo[*b*]thiophene suffers from low selectivity. On the other hand, C-H iodination of 4- to 7-positions generally demands a proximal directing group and/or appropriate protection of the reactive 2- and 3-positions. Thus, adequate activation using carbon-heteroatom bond, typically carbon-metal bond, is of use for selective iodination of 2- to 7- positions. Typical methods for C-Li bond formation is (i) deprotonation of C-H bond or (ii) halogen-lithium exchange of C-halogen bond. Both methods are used in preparation of iodobenzo[*b*]thiophenes.

(i) By deprotonation

In most cases deprotonation occurs at C-2 position (Scheme 11). Typical bases are BuLi, LDA, LiTMP, *etc.*, while typical iodination reagents are I₂, ICl, 1,2-diiodoethane, iodomethylactone, *etc.*^{22,23}

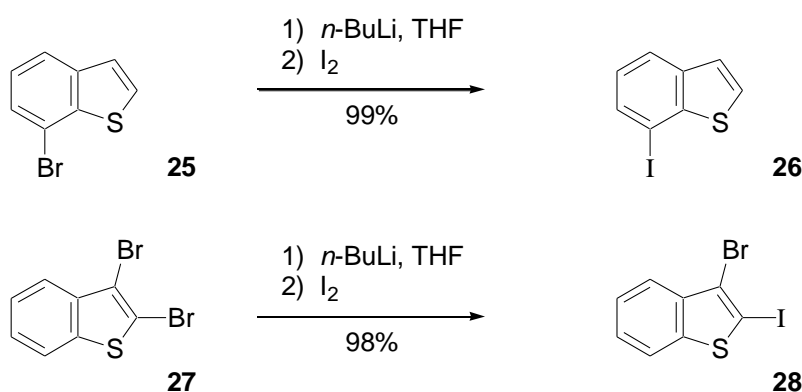


Scheme 11

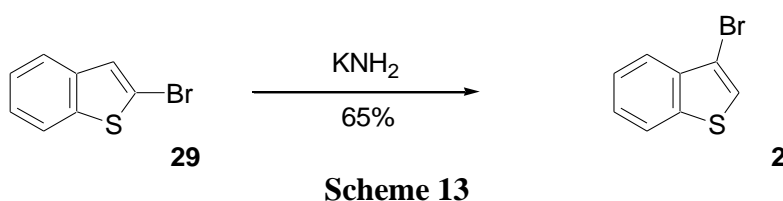
When the 2-position is substituted as is the case of **24**, deprotonation may occur at other positions such as the C-7 position, of which lithiation is facilitated probably by coordination of the sulfur lone pair.^{24,25}

(ii) By halogen-lithium exchange

Halogen-lithium exchange is a useful tool for selective lithiation of desired positions, even if the 2,3-positions are not substituted (Scheme 12, compound **25** to **26**).²⁶ In some specific cases, the regioselectivity is very good as shown in the case of 2,3-dibromo derivative **27** to the 3-bromo-2-iodo form **28**.²⁷

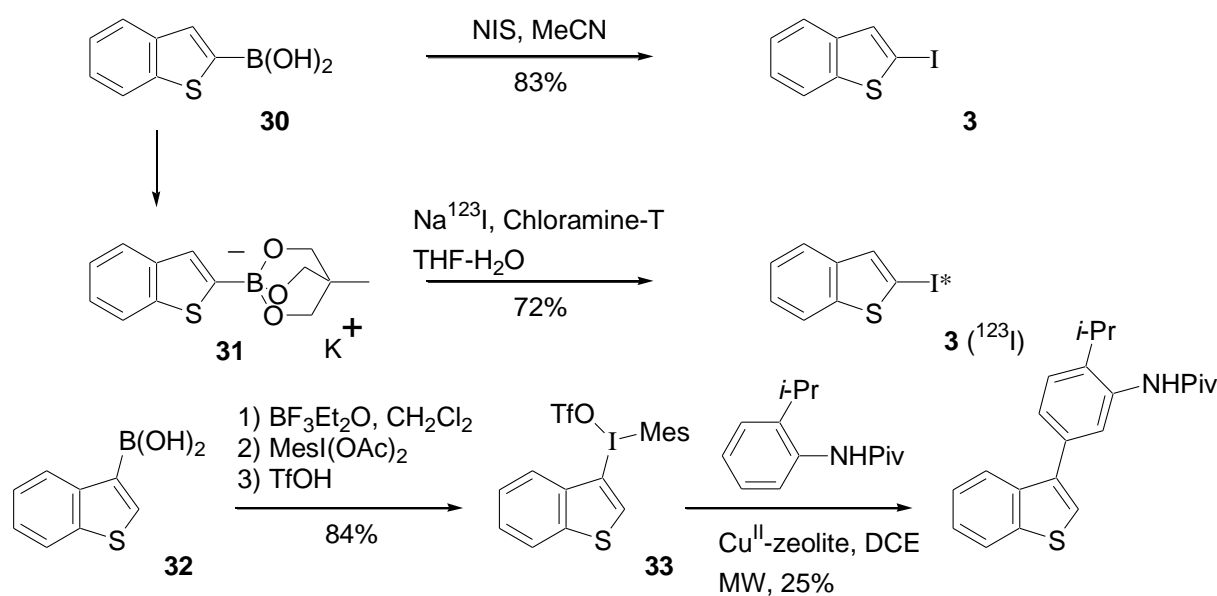


For use of organolithium reagents and alkali metal amides, possibility of so-called ‘halogen dance’ reaction should be kept in mind. In the case of 2-bromobenzo[b]thiophene **29**, halogen dancing with KNH₂ or LDA leading to **2** was reported (Scheme 13).^{28,29}



2.1.1.3. Iodination via C-B bond

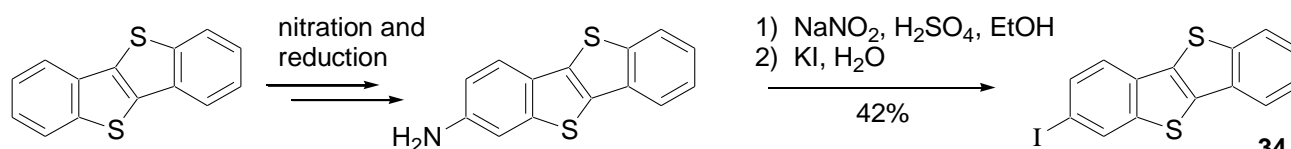
This iodination process of C-B bond can be preceded by Hartwig-Miyaura C-H borylation, Miyaura-Ishiyama C-X borylation, or lithiation-borylation process. For iodination of C-2 position of benzo[*b*]thiophene boronic acid **30**, NIS / MeCN is often used (Scheme 14).³⁰ Various iodine reagents such as I₂ / KF,³¹ PhI(OH)(OTs),³² and (CF₃)₂CFI / hydroquinone / Cu³³ have also been applied. Not only boronic acid but also trifluoroborate³⁴ and triolborate like **31**³⁵ were subjected to iodination. The latter was applied to radioiodination using Na¹²³I.³⁶ Iodonium salts such as **33** were also prepared from boronic acid **32** and in some cases used for further transformation.^{32,37,38}



Scheme 14

2.1.1.4. Iodination via C-N bond

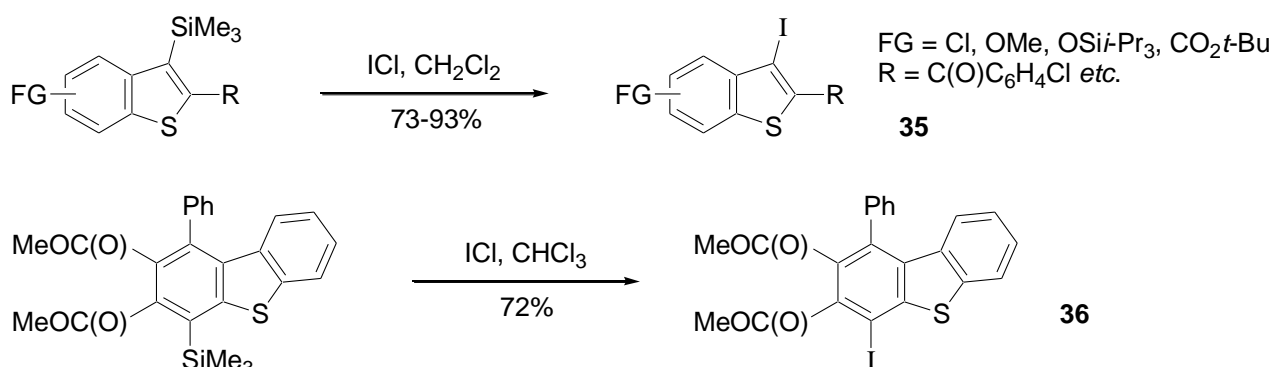
Most reactions of this category are those of diazonium salts. KI and NaI are typical iodine sources. Simple 5-aminobenzo[*b*]thiophene sulfate was subjected to diazotization and reaction with KI to produce 5-iodo derivative in 49% yield.³⁹ Similarly, compound **34** was prepared as shown in Scheme 15.⁴⁰



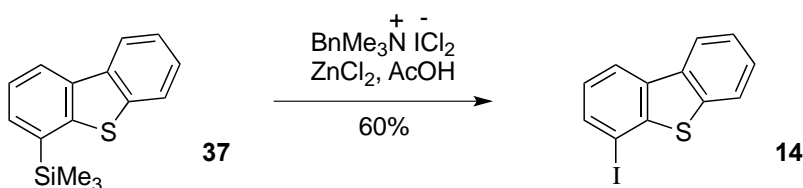
Scheme 15

2.1.1.5. Iodination via C-Si bond

Typically, ICl / CH₂Cl₂ (or CHCl₃) is used for this conversion giving **35** and **36**, for instance^{41–45} (Scheme 16, see also Scheme 44). Iodination of **37** by BnMe₃N⁺ Cl₂I⁻ was also reported (Scheme 17).⁴⁶



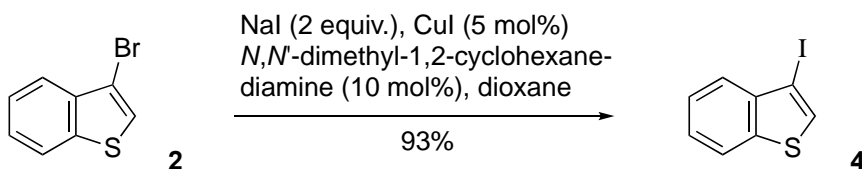
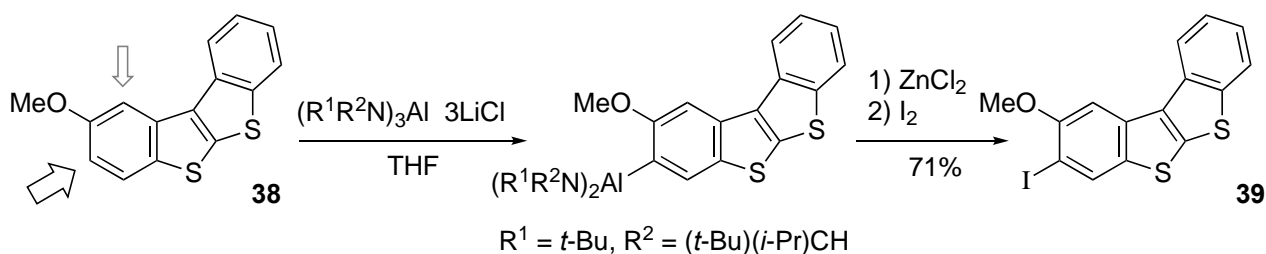
Scheme 16



Scheme 17

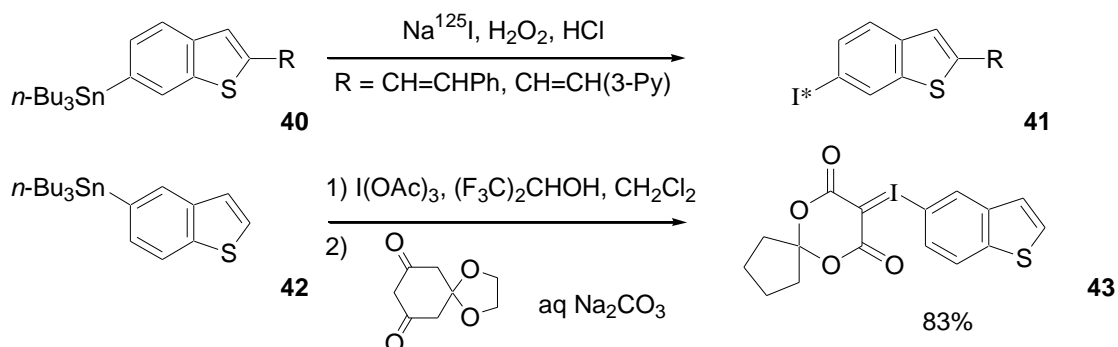
2.1.1.6. Iodination via other C-Metal bonds

Iodination reaction of benzothienobenzothiophene **38**, by MeO group-directed aluminatation followed by transmetallation with ZnCl_2 and quenching with I_2 , was reported to form **39**, (Scheme 18).⁴⁷ Halogen exchange reactions using copper catalyst were reported: Typical conditions for this exchange are NaI / *cat.* CuI / ethylenediamine ligand.⁴⁸⁻⁵⁰



Scheme 18

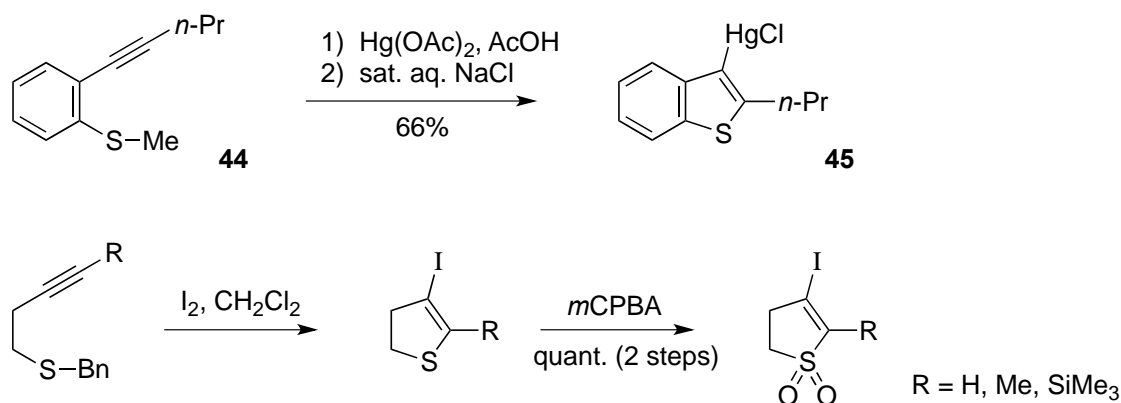
Tributylstannylbenzo[*b*]thiophenes were prepared from the corresponding bromobenzothiophenes using $(n\text{-Bu}_3\text{Sn})_2$ / *cat.* $\text{Pd}(\text{PPh}_3)_4$ and then iodinated with I_2 in CHCl_3 .⁵¹ Some radioactive iodo compounds (^{125}I or ^{131}I) such as **41** were prepared from the stannanes **40**, for example using Na^{125}I and H_2O_2 (Scheme 19).^{51,52} Trivalent iodo compound **43** was obtained via tributylstannanes **42**.⁵³



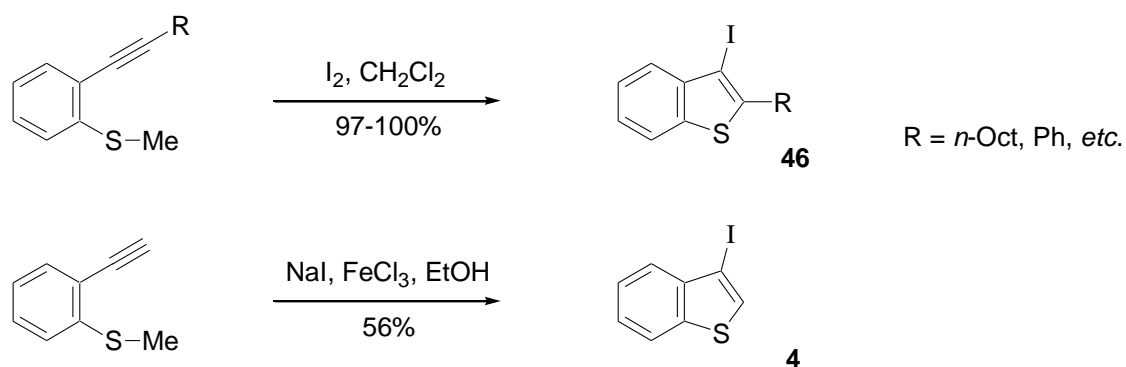
Scheme 19

2.1.2. By iodocyclization of (ethynyl)(sulfanyl)benzenes

In 1984, Larock and Harrison reported mercuration product **45** of *o*-(ethynyl)(sulfanyl)benzene **44** (Scheme 20).⁵⁴ Later, Turos *et al.* described aliphatic iodocyclization of (benzylsulfanylethyl)alkynes leading to five-membered ring compounds.^{55,56} In 2001, Flynn *et al.* and Larock *et al.* reported preparation 3-iodobenzo[*b*]thiophenes such as **46** by iodocyclization of *o*-(ethynyl)(sulfanyl)benzene (Scheme 21).^{57,58} In some cases, in situ generated I₂, for example from FeCl₃ and NaI, was used.⁵⁹ Thus, if the target compound is 2-substituted-3-iodobenzo[*b*]thiophene derivative, the iodocyclization is a candidate.⁶⁰ Compared to cyclization of internal alkynes, iodocyclization of a terminal alkyne to 2-unsubstituted 3-iodobenzo[*b*]thiophene derivative has been scarcely reported.^{59,61}



Scheme 20

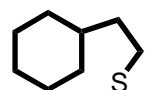


Scheme 21

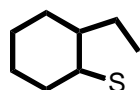
2.2. Precursors for benzo[*b*]thiophene core; with or without iodine

Classification of the '8 carbon - 1 sulfur' framework of benzo[*b*]thiophene precursors based on retrosynthesis-like bond cleavage (*i.e.*, bond formation in actual synthesis)

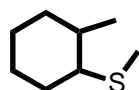
Single-component precursors



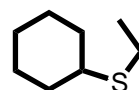
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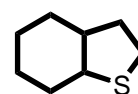
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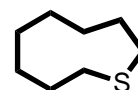
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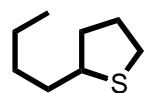
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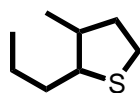
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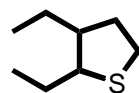
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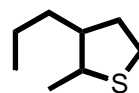
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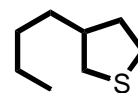
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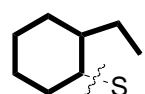


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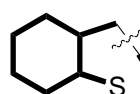


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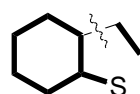
Two-component variation of the above precursors (examples)



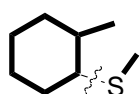
Type 2-v1



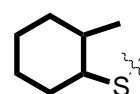
2-v3



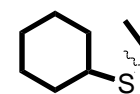
2-v4



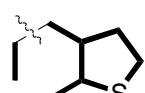
3-v1



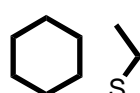
3-v2



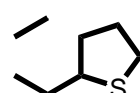
4-v2



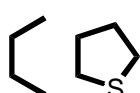
Type 9-v7



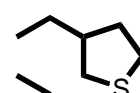
Type (1,4)



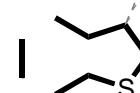
(6,8)



(6,10)



(8,10)



(5,7,9)

Figure 2. Classification of benzo[*b*]thiophene precursors

Figure 2 illustrates some possible precursors of benzo[*b*]thiophenes as those of '8 carbon - 1 sulfur' frameworks. Compared to the 5-membered ring moiety of benzo[*b*]thiophenes, the 6-membered ring moiety generally exhibits lower reactivity, as mentioned in section 2.1. Moreover, introduction of substituents to the benzene moiety demands highly regioselective method, reflecting the low symmetry of benzo[*b*]thiophene core. Thus, introduction of iodine atom to the 6-membered ring after completion of benzo[*b*]thiophene skeleton does not seem to be a good idea, unless a directing group exists.

In contrast, if we use iodine-containing precursors of benzo[*b*]thiophene, some reported preparative methods for benzothiophenes may be applicable and the synthesis will become easier. However, there are several restrictions due to high reactivity of iodine: it will be better to avoid halogen-metal exchange,

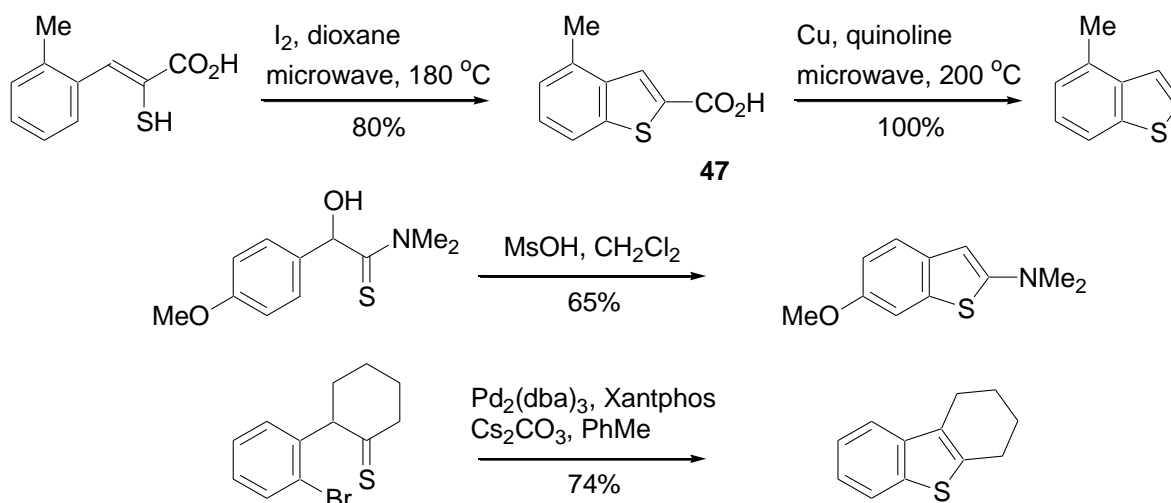
cross coupling reactions, and analogous reactions mediated by transition metals such as Pd, Cu, or Ni, throughout the synthetic process to iodobenzothiophenes, because reaction of iodine is easier than other halogens such as bromine and chlorine in these reactions. Furthermore, there may be a possibility of so-called halogen-dance side reaction in the case of halogen-metal exchange, and homo coupling side reaction in the case of cross coupling reactions. Other demerit of this strategy is possible increase in the number of synthetic steps. Consequently, iodine substituent is often used for preparation of *precursors*, and consumed prior to the conversion into the target benzothiophenes in many reported cases. Nevertheless, syntheses from iodine-containing precursors may prevail over the demerits in some appropriate cases. In order to help planning synthetic routes, this section lists some typical preparative methods of benzo[*b*]thiophenes, no matter whether the target compounds contain iodine or not.

2.2.1. Benzene-based precursors for preparation of benzo[*b*]thiophenes

If the target molecule contains iodine at the 6-membered ring moiety of benzo[*b*]thiophene, transformation of iodobenzene precursors will be practical. Among the possible precursors of types 1-4, those of types 2 and 3 have been utilized in many reports, as shown below.

Type 1 precursors

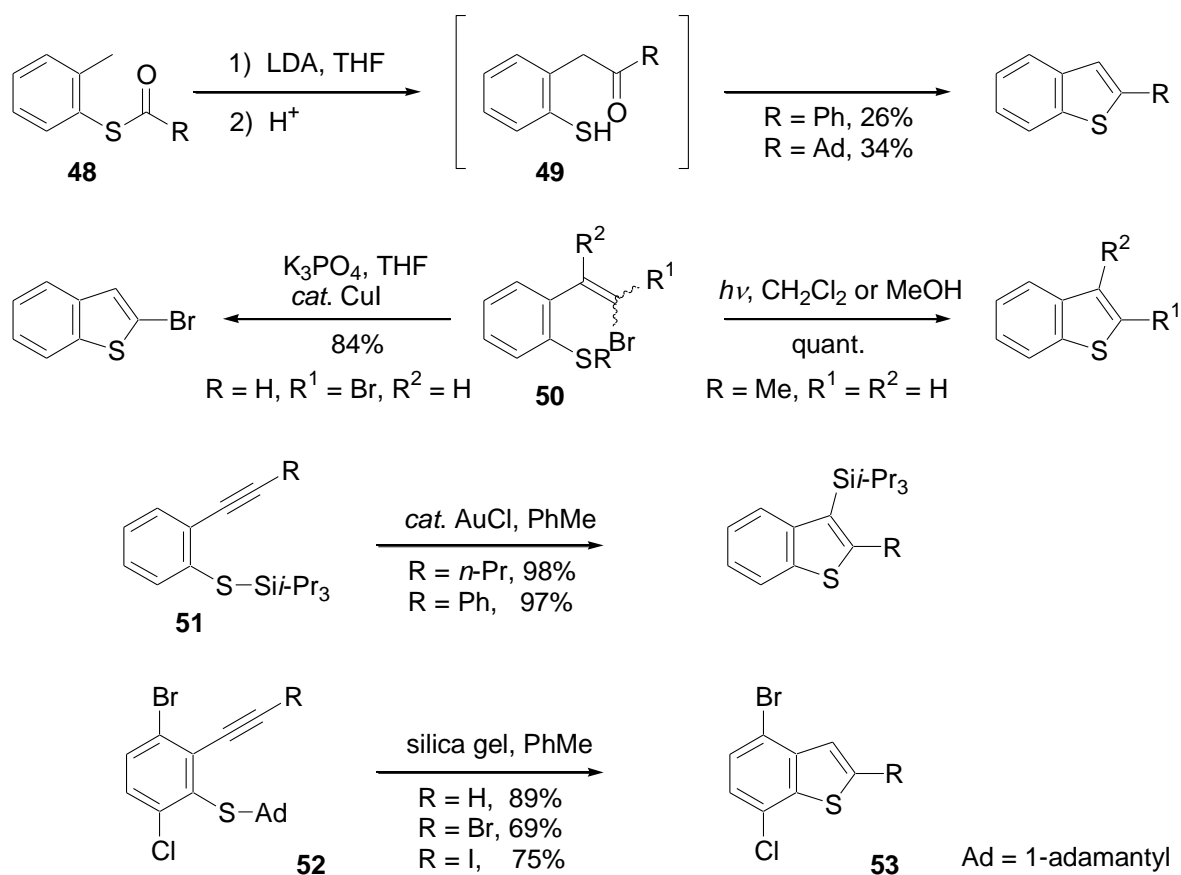
In general, this type of precursors possesses aliphatic sulfur functional group (Scheme 22).⁶²⁻⁶⁷ The number of reports is not so large, compared to that of precursors containing arylsulfanyl functional groups such as thiophenol. Regioselectivity may be a problem in some specific cases (see Type 4 precursors part). Heating with Cu / quinoline is a standard method for decarboxylation of benzo[*b*]thiophene-2-carboxylic acid derivatives such as **47**.⁶⁸



Scheme 22

Type 2 precursors

Various methods belong to this category (Scheme 23).⁶² Iodocyclization^{57,58} is also included in this class (see section 2.1.2.). *o*-(Sulfanylbenzyl)ketones **49** are supposed to be intermediates in the reaction of *o*-tolyl thioesters **48** (type 3 precursor) with LDA followed by protonation.⁶⁹

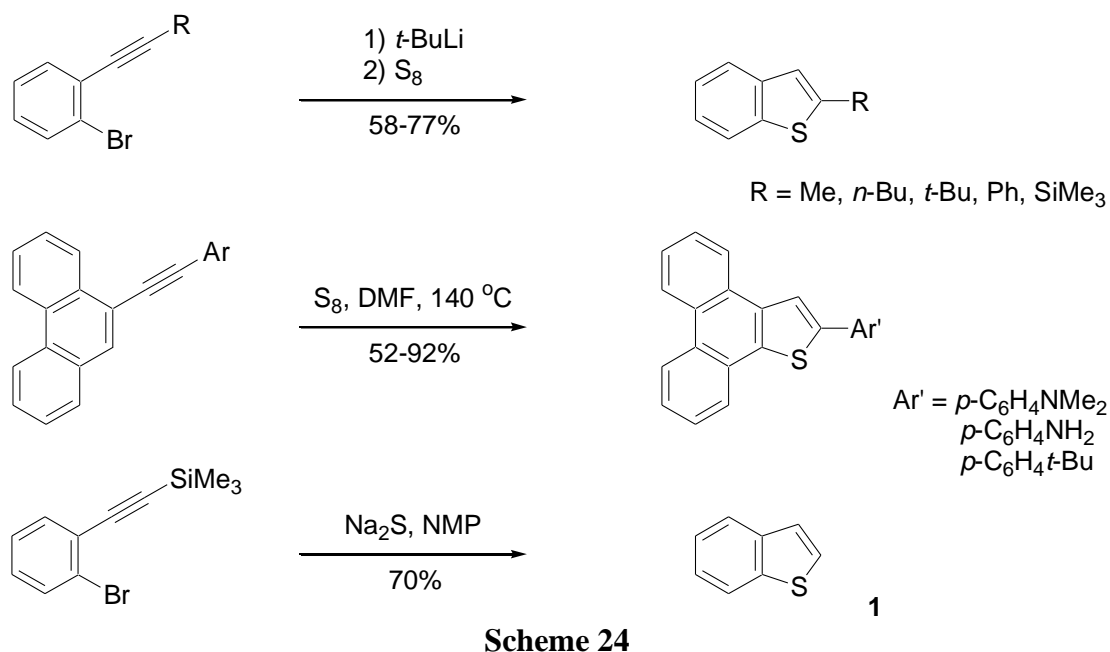


Scheme 23

Syntheses from *o*-(2-bromoethenyl)(sulfanyl)benzenes **50** in the presence of CuI catalyst⁷⁰ or under UV irradiation^{71,72} were reported. Concerning alkynes, cyclization of *o*-(ethynyl)(sulfanyl)benzenes **51** in the presence of Lewis acid catalysts has been investigated.^{73,74} Silica gel-assisted preparations of benzo[b]thiophenes **53** from alkynes **52** (terminal alkynes or haloalkynes) have also been reported.⁷⁵

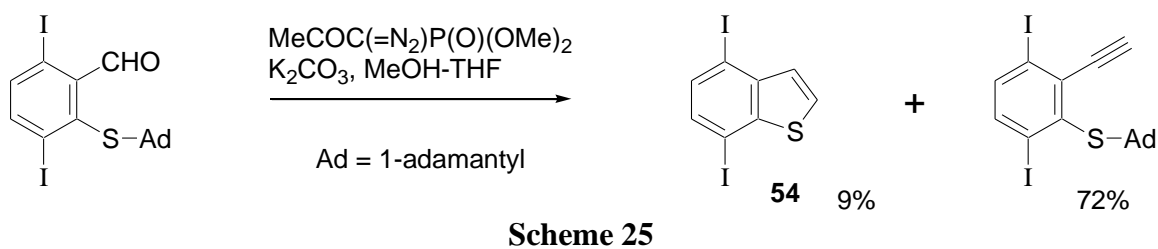
Type 2-v1 precursors

Some synthetic methods using elemental sulfur in the final step were reported.^{76–78} Two of them are shown in Scheme 24. In these reactions, intermediates similar to the type 2 precursors are supposed. As a related preparation, Na₂S was also used as a sulfur source (Scheme 24).⁷⁹ For analogous but different combination of bromophenyl–sulfur–alkynyl precursor system of the type 2 class, see Scheme 26 (Type 2-v4).



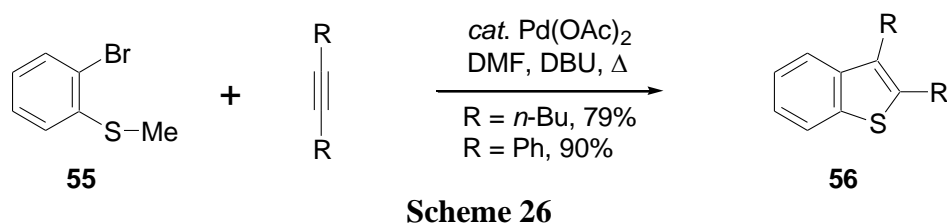
Type 2-v3 precursors

Ohira-Bestmann reagent is normally used for conversion of aldehyde into terminal alkynes. However, in the reaction shown in Scheme 25, benzo[*b*]thiophene **54** was generated as a by-product.⁸⁰ Substituents at the both *o*-positions of the CHO seems to be necessary for production of benzothiophenes. A combination of *o*-(acyl)(sulfanyl)benzene with a ylide $^-\text{CH}_2\text{S}^+\text{Me}_2$ is another example of this class.⁸¹



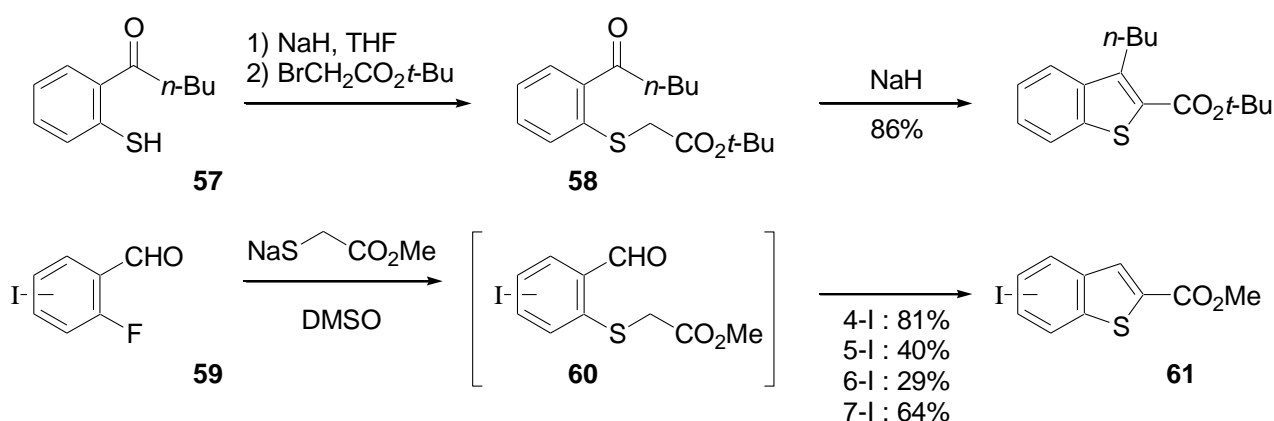
Type 2-v4 precursors

Transition metal-mediated reactions of *o*-bromo(sulfanyl)benzene with alkynes led to benzothiophenes.⁸² In the case of **55** with unsymmetrical internal alkynes ($\text{R}-\text{C}\equiv\text{C}-\text{R}'$), the products **56** tend to be mixtures of isomers bearing the larger substituents at the C-2 position (Scheme 26).⁸³

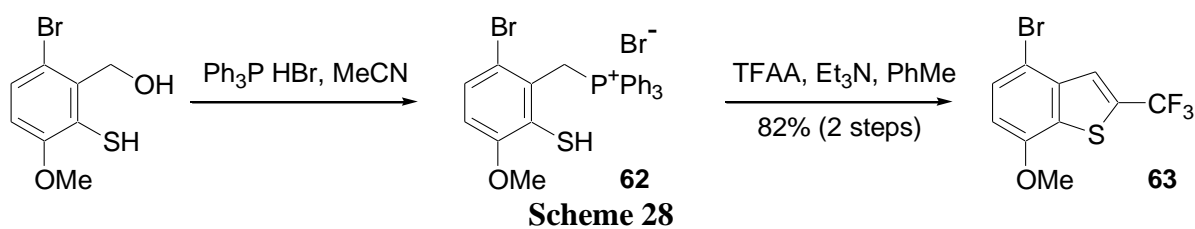


Type 3 and related precursors (Type 3-v1, Type 3-v2)

One example of Type 3 precursor has been shown in Scheme 23.⁶⁹ Knoevenagel-type condensation of *o*-(β -ketoalkylsulfanyl)phenyl carbonyl compounds is one of the typical traditional methods for preparation of 2-substituted benzo[*b*]thiophenes.^{84,85} *o*-(Acyl)thiophenols and *o*-fluorobenzaldehydes such as **57** and **59**, respectively, are often used as starting materials (Scheme 27).^{86,87} Benzothiophene-2-carboxylates **61** containing iodine at the benzene moiety were prepared by this method.⁸⁷

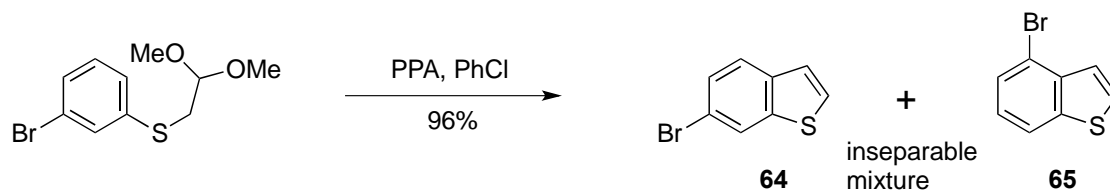


The following reaction of **62** can be regarded as a formal Wittig reaction between in situ generated $\text{CH}=\text{PPh}_3$ and $\text{S}-\text{COCF}_3$ groups, leading to **63** (Scheme 28).⁸⁸ See also the related references.⁸⁹

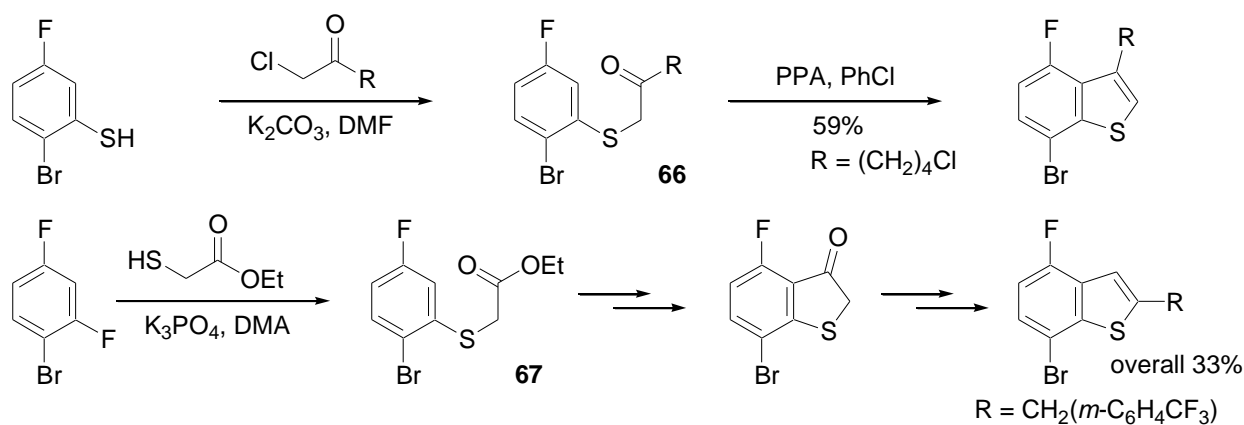


Type 4 and related precursors

Preparation of the precursors of this category may be easier than other methods.⁹⁰⁻⁹⁶ However, regioselectivity become a problem in specific cases. For example, products **64** and **65** in Scheme 29 were not separated through column chromatographic treatment.⁹⁵ In Scheme 30, structurally similar ketone **66**⁹² and ester **67**⁹³ were prepared from different sulfur compounds and converted into 3- and 2-substituted benzo[*b*]thiophenes, respectively. Reaction of thiophenol with substituted propiolates in the presence of iodine and di-*t*-butyl peroxide (DTBP) led to benzo[*b*]thiophenes (Scheme 30).⁹⁶ In these reactions, intermediates analogous to type 4 precursor were proposed (see also, Scheme 26).



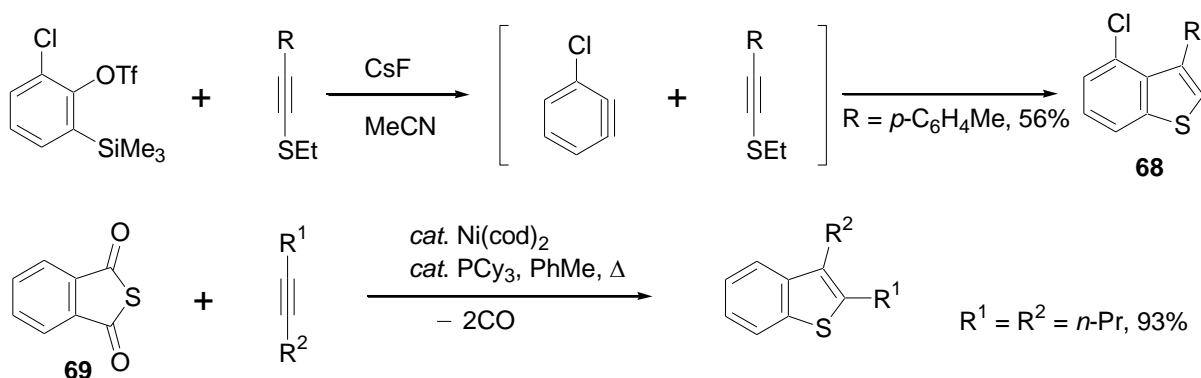
Scheme 29



Scheme 30

Type (1,4) and related precursors

Some syntheses via benzyne derivatives were reported (Scheme 31). In this type of reactions, ketene dithioacetal⁹⁷ or sulfanylacetylene⁹⁸ were used as '2 carbon – 1 sulfur' moieties. The regioselectivity was relatively good for some mono-substituted benzyne to give benzothiophenes like **68**.^{98,99} A unique sulfur source related to this type of precursor is thiophthalic anhydride **69**, which led to benzothiophene via double decarbonylation with Ni catalyst.⁹⁹ The formation of the product depends on the choice of trialkylphosphines and a problem of regioisomers exists in the case of unsymmetrical alkynes.



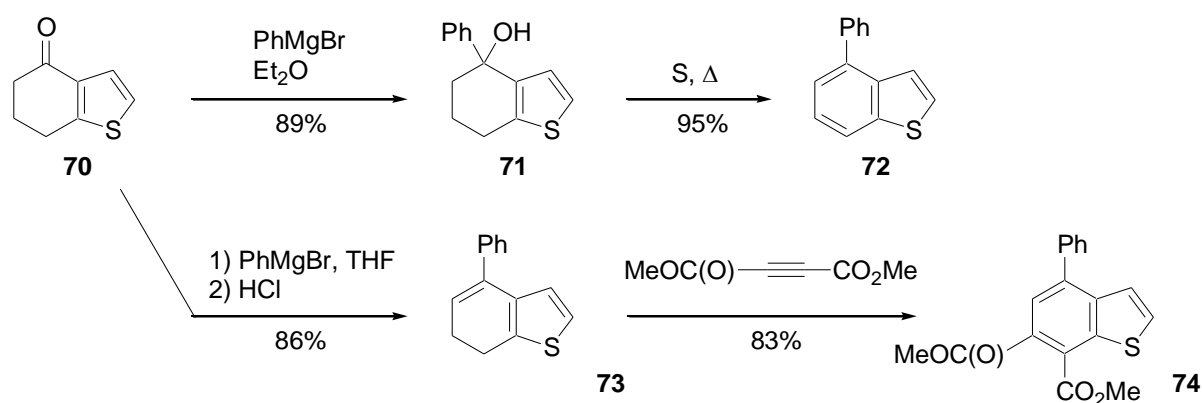
Scheme 31

2.2.2. Thiophene-based precursors for preparation of benzo[*b*]thiophenes

As mentioned in Section 2.1.1.1., iodination at 2- and/or 3-positions of benzo[*b*]thiophene is not so difficult, compared to that at 4- to 7-positions. Thus, for the purpose of preparation of 2- or 3-iodobenzo[*b*]thiophenes, multi-step conversion from iodothiophene-based precursors is not so practical. Furthermore, relatively high reactivity of iodothiophene makes the route difficult: The reactions in this section are those for preparation of iodine-free benzo[*b*]thiophene derivatives.

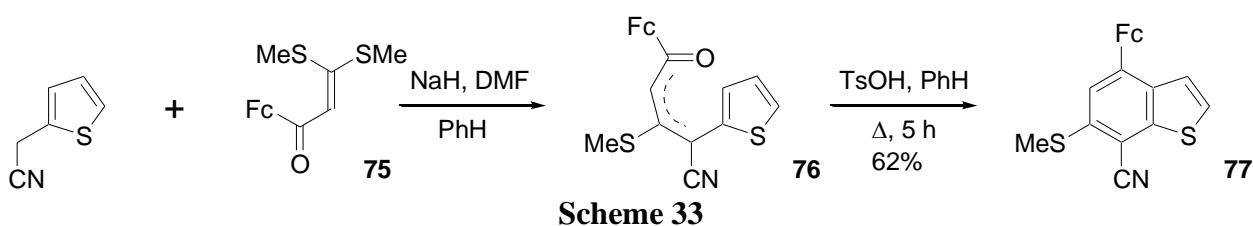
Type 0 and related Type (8,10) precursors

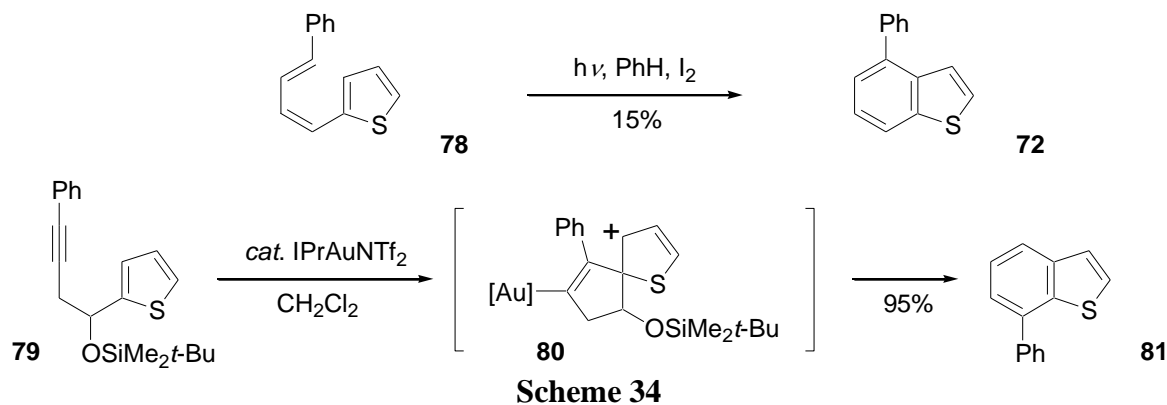
Bicyclic precursors such as tetrahydrobenzothiophenone **70** have been utilized (Scheme 32).^{100–102} After introduction of phenyl group, compound **71** was dehydrated and dehydrogenated with sulfur to give benzothiophene **72**.¹⁰⁰ A combination of **73** and a symmetrical alkyne was used as the ‘two-component’ type (8,10) precursor, which led to benzothiophene **74** via Alder-Rickert reaction.¹⁰³



Type 6 precursors

Reaction of 2-thienylacetonitrile anion with a ketene dithioacetal **75** followed by acid-catalyzed cyclization of **76** gave a 4-ferrocenylbenzo[*b*]thiophene **77** (Scheme 33).¹⁰⁴ An analogous cyclization occurred, when 3-thienylacetonitrile was used (see Type 10 precursors section). As shown in Scheme 34, formation of 4-phenylbenzo[*b*]thiophene **72** by oxidative-photocyclization of phenyl(thienyl)butadiene **78** was reported (for analogous reaction, see Scheme 40).¹⁰⁵ This type of photocyclization have been used for construction of multi-annulated heteroacenes.^{106,107}

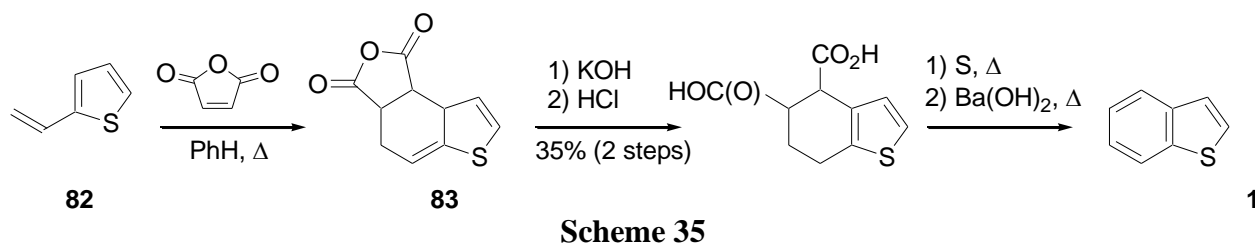




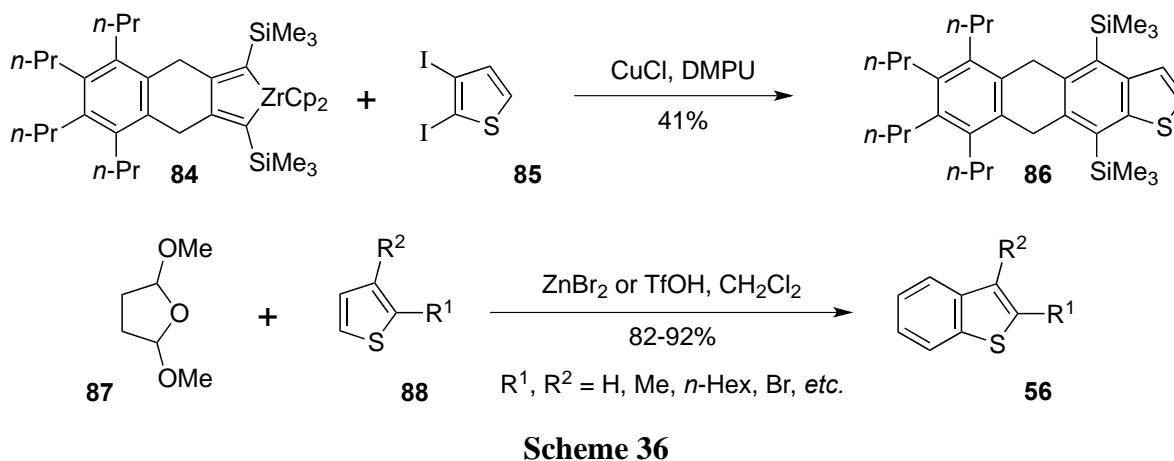
Interestingly, activation of the triple bond in **79** with Au catalyst induced a nucleophilic attack of the thiophene π electrons leading to 7-phenyl derivative **81**, after rearrangement of **80** (Scheme 34).¹⁰⁸

Type (6,8) and Type (6,10) precursors

Diels-Alder reaction of 2-vinylthiophene **82** with maleic anhydride followed by hydrolysis of the adduct **83**, dehydrogenation, and decarboxylation, forming benzo[*b*]thiophene **1** was reported (Scheme 35).^{109,110}

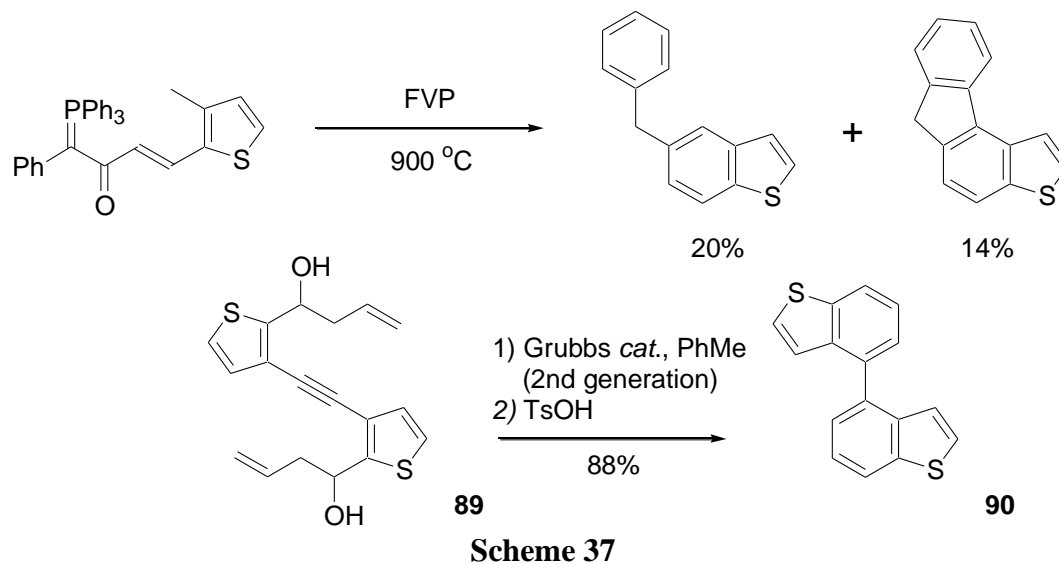


Reaction of 2,3-diiodothiophene **85** with zirconacyclopentadiene **84** afforded benzothiophene **86** (Scheme 36).⁴³ 2,2'-Diodobiphenyl reacted with 2,3-diphenylthiophene in the presence of AgOPiv, TfOH, and Pd catalyst to give phenanthrothiophene in 40% yield.¹¹¹ Reactions of 2,5-dimethoxytetrahydrofuran **87** with thiophenes **88** were mediated by ZnBr₂ or TfOH.¹¹²



Type 7 precursors

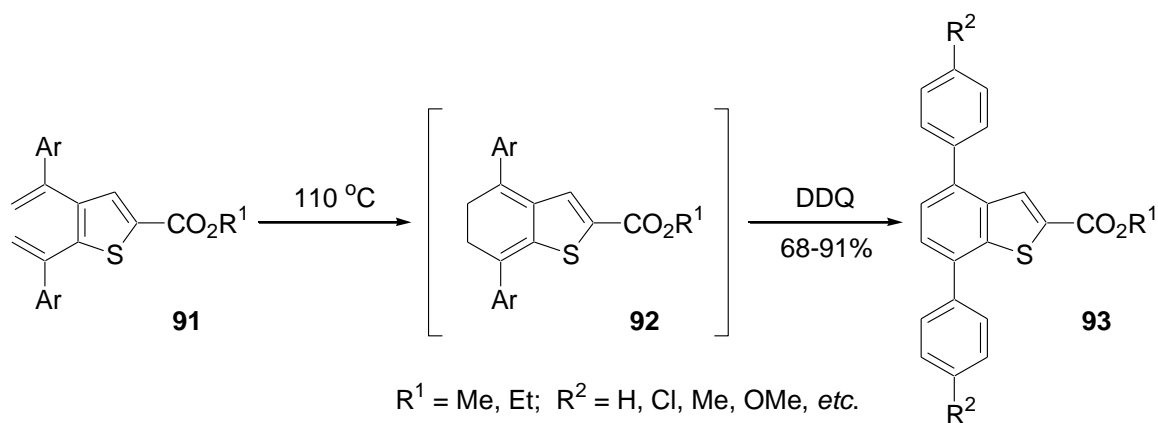
Two unique examples are shown below (Scheme 37).^{113,114} The latter adopted ring-closing metathesis of **89** using Grubbs second generation catalyst to give simple 4,4'-bibenzo[*b*]thiophene **90**.



Scheme 37

Type 8 precursors

A sigmatropic rearrangement of **91** was effectively applied to form 6-membered ring of **92**, followed by oxidation leading to **93** (Scheme 38).¹¹⁵

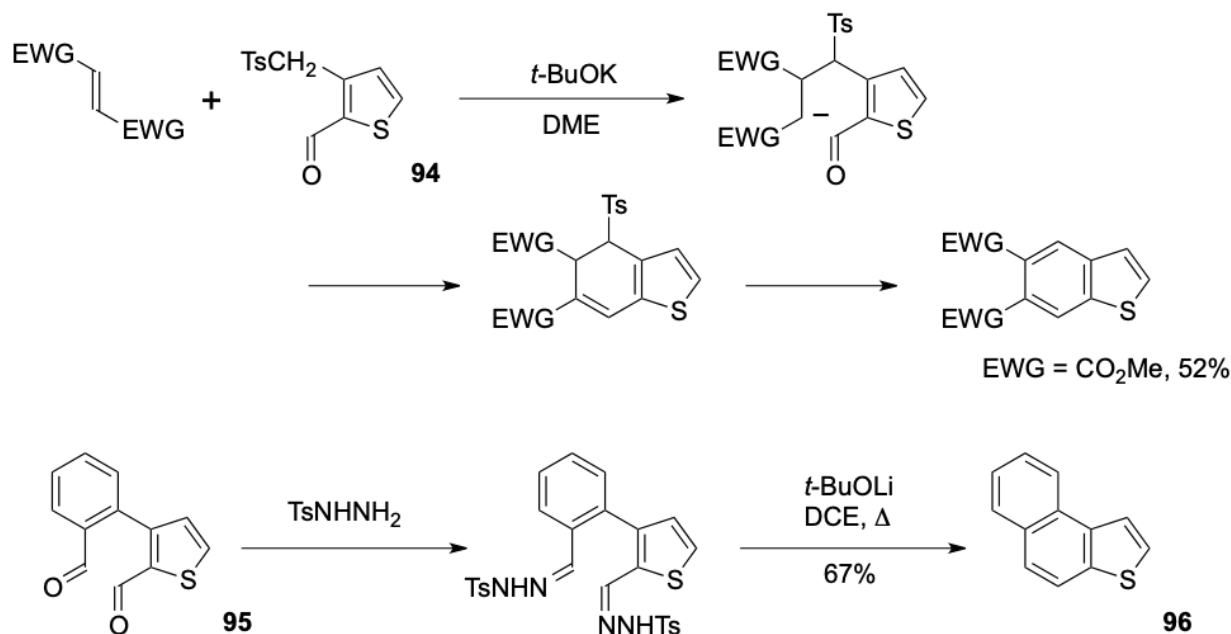


Scheme 38

Type 9 and the related Type 9-v7 precursors

3-Substituted 2-thiophenaldehyde **94** reacted with a base and dimethyl fumarate to give 5,6-disubstituted benzo[*b*]thiophene (Scheme 39).¹¹⁶ The precursor of type 9 was supposed to be generated in situ.

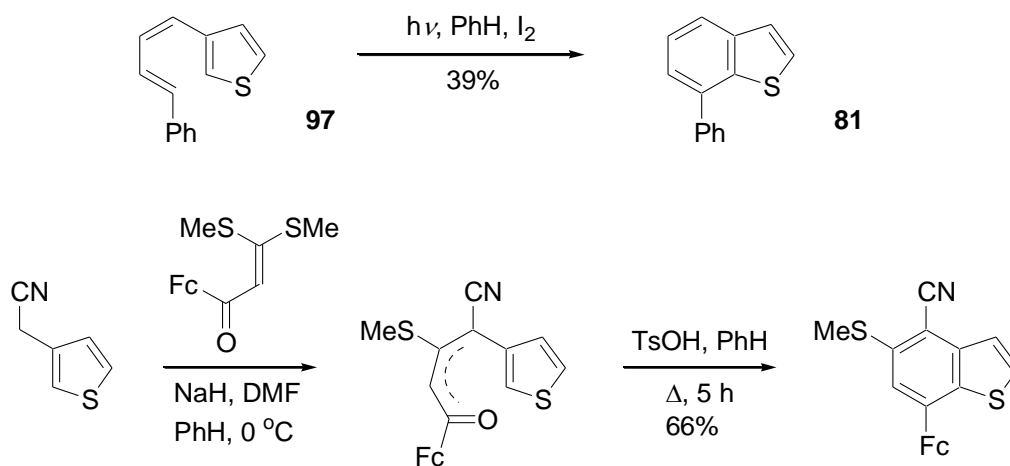
Starting from dialdehyde **95**, naphthothiophene **96** was produced by detosylative cyclization of bis-*N*-tosylhydrazone.¹¹⁷ This type of detosylative cyclization was also performed using a gold catalyst in 77% yield.



Scheme 39

Type 10 precursors

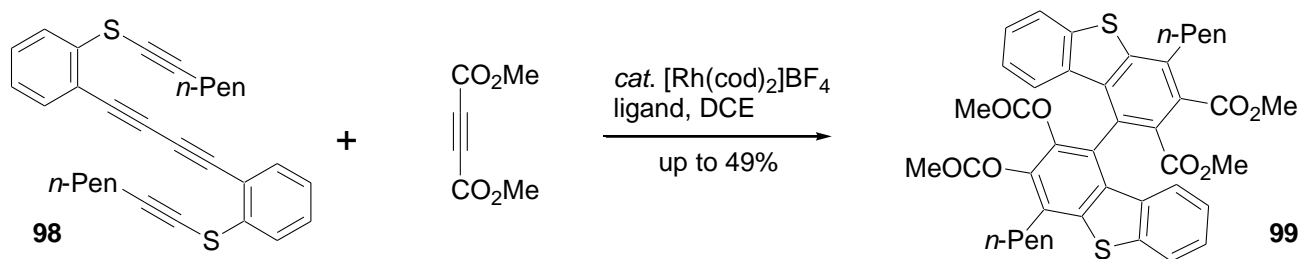
Oxidative-photocyclization of 1-phenyl-4-(3-thienyl)butadiene **97** afforded 7-phenylbenzothiophene **81** in 39% yield (Scheme 40, see also type 6 precursor part).¹⁰⁵ Ferrocenyl-substituted benzo[*b*]thiophene was prepared from 3-thienylacetonitrile, by analogous reaction shown in Scheme 33.¹⁰⁴



Scheme 40

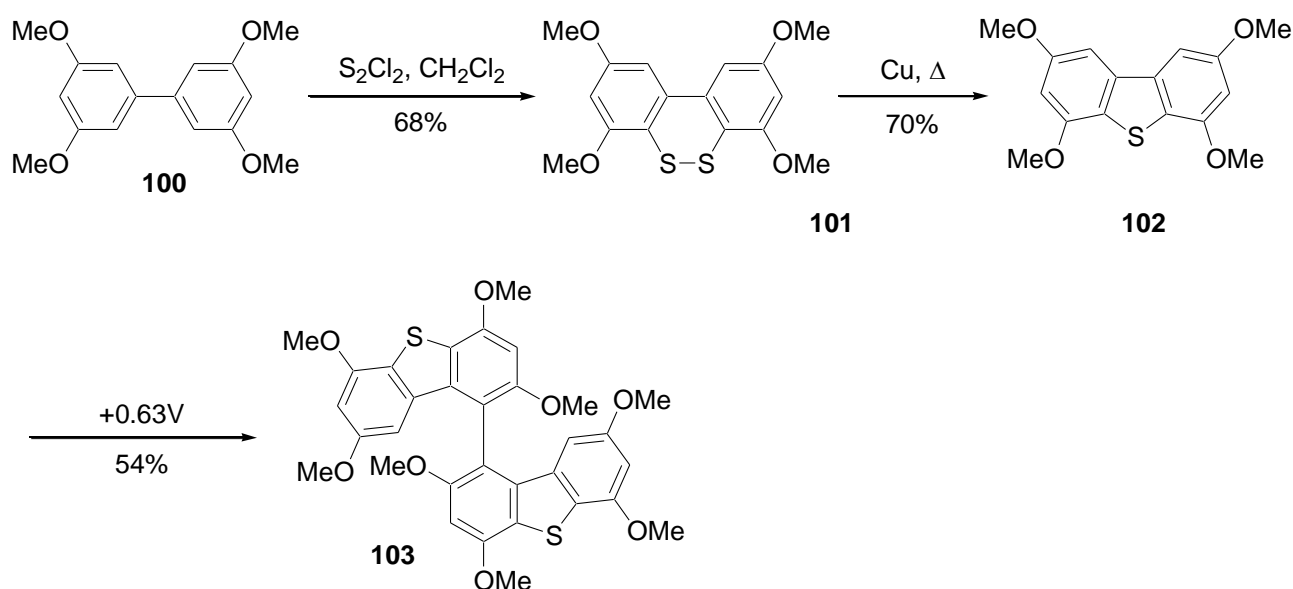
2.2.3. Other precursors

A unique precursor **98** was utilized in preparation of a chiral 1,1'-bidibenzothiophene species **99** as shown in Scheme 41.⁴⁵ The precursor **98** seems to be a benzene-based type 3 precursor, however, it can be regarded also as a part of two-component type (5,7,9) precursor: Thiophene and benzene rings were constructed at the same time by metal-catalyzed [2+2+2] cycloaddition in the presence of a chiral ligand.



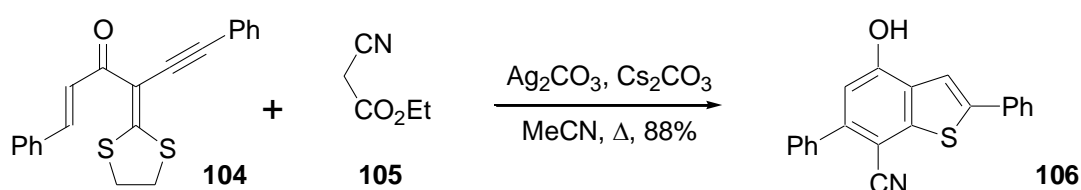
Scheme 41

Another 1,1'-bidibenzothiophene derivative **103** was prepared by anodic oxidation of dibenzothiophene **102** (Scheme 42).¹¹⁸ In this case, the π -system of the starting biphenyl **100** is similar to the type 2-v1 precursor in Scheme 24, however, the disulfide **101** can be regarded also as a precursor. Desulfurization of **101** was performed with copper.



Scheme 42

Scheme 43 exhibits a construction of benzothiophene **106** by a kind of tandem cyclization of two-component precursor **104** and **105**, using the ketene dithioacetal **104** as a sulfur source.¹¹⁹



Scheme 43

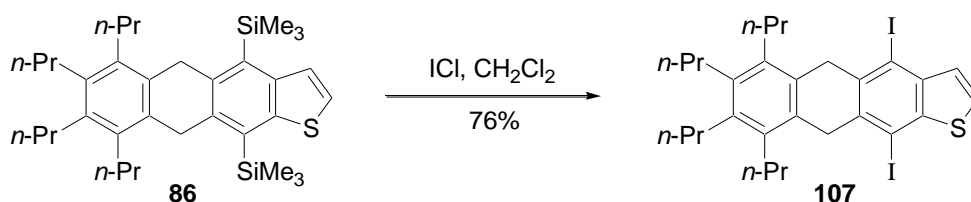
3. PREPARATION AND REACTIONS OF 4,7-DIHALOBENZO[*b*]THIOPHENES CONTAINING IODINE

Despite the variety of preparative methods for benzo[*b*]thiophenes, syntheses of *iodine-containing* 4,7-dihalobenzo[*b*]thiophene building blocks have been limited. One reason is that iodine atoms in the precursor are often utilized for construction of benzothiophene skeleton and ‘consumed’ before completion of the final product. For purpose of making valuable multi-functional scaffolds in artificial molecular architecture, building blocks containing both iodine and other halogen atoms are desirable for regioselective transformations. Most of the reported preparations and reactions of iodine-containing 4,7-dihalobenzo[*b*]thiophene building blocks are summarized in this review as follows.

3.1. Preparation of 4,7-dihalobenzo[*b*]thiophenes containing iodine

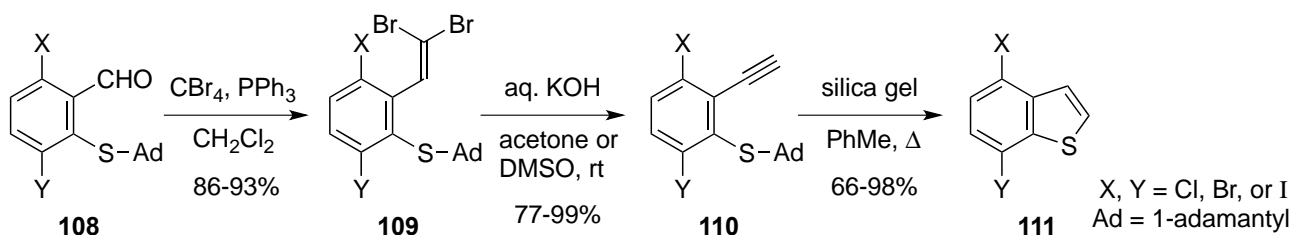
3.1.1. Iodine at the 6-membered ring

4,7-Diiodobenzo[*b*]thiophene derivative **107** was prepared by iodination of bis(trimethylsilyl) derivative **86** (Scheme 44).⁴³



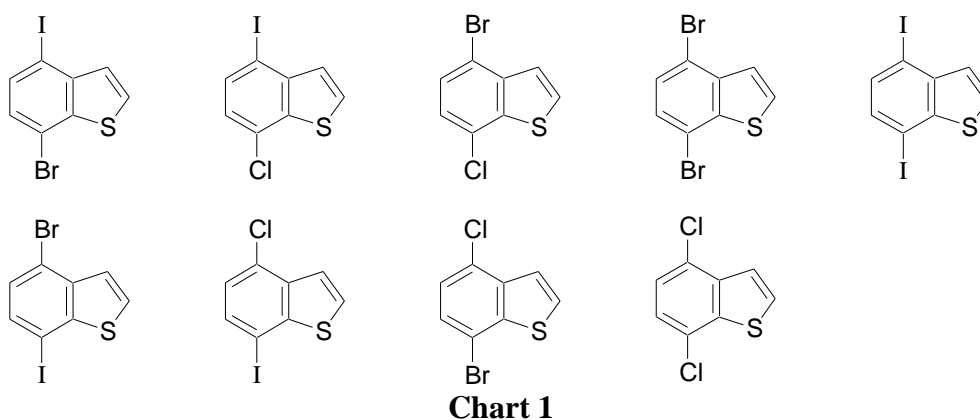
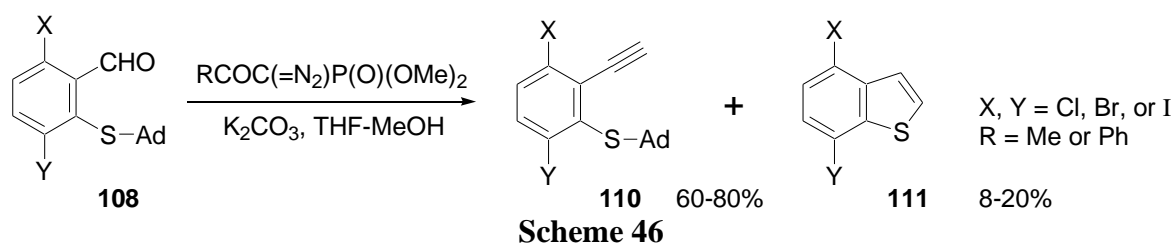
Scheme 44

Regioselective transformation of a single iodine from unsymmetrical diiodo compounds (such as **107**) may be possible in some specific situations, utilizing the electronic effect of the proximate sulfur atom. However, for cross coupling reactions, (bromo)(iodo)derivative or (chloro)(iodo)derivative seems to be advantageous (see section 3.2.). For preparation of such dihalo-compounds, transformation from (halo)(iodo)benzene precursors is practical, by reason mentioned in section 2.1.1.1., and this was realized by adopting silica gel-assisted cyclization of (ethynyl)(sulfanyl)dihalobenzenes **110** to **111** (Scheme 45).⁷⁵ In the preparation of **110** from the dibromoalkene **109**, mild (formal) Corey-Fuchs reaction conditions using KOH / H₂O in acetone or DMSO was applied in order to keep the halogen atoms X and Y.^{61,75}

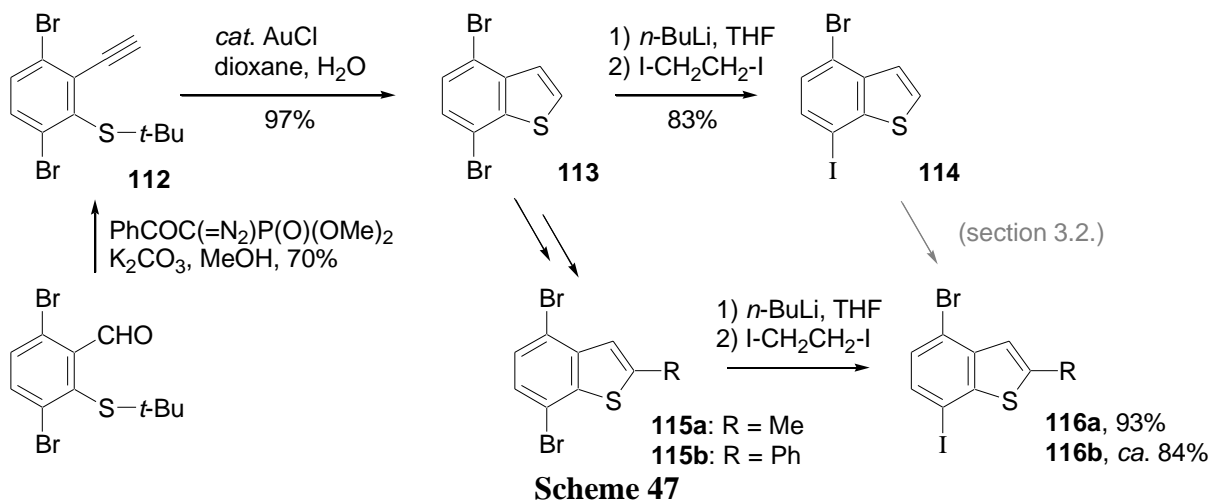


Scheme 45

Reaction of the aldehyde **108** with Ohira-Bestmann reagent also afforded the 4,7-dihalobenzothiophenes **111** as minor products (Scheme 46).⁸⁰ 4,7-Dihalobenzo[*b*]thiophenes obtained by silica gel-assisted cyclization and/or by Ohira-Bestmann reagents are listed in Chart 1.

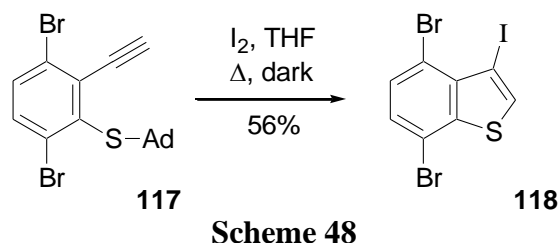


4,7-Dibromo derivative **113** was alternatively prepared from the corresponding (*t*-butylsulfanyl)ethynylbenzene **112** by using AuCl catalyst in 1,4-dioxane-H₂O (Scheme 47).⁷⁴ Bromine-lithium exchange of **113** occurred selectively at C-7 position and afforded 4-bromo-7-iodo derivative **114**. This type of iodination is also applicable to 2-substituted derivatives, if the substituents are tolerable to butyllithiums, as shown in the cases of **115a,b** to **116a,b**, respectively.⁸⁰

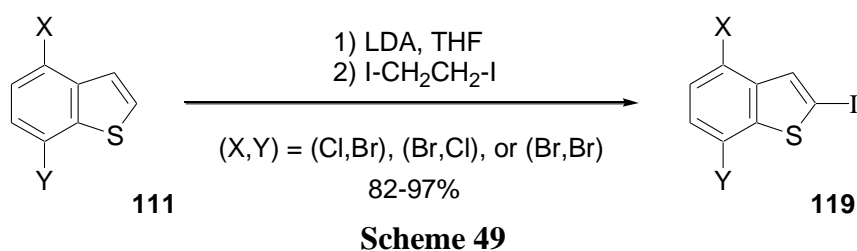


3.1.2. Iodine at the 5-membered ring

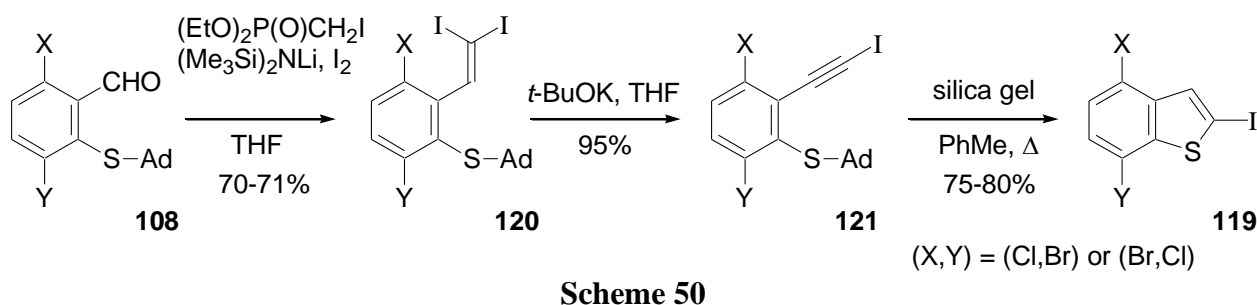
3-Iodo-4,7-dibromobenzothiophene **118** was prepared by iodocyclization of **117** (Scheme 48).⁶¹



2-Iodo-4,7-dihalobenzo[*b*]thiophenes **119** were prepared by deprotonation of **111** with LDA followed by reaction with 1,2-diiodoethane (Scheme 49).^{75,80} In general, this method using LDA can be applicable to other electrophiles and does not seem to affect the halogen atoms on the benzene ring.



Silica gel-assisted cyclization was effectively applied to preparation of 2,4,7-trihalobenzo[*b*]thiophenes: (iodoethynyl)(sulfanyl)benzenes **121** were generated from the corresponding diiodoalkenes **120** and then converted into 2-iodobenzo[*b*]thiophenes **119** (Scheme 50).⁷⁵ 2,4,7-Trihalobenzo[*b*]thiophenes obtained by analogous silica gel-assisted cyclization are listed in Chart 2.^{75,80}



(Iodoethynyl)(sulfanyl)benzene **122** was also prepared from the corresponding terminal alkyne **117** using I_2 / 2,2,6,6-tetramethylpiperidine (TMP), and converted into benzothiophene **123** (Scheme 51).⁶¹ This method was applicable to other electrophiles, such as DMF, leading to 2-substituted benzothiophenes after silica gel-assisted cyclization.

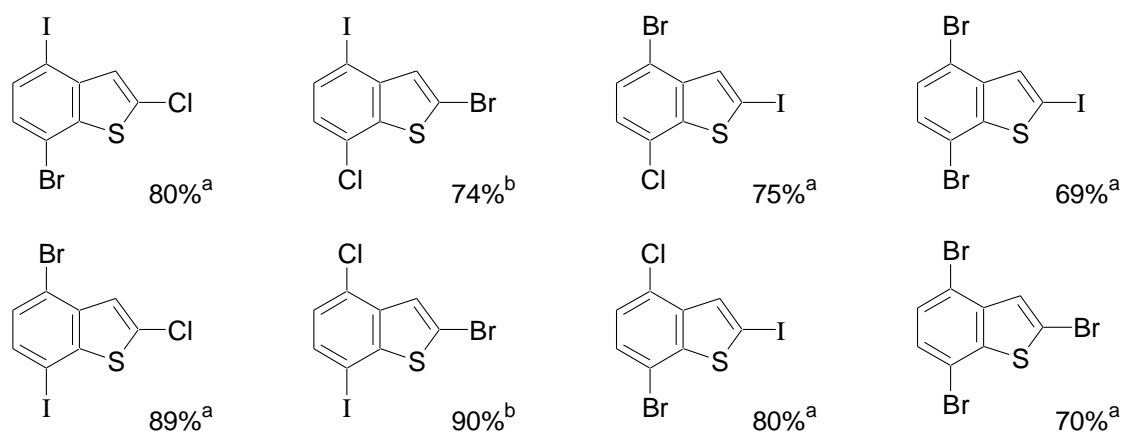
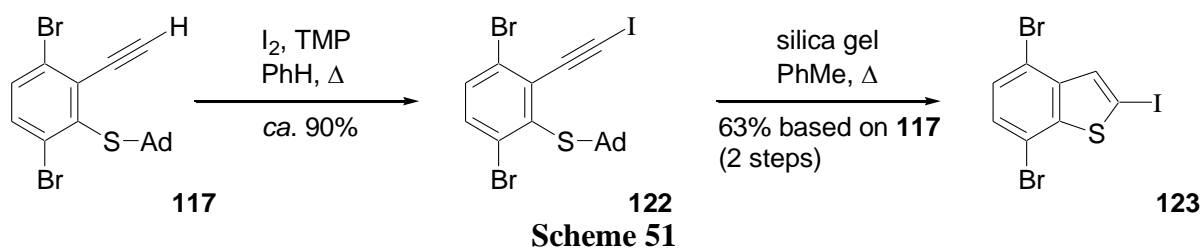
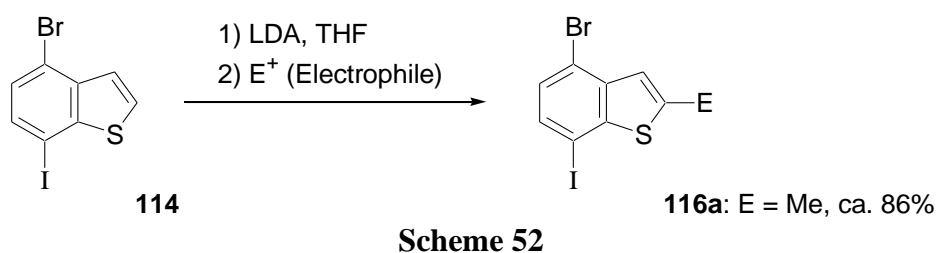


Chart 2 (Yields based on the corresponding (a) haloalkynes or (b) dihaloalkenes (2 steps) are shown.)

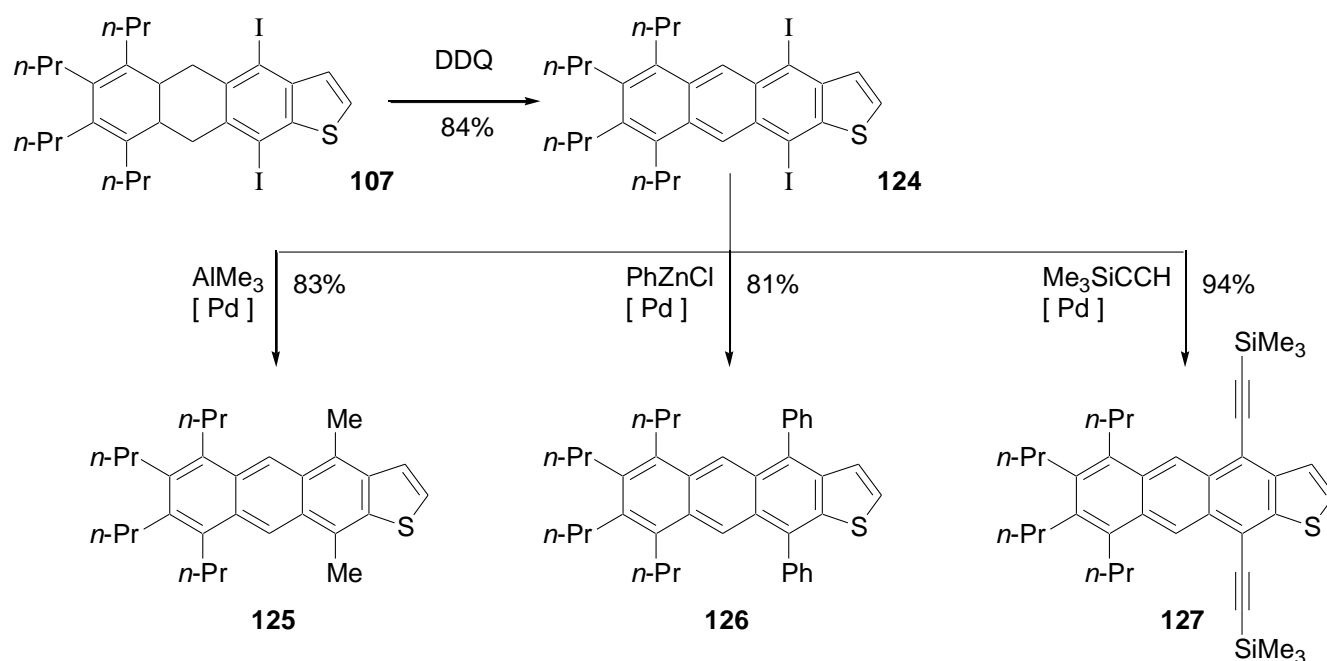


3.2. Reactions of 4,7-dihalobenzo[*b*]thiophenes containing iodine

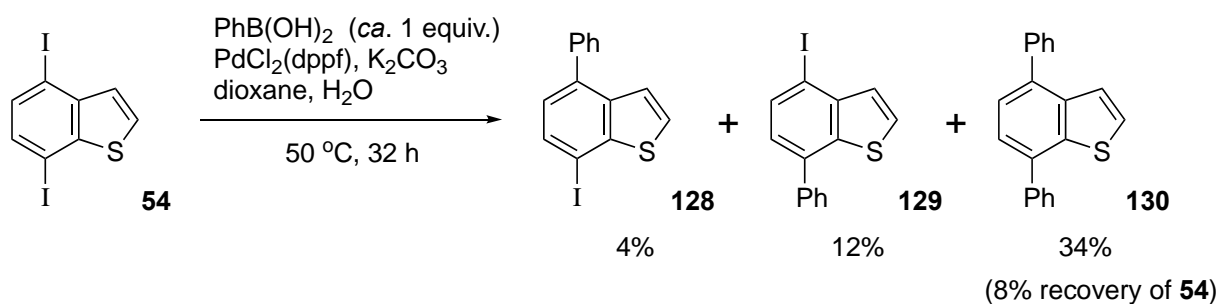
Reaction of the (bromo)(iodo) derivative **114** with LDA followed by treatment with iodomethane afforded **116a** in good yield (Scheme 52; S. Mikami and K. Toyota, unpublished results). As the lithiation of 4,7-dihalobenzo[*b*]thiophene with LDA at C-2 position does not generally affect the halogen atoms at the 4,7-positions, succeeding reactions seem to be applicable to various electrophiles and the iodine atom can be ‘reserved’ until it is subjected to cross couplings.



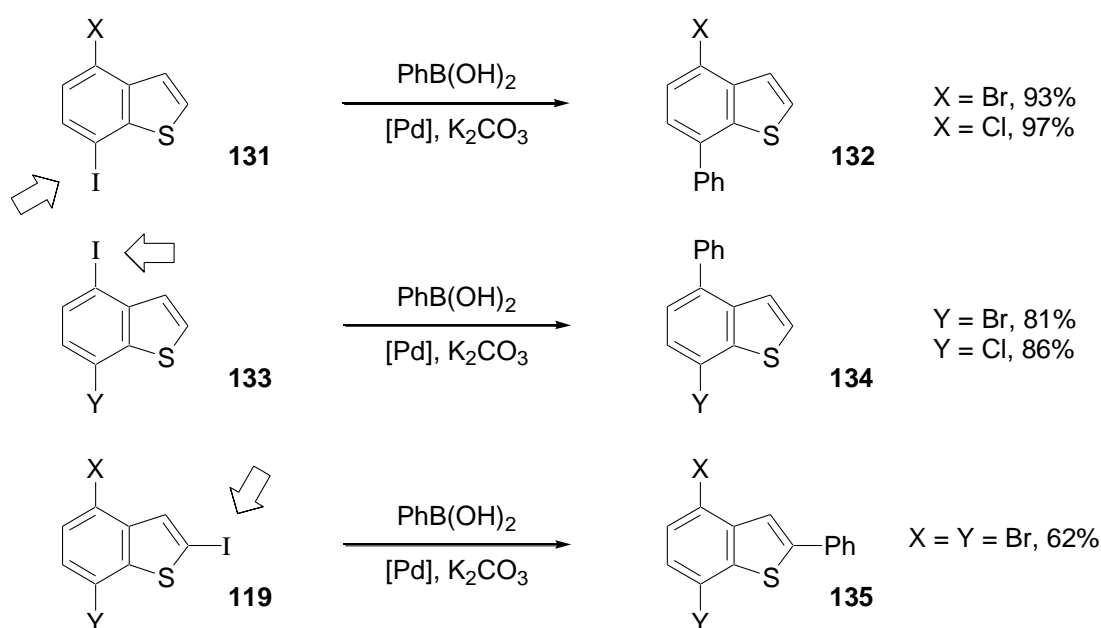
The iodine-containing derivatives are expected to take important roles in cross coupling reactions. Takahashi *et al.* reported cross coupling reactions of diiodoanthrathiophene derivative **124** using 2.5 molar amount of the coupling partner to give the products **125–127** in good yields (Scheme 53).⁴³



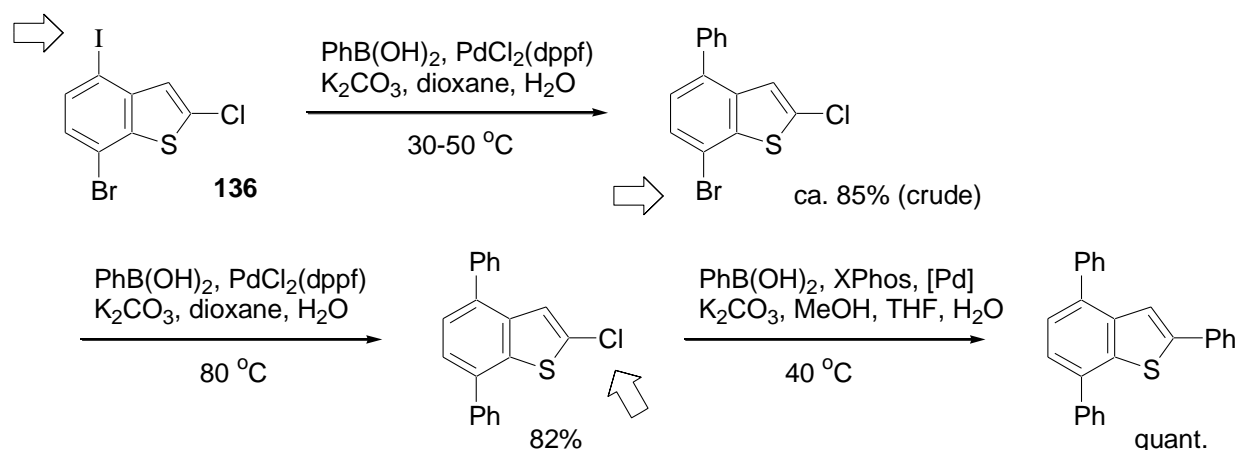
In the case of an equimolar reaction of diiodo derivative, however, regioselectivity will become a problem. In fact, a cross coupling reaction of simple 4,7-diiodobenzo[*b*]thiophene **54** with *ca.* 1 molar equivalent of phenylboronic acid resulted in a mixture of 4-phenyl, 7-phenyl, and 4,7-diphenyl derivatives **128–130** with a significant amount of recovery of the substrate (Scheme 54).⁸⁰



In contrast, reactions of (bromo)(iodo)- or (chloro)(iodo)-derivatives gave single products **132**, **134**, and **135** in medium to very good yields (Scheme 55).⁸⁰ Furthermore, stepwise introduction of phenyl groups using (bromo)(chloro)(iodo)benzo[*b*]thiophene **136** demonstrated good yield for each step (Scheme 56).¹²⁰



Scheme 55



Scheme 56

Introduction of different substituents have also been performed using (bromo)(iodo) derivative, which led to peptide- or α helix-inspired molecules.⁷⁴ Chart 3 exhibits an α helix mimicking-oligoarene **137**^{121,122} and oligonaphthalene **138**.¹²³ The 4-bromo-7-iodo-2-methyl derivative **116a** (Scheme 52, E = Me) was converted into oligoarene **140** containing five side chains [four (triisopropylsilyl)ethynyl groups and a methyl group] with main axis of *ca.* 3 nm length.⁷⁴ Stepwise Suzuki coupling afforded a sequence-defined oligoarene **139** with three different side chains (Chart 3). Further elongation of the functionalized oligoarenes is expected by using the 2-substituted 4,7-dihalobenzo[*b*]thiophene scaffolds.

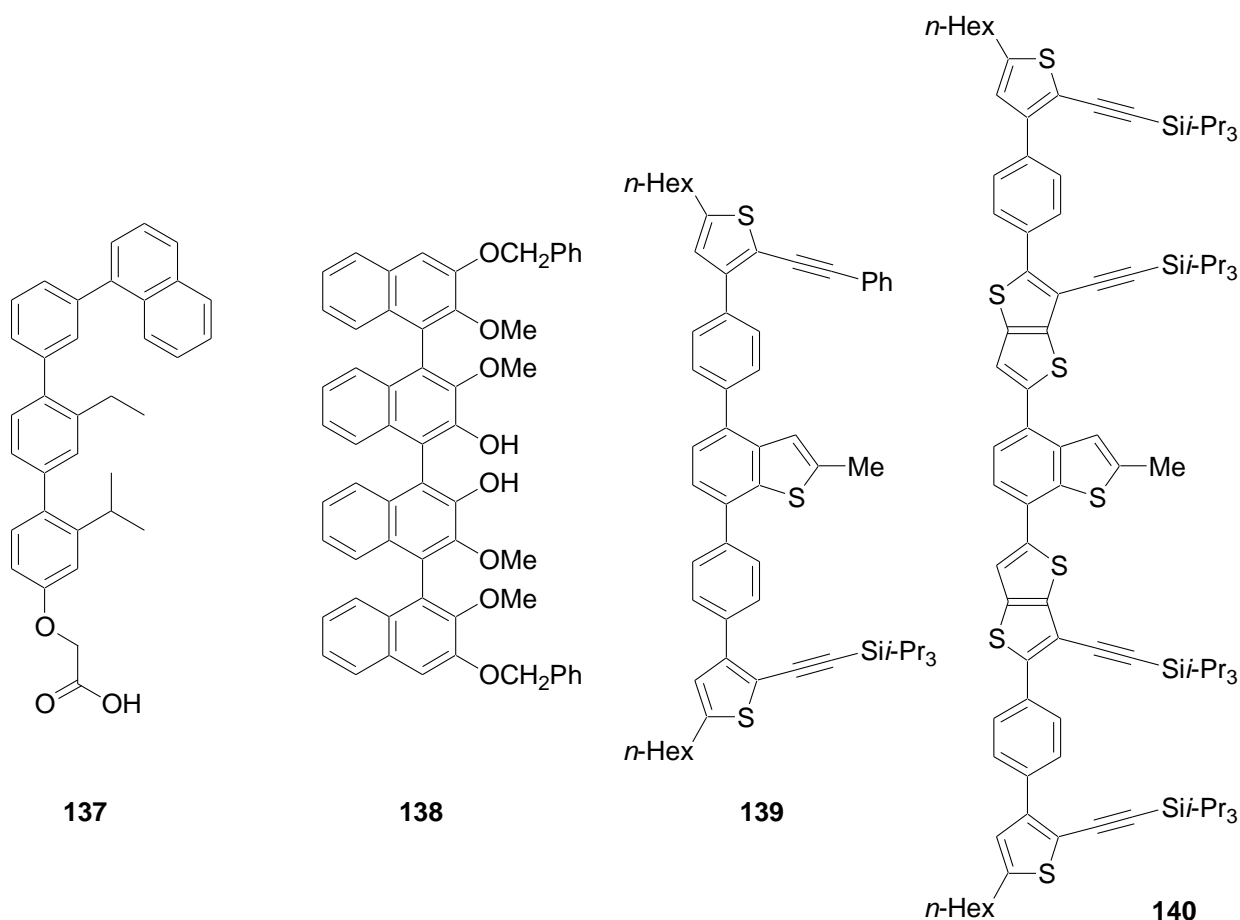


Chart 3

4. CONCLUSION

In section 2.1., preparations of iodobenzo[*b*]thiophenes from iodine-free compounds were described. In section 2.2., synthetic methods for benzo[*b*]thiophenes were briefly surveyed based on a skeletal classification of the precursors. Apparently, several methods and reagents in section 2.2. do not match for preparation of iodine-containing benzo[*b*]thiophenes, mainly because of the high reactivity of the iodo-substituent. Nevertheless, various iodobenzo[*b*]thiophenes have been reported and some of them are described in section 2.2. In section 3, preparations of iodinated 4,7-dihalobenzo[*b*]thiophenes were summarized. Reactions of the iodine-containing 4,7-dihalobenzo[*b*]thiophene scaffolds as well as their application to artificial molecular architecture are also shown in this review.

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