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Preparation of Benzothiophenes and Benzoselenophenes from Arylamines and Alkynes *via* Radical Cascade Reactions

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Abstract: An intermolecular radical cascade reaction between readily prepared *o*-methylthio-arylamines or *o*-methylselanyl-arylamines and alkynes for the preparation of valuable benzothiophenes or benzoselenophenes is reported. These transformations occur efficiently with complete regioselectivity and the products are obtained in moderate to good yields. The current protocol is successfully applied to the synthesis of the key intermediates of the drug raloxifene and an AT_1 receptor antagonist.

Keywords: arylamines; benzoselenophenes; benzothiophenes; one-pot processes; radical reactions

Benzothiophene and its derivatives represent a highly important and valuable class of heterocyclic compounds widely present in many medicinally relevant molecules. For example, raloxifene,[1] arzoxifene,[2] and zileuton[3] are all active drugs on the market. On the other hand, the structural motif of benzothiophene can be found in various bioactive molecules, which exhibit prominent bioactivities (Figure 1).[4] In addition, benzothiophenes have found wide application in material science.[5] Accordingly, a variety of synthetic methods for the preparation of substituted benzothiophenes have been developed.[6] Most of these approaches mainly focus on electrophilic cyclization and coupling cyclization reactions to construct the benzothiophene core.[7,8] However, the development of simple and novel synthetic methods for a facile access to benzothiophenes is still highly desirable.

In recent years, the preparation of benzothiophenes *via* radical cascade reactions has attracted considerable attention since it offers a simple and efficient approach to construct the benzothiophene ring.[9] Zanardi's group[9a] and McDonald's group[9b] independently reported the synthesis of benzothiophenes from *o*-methylthio-arenediazonium salts and alkynes *via* radical cascade reactions. Moreover, Schiesser and co-workers described a similar sequence for the preparation of benzoselenophenes from diazonium salts [Scheme 1A, Eq. (1)].[9c] However, all of these methods require the introduction of stoichiometric amounts of transition metals. To overcome this drawback, König and co-workers recently demonstrated a metal-free synthesis of benzothiophenes by reacting diazonium salts with alkynes using visible-light photoredox catalysis [Scheme 1A, Eq. (2)].[9d] Despite advances in synthetic methodology, the use of diazoni-

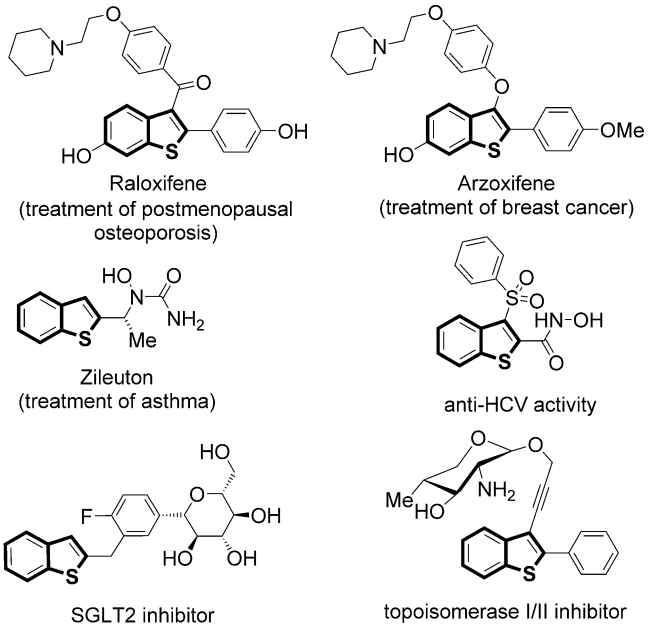
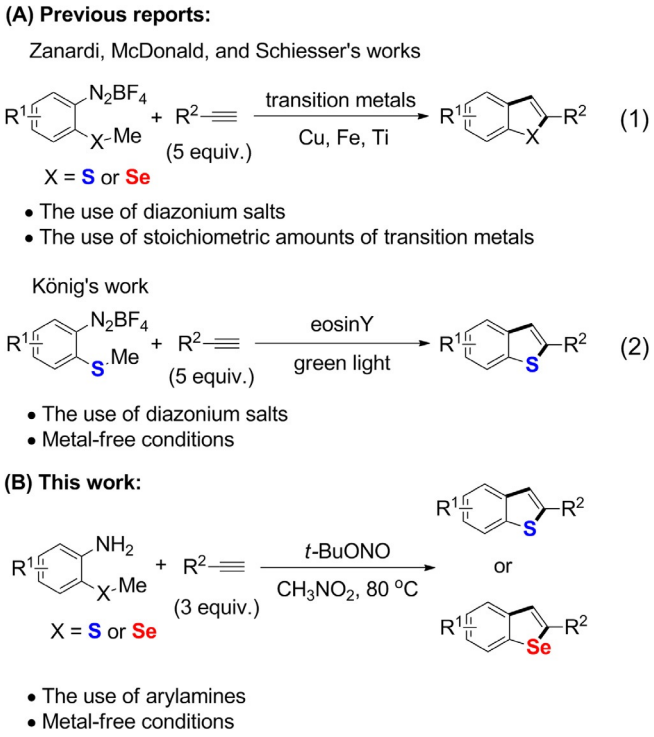


Figure 1. Representative drugs and biologically active molecules containing benzothiophene motif.



Scheme 1. Strategies for the preparation of 2-substituted benzothiophenes or benzoselenophenes *via* radical cascade reactions.

um salts as aryl radical precursors may limit the further application of such a method, because not every arylamine can be easily converted to the corresponding aryldiazonium salt. In addition, isolation or storage of diazonium salts is problematic because of their limited stability.

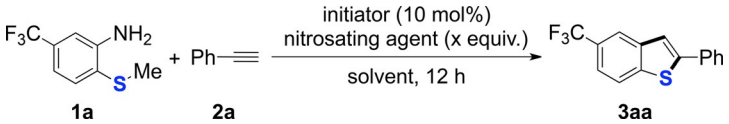
To avoid the preparation of diazonium salts and to enhance overall reaction efficiency, we envisioned that the preparation of benzothiophenes might be realized by combining the diazotization and cyclization steps in a one-pot protocol. The advantage for the use of arylamines as aryl radical precursors is that arylamines are easy to obtain and are stable. Herein, we describe a simple and efficient method for the preparation of valuable benzothiophenes starting with readily available arylamines and alkynes *via* radical cascade reactions. It is important to note that the current protocol can also be applied to the preparation of benzoselenophenes (Scheme 1B).

Recently, several organic molecules such as BPO,[10] iodide,[11] ascorbic acid,[12] and porphyrin[13] have been identified as efficient initiators to generate aryl radicals from the corresponding diazonium salts. Inspired by these successful examples, our investigation commenced with the radical cascade reactions of commercially available *o*-methylthio-arylamine **1a** with phenylacetylene **2a** in the presence of $(n\text{-Bu})_4NI$ as an initiator and *t*-BuONO as a nitrosating agent in DMSO at room temperature under N_2 for 12 h. The targeted product **3aa** was isolated in 41% yield (Table 1, entry 1). Encouraged by this promising result, we next screened a range of organic initiators under the same conditions. The results showed that KI, $(n\text{-Bu})_4NBr$, BPO, and ascorbic acid gave similar yields (Table 1, entries 2–5). Notably, when this reaction was run without an initiator, a similar result was obtained (Table 1, entry 6). It is shown that an initiator is not essential for this transformation. Alternative nitrosating agents, such as $TABNO_2$, amylONO, and $NaNO_2$ provided worse results (Table 1, entries 7–9). Different solvents were subsequently surveyed, and we found that CH_3NO_2 is the best solvent for running this reaction (Table 1, entry 12). The yield of **3aa** was significantly improved to 57% by using 2.0 equiv. of *t*-BuONO (Table 1, entry 13). Further investigation showed that a higher reaction temperature can promote this transformation, and **3aa** was obtained in 70% yield at 80 °C (Table 1, entry 15). It is noteworthy that the amount of **2a** was further lowered to 3.0 equiv. without affecting the yield, but a lower yield was achieved with 2.0 equiv. of **2a** (Table 1, entries 16 and 17). When the reaction was carried out in a non-dry solvent, **3aa** was obtained in 63% yield (Table 1, entry 18).

With the optimized reaction conditions in hand, we next explored the scope of the benzothiophene synthesis with regard to *o*-methylthio-arylamines (Scheme 2). *o*-Methylthio-arylamines bearing electron-donating substituents (methyl, methoxy) underwent this transformation smoothly to afford the corresponding products in moderate yields (41–47%). Moreover, *o*-methylthio-arylamines carrying halogen substituents were compatible with the reaction conditions, providing the corresponding products in moderate to good yields (48–55%). Notably, the halogen substituents such as Cl and Br are useful for further functionalization. *O*-Methylthio-aniline worked well and gave the desired product **3ja** in 48% yield.

We next examined the scope of the reaction with respect to the alkynes (Scheme 2). Phenylacetylene derivatives bearing electron-donating substituents at the *para*-position of the arene provided the corresponding products **3ab** (4-Me) and **3ac** (4-OMe) in excellent yields (**3ab**: 68%, **3ac**: 71%). The *ortho*- and *meta*-substituted congeners gave similar results (**3ah**: 65%, **3ai**: 65%). Phenylacetylene derivatives bearing halogen substituents such as F, Cl, and Br performed well with excellent yields (**3ad**: 70%, **3ae**: 68%, **3af**: 71%). The substrate containing an electron-withdrawing substituent such CF_3 was successfully converted into the corresponding product **3ag** in 75% yield. A heteroaryl-substituted alkyne, 3-ethynylthiophene afforded the product **3aj** in 60% yield. In addition, alkyl, ester, and TMS-substituted alkynes were

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3aa

Entry	Initiator	Nitrosating agent (equiv.)	Amount of **2a** (equiv.)	Solvent	Yield [%][b]
1	$(n\text{-Bu})_4NI$	*t*-BuONO (1.5)	5	DMSO	41
2	KI	*t*-BuONO (1.5)	5	DMSO	44
3	$(n\text{-Bu})_4NBr$	*t*-BuONO (1.5)	5	DMSO	40
4	BPO	*t*-BuONO (1.5)	5	DMSO	44
5	ascorbic acid	*t*-BuONO (1.5)	5	DMSO	48
6	none	*t*-BuONO (1.5)	5	DMSO	46
7	none	$TBANO_2$ (1.5)	5	DMSO	0
8	none	amylONO (1.5)	5	DMSO	33
9	none	$NaNO_2$ (1.5)	5	DMSO	trace
10	none	*t*-BuONO (1.5)	5	DMF	40
11	none	*t*BuONO (1.5)	5	CH_3CN	40
12	none	*t*-BuONO (1.5)	5	CH_3NO_2	48
13	none	*t*BuONO (2.0)	5	CH_3NO_2	57
14[c]	none	*t*-BuONO (2.0)	5	CH_3NO_2	62
15[d]	none	*t*-BuONO (2.0)	5	CH_3NO_2	70
16[d]	**none**	***t*-BuONO (2.0)**	**3**	**CH_3NO_2**	**70**
17[d]	none	*t*-BuONO (2.0)	2	CH_3NO_2	62
18[e]	none	*t*-BuONO (2.0)	3	CH_3NO_2	63

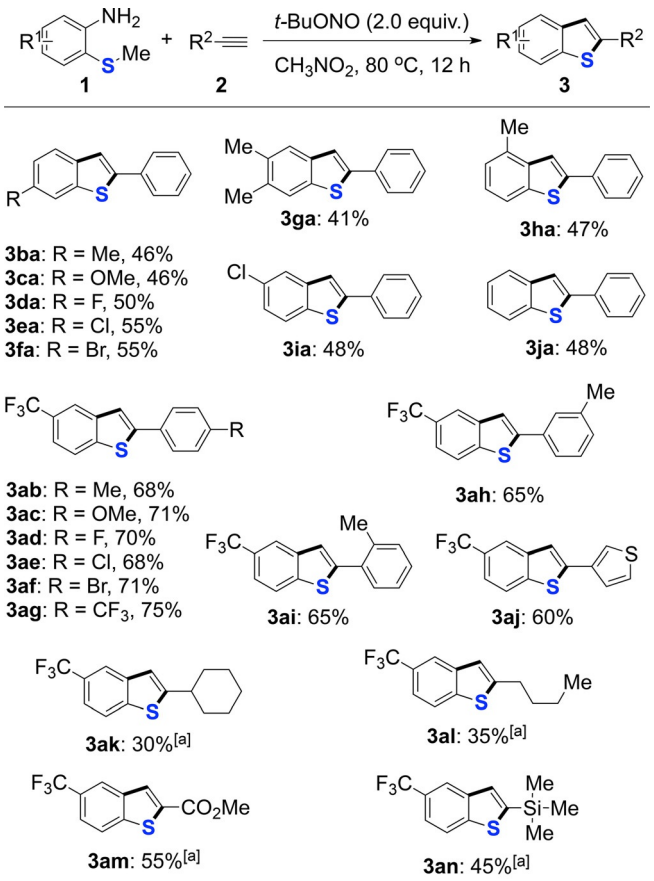
[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (2.0 mmol), initiator (0.04 mmol), and nitrosating agent (0.6 mmol) in dry solvent (1.0 mL) at room temperature under N_2 for 12 h.
[b] Isolated yields.
[c] The reaction was conducted at 60 °C.
[d] The reaction was conducted at 80 °C.
[e] The commercial CH_3NO_2 (1.0 mL) was directly used. BOP = benzoyl peroxide, $TBANO_2$ = tetrabutylammonium nitrite.

proved to be competent, leading to the products **3ak**–**3an** in moderate to good yields (30–55%).

Benzoselenophenes are also an important class of heterocycles, which have found wide application in organic synthesis, medicinal chemistry, and materials science.[9c,14] In light of this importance, we subsequently extended the present protocol to prepare benzoselenophenes starting with readily prepared *o*-methylselanyl-arylamines and alkynes under metal-free conditions (Scheme 3). Reactions with *o*-methylselanyl-arylamines carrying electron-donating and electron-withdrawing substituents proceeded well, and the corresponding products **5aa**–**5da** were obtained in good yields (50–60%). Moreover, a variety of alkynes bearing different substituents were tested. We found that electron-donating (methyl, methoxy) and also electron-withdrawing substituents (halides) were well tolerated, affording the corresponding products **5db**–**5df** in good yields (57–60%). With heteroaryl, alkyl, and TMS substituents on the alkynes, moderate yields were obtained (**5dj**: 43%, **5dl**: 36%, **5dn**: 34%).

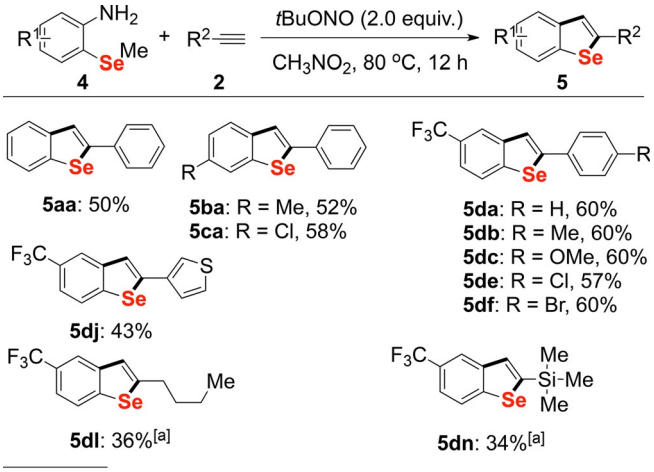
The current method provides many opportunities for application to organic synthesis. For example, the key intermediate **6** of the raloxifene synthesis can be easily prepared by using this metal-free route.[9b,d] We prepared **1c** from commercially available 2-amino-6-methoxybenzothiazole **1c′** and reacted it with alkyne **2c** under our conditions to afford the benzothiophene **6** in 50% yield (Scheme 4, a). In addition, this method can also be successfully applied to the synthesis of the key intermediate **8** of AT_1 receptor antagonist.[9c] The *o*-methylselanyl-aniline **4a** was easily prepared in two steps from 1-fluoro-2-nitrobenzene **4a′**, which reacted with alkyne **2o** to form the benzoselenophene **8** in 45% (Scheme 4, b).

To gain mechanistic insights into the reaction pathway, some preliminary studies were conducted. Radical trapping experiment was conducted by using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical trap, and the TEMPO-trapped product **11** could be identified by high-resolution mass spectrometry [Scheme 5a, Eq. (1)]. This result suggested that aryl radicals are likely involved in these reactions. In addition, the *o*-methylthio-benzenediazonium salt was prepared independently and used under our standard conditions, affording traces of the targeted product **3ja**. This result indicated that diazonium salts as the key intermediates in the reaction mechanism appear rather unlikely [Scheme 5a, Eq. (2)]. Moreover, the



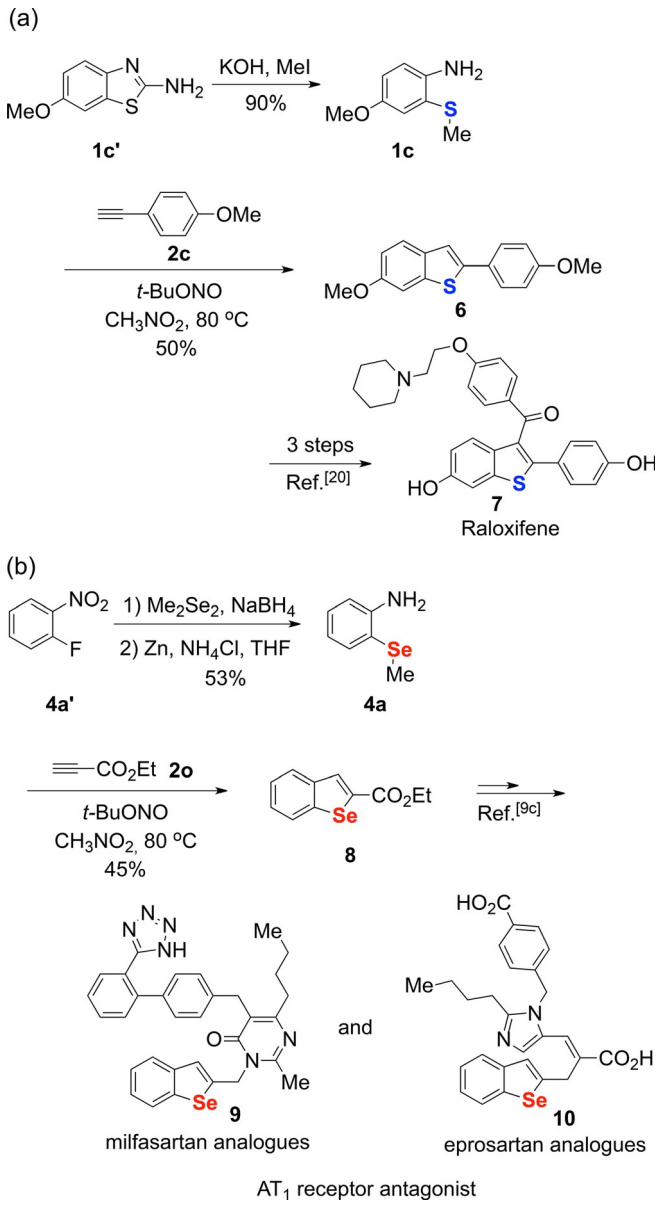
[a] The reaction was conducted in a sealed tube.

Scheme 2. Various 2-substituted benzothiophenes prepared. *Reaction conditions:* see entry 16, Table 1. The yields given are for the isolated products.



[a] The reaction was conducted in a sealed tube.

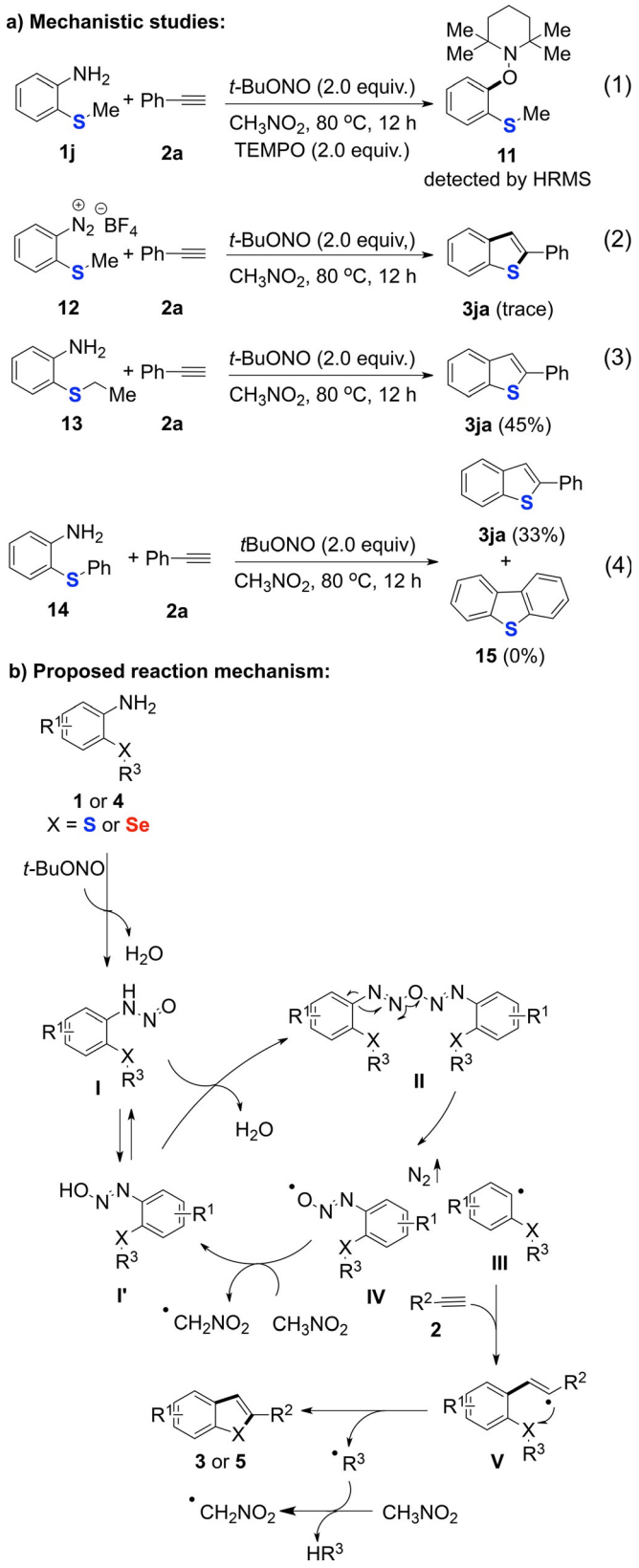
Scheme 3. Various 2-substituted benzoselenophenes prepared. *Reaction conditions:* see entry 16, Table 1. The yields given are for the isolated products.



Scheme 4. Synthetic applications.

reactions of 2-(ethylthio)aniline **13** and 2-(phenylthio)aniline **14** were investigated. When the reaction was conducted on 2-(ethylthio)aniline **13**, the product **3ja** was obtained in 45% yield [Scheme 5a, Eq. (3)]. When the reaction was conducted on 2-(phenylthio)-aniline **14**, the product **3ja** was obtained in 33% yield [Scheme 5a, Eq. (4)]. In this reaction, the product **15** that was likely generated *via* intramolecular cyclization could not be observed. In addition, benzene could be detected by GC-MS from reaction mixture.

On the basis of the above experiments and previous reports,[9a,d,15,16] a plausible mechanism is proposed in Scheme 5b. First, arylamine **1** or **4** is transformed with *t*-BuONO to the corresponding nitrosamine **I**, which



Scheme 5. a) Mechanistic studies. b) Proposed reaction mechanism.

undergoes self-condensation to generate diazo anhydride **II**. It is important to note that the formation of this type of dimeric diazo anhydride structure is well established in the literature.[16–18] N–O homolysis of **II** provides aryl radical **III** along with azoxy radical **IV** and nitrogen. Addition of **III** to alkyne **2** leads to the vinyl radical **V**, which reacts *via* intramolecular homolytic substitution at the sulfur atom or selenium atom to form the final products **3** or **5** along with a R^3 radical.[19] The R^3 radical can further react *via* H-abstraction from the solvent. In addition, the generated azoxy radical **IV** abstracts a hydrogen atom from the solvent to afford the diazo hydroxide **I′** (the species **I** and **I′** are in equilibrium and can thus be readily interconverted),[16c] which can further react to generate the aryl radical **III**.

In summary, we have developed a simple, efficient, and unified strategy for the preparation of benzothiophenes and benzoselenophenes from readily prepared starting materials. Notably, these transformations occur efficiently without the help of any transition metal or additive. Reactions are very easy to conduct and products are obtained in moderate to good yields with a good functional group tolerance. The applications of the method are demonstrated by the synthesis of the key intermediates of the drug raloxifene and AT_1 receptor antagonist. Further studies on the scope, mechanism, and synthetic application are ongoing in our laboratory.

Experimental Section

General Procedure for the Preparation of Benzothiophenes

o-Methylthio-arylamines **1** (0.4 mmol, 1.0 equiv.) were placed in a dry standard Schlenk tube or a dry sealed tube under N_2. Dry CH_3NO_2 (1.0 mL) was added, followed by the addition of alkynes **2** (1.2 mmol, 3.0 equiv.) and *t*-BuONO (0.8 mmol, 2.0 equiv.). The reaction mixture was stirred at 80 °C for 12 h, and the reaction was monitored with TLC. The crude reaction mixture was purified by flash column chromatography on silica gel to afford the corresponding product.

General Procedure for the Preparation of Benzoselenophenes

o-Methylselanyl-arylamines **4** (0.4 mmol, 1.0 equiv.) were placed in a dry standard Schlenk tube or a dry sealed tube under N_2. Dry CH_3NO_2 (1.0 mL) was added, followed by the addition of alkynes **2** (1.2 mmol, 3.0 equiv.) and *t*-BuONO (0.8 mmol, 2.0 equiv.). The reaction mixture was stirred at 80 °C for 12 h, and the reaction was monitored with TLC. The crude reaction mixture was purified by flash column chromatography on silica gel to afford the corresponding product.

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