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Palladium-Catalyzed Regioselective C–S Bond Cleavage of Thiophenes

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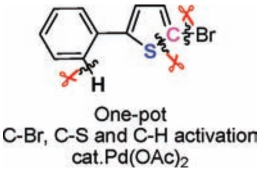
ABSTRACT

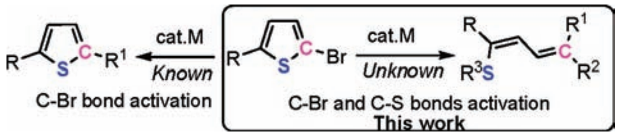


Herein, a Pd-catalyzed reaction of simple and diverse bromothiophenes with alkynes via regioselective C–S bond activation is reported. This provides a new approach to prepare sulfur-based heterocycles and fulvenes.

The unique electronic, optical, and redox properties of thiophenes have attracted sigificant interest among researchers all over the world and have actually been advanced to be among the most frequently used π-conjugated materials, particularly as active components in organic electronic devices and molecular electronics.[1] Transition-metal-catalyzed cross-coupling reactions of bromothiophenes serve as key methods to introduce thiophene units into organic molecular materials (Scheme 1).[2]

Herein, we describe an unprecedented palladium-catalyzed ring rearrangement of bromothiophenes with alkynes through carbon–sulfur bond activation. To the best of our knowledge, this is the first example of the synthesis of sulfur-containing heterocyclic compounds through catalytic ring-opening reaction of thiophenes. This novel reaction provides not only a new method to obtain sulfur-containing compounds but also valuable supplementary mechanistic insights into the C–S bond activation of thiophene, a key step in hydrodesulfurization (HDS).[4]

Scheme 1



Recently, we developed an efficient method to synthesize benzothiophenes from bromothiophenes and alkynes.[3] During the course of this work, we found that the reaction of **1a** with alkyne **2a** provided the interesting product **3a** (Scheme 2). The structure of **3a** was further confirmed by X-ray crystal structure analysis (see the Supporting Information for details). Surprisingly, one of the C–S bonds was cleaved selectively during the reaction.

According to an extensive literature survey, homogeneous reactions of thiophene with transition metals are used as models for mechanistic understanding of hydrodesulfurization

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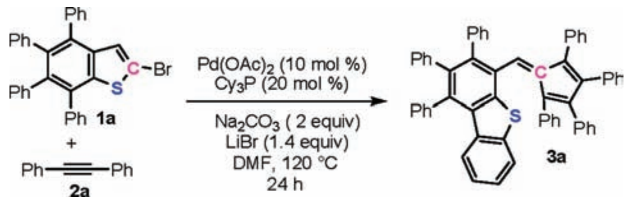
Scheme 2

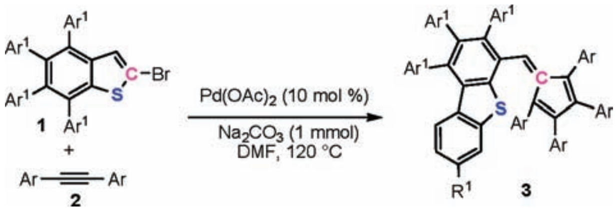


(HDS), a very important industrial heterogeneous process to produce sulfur-free petroleum products.[4] Significantly, the reactions of thiophene with transition-metal complexes have usually led to the cleavage of the C–S bond and thus to the formation of various new transition-metal complexes, which contain metal–sulfur and metal–carbon bonds.[5–8] However, there is no application of these C–S bond cleavage reactions catalytically in organic synthesis.[9,10] We hypothesized the formation of **3a** occurs through the catalytic cleavage of C–S bond and the rearrangement of benzothiophene **1a** with alkyne **2a**. A new C–S bond is formed between the sulfur fragment and the neighboring phenyl group through C–H bond activation, which give the dibenzothiophene moiety, while the reactive carbon part is trapped by alkynes to form the fulvene moiety.

A brief screening of various reaction conditions revealed that this reaction did not proceed in the absence of Pd(OAc)$_2$ or Na$_2$CO$_3$. Moreover, this transformation can be accomplished without addition of phosphine (see STable 1 of the Supporting Information for details). Simply heating the DMF (5 mL) solution of **1a** (0.5 mmol), **2a** (1.5 mmol), Pd(OAc)$_2$ (10 mol %), and Na$_2$CO$_3$ (1.0 mmol) at 120 °C resulted in the formation of the dibenzothiophene **3a** in a 76% yield (Table 1, entry 1). With this optimized catalytic system in hand, the scope of the substrates was evaluated with a variety of substituted benzothiophenes and alkynes (Table 1). The electronic densities of Ar (entries 1–4) and Ar^1 groups (entries 5–7) did not affect the yields of the reaction to a significant extent, allowing for dibenzothiophenes **3a**–**g** to be isolated in 54–76% yields. The crystal structure of **3g** (Figure 1) clearly shows that the C(Br)–S bond of the thiophene moiety was cleaved regioselectively and a new C–S bond was formed with neighboring Ar^1 group (entry 7, R^1 = F).

Encouraged by the above selective cleavage of the C–S bond and the consequent intramolecular C–S coupling process, we conducted further experiments with simple bromothiophenes **4a** and **4b**. Interestingly, these reactions provided thiopyran derivatives **5a** and **5b**, respectively (Scheme 3). Product **5b** was confirmed by X-ray crystal analysis (Figure 2). Notably, the formation of thiopyran ring occurred regioselectively, and only the C(Br)–S bond of thiophene was cleaved. The sulfur-containing species were trapped by an intermolecular carbothiolation of alkyne. These results highlighted that this regioselective C–S cleavage reaction of bromothiophene has a wide reaction spectrum.

Table 1. Reactions of Bromobenzothiophenes with Alkynes



entry	4	2	time (h)	product	isolated yield (%)
1	**1a** (Ar^1 = *p*-H-Ph)	**2a** (Ar = Ph)	13	**3a** (R^1 = H)	76
2	**1a**	**2b** (Ar = *p*-Me-Ph)	10	**3b** (R^1 = H)	54
3	**1a**	**2c** (Ar = *p*-OMe-Ph)	14	**3c** (R^1 = H)	75
4	**1a**	**2d** (Ar = *p*-F-Ph)	14	**3d** (R^1 = H)	58
5	**1b** (Ar^1 = *p*-Me-Ph)	**2a**	17	**3e** (R^1 = Me)	57
6	**1c** (Ar^1 = *p*-OMe-Ph)	**2a**	17	**3f** (R^1 = OMe)	76
7	**1d** (Ar^1 = *p*-F-Ph)	**2a**	18	**3g** (R^1 = F)	72

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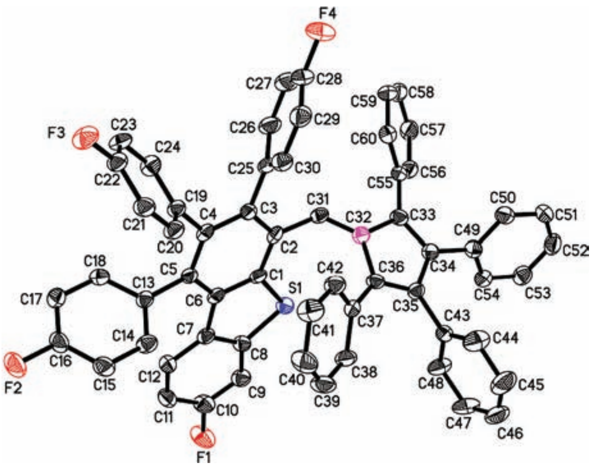
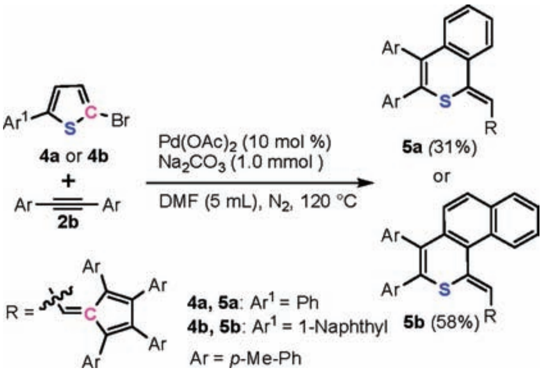


Figure 1. ORTEP drawing of **3g** (50% probability for thermal ellipsoids). Hydrogen atoms and solvents are omitted for clarity.

Scheme 3. Formation of Thiopyran Derviatives



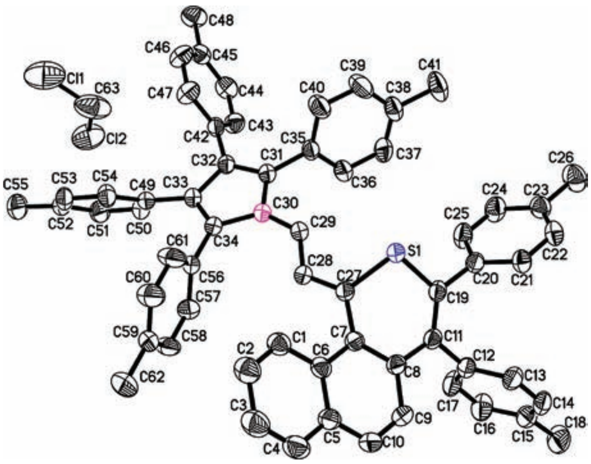
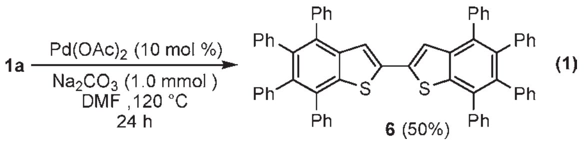


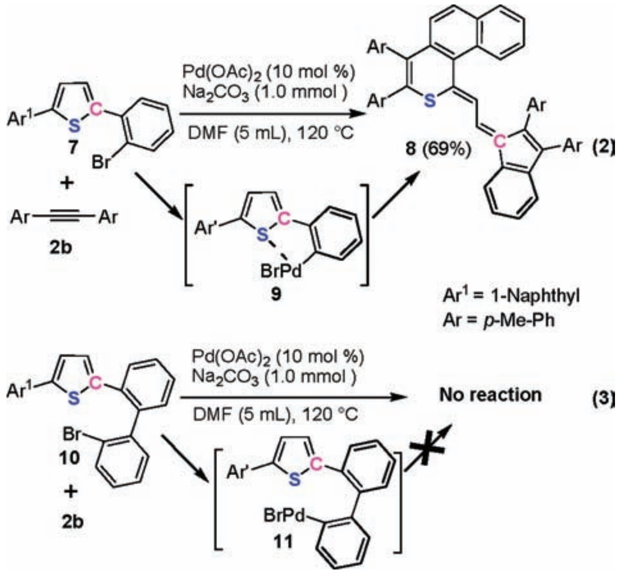
Figure 2. ORTEP drawing of **5b** (50% probability for thermal ellipsoids). Hydrogen atoms are omitted for clarity.

Some control experiments were preformed to gain mechanistic insights into this C–S bond cleavage reaction. Under the same reaction conditions, bromobenzothiophene **1a** alone provided the homocoupling product **6** in a 50% yield (eq 1).



The reaction of thiophene **7** with alkyne **2b** provided **8** in a 69% yield (Scheme 4, eq 2). The crystal structure of **8** (Figure 3) clearly shows that the C–S bond closer to bromine was cleaved selectively. Finally, no reaction was observed with thiophene **10** (Scheme 4, eq 3). We postulated

Scheme 4



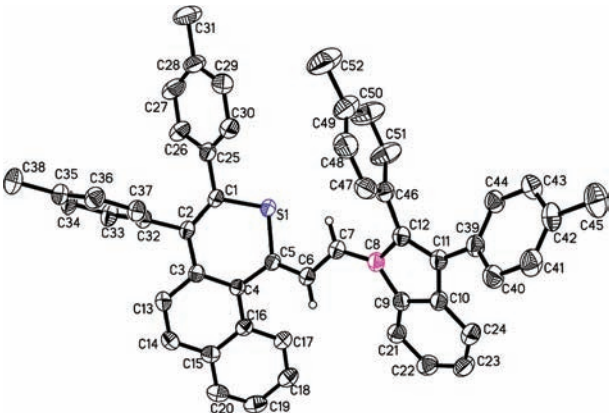
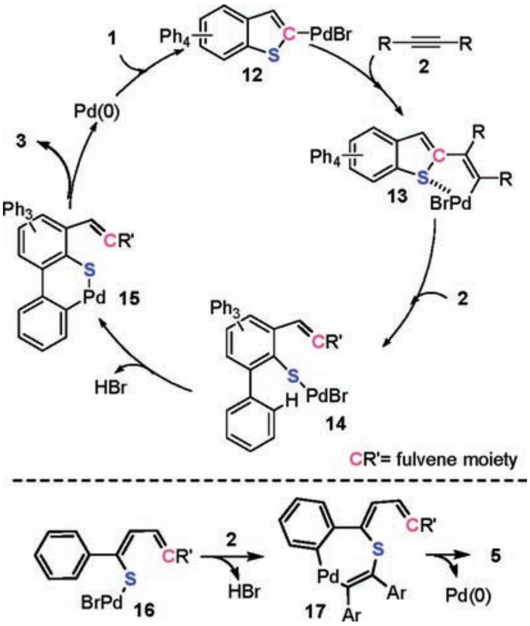


Figure 3. ORTEP drawing of **8** (50% probability for thermal ellipsoids).

Scheme 5. Proposed Reaction Mechanism



therefore that the C–Br bond of **7** acts as a directing group and the in situ formed Pd(II) intermediate **9** brings the active catalyst next to the C–S bond. The failure of **10** might be due to the weak interaction between the palladium center and the C–S bond in **11**.

Based on these results, we propose the following reaction mechanism (Scheme 5): (1) oxidative addition of Pd(0) to bromobenzothiophene **1** gives a thienylpalladium(II) intermediate **12**; (2) *cis*-carbopalladation with one alkyne gives a vinylic palladium intermediate **13** (allowing Pd to reach the C–S bond regioselectively); (3) next, though the detailed mechanism is not clear yet, C–S bond activation and cycloaddition with alkyne give **14**; (4) the cyclopalladation with the neighboring Ph group affords a six-membered palladacycle **15**; (5) the subsequent reductive elimination affords the product **3** with regeneration of Pd(0) species. In the thiopyran case (Scheme 5, bottom), the Pd–sulfur species **16** reacts with alkyne **2** through carbothiolation to form a seven-membered palladacycle **17**, which produces thiopyran **5**.

In summary, we have developed a palladium-catalyzed highly regioselective ring-rearrangement reaction of readily available bromothiophenes with alkynes. Our reaction utilizes bromothiophene as a new type building block in organic and material chemistry. Further investigation on the scope and the mechanism of this reaction is in progress in our laboratory.

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Supporting Information Available. Experimental procedures, spectroscopic and analytical data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.