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Metal-free sp^3 C–H functionalization: a novel approach for the syntheses of selenide ethers and thioesters from methyl arenes†

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A DTBP-promoted metal-free and solvent-free formation of C–Se and C–S bonds through sp^3 C–H functionalization of methyl arenes with diselenides and disulfides is described.

From an atom-economy point of view, the construction of carbon–carbon[1,2] and carbon–heteroatom[3] bonds through C–H functionalization has been an attractive research area in organic synthesis.[1–3] Regarding the carbon–heteroatom bond formation, the synthesis of aryl chalcogenides[4,5] has been less studied when compared with other carbon–heteroatom bond forming processes. Although the direct C–S and C–Se bond formation through C–H functionalization of arenes is known with[6] or without[7] transition metals, the C–S and C–Se bond formations through the C–H functionalization of sp^3 carbon are not documented. Organo-selenium compounds are important motifs in organic synthesis and in the chemical industry[8] as well as serve as potential drug candidates.[9,10] In recent years, the preparation of thioesters have also received much attention due to the importance of thioesters as acyl transfer reagents in organic synthesis[11] and chemical biology.[12] Traditionally, thioesters have been prepared through the condensation reaction of carboxylic acid derivatives such as acyl chlorides and anhydrides. For example, acyl chlorides are moisture-sensitive, and this approach will produce an equal amount of halide anion when an acyl halide is used.[13] Recently, the coupling reaction of thiols or disulfides with aldehydes has been reported for the preparation of thioesters.[14] Notably, coupling of methyl arenes with thiol surrogates would be the most attractive approach from an atom-economy point of view. Here, we report the DTBP-promoted syntheses of selenide ethers and thioesters from methyl arenes for the first time.

Initially, mesitylene (**1a**) was selected as the model, and treated with diphenyl diselenide (**2a**) under the influence of *tert*-butyl hydroperoxide (TBHP)[14a] at 120 °C for 24 h (Table 1, entries 1 and 2); however, only a trace amount of **3a** was detected using GC-MS.

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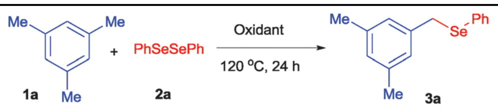
Table 1 Optimization of the reaction conditions[a]



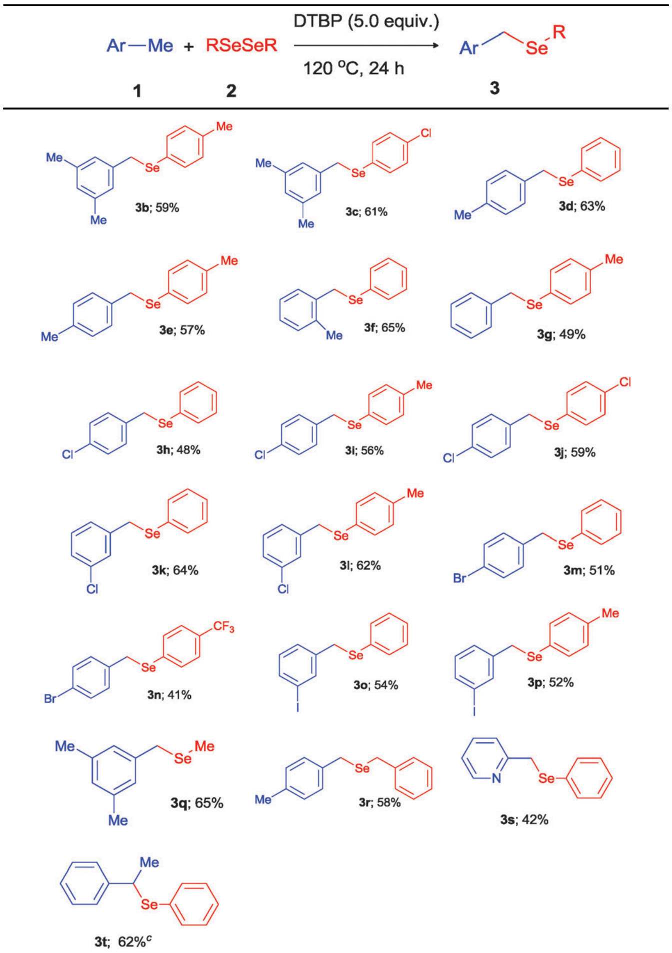
Entry	Oxidant (equiv.)	Yield (%)
1[b]	TBHP (3.0)	Trace
2[c]	TBHP (3.0)	Trace
3	H_2O_2 (3.0)	Trace
4	BPO (3.0)	14
5	TBPB (3.0)	Trace
6	DTBP (3.0)	38
7	DTBP (5.0)	68
8	DCP (5.0)	58
9[d]	DTBP (5.0)	60
10[e]	DTBP (5.0)	37
11[f]	DTBP (5.0)	69
12[g]	DTBP (5.0)	71

[a] Reaction conditions: mesitylene (1.0 mL), diphenyl diselenide (0.5 mmol) and oxidant (5.0 mmol) were reacted at 120 °C for 24 h. [b] TBHP solution in decane. [c] TBHP solution in water. [d] 140 °C. [e] 0.5 mL mesitylene was used. [f] 1.5 mL mesitylene was used. [g] 2.0 mL mesitylene was used. (TBHP = *tert*-butyl hydroperoxide, TBPB = *tert*-butyl peroxybenzoate, BPO = benzoyl peroxide, DTBP = di-*tert*-butyl peroxide, DCP = dicumyl peroxide).

Screening other oxidants (Table 1, entries 3–6) showed that di-*tert*-butyl peroxide (DTBP) is the best and gives the product in 38% yield (Table 1, entry 6). To our delight, 68% yield of the product was obtained when a higher amount of DTBP was employed (Table 1, entry 7). 58% of the product was obtained when dicumyl peroxide (DCP) was used as the oxidant (Table 1, entry 8).[2] It was found that a higher reaction temperature (Table 1, entry 9) and lower amount of mesitylene (Table 1, entry 10) diminished the yield of **3a**. Increasing the amount of mesitylene provided little enhancement in the chemical yields (Table 1, entries 11 and 12, respectively). Notably, no selenoxide was formed during the reaction.

With the optimized reaction conditions in hand, we then studied the scope of this system for a variety of substrates. As demonstrated in Table 2, various methyl arenes **1** were worked smoothly with diaryl diselenides **2** to provide selenide ethers (**3b–3s**) in good yields. This system shows good functional group tolerance, and functional groups including chloro (**3c**, **3h–3l**), bromo (**3m**, **3n**), iodo (**3o**, **3p**)

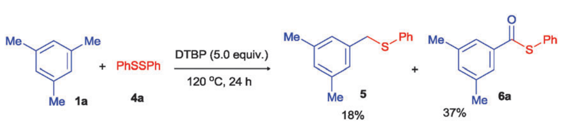
Table 2 DTBP-promoted C–Se bond formation between methyl arenes and diselenides *via* sp^3 C–H functionalization[a,b]



[a] Reaction conditions: methyl arenes (1.0 mL), diselenide (0.5 mmol) and DTBP (5.0 mmol) were reacted at 120 °C for 24 h. [b] Yields are based on diselenides. [c] Trace amount of isomer was also observed.

and trifluoromethyl (**3n**) are tolerated under the reaction conditions. Not only diaryl diselenide but also dialkyl diselenide could be used as the coupling partner (**3q**, **3r**). 2-Methylpyridine was also coupled with diphenyl diselenide to form selenide ether **3s**. The coupling reaction of ethyl benzene with diphenyl diselenide could give selenide ether **3t** as the major product along with the isomer (at the position of the methyl carbon).

Based on the promising results for C–Se bond formation, we then turned our attention towards C–S bond formation *via* sp^3 C–H functionalization of methyl arenes. The thioether (**5**) was obtained along with the formation of a thioester (**6a**) when mesitylene (**1a**) was treated with diphenyl disulfide (**4a**) by using DTBP as the oxidant at 120 °C for 24 h (eqn (1)).

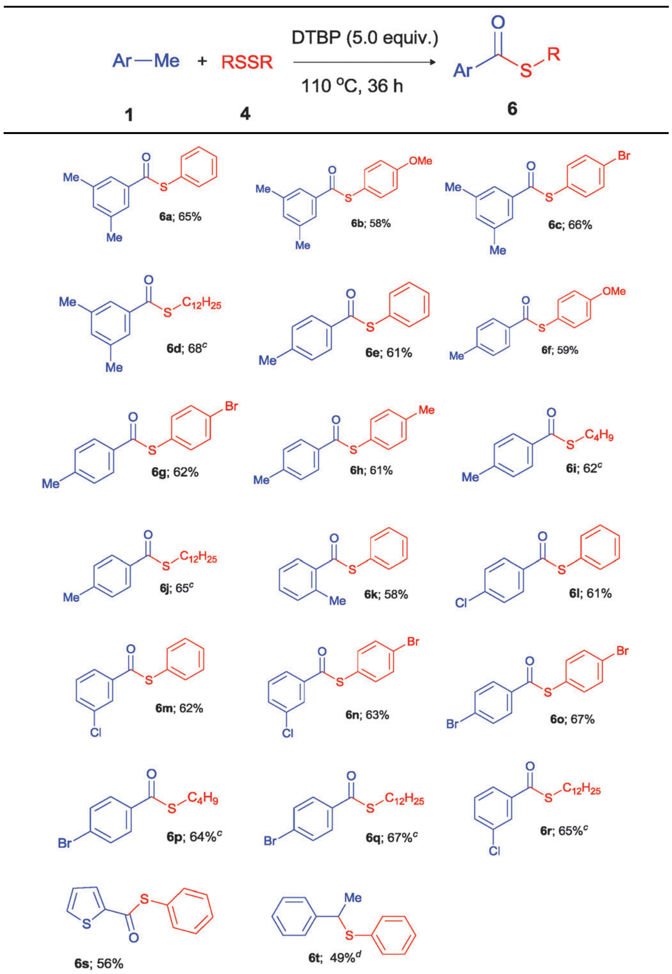


(1)

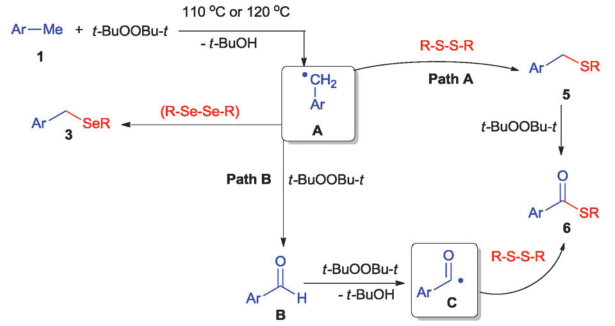
To our delight, 65% yield of **6a** was obtained when the reaction was carried out at 110 °C for 36 h. We have extended this selective formation of a thioester to various methyl arenes with disulfides under the influence of DTBP at 110 °C for 36 h to give thioesters in good yields. Remarkably, both diaryl- and dialkyl disulfides were coupled with methyl arenes. Functional groups including bromo (**6c**, **6g**, **6n–6q**), chloro (**6l–6n** and **6r**) and methoxy (**6b** and **6f**) were tolerated under the reaction conditions employed. 2-Methylthiophene was also coupled with diphenyl disulfide to provide **6s** in 56% yield. The coupling of ethyl benzene with diphenyl disulfide provided the thioether **6t** instead of the thioester (Table 3).[7d]

The control experiment showed that dimerization of mesitylene and trace amounts of aldehyde were detected when mesitylene (**1a**) was treated with DTBP at 110 °C for 24 h without diselenide or disulfide (eqn (2)). Based on this result, we proposed a plausible mechanism for this reaction (Scheme 1). In the case of C–Se formation, the benzyl radical **A** was coupled with diselenide to provide a selenide ether (**3**), and no selenide ester was determined in this reaction even when the reaction was performed for 48 h. Two potential reaction pathways are involved in the case of C–S coupling. First, the benzyl radical **A** reacted with disulfide to

Table 3 DTBP-promoted synthesis of thioesters from methyl arenes **1** and disulfides **4**[a,b]

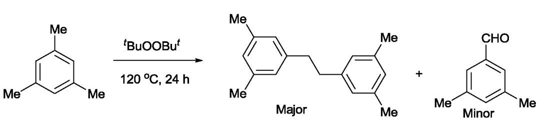


[a] Reaction conditions: methyl arene (1.0 mL), disulfide (0.5 mmol) and DTBP (5.0 mmol) were reacted at 110 °C for 36 h. [b] Yields are based on disulfides. [c] 48 h. [d] Thioester was not obtained.

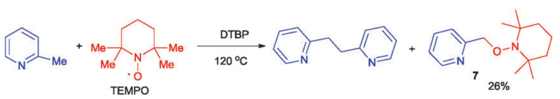


Scheme 1 Plausible mechanism.

provide thioether **5** which was further oxidized to give thioester **6** (path **A**). Second, the thioester **6** was obtained *via* the coupling between the *in situ* generated aldehyde radical **C** and disulfide (path **B**).[14b] When the reaction was carried out using mesitylene and diphenyl disulfide in the presence of DTBP at 110 °C with different reaction times, GC-MS showed a mixture of thioether and thioester for 12 h and 24 h. Only thioester was detected after 36 h. This result supports that the thioether is the intermediate for the formation of the thioester through path **A**. In further support of the radical pathway, 2-methylpyridine was reacted with TEMPO (1,1,5,5-tetramethylpentamethylene nitroxide) in the presence of DTBP to give the coupled product **7** in 26% yield (eqn (3)), along with the unreacted TEMPO and dimerized product. The compound **7** was isolated and the structure was confirmed using ^{1}H, ^{13}C NMR and HRMS. The dimerization of methyl arene in the reaction also supports a radical pathway.[15]



(2)



(3)

In conclusion, we have reported the first C–Se and C–S bond formations through sp^3 C–H functionalization of methyl arenes with diselenides and disulfides under metal-free and solvent-free conditions. Our efforts to obtain understanding of the details of the mechanism and applications of this system to other substrates are currently underway in our laboratory.

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