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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

Satpal Singh Badsara, Yi-Chen Liu, Ping-An Hsieh, Jing-Wen Zeng, Shao-Yi Lu, Yi-Wei Liu and Chin-Fa Lee*

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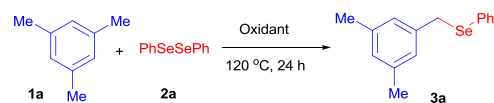
A DTBP-promoted metal-free and solvent-free C-Se and C-S bond formation through a sp^3 C-H functionalization of methyl arenes with diselenides and disulfides is described.

From an atom-economy point of view, construction of carbon-carbon^{1,2} and carbon-heteroatom³ bonds through C-H functionalization have been attractive research area in organic synthesis.¹⁻³ Regarding the carbon-heteroatom bond formation, the synthesis of aryl chalcogenides^{4,5} have been less studied when compared with other carbon-heteroatom bond forming processes. Although the direct C-S and C-Se bond formations through C-H functionalization of arenes is known with⁶ or without⁷ transition metals. However, 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, chemical industry⁸ 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 an acyl transfer reagents in organic synthesis¹¹ 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 acyl halide is used.¹³ Recently, coupling reaction of thiols or disulfides with aldehydes have 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 trace amount of **3a** was detected by GC-MS. Screening other oxidants (Table 1, entries 3-6) showed that di-*tert*-butyl peroxide (DTBP) is the best to give the product in 38% yield (Table 1, entry 6). To

our delight, a 68% yield of product was obtained when higher amount of DTBP was employed (Table 1, entry 7). A 58% of product was obtained when dicumyl peroxide (DCP) was used as an oxidant (Table 1, entry 8).² It was found that 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 the little enhancement in chemical yields (Table 1, entries 11 and 12, respectively). Notably, no selenoxide was formed during the reaction.

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 ₂ O ₂ (3.0)	Trace
4	BPO (3.0)	14
5	TBHP (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).

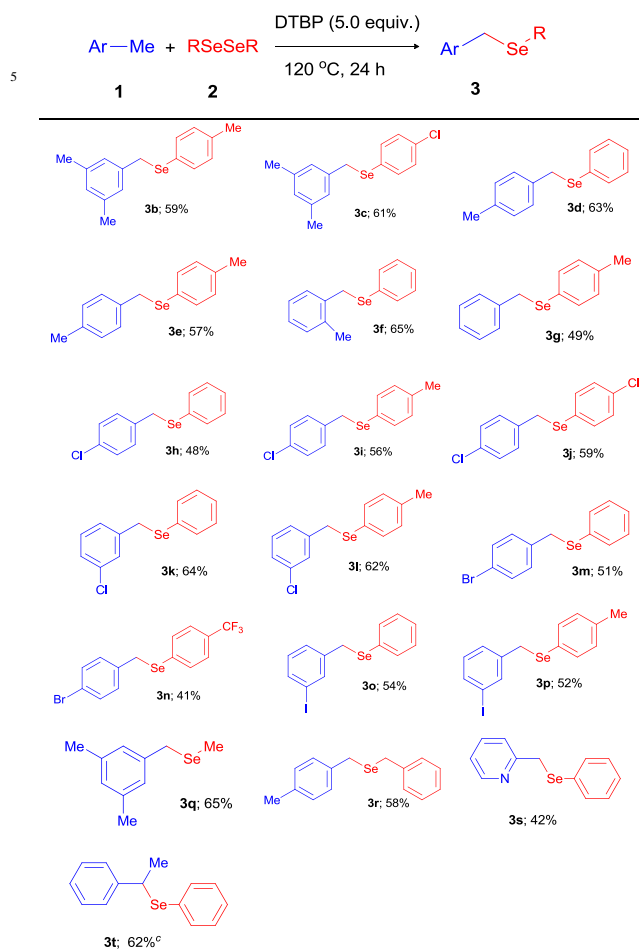
With the optimized reaction conditions in hand, we then studied the scope of this system for a variety of substrates. As demonstrated in Table 2, various methyl arenes **1** were worked smoothly with diaryl diselenides **2** to provide selenide ethers (**3b-3s**) in good yields. This system shows good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

Department of Chemistry, National Chung Hsing University, Taichung, Taiwan 402, R.O.C

E-mail: cfalee@dragon.nchu.edu.tw; Fax: +886 4 2286-2547; Tel: +886 4 2284-0411 ext. 810

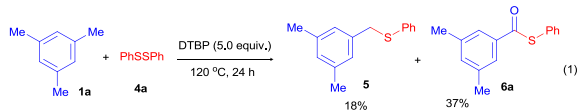
† Electronic Supplementary Information (ESI) available: Experimental details, spectral data for new products. See DOI: 10.1039/b000000x/

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



^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.

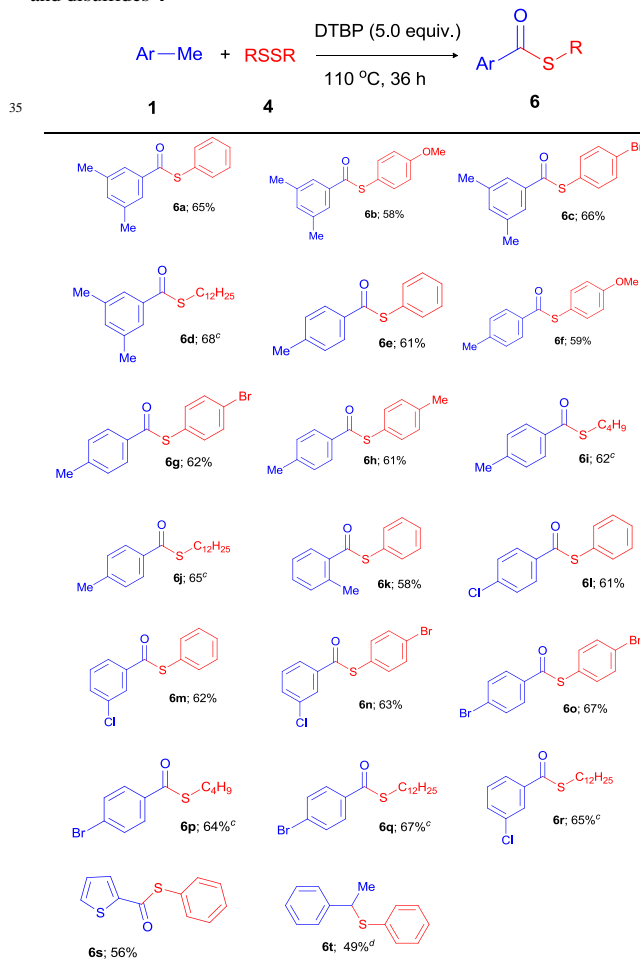
10 Based on the promising results for C-Se bond formation, we then turned our attention towards C-S bond formation via sp^3 C-H functionalization of methyl arenes. The thioether (**5**) was obtained along with the formation of thioester (**6a**) when mesitylene (**1a**) was treated with diphenyl disulfide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



To our delight, a 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 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

30 provided the thioether **6t** instead of thioester.^{7d}

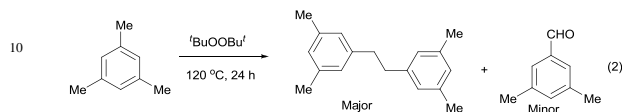
Table 3 DTBP-promoted synthesis of thioesters from methyl arenes **1** and disulfides **4**^a



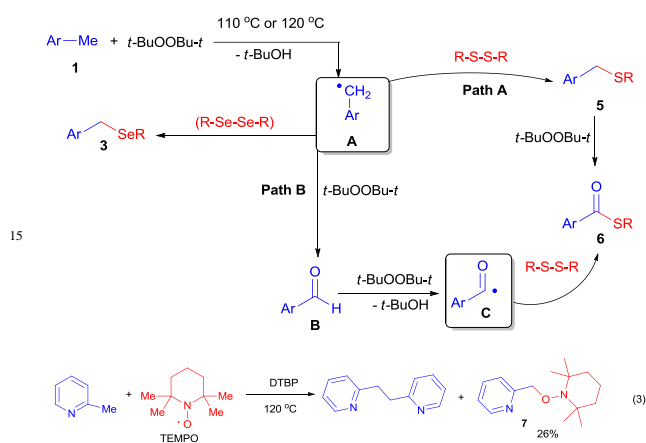
^a Reaction conditions: methyl arene (1.0 mL), disulfide (0.5 mmol) and DTBP (5.0 mmol) were reacted at 110 °C for 36 h. ^b Yields are based on disulfides. ^c 48 h. ^d Thioester was not obtained.

The control experiment showed that a dimerization of mesitylene and trace amount 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, benzyl radical **A** was coupled with diselenide to provide selenide ether (**3**), 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 provide thioether **5** which will further oxidize to thioester **6** (Path **A**). Second, the thioester **6** was obtained via the coupling between *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 thioester through path A. For further support of 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 unreacted TEMPO and dimerized product. The compound **7** was isolated and the structure was confirmed by ^1H , ^{13}C NMR and HRMS. The dimerization of methyl arene in the reaction also support a redical pathway.¹⁵



Scheme 1 Plausible Mechanism



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 understanding the details of mechanism and applications of this system to other substrates are currently underway in our laboratory.

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