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# Metal-Free Preparation of Cycloalkyl Aryl Sulfides via Di-tert-butyl Peroxide-Promoted Oxidative C(sp3)[BOND]H Bond Thiolation of Cycloalkanes

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## Abstract

A concise thiolation of C($sp^3$)–H bond of cycloalkanes with diaryl disulfides in the presence of oxidant of di-*tert*-butylperoxide (DTBP) has been developed. This reaction without using any of metal catalyst, tolerates varieties of disulfides and cycloalkanes substrates, giving good to excellent chemical yields, which provides a useful approach to cycloalkyl aryl sulfides from unactivated cycloalkanes.

### Keywords

metal-free; thiolation; oxidative; C($sp^3$)–H activation; cycloalkane

The formation of C–S bonds represents an active research area in general organic chemistry, material science as well as biological and pharmaceutical chemistry.[1] In the past decade, a number of methodologies have been developed in this field. In particular, transition-metal-catalyzed cross-coupling reactions of thiols with aryl halides provided the most general strategies for constructing C–S bonds.[2] Recently, metal-catalyzed C–S bonds formation through C($sp^2$)–H bond activation has become an alternative and intriguing methods for preparation of sulfides due to its high atom-economy and efficiency.[3] However, the cleavage of C($sp^3$)–H bond leading to the C–S bond formation is less studied. Very recently, Xiang and co-workers reported a novel thiolation of C($sp^3$)–H bond adjacent to a nitrogen or oxygen atom (Scheme 1a and 1b).[4] To date, the thiolation of C($sp^3$)–H bond of unactivated alkanes still have not been developed.

Direct C($sp^3$)–H transformation of alkanes, which is a great challenge due to their low reactivity and the lack of a coordination site for the metal catalyst, has attracted many generations of organic chemists in recent years.[5] However, C($sp^3$)–H bond activation of cycloalkanes to form C–C,[6] C–O,[7] C–N[8] bonds still has not been well reported because

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C($sp^3$)–H bond activation of cycloalkanes is more difficult than C($sp^3$)–H bond activation adjacent to heteroatoms, double bonds, phenyl or electron withdrawing groups. Li and others have done elegant work in this field using a transition-metal catalyst (such as Ru, Sc, Fe, etc.) both for activating the C($sp^3$)–H bond of cycloalkanes and subsequent coupling to form C–Y (Y = O, N, C) bonds.[9] Recently, our group also developed a Fe-catalyzed decarboxylative alkenylation of cycloalkanes via a radical process.[10] The metal-free C($sp^3$)–H bond functionalization progress for C($sp^2$)–C($sp^3$) bond formation of heteroaromatics and cycloalkanes promoted by DTBP have also been reported (Scheme 1c).[11,12] To the best of our knowledge, no reports for the construction of C–S bond through C($sp^3$)–H bond functionalization of cycloalkanes are described. Herein, we would report the first realization on the thiolation of C($sp^3$)–H bond of cycloalkanes through DTBP-mediated oxidative C($sp^3$)–H bond functionalization without the aid of transition-metal catalyst (Scheme 1d).

Initially, we conducted our investigation by reacting 1,2-diphenyldisulfane **1** (0.5 mmol) with cyclohexane **2a** (2 mL) in the presence 4.0 equiv of tert-butylhydroperoxide (TBHP) at 120 °C for 24 h. The reaction could happen, and afforded the expected product of cyclohexyl(phenyl)sulfane **3a** in a poor yield (23%, Table 1, entry 1). Replacing TBHP with DTBP, the yield dramatically increased to 88% without the aid of any metal catalyst or other additives (Table 1, entry 2). The use of other oxidants such as DDQ, $K_2S_2O_8$, $H_2O_2$ (30% aqueous solution) or TBPB did not provide better results (Table 1, entries 3–6). A decreased loading of DTBP to 2.0 equiv or a lower temperature to 100 °C, the lower yield would be obtained in 75% and 69%, respectively (Table 1, entries 7 and 8). No significant effect in yield of **3a** was found with 6.0 equiv of DTBP or a higher temperature (Table 1, entries 9 and 10). Furthermore, the addition of metal-catalyst, $Cu(OAc)_2$ (10 mol %), did not result any improvement on the yield (79%, Table 1, entry 11). Further optimization of the conditions showed that the reaction could not proceed without the use of oxidant DTBP (Table 1, entry 12).

With the optimized reaction conditions in hand, this approach was then applied to the coupling of cyclohexane to a variety of diaryl disulfides (Scheme 2). As shown in Scheme 2, the process has a broad scope and high compatibility with functional groups, such as methyl, methoxy, halo and nitro substituent groups. *Ortho*-, *meta*- and *para*-substituted diaryl disulfides were well tolerated, and the reactions gave the corresponding products with good to excellent yields of 71–92% (**3a-h**). The lower yields observed in the case of *ortho*-substituted diaryl disulfides compared to its *para*- or *meta*- analogues, is possibly due to the steric hindrance (**3d-f**). The reaction with *p*-methyl and *p*-methoxy substituted diaryl disulfides afforded the expected product with excellent yields (**3b** and **3c**). However, when *p*-fluoro and *p*-nitro substituted diaryl disulfides were used as the coupling partner the product yields dropped (85% for **3d** and 75% for **3h**). These results imply that the electronegativity of the substituents in the diaryl disulfides has an obvious effect on the chemical yields. In addition, the disubstituted diaryl disulfide is also well tolerated in this reaction to give the target product with a slightly lower yield of 80% (**3i**). Notably, the heterocyclic disulfides thienyl or pyridinyl disulfide can work well in the reaction to provide the corresponding alkyl heteroaryl sulfide (**3j-k**). It is worth to note that the reaction with

complex heterocyclic disulfides 2,2'-dithiobis(benzothiazole) and 5,5'-dithiobis(1-phenyl-1*H*-tetrazole) also proceed successfully under the optimized condition (**3l-m**). Disappointingly, 1,2-dibenzyldisulfane was not a suitable substrate for the current thiolation system (**3n**).

Subsequently, other cycloalkanes, including cyclopentane, cycloheptane and cyclooctane were employed as substrates for this reaction to further examination of the reaction scope (Scheme 3). Fortunately, they work well in the system under the optimized conditions, and can react with different diaryl disulfides **1**, giving the corresponding products **4a–j** in 67–89% chemical yield. Comparing with the results shown in Scheme 2 for cyclohexane as a substrate, the reaction with cyclopentane showed a lower efficiency, and obvious lower yields were found (67–82%, **4a**–**g**). However, for the cases of larger cycloalkanes, such as cycloheptane and cyclooctane, comparative chemical yields were obtained (**4h**–**j**).

Then intramolecular and intermolecular competition experiments were carried out. Firstly, heteroaryl aryl disulfide **1o** was used for the investigation of the intramolecular competition reaction (Scheme 4). We found both of these two ArS• could react with cyclohexane well, giving the cross-coupling products **3l** and **3b** in 85% and 86% chemical yields respectively.

Then, the examination of the intramolecular competition reaction was performed with the using of disulfides **1l** and **1b** as substrates at the same time (Scheme 5). The reaction with both of these two disulfides proceeded very well, and good chemical yields were obtained (**3l** and **3b** in 82% and 84% respectively).

To gain insight into the reaction mechanism, several control experiments were carried out (Scheme 6). Addition of the radical-trapping reagents 2,2,6,6 tetramethylpiperidine *N*-oxide (TEMPO) or azobisisobutyronitrile (AIBN) can completely inhibit the reaction and almost no desired product was observed. These results indicate that the transformation may proceed via a radical course.

Based on the above results and literature reports,[4, 10, 13] a possible mechanism for the cycloalkane thiolation reaction is illustrated in Scheme 7, which includes a key radical oxidative coupling step. At the beginning, homolysis of DTBP give *tert*-butoxy radical intermediate **A** under the condition of heating. Then, cyclohexane radical intermediate **B** is generated via reaction of intermediate **A** and cyclohexane **2a** through a C–H bond cleavage. The following step is the reaction between intermediate **B** and 1,2-diphenyldisulfane **1**, affording the final target product **3a**, along with the formation of PhS• free radical intermediate **C**. Finally, the free radical **C** couples with cyclohexane readical **B**, giving another molecular of product **3a**.

In conclusion, we have presented a novel and highly efficient method for C–S cross-coupling through direct C($sp^3$)–H bond functionalization of cycloalkanes with diaryl sulfides using DTBP as the oxidant without use of any metal catalyst. Varieties of substituted diphenyl disulfides and heterocyclic disulfides could be tolerated and coupled with cycloalkanes, giving the cycloalkyl aryl sulfides in good to excellent yields. Moreover,

this synthetic strategy for direct C–S bond formation might be very valuable and attractive in radical chemistry.

## Experimental Section

### General procedure for thiolation of cycloalkanes

A sealable reaction tube equipped with a magnetic stirrer bar was charged with diaryl disulfides (0.5 mmol), DTBP (di-*tert*-butyl peroxide, 2.0 mmol, 377 μL), and cycloalkanes (2.0 mL). The rubber septum was then replaced by a Teflon–coated screw cap, and the reaction vessel placed in an oil bath at 120 °C. After stirring at this temperature for 24 h, it was cooled to room temperature and diluted with ethyl acetate, washed with water, dried over $MgSO_4$. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum) to afford the direct cross–coupling product, cycloalkyl aryl sulfides. In this reaction, 0.5 mol of diaryl disulfides can afford 1 mol of PhS• free radical as shown by Scheme 7, which finally can give 1 mol of cross-coupling product. So the yields and amounts of products are given based on this.

Heating of organic peroxide could be potentially dangerous.

## Acknowledgments

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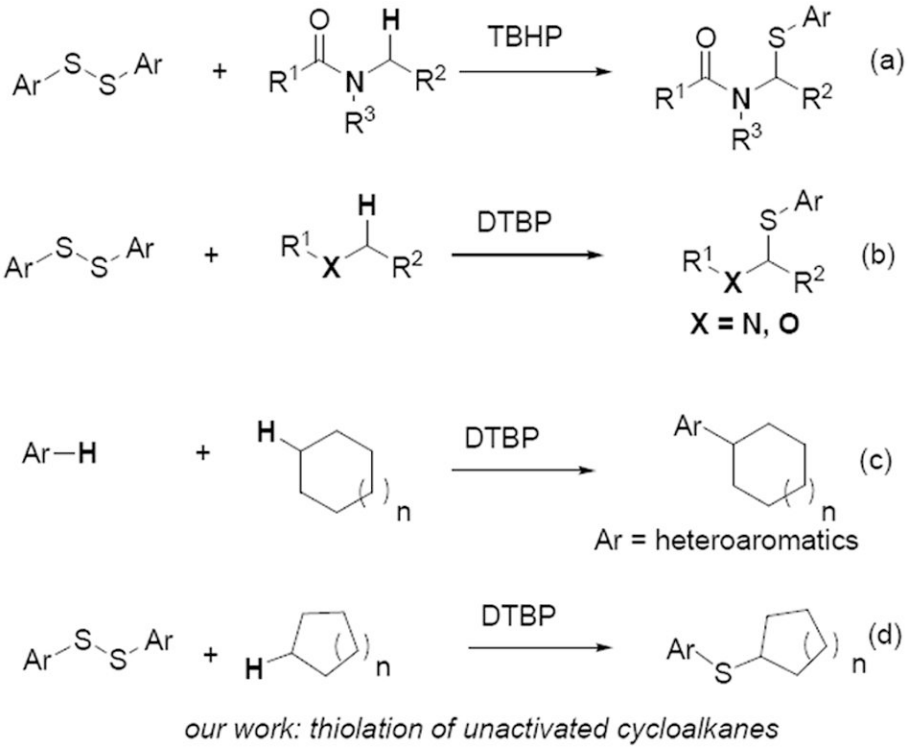
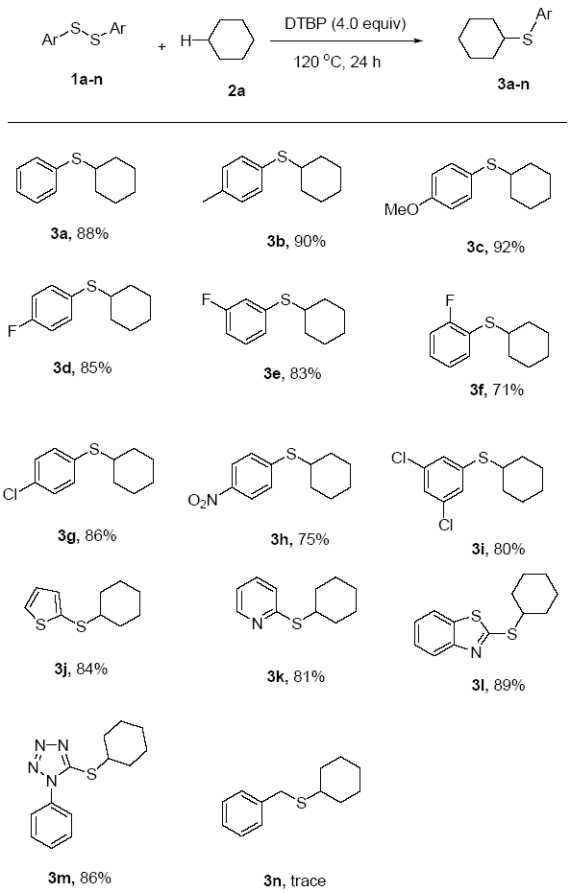
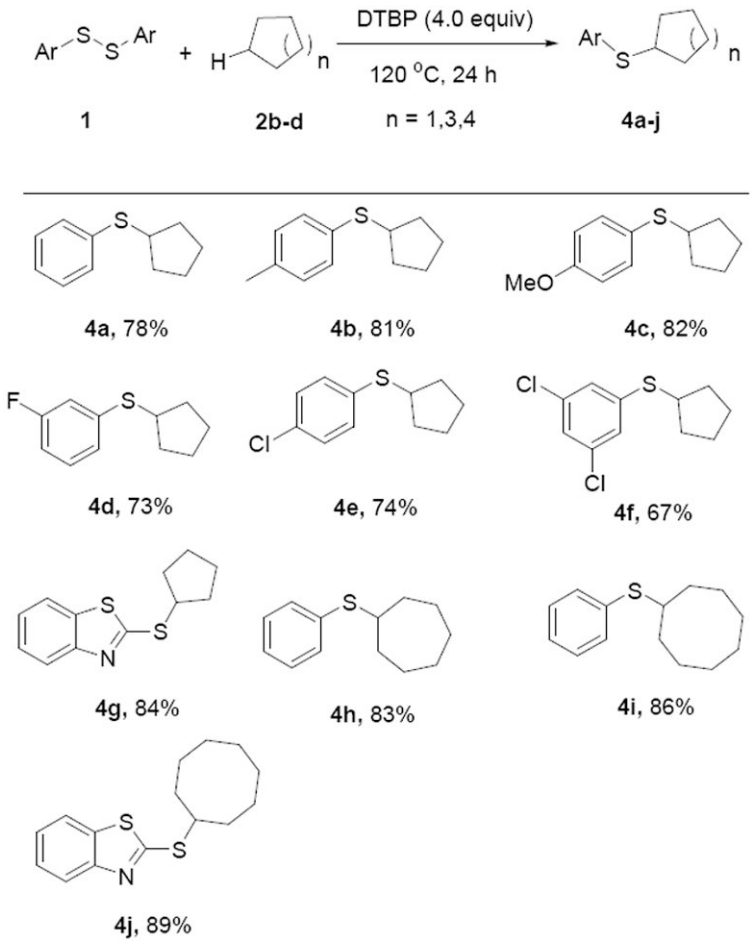



**Scheme 1.**
C($sp^3$)–H bond functionalization.



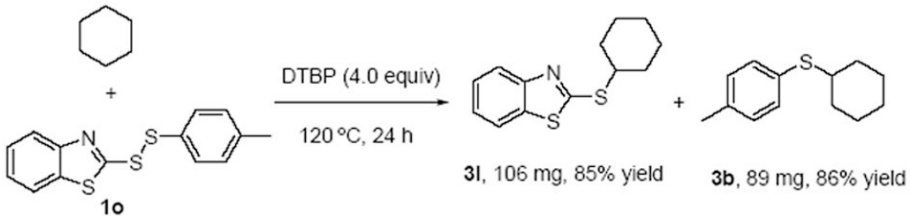

**Scheme 2.**

Thiolation of cyclohexane with disulfides. Reaction conditions: **1** (0.5 mmol), cyclohexane (2 mL), DTBP (4.0 equiv), 120 °C, 24 h. Isolated yields based on **1**.



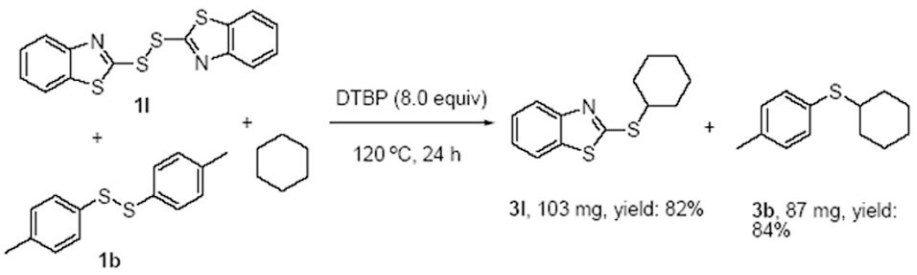

**Scheme 3.**

Thiolation of cyclopentane with disulfides. Reaction conditions: **1** (0.5 mmol), cycloalkanes (2 mL), DTBP (4.0 equiv), 120 °C, 24 h. Isolated yields based on **1**.



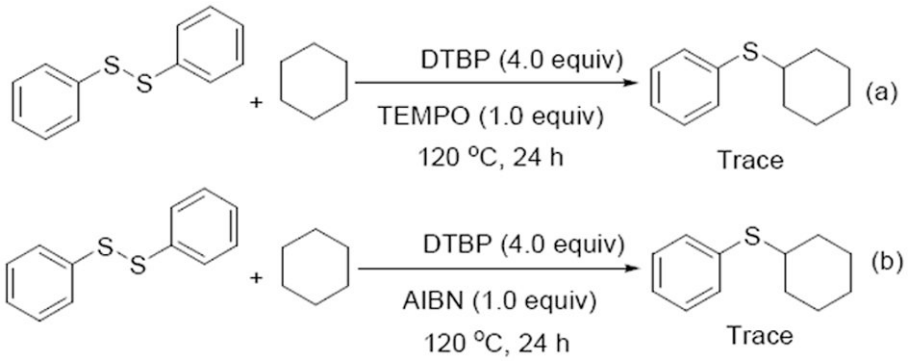

**Scheme 4.**

Investigation of the intramolecular competition reaction. Reaction conditions: **1o** (0.5 mmol), cyclohexane (2 mL), DTBP (4.0 equiv), 120 °C, 24 h.

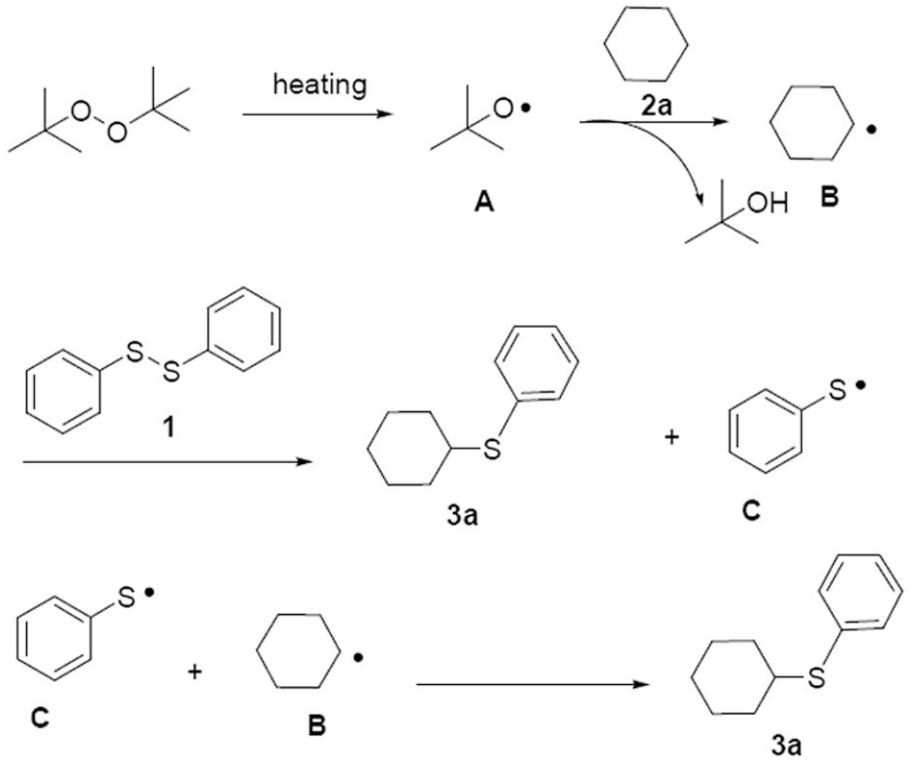



**Scheme 5.**

Investigation of the intermolecular competition reaction. Reaction conditions: **1l** (0.25 mmol), **1b** (0.25 mol), cyclohexane (2 mL), DTBP (8.0 equiv), 120 °C, 24 h.



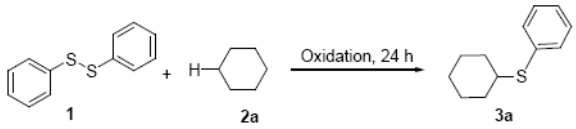

**Scheme 6.**
Insights into the mechanism.




**Scheme 7.**
A possible reaction mechanism.

## Table 1

Optimization of reaction condition [a]




| Entry | Oxidant (equiv) | *T* (°C) | Yield (%)[b] |
|---|---|---|---|
| 1 | TBHP (4.0) | 120 | 23[c] |
| 2 | DTBP (4.0) | 120 | 88 |
| 3 | DDQ (4.0) | 120 | N.D. |
| 4 | $K_2S_2O_8$ (4.0) | 120 | N.D. |
| 5 | $H_2O_2$ (4.0) | 120 | Trace[d] |
| 6 | TBPB (4.0) | 120 | 18 |
| 7 | DTBP (2.0) | 120 | 75 |
| 8 | DTBP (4.0) | 100 | 69 |
| 9 | DTBP (6.0) | 120 | 86 |
| 10 | DTBP (4.0) | 140 | 87 |
| 11 | DTBP (4.0) | 120 | 79[e] |
| 12 | – | 120 | N.D. |

[a] Catalytic conditions: **1** (0.5 mmol), cyclohexane (2 mL), oxidant, 24 h.

[b] Isolated yields based on **1**.

[c] 70% in water solution.

[d] 30% aqueous solution.

[e] $Cu(OAc)_2$ (0.05 mmol) was added.