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Metal-Free Preparation of Cycloalkyl Aryl Sulfides *via* Di-*tert*-butyl Peroxide-Promoted Oxidative C(sp^3)–H Bond Thiolation of Cycloalkanes

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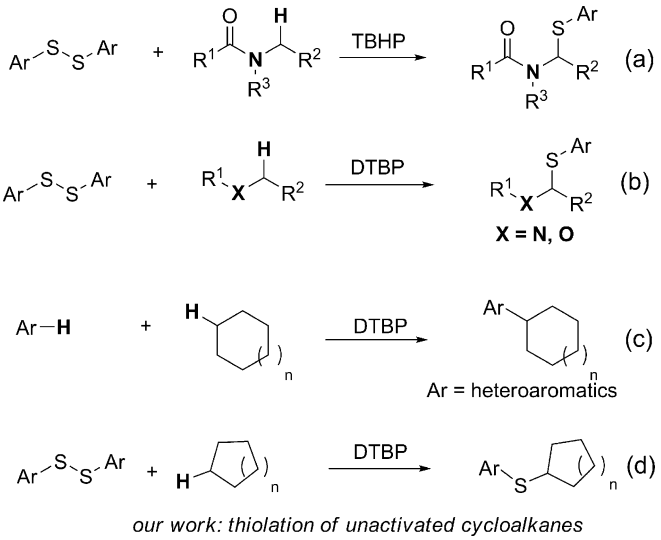
Abstract: A concise thiolation of the C(sp^3)–H bond of cycloalkanes with diaryl disulfides in the presence of the oxidant di-*tert*-butyl peroxide (DTBP) has been developed. This reaction, without using any metal catalyst, tolerates varieties of disulfides and cycloalkanes substrates, giving good to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

Keywords: C(sp^3)–H activation; cycloalkanes; metal-free conditions; oxidative process; thiolation

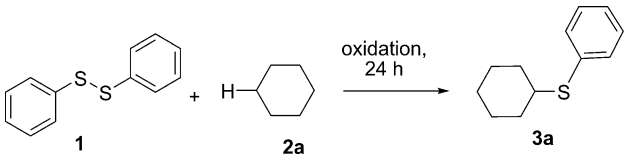
The formation of C–S bonds represents an active research area in general organic chemistry, material science as well as biological and pharmaceutical chemistry.[1] In the past decade, a number of methodologies have been developed in this field. In particular, transition metal-catalyzed cross-coupling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

The 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 considerable interest 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 the 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 an 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 has also been reported



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

Table 1. Optimization of reaction conditions.[a]



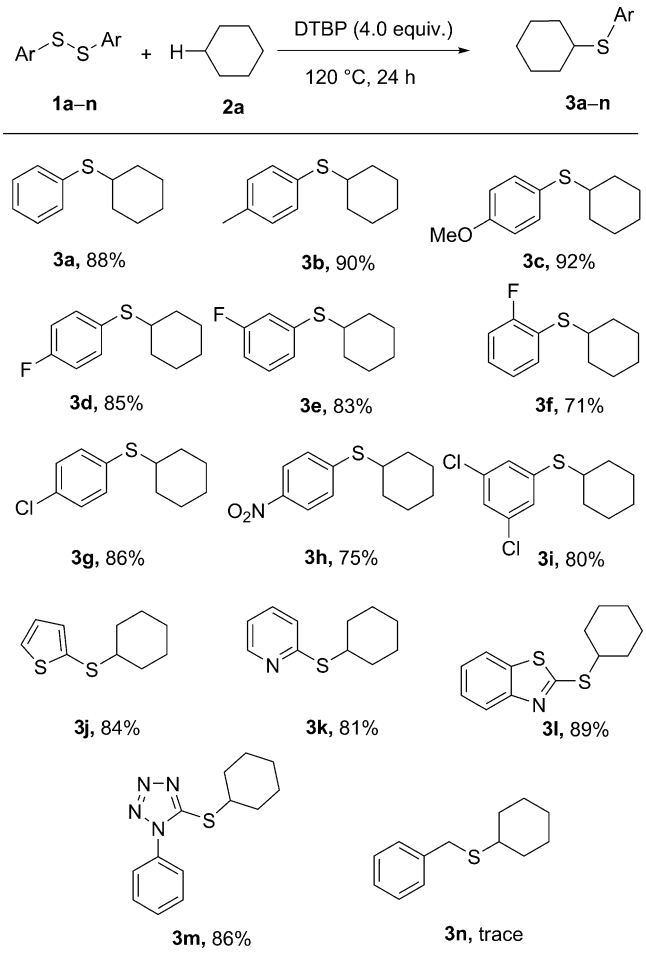
Entry	Oxidant (equiv.)	T [°C]	Yield [%][b]
1	TBHP (4.0)	120	23[c]
2	DTBP (4.0)	120	88
3	DDQ (4.0)	120	N.D.
4	$K_2S_2O_8$ (4.0)	120	N.D.
5	H_2O_2 (4.0)	120	trace[d]
6	TBPB (4.0)	120	18
7	DTBP (2.0)	120	75
8	DTBP (4.0)	100	69
9	DTBP (6.0)	120	86
10	DTBP (4.0)	140	87
11	DTBP (4.0)	120	79[e]
12	–	120	N.D.

[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.

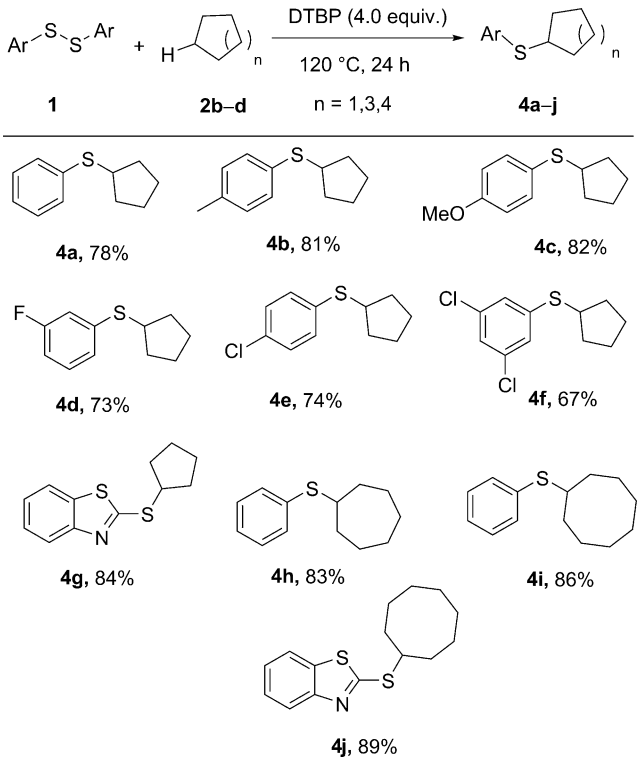
(Scheme 1c).[11,12] To the best of our knowledge, no examples for the construction of a C–S bond through C(sp^3)–H bond functionalization of cycloalkanes have been described. Herein, we now report the first realization of the thiolation of C(sp^3)–H bonds of cycloalkanes through DTBP-mediated oxidative C(sp^3)–H bond functionalization without the aid of a 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*-butyl hydroperoxide (TBHP) at 120 °C for 24 h. The reaction did happen, and afforded the expected product of cyclohexyl(phenyl)sulfane **3a** in a poor yield (23%, Table 1, entry 1). On 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 any better results (Table 1, entries 3–6). With a decrease in the loading of DTBP to 2.0 equiv. or at a lower temperature of 100 °C, lower yields were obtained, 75% and 69%, respectively (Table 1, entries 7 and 8). No significant effect on the yield of **3a** was found with use of 6.0 equiv. of DTBP or at a higher temperature (Table 1, entries 9 and 10). Furthermore, the addition of a metal catalyst, $Cu(OAc)_2$ (10 mol%), did not result in any improvement of the yield (79%, Table 1, entry 11). Further optimization of the conditions showed that the reaction could not proceed without the use of DTBP as oxidant (Table 1, entry 12).

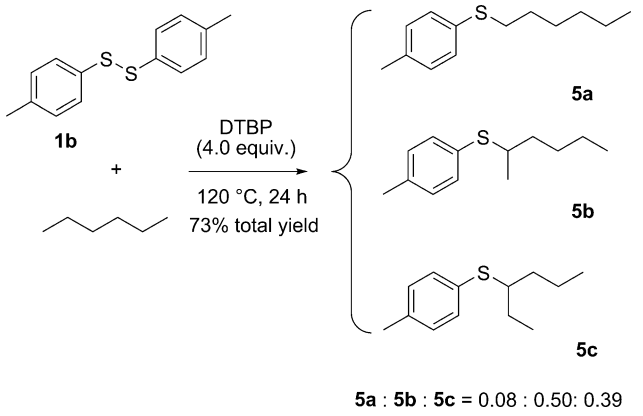
With the optimized reaction conditions in hand, this approach was then applied to the coupling of cyclohexane to a variety of diaryl disulfides (Scheme 2). As shown in Scheme 2, the process has a broad scope and high compatibility with functional groups such as methyl, methoxy, halo and nitro substituents. Also, *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 the *para*- or *meta*- analogues, is possibly due to the steric hindrance (**3d–f**). The reaction with *para*-methyl- and *para*-methoxy-substituted diaryl disulfides afforded the expected products with excellent yields (**3b** and **3c**). However, when *para*-fluoro and *para*-nitro-substituted diaryl disulfides were used as the coupling partner the product yields dropped (85% for **3d** and 75%



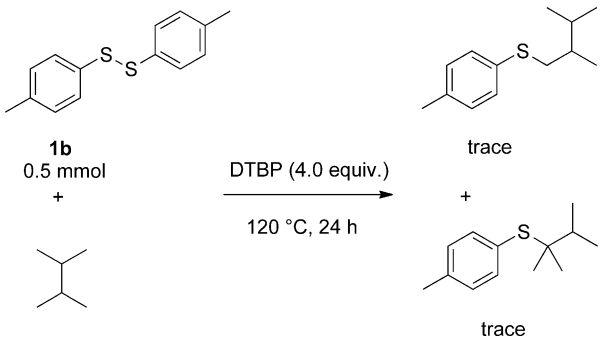
Scheme 2. Thiolation of cyclohexane with disulfides. *Reaction conditions:* **1** (0.5 mmol), cyclohexane (2 mL), DTBP (4.0 equiv.), 120 °C, 24 h. Isolated yields based on **1**.



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. Thiolation of hexane with disulfides. *Reaction conditions:* **1b** (0.5 mmol), hexane (2 mL), DTBP (4.0 equiv.), 120 °C, 24 h.



Scheme 5. Thiolation of 2,3-dimethylbutane with disulfides. *Reaction conditions:* **1b** (0.5 mmol), 2,3-dimethylbutane (2 mL), DTBP (4.0 equiv.), 120 °C, 24 h.

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

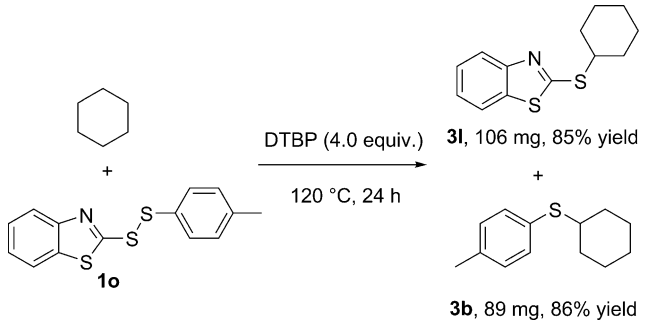
Subsequently, other cycloalkanes, including cyclopentane, cycloheptane and cyclooctane were employed as substrates for this reaction to further examine the reaction scope (Scheme 3). Fortunately, they work well in the system under the optimized conditions, and can react with different diaryl disulfides **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 reactions 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, a linear substrate, hexane was tried in this reaction (Scheme 4). The reaction could proceed well and give in total a 73% chemical yield, however, three isomers **5a**–**5c** were obtained in the ratio of 0.08:0.50:0.39, and could not be isolated.

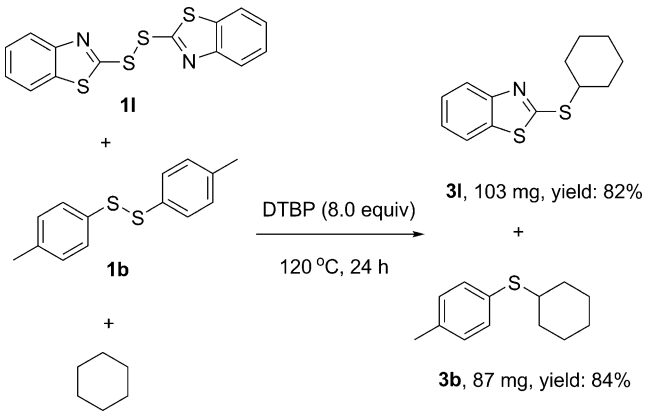
Also, the examination of branched alkane was carried out. 2,3-Dimethylbutane was tried as substrate for this reaction (Scheme 5). It was unfortunate to find that 2,3-dimethylbutane was not a suitable substrate for the current reaction, and only a trace amount of the desired product was found.

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 6). 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.

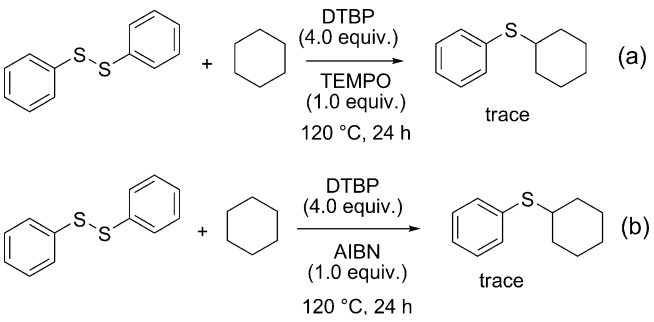
Then, the examination of the intramolecular competition reaction was performed with the using of di-



Scheme 6. Investigation of the intramolecular competition reactions. *Reaction conditions:* **1o** (0.5 mmol), cyclohexane (2 mL), DTBP (4.0 equiv.), 120 °C, 24 h.



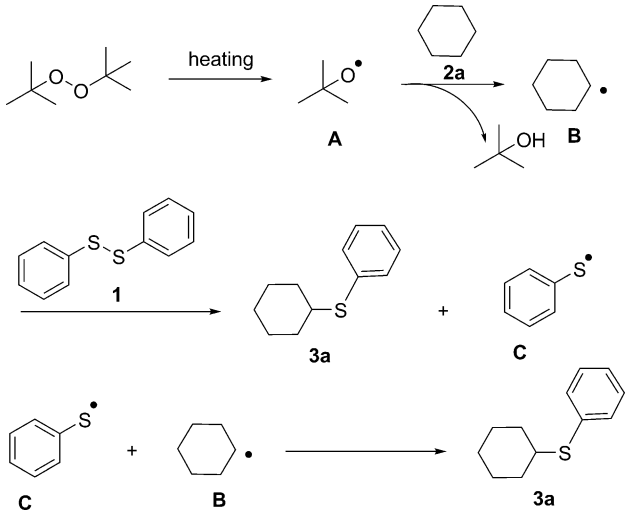
Scheme 7. Investigation of the intermolecular competition reactions. *Reaction conditions:* **1l** (0.25 mmol), **1b** (0.25 mol), cyclohexane (2 mL), DTBP (8.0 equiv.), 120 °C, 24 h.



Scheme 8. Insights into the mechanism.

sulfides **1l** and **1b** as substrates at the same time (Scheme 7). 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 insights into the reaction mechanism, several control experiments were carried out (Scheme 8). Addition of the radical-trapping reagents 2,2,6,6 tetramethylpiperidine *N*-oxide (TEMPO) or azobisisobutyronitrile (AIBN) can completely inhibit the reaction



Scheme 9. A possible reaction mechanism.

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 9, which includes a key radical oxidative coupling step. At the beginning, homolysis of DTBP gives *tert*-butoxy radical intermediate **A** under the conditions 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$^{\bullet}$ free radical intermediate **C**. Finally, the free radical **C** couples with cyclohexane radical **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, the reaction mixture was cooled to room temperature and diluted with ethyl acetate, washed with water, dried over $MgSO_4$. After the solvent had been 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 in Scheme 9, which finally can give 1 mol of cross-coupling product. So the yields and amounts of products are given based on this.

Caution: Heating of organic peroxides could be potentially dangerous.

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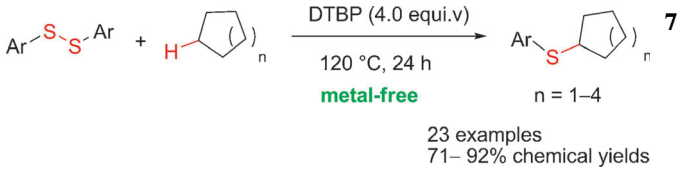

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