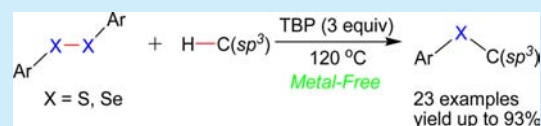


Syntheses of Sulfides and Selenides through Direct Oxidative Functionalization of C(sp<sup>3</sup>)–H BondBingnan Du,<sup>†</sup> Bo Jin,<sup>†</sup> and Peipei Sun<sup>\*,†,‡</sup><sup>†</sup>Jiangsu Key Laboratory of Biofunctional Materials, College of Chemistry and Materials Science, Nanjing Normal University, Nanjing 210097, China<sup>‡</sup>Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing 210023, China

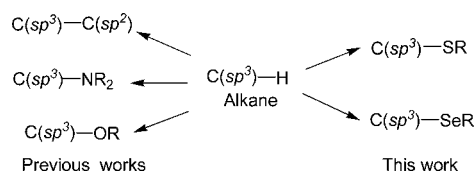
## S Supporting Information

**ABSTRACT:** A new protocol for C–S and C–Se bond formation by the direct functionalization of the C(sp<sup>3</sup>)–H bond of alkanes under metal-free conditions was developed. Using <sup>t</sup>BuOO<sup>t</sup>Bu as the oxidant, the reaction of disulfides or diselenides with alkanes gave sulfides or selenides in moderate to good yields. The method was very simple and atom-economical.



The functionalization of C(sp<sup>3</sup>)–H bonds has been an extremely remarkable project in recent years because of the atom-economics and the environmental sustainability.<sup>1</sup> Direct functionalization of saturated C–H bonds to form C–C or C–heteroatom bonds via metal-catalyzed atom/group transfer reactions is becoming an appealing methodology in modern organic synthesis.<sup>2</sup> One of the most attractive approaches on the functionalization of the C(sp<sup>3</sup>)–H bond is the activation of purely isolated and unactivated C(sp<sup>3</sup>)–H bonds of alkanes under the oxidation conditions.<sup>3</sup> By this strategy, vast lowcost feedstock of hydrocarbons could be turned into synthetically useful compounds. Several oxidative cross-couplings of simple alkanes with C(sp<sup>2</sup>) of arenes, heteroarenes, or olefins by the C(sp<sup>3</sup>)–H bond activation to form the C–C bond were reported recently.<sup>4</sup> Moreover, a series of encouraging progresses on oxidative functionalization of C(sp<sup>3</sup>)–H bonds of simple alkanes to form C(sp<sup>3</sup>)–heteroatom bonds also have been achieved in recent years. For example, the peroxide-mediated amination with nitroarenes,<sup>5</sup> Cu-catalyzed C–H amination/amidation with aromatic amines/amides,<sup>6</sup> Fe-catalyzed C–H amination with hypervalent iodides,<sup>7</sup> direct amination of alkanes by hypervalent bromides,<sup>8</sup> direct azidation of alkanes by azidobenziodoxoles,<sup>9</sup> Fe-catalyzed C–H hydroxylation of alkanes,<sup>10</sup> Cu-catalyzed C–H etherification with <sup>t</sup>BuOO<sup>t</sup>Bu,<sup>11</sup> etc. Until now, the oxidative functionalization of C(sp<sup>3</sup>)–H bonds of simple alkanes mainly focused on the formation of C–C, C–N, and C–O bonds (Scheme 1). Thus, it would be highly desirable if this strategy could be expanded to the construction of various C(sp<sup>3</sup>)–heteroatom bonds.

The importance of organosulfur compounds in general organic synthesis, in the pharmaceutical industry, in food chemistry, as well as in material science is well-known.<sup>12</sup> The most striking development on the construction of the C–S bond is transition metal-catalyzed cross-coupling reactions in recent years except the traditional methods.<sup>13</sup> To develop new, efficient, and environmentally benign routes for the syntheses

Scheme 1. Oxidative Functionalization of C(sp<sup>3</sup>)–H Bonds of Simple Alkanes

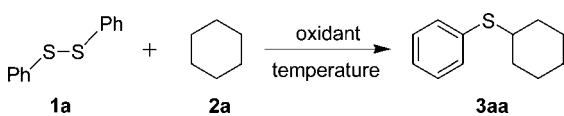
of sulfides is an important and challenging task because of the significance of such compounds. In particular, the reactions under metal-free conditions are desired in the pharmaceutical synthesis. We report here the straightforward, mild, and convenient protocol for the syntheses of sulfides and selenides through the direct oxidative cross-couplings of simple alkanes with disulfides or diselenides in the absence of a transition metal.

We began our investigations by using diphenyl disulfide **1a** and cyclohexane **2a** as the substrates to optimize the reaction conditions (Table 1). The copper salt was initially employed as the catalyst for this oxidative coupling reaction. We were pleased to find that in argon atmosphere and using 2.0 equiv of *tert*-butyl peroxide (TBP) as the oxidant, this reaction provided the desired product **3aa** in the yields of 46–71% after 18 h at 100 °C in the presence of 10 mol % various copper salts (entries 1–6). We also noticed that without any catalyst, the reaction still gave a 55% yield (entry 7). So we decided to carry out the reaction under metal-free conditions. To our delight, when the reaction temperature was increased to 120 °C, a yield of 81% was obtained only in the presence of 2.0 equiv of TBP (entry 8). Further increasing the amount of oxidant TBP to 3.0 equiv brought a yield of 88% (entry 9). When other oxidants, such as dicumyl peroxide (DCP), *tert*-butyl hydroperoxide (TBHP) and benzoyl peroxide (BPO) were used instead of

Received: April 21, 2014

Published: May 16, 2014

Table 1. Selected Results for Screening the Optimized Reaction Conditions<sup>a</sup>

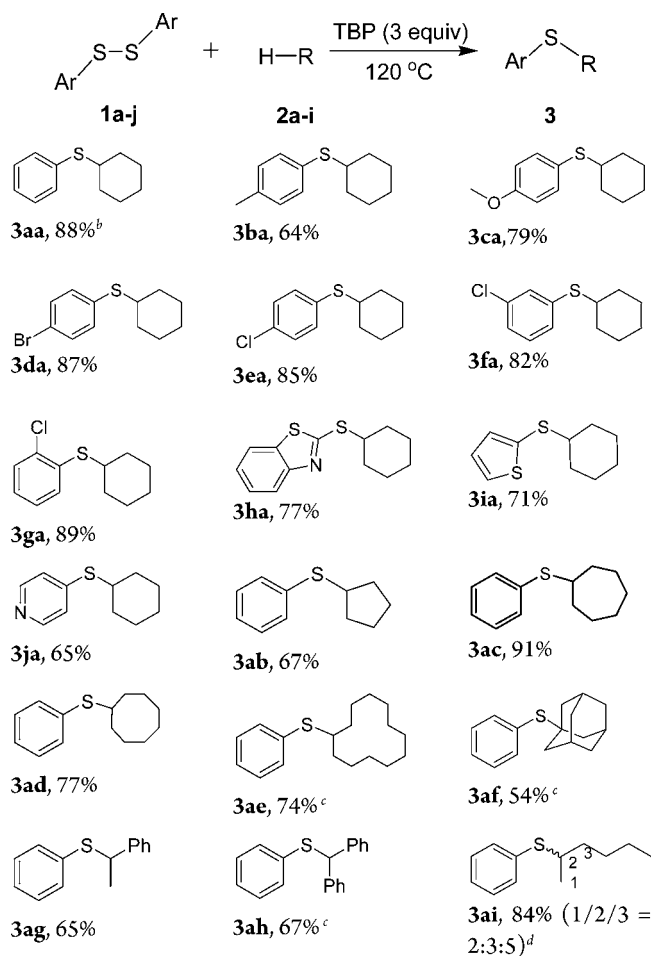
				
entry	additive (mol %)	oxidant <sup>b</sup> (equiv)	temp (°C)	yield <sup>c</sup> (%)
1	Cu(OTf) <sub>2</sub> (10)	TBP (2)	100	47
2	Cu(OAc) <sub>2</sub> (10)	TBP (2)	100	54
3	CuO (10)	TBP (2)	100	46
4	CuI (10)	TBP (2)	100	65
5	CuBr (10)	TBP (2)	100	71
6	CuCl (10)	TBP (2)	100	63
7		TBP (2)	100	55
8		TBP (2)	120	81
9		TBP (3)	120	88
10		DCP (3)	120	59
11		TBHP (3)	120	17
12		BPO (3)	120	35
13		BQ (3)	120	0
14		H <sub>2</sub> O <sub>2</sub> (3)	120	0
15		K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (3)	120	0
16		O <sub>2</sub> (1 atm)	120	0
17 <sup>c</sup>		TBP (3)	120	23
18 <sup>d</sup>		TBP (3)	120	64

<sup>a</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mL) and the oxidant, in a sealed tube under Ar for 18 h. <sup>b</sup>TBP: *tert*-butyl peroxide, DCP: Dicumyl peroxide, TBHP: *tert*-butyl hydroperoxide 70% in water, BPO: benzoyl peroxide, BQ: 1,4-benzoquinone. <sup>c</sup>Under O<sub>2</sub> atmosphere. <sup>d</sup>Under air atmosphere. <sup>e</sup>Isolated yield.

TBP, the reaction gave the poor yields (entries 10–12). And also, the reaction could not take place at all if 1,4-benzoquinone (BQ), H<sub>2</sub>O<sub>2</sub>, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, or O<sub>2</sub> was employed as the oxidant (entries 13–16). Furthermore, O<sub>2</sub> and air showed significant inhibition to the reaction. When the reaction was performed under O<sub>2</sub> or air atmosphere, the lower yield of 23% or 64% was obtained, respectively (entries 17–18).

With the optimized reaction conditions in hand, a series of other disulfides and alkanes as the substrates were investigated (Scheme 2). Aryl disulfides bearing both electron-donating groups (R = Me, OMe) and electron-withdrawing groups (R = Br, Cl) reacted with cyclohexane to give the desired sulfides in moderate to good yields (**3ba–ga**), and the connection position of substituent on the benzene ring had no significant influence on the reaction (**3ea–ga**). It is worth noting that this protocol is also applicable to a range of heterocyclic aromatics such as benzothiazole, thiophene and pyridine (**3ha–ja**). Next we employed a round of cycloalkanes, including cyclopentane, cycloheptane, cyclooctane, cyclododecane and adamantane as the coupling partner, and the results did not show evident difference compared with the reaction of cyclohexane (**3ab–af**). Finally, open chain compounds were also investigated, and the corresponding oxidative coupling products were obtained (**3ag–ai**). It is interesting that the reactions showed evident regioselectivity, in which tertiary C–H of alkane had a higher reactivity than secondary C–H (**3af**), and secondary C–H was more active than primary C–H (**3ag**, **3ai**), which is consistent with the stability order of the radicals.

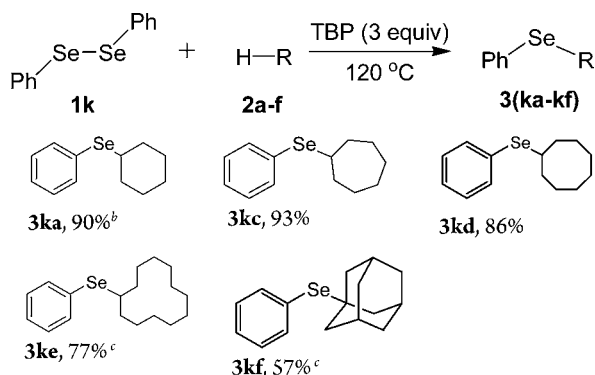
Organoselenium compounds are also attractive synthetic targets not only owing to their chemo-, regio-, and stereo-selective reactions but also because of their biological

Scheme 2. Results of Oxidative Coupling Reaction of Alkanes with Disulfides<sup>a</sup>

<sup>a</sup>Reaction conditions: **1** (0.2 mmol), **2** (1.0 mL) and TBP (3.0 equiv), in a sealed tube under Ar at 120 °C for 18 h. <sup>b</sup>Isolated yields. <sup>c</sup>**2** (3.0 equiv) in benzene (1.0 mL). <sup>d</sup>Determined by <sup>1</sup>H NMR analysis.

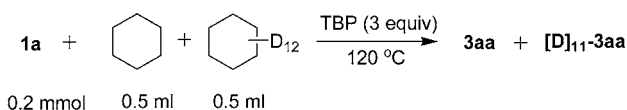
activities.<sup>14</sup> Barton et al.<sup>15</sup> reported a Fe-mediated phenylselenation of saturated hydrocarbons to generate phenylselenocyclohexane, in which saturated hydrocarbons were oxidized synergistically with H<sub>2</sub>S and O<sub>2</sub> in the presence of Fe. Encouraged by the successful synthesis of sulfides under the metal-free oxidation conditions above, we decided to expend this strategy to the synthesis of selenides (Scheme 3). Under the same reaction conditions, the oxidative coupling of diselenide with alkanes gave the corresponding products phenylselenides in yields of 57–93% (**3ka–kf**).

For understanding the pathway of the present reaction, an intermolecular kinetic isotope experiment was carried out (Scheme 4).<sup>4c,g,h</sup> The results showed that when equivalent cyclohexane (**2a**) and [D<sub>12</sub>]cyclohexane ([D]<sub>12</sub>-**2a**) were employed to react with diphenyl disulfide (**1a**) under the standard reaction conditions for several reaction times a significant isotopic effect could be observed (Scheme 4), which indicated that the C(sp<sup>3</sup>)–H bond cleavage should be the rate-determining step in this transformation. In addition, only **3aa** and [D]<sub>11</sub>-**3aa** were observed as the products, which revealed that the process of C(sp<sup>3</sup>)–H bond cleavage is irreversible. When 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidin-1-oxyl (TEMPO, a radical-trapping reagent) was added, the

Scheme 3. Results of Oxidative Coupling Reaction of Alkanes with Diselenide<sup>a</sup>

<sup>a</sup>Reaction conditions: **1k** (0.2 mmol), **2** (1.0 mL) and TBP (3 equiv), in a sealed tube under Ar at 120 °C for 18 h. <sup>b</sup>Isolated yields. <sup>c</sup>**2** (3.0 equiv) in benzene (1.0 mL).

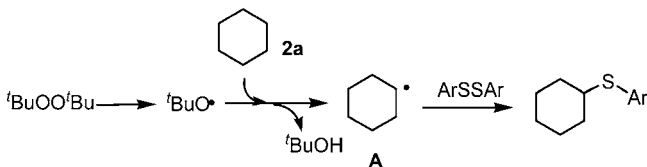
Scheme 4. KIE Study



For 2 h (yield 21%), **3aa**:**[D]<sub>11</sub>-3aa** = 5.7  
 For 6 h (yield 46%), **3aa**:**[D]<sub>11</sub>-3aa** = 5.2 (Determined by <sup>1</sup>H NMR spectra)  
 For 18 h (yield 85%), **3aa**:**[D]<sub>11</sub>-3aa** = 4.8

reaction was totally suppressed, which indicated that the radicals were generated in this transformation. On the basis of these experimental results and previous related reports,<sup>4d,9a,11</sup> a plausible mechanism is depicted in Scheme 5. First, the

Scheme 5. Proposed Reaction Mechanism



homolytic cleavage of TBP produced *tert*-butoxyl radical. The *tert*-butoxyl radical then abstracted hydrogen from the C–H bond of alkane to afford alkyl radical (**A**). Radical **A** finally reacted with ArSSAr to release the product.

In summary, an unprecedented C–S and C–Se bond formation based on the direct oxidative cross-couplings of simple alkanes with disulfides or diselenides in the absence of a transition metal was developed. This method provides a very simple and atom-economic route for the syntheses of sulfides and selenides. Moreover, a KIE experiment showed that the irreversible C(sp<sup>3</sup>)–H bond cleavage should be involved in the rate-determining step.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and full characterization for all compounds; copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Project 21272117 and 20972068) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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