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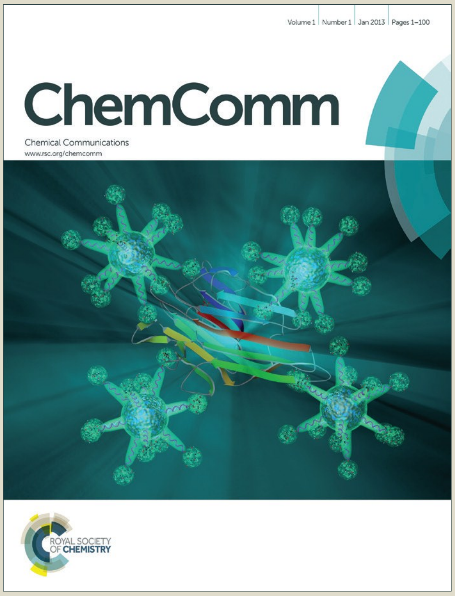

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COMMUNICATION

Copper-Mediated Stereospecific C-H Oxidative Sulfenylation of Terminal Alkenes with Disulfides

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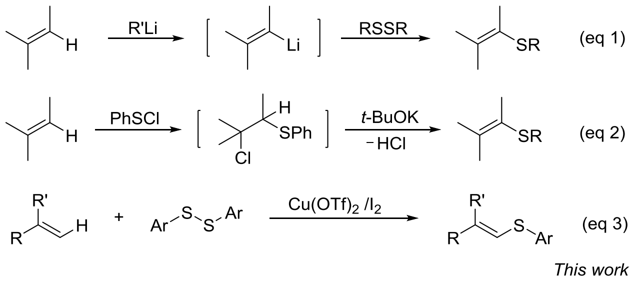
A copper and iodine-mediated C-H oxidative sulfenylation of olefins with diaryl disulfides has been developed for the stereospecific synthesis of vinyl thioether. With the combination of $Cu(OTf)_2$ and I_2, a variety of terminal alkenes underwent the oxidative coupling reaction with various diaryl disulfides successfully to afford the corresponding *E*-vinyl sulfides in moderate to good yields.

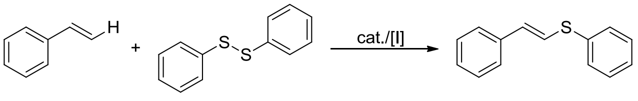
Vinyl sulfides are essential structural motifs which can be found in many biologically active molecules and natural products,[1] and also are versatile building blocks or intermediates in organic synthesis,[2] such as enol substitutes,[3] Michael acceptors[4] and olifen metathesis.[5] Consequently, the preparation of vinyl sulfides has received much attention, and two common methods are frequently utilized for their synthesis, including transition-metal-catalyzed cross-coupling of vinyl halides with thiol [6] and hydrothiolation of alkynes.[7] Traditionally, the vinylic C-H bond sulfenylation could also be realized through deprotonation by organolithium reagent followed by quenching with disulfides (eq 1, Scheme 1).[8] The tandem addition/elimination reactions of PhSCl with olefins in the presence of strong base also afford olefinic C-H thiolated products (eq 2).[9] Recently, Deng and co-worker developed a silver-mediated vinylic C-H bond sulfenylation of enamides with disulfides.[10] However, the utility and applicability of the above reactions was limited by prefunctionalization of starting materials or/and the harsh reaction conditions. Herein, we report a convenient and practical method for the stereospecific synthesis of *E*-vinyl sulfides by copper-catalyzed, iodine-mediated C-H bond sulfenylation of terminal olefins with aryl disulfides (eq 3).

Scheme 1. Intermolecular vinylic C-H sulfenylation.



The reaction between styrene **1a** and 1,2-diphenyldisulfane **2a** was selected as a model reaction to optimize the reaction conditions, and the results were summarized in Table 1. We initially carried out the reaction of styrene **1a** with disulfide **2a** and 1 equiv of I_2 in DMSO at 120 ℃ for 6h, the target product **3** was isolated in 12% yields (entry 1). Subsequently, a variety of copper catalysts were examined with the aim to enhance the reaction yield. The results disclosed that both copperic and

Table 1. Screening conditions [a]



1a **2a** **3**

Entry	Catalyst	[I] source	Base	Solvent	Yield (%)
1	-	I_2	-	DMSO	12
2	CuI	I_2	-	DMSO	38
3	CuBr	I_2	-	DMSO	61
4	CuCl	I_2	-	DMSO	46
5	$Cu(OAc)_2$	I_2	-	DMSO	60
6	$Cu(TFA)_2$	I_2	-	DMSO	64
7	$Cu(OTf)_2$	I_2	-	DMSO	76
8	$Cu(OTf)_2$	NIS	-	DMSO	52
9	$Cu(OTf)_2$	TBAI	-	DMSO	11
10	$Cu(OTf)_2$	$PhI(OAc)_2$	-	DMSO	0
11	$Cu(OTf)_2$	-	-	DMSO	0
12	$Cu(OTf)_2$	I_2	*t*-BuOK	DMSO	Trace
13	$Cu(OTf)_2$	I_2	K_2CO_3	DMSO	16
14	$Cu(OTf)_2$	I_2	NEt_3	DMSO	22
15	$Cu(OTf)_2$	I_2	-	DMF	27
16	$Cu(OTf)_2$	I_2	-	DMAc	18
17	$Cu(OTf)_2$	I_2	-	NMP	0
18[b]	$Cu(OTf)_2$	I_2	-	DMSO	42

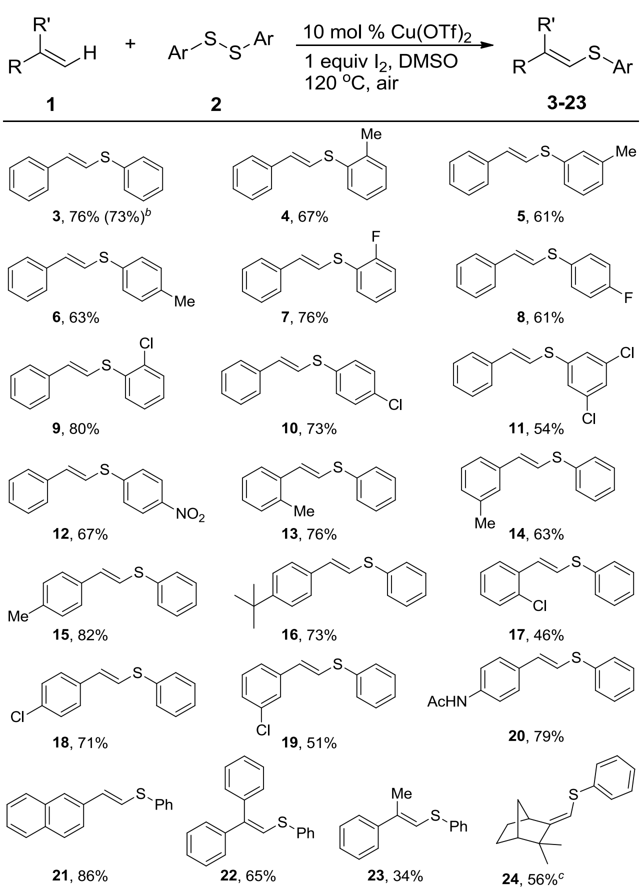
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.25 mmol), $Cu(OTf)_2$ (10 mol %), I_2 (0.5 mmol) in DMSO (2 mL) under air atmosphere at 120 ℃ for 6 h, isolated yield. [b] At 100 ℃.

copperous salts could promote the oxidative coupling reaction to provide product in 38-76% yields (entries 2-7). Treatment of substrate **1a** with **2a**, elemental iodine and 10 mol % of $Cu(OTf)_2$ in DMSO at 120 ℃ afforded the desired product 3 in 76% yield (entry 7). These results prompted us to investigate various iodine sources, such as NIS, TBAI and $PhI(OAc)_2$. Lower yields were found for NIS and TBAI, but $PhI(OAc)_2$ was ineffective for this reaction (entries 8-10). It is noteworthy that reaction did not proceed completely in the absence of I_2 (entry 11), which suggested that elemental iodine played a key role in the sulfenylation. Considering that base could facilitate some elimination reactions, we tested some bases including *t*-BuOK, K_2CO_3 and NEt_3. However, all bases disfavoured the transformation and low yields were obtained (entries 12-14). Some polar solvents were also tested, including DMF, DMAc and NMP, but all were less effective than DMSO (entries 15-17). Further investigation revealed that the reaction yield was reduced sharply to 42% when the reaction was performed at 100 ℃ (entry 18).

Under these optimized conditions, the substrate scopes of olefins and diaryl disulfides for this vinylic C-H bond sulfenylation were explored, and the results were shown in Table 2. Firstly, the reaction between styrene **1a** and a number of diaryl disulfides were investigated under the standard conditions. The results disclosed that all *ortho*-substituted, *meta*-substituted and *para*-substituted disulfide were suitable substrates and afforded the corresponding products in moderate to good yields. For example, *ortho*-tolyl disulfide provided the product **4** in 67% yield, *meta*- and *para*-tolyl disulfides gave the products **5** and **6** in 61% and 63% yields, respectively. *mono*-Fluorinated and chlorinated diphenyl disulfides afforded the products **7-10** in 61% - 80% yields. 3.5-Dichlorophenyl disulfide afforded the product **11** in 54% yield. It should be mentioned that electron-deficient 4-nitrophenyl disulfide provided the product **12** in 67% yield. Subsequently, we investigated the substrate scope of olefins by examining their reaction with diphenyl disulfide **2a** under the optimal conditions. As expected, *ortho*-, *meta*- and *para*-substituted styrenes produced vinyl sulfides **13**, **14** and **15** in good yields (76%, 63% and 82%). A 73% yield was obtained for 4-*tert*-butylstyrene. Moderate yields were observed when 2-chloro, 3-chloro and 4-chloro styrenes were used as substrates (46%-71%, **17-19**). Styrene with an acetamido group was also transformed to the target product **20** in 79% yield. 2-Vinylnaphthalene provided the corresponding product **21** in 86% yield. During the investigation of *gem*-disubstituted ethylenes, a 65% yield was found for ethene-1,1-diyldibenzene, while prop-1-en-2-ylbenzene gave the product **23** in a 34% yield. Most notably, a natural product, β-pinene also underwent the C-H sulfenylation successfully to produce the desired product **24** in 56% yield.

To probe the mechanism of this C-H oxidative sulfenylation, some control experiments were conducted as shown in Scheme 2. Styrene **1a** was treated with $Cu(OTf)_2$ and 1 equiv of I_2 in DMSO in the absence of disulfide under the standard conditions, but the iodized product **25** could not be observed (eq 1, Scheme 2).

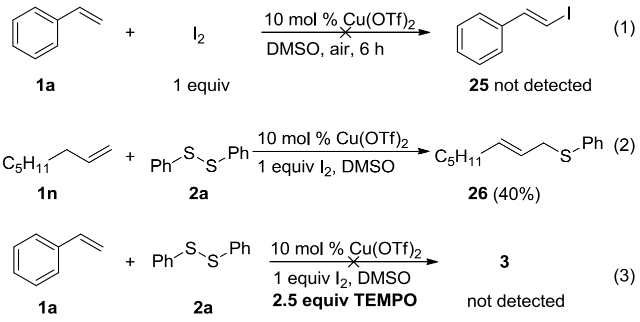
Table 2. Copper-Mediated C-H Oxidative Sulfenylation of Terminal Alkenes with Disulfides [a]



[a] Reaction conditions: **1** (0.5 mmol), **2** (0.25 mmol), $Cu(OTf)_2$ (10 mol %), I_2 (0.5 mmol) in DMSO (2 mL) under air atmosphere at 120 ℃ for 6 h, isolated yield. [b] At 2 mmol sacles. [c] For 10 h

These results demonstrated that the sulfenylation did not undergo a coupling reaction of vinyl iodide with disulfide. Subsequently, we carried out the reaction of 1-octene with disulfide **2a**, 10 mol % $Cu(OTf)_2$, 1 equiv I_2 in DMSO. However, the expected vinylic C-H thiolation product could not be obtained, instead, allyl C-H sulfenylated product **26** was isolated exclusively in 40% yield (eq 2). This finding implied that allyl radical are probably key intermediate during the sulfenylation of aliphatic olefins.[11] Then, the reaction of styrene **1a** with **2a**, $Cu(OTf)_2$, I_2 in DMSO was performed under the standard conditions by adding 2.5 equiv of 2,2,6,6-tetramethylpiperidine oxide (TEMPO), a radical

Scheme 2. Control experiments.



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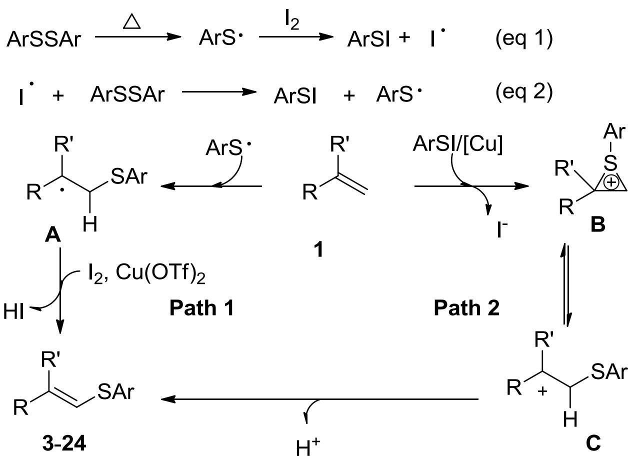
scavenger (eq 3). As expected, the reaction did not proceed and the product **3** could not be detected. These results indicated that the C-H oxidative sulfenylation might be involved a free radical process.

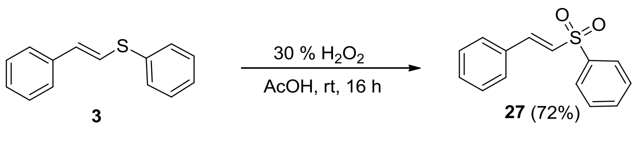
Scheme 3. Possible mechanism.



On the basis of the present results and former reported results,[12] a plausible mechanism was outlined in Scheme 3. Vinyl iodide could not be detected in the presence of disulfide and the reaction did not proceed in the presence of TEMPO (Scheme 2). These results suggest that the reaction may proceed through a free radical pathway. Firstly, aryl disulfide might decompose at high temperature to form free radical RS·,[13] which reacts with iodine to produce the RSI and iodine radical (eq 1, Scheme 3).[14] The chain propagation of iodine radical with aryl disulfide affords active RSI and radical RS· (eq 2). The addition of radical RS· to alkene **1** produces an alkyl radical **A**. The following oxidation by I_2 and $Cu(OTf)_2$ produces the corresponding carbocation, which loses a H^+ to yield desired product **3**-**24** (Path 1). Alternatively pathway is also possible (Path 2). The electrophilic addition of RSI to the double bond of alkene **1** with aid of $Cu(OTf)_2$ affords unstable three-numbered cyclic sulfonium **B**, which can be transformed easily to carbocation C. Finally, the deprotonation of intermediate **C** gives the desired product **3**-**24**.

Vinyl sulfone derivatives show a wide range of useful biological and pharmacological activities.[15] To demonstrate the applicability of this reaction in the synthesis of these types of molecules, the further transformations of vinyl sulfides was explored as outlined in Scheme 4. Treatment of product **3** with 30 % H_2O_2 in AcOH at room temperature afforded *E*-vinyl sulfone **27** in 72% yield.[16]

Scheme 4. Synthetic applications of **3**.



In summary, a convenient and efficient method for stereospecific synthesis of *E*-vinyl sulfides has been developed by copper-mediated vinylic C-H oxidative sulfenylation. A variety of terminal alkenes underwent the oxidative coupling reaction with various disulfides successfully to afford the corresponding vinyl sulfides in moderate to good yields. This atom-economic transformation was realized by incorporation of both sulfur atoms of aryl sulfides onto olefins. The utilization of alkenes without prefunctionalization and commercially available disulfides as coupling partners are significant advantages for the usefulness of this C-H oxidative coupling reaction. The present reaction has broad substrate scope of alkenes and sulfides with excellent functional group tolerance, which provides a new valuable one-pot shortcut for stereospecific preparation of vinyl sulfides.

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Notes and references

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