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Copper-Catalyzed Synthesis of Vinyl Sulfides

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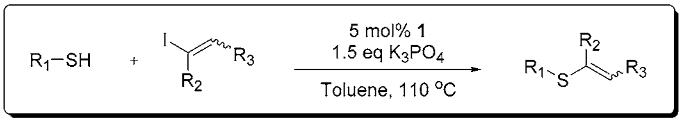
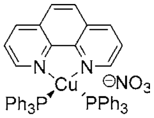
ABSTRACT





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We report a method for the synthesis of vinyl sulfides using the soluble copper(I) catalyst [Cu(phen)(PPh$_3$)$_2$]NO$_3$. The desired vinyl sulfides are obtained in good to excellent yields, with retention of stereochemistry. This protocol tolerates a wide variety of functional groups or substrates, is palladium-free, and does not require the use of expensive or air-sensitive additives.

Vinyl sulfides play an important role as synthetic intermediates in organic chemistry. They are used as equivalents of enolate ions[1] and Michael acceptors.[2] They are important intermediates in the synthesis of oxetanes,[3] cyclopentanones,[4] and cyclopentanes.[5] Many natural products and compounds exhibiting interesting biological properties contain the vinyl sulfide moiety.[6]

Because of the importance of these compounds, there have been a number of reported methods for synthesizing vinyl sulfides.[7] The most noteworthy among them involves the addition of a thiol to an alkyne. This can occur either under radical conditions,[8] affording the anti-Markovnikov product containing a mixture of regioisomers, or through the employment of transition metal catalysts (Mo, Pd, Pt, Rh, Ru).[9] The Wittig reaction has also been utilized in the synthesis of vinyl sulfides.[10] This approach requires the use of strong bases, and the synthesis of the appropriate Wittig reagents can be problematic.[7a] Vinyl sulfides have also been prepared from the cross-coupling of vinyl halides and sodium or lithium benzenethiolates or their tin analogues.[11] However, the scope and functional group tolerance of these cross-coupling reactions have not been fully explored.

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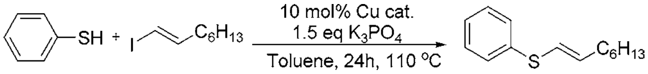
Recently there has been a resurgence in interest in developing copper-catalyzed cross-coupling reactions.[12] These methods are mild and tolerate a variety of functional groups or substrates. These copper-based methods work extremely well with soft nucleophiles such as sulfur, selenium, and phosphorus.[13] Because of the importance of vinyl sulfides and the lack of a general protocol for their synthesis, we felt that the copper-based protocols may be readily extended to the synthesis of vinyl sulfides. However, the extension was not trivial and required a thorough reoptimization of the reactions conditions with respect to catalyst, base, and solvent. We now report a general, stereospecific copper-based protocol for the cross-coupling of vinyl iodides and thiols for the synthesis of vinyl sulfides.

The optimization process was performed using the cross-coupling of thiophenol and (*E*)-1-iodooctene. We first screened a variety of bases using 10 mol % [Cu(neocup)-PPh_3Br] as the catalyst. It was observed that bases such as K_3PO_4, K_2CO_3, Cs_2CO_3, and CsOAc were very effective. Other bases such as Na_2CO_3, NaO*t*Bu, KO*t*Bu, and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were less effective (see Supporting Information). We then examined a variety of copper(I) complexes, copper(I) salts, and copper(I) salts with certain additives in toluene at 110 °C with 1.5 equiv of K_3PO_4 as the base (Table 1).

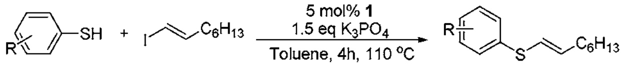
Table 1. Comparison of Well-Defined Copper(I) Complexes, Copper(I) Salts, and Additives as Catalysts for the Cross-Coupling of Thiophenol and (*E*)-1-Iodooctene



catalyst	GC yield (%)
well-defined complexes	
$[Cu(phen)(PPh_3)_2]NO_3$	>99
$[Cu(phen)PPh_3Br]$	97
$[Cu(neocup)PPh_3Br]$	93
$[Cu(CH_3CN)_4]PF_6$	16
$[Cu(bipy)PPh_3Br]$	16
$[Cu(PPh_3)_3Br]$	14
copper(I) salts/additives	
CuI/phen/PPh_3 (1:1:2)	97
CuI/phen (1:1)	96
CuI	0

The copper(I) complexes $[Cu(phen)(PPh_3)_2]NO_3$, [Cu(phen)-PPh_3Br], and $[Cu(neocup)PPh_3Br]$ demonstrated an excellent ability to catalyze the reaction. The use of copper(I) iodide and 1,10-phenanthroline as an additive also exhibited similar results. However, when we compared the rate of product formation with $[Cu(phen)(PPh_3)_2]NO_3$ and CuI/phen as the catalyst, it was seen that the well-defined complex [Cu(phen)-$(PPh_3)_2]NO_3$ was more active. After only 2 h the yield of

Table 2. Copper-Catalyzed Cross-Coupling of Various Aryl Thiols with (*E*)-1-Iodooctene Using the Standard Protocol



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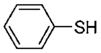
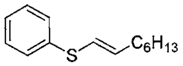
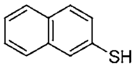
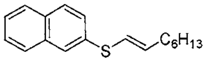
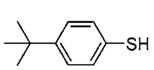
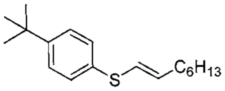
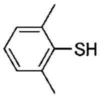
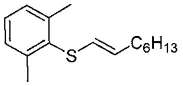
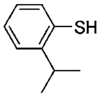
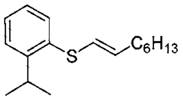
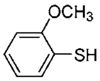
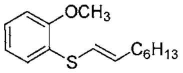
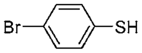
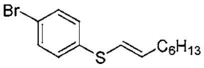
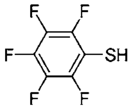
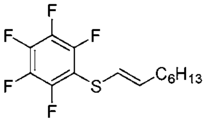
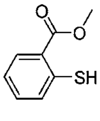
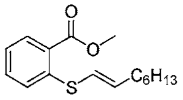
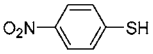
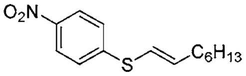
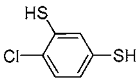
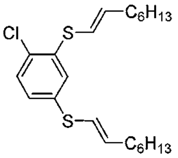
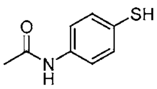
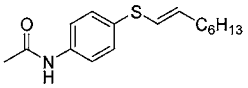
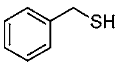
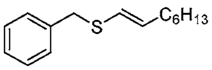
1			93
2			97
3			92
4			99
5			97
6			94
7			96
8			98
9			94
10			93
11			91
12			97
13			99

[a] Isolated yields. [b] The starting vinyl iodide (*E*)-1-iodooctene contained ~10% of the (*Z*)-isomer; this led to ~10% of the *cis*-isomer in the product.

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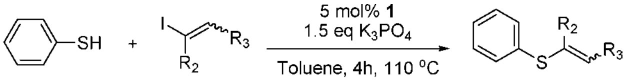
Table 3. Copper-Catalyzed Cross-Coupling of Thiophenol with an Assortment of Vinyl Iodides Using the Standard Protocol



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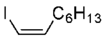
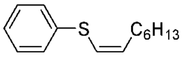
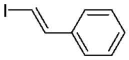
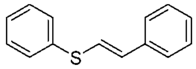
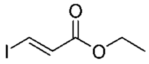
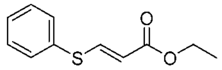
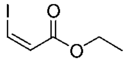
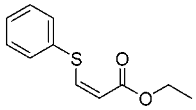
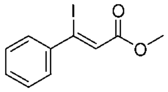
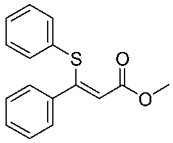
1			93
2			97
3			98
4			98
5			96

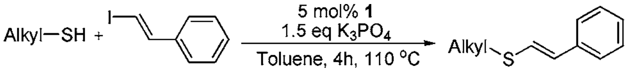
[a] Isolated yields.

the product was 99% using [Cu(phen)(PPh$_3$)$_2$]NO$_3$. This compares to an 80% yield using CuI/phen. Lowering the catalytic loading of [Cu(phen)(PPh$_3$)$_2$]NO$_3$ to 5 mol % using 1.5 equiv of K$_3$PO$_4$ as the base had no observed effect on the yield after 4 h. When the reaction was run either in the absence of catalyst or in the absence of base the desired product was not observed by GC. We also observed that the toluene could be used "as is" without further purification.[14] When toluene was replaced with 2-propanol, the reaction did proceed but after 4 h the yield of the desired product was only 60%. It took 24 h for the reaction to afford yields similar to those using toluene. On the basis of these optimization experiments we decided to use 5 mol % [Cu(phen)(PPh$_3$)$_2$]NO$_3$[15] as the catalyst and 1.5 equiv of K$_3$PO$_4$ as the base in toluene as our protocol for the copper-catalyzed synthesis of vinyl sulfides.

To determine the scope of the reaction, we first examined the cross-coupling of a variety of aryl thiols to (*E*)-1-iodooctene using the developed procedure (Table 2). It was discovered that a wide range of aryl thiols could be coupled in high yields. Electron-rich and electron-poor thiols were easily tolerated using this procedure. Sterically hindered thiols such as 2,6-dimethylthiophenol and 2-isopropylthiophenol (Table 2, entries 4 and 5, respectively) could be coupled to (*E*)-1-iodooctene in high yields. Base-sensitive thiols such as a methyl ester (Table 2, entry 9) and an amide (Table 2, entry 12) also coupled very nicely. Thiols bearing bromine, chlorine, and fluorine (Table 2, entries 7, 8, and 11, respectively) were also tolerated in this protocol. Furthermore, the stereochemistry of the vinyl iodide was retained in the product. We then explored the coupling of various vinyl iodides to thiophenol using the standard protocol. It was seen that the corresponding vinyl sulfides were obtained in very good yields (Table 3). It was observed that both (*E*)- and (*Z*)-isomers were well tolerated. The standard protocol also worked well for a variety of β-iodo-α,β-unsaturated esters (Table 3, entries 3−5).

The ability to couple alkanethiols to *trans*-β-iodostyrene was also investigated (Table 4). We successfully coupled a variety of primary, secondary, and tertiary thiols in excellent yields. The presence of an ester and an alkanethiol attached to a furan were also tolerated (Table 4, entries 5 and 7, respectively). We also discovered that this method shows excellent selectivity in the presence of a hydroxyl group without the need of protection; there was no observed cross-coupling between the vinyl iodide and the alcohol. These coupling reactions were typically complete within 4 h, but

Table 4. Copper-Catalyzed Cross-Coupling of Various Alkyl Thiols with *trans*-β-Iodostyrene Using the Standard Protocol



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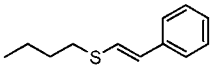
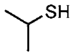
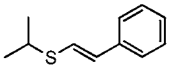
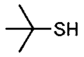
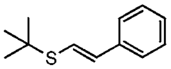
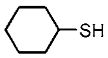
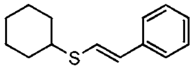
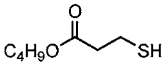
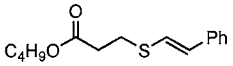
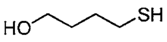
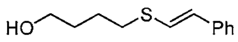
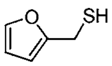
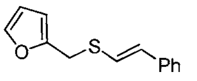
1			99
2			90
3			80
4			95
5			98
6			97[b]
7			97

[a] Isolated yields. [b] Reaction run for 8 h.

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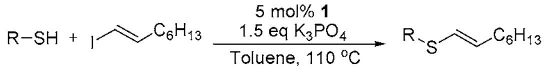
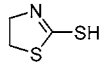
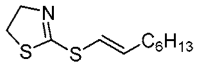
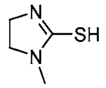
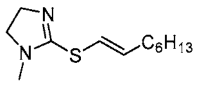
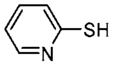
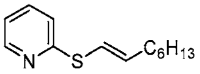
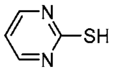
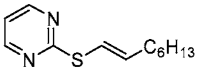
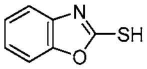
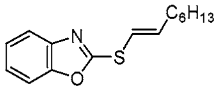
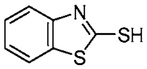
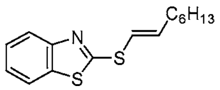
(13) (a) Van Allen, D.; Venkataraman, D. *J. Org. Chem.* **2003**, *68*, 4590. (b) Gujadhur, R. K.; Venkataraman, D. *Tetrahedron Lett.* **2003**, *44*, 81. (c) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315. (d) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (e) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803.

(14) Identical yields were obtained when the reaction was set up outside of the glovebox using standard Schlenk techniques.

(15) For the preparation of [Cu(phen)(PPh$_3$)$_2$]NO$_3$ see *Supporting Information*. This copper complex is also commercially available through Strem Chemicals Inc.

Table 5. Copper-Catalyzed Cross-Coupling of Various Heterocyclic Thiols with (*E*)-1-Iodooctene Using the Standard Protocol



entry	thiol	product	yield[a]
1			88^b
2			99^c
3			99^c
4			97^c
5			99^d
6			98^d

[a] Isolated yields. [b] Reaction run for 12 h. [c] Reaction run for 24 h. [d] Reaction run for 8 h.

4-mercapto-1-butanol required 8 h for completion (Table 4, entry 6).

Because of the occurrence of heterocycles in many compounds that are of biological and materials interest, we decided to examine the ability of this method to tolerate a variety of heterocyclic thiols (Table 5). It was found that a wide-range of heterocyclic thiols could be coupled to (*E*)-1-iodooctene in excellent yields. However, in contrast to the coupling of aryl and alkanethiols, the coupling reactions were slower. It was also observed that the coupling of thiadiazole-based thiols to (*E*)-1-iodooctene was unsuccessful.

In conclusion, we have developed a copper-catalyzed method for the stereospecific synthesis of vinyl sulfides in excellent yields using a combination of 5 mol % [Cu(phen)-$(PPh_3)_2$]NO_3 (**1**) and 1.5 equiv of K_3PO_4 in toluene. This method tolerates a wide range of functional groups and substrates. We have also demonstrated the ability to couple both alkanethiols and heterocyclic thiols to vinyl iodides, the latter being especially useful for the potential synthesis of biologically important compounds. Additionally, the reaction avoids the use of palladium and/or expensive additives.

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Supporting Information Available: Synthetic procedures, additional optimization data, and complete characterization data for entries in Tables 2−5. This material is available free of charge via the Internet at http://pubs.acs.org.

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