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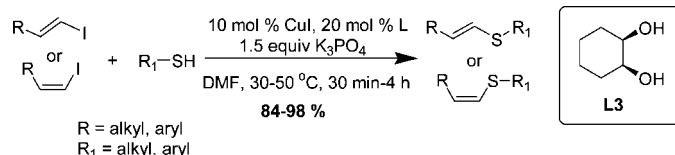
Stereo- and Regiospecific Cu-Catalyzed Cross-Coupling Reaction of Vinyl Iodides and Thiols: A Very Mild and General Route for the Synthesis of Vinyl Sulfides

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ABSTRACT



A mild and efficient method for the copper-catalyzed formation of vinylic carbon–sulfur bonds has been developed. The desired vinyl sulfides are obtained in good to excellent yields, with full retention of stereochemistry. This method is particularly noteworthy given its mild reaction conditions, simplicity, and generality, as well as low cost of the catalyst system.

In the past few years, the efficiency of metal-catalyzed methods for the preparation of aryl ethers¹ and thioethers² using both palladium and copper catalysis has increased greatly. In contrast, metal-catalyzed preparation of vinyl sulfides of synthetic³ and biological⁴ importance in organic chemistry has lagged behind.

Vinyl sulfides are used as enolate ion⁵ equivalents and Michael acceptors.⁶ They are also important intermediates in the synthesis of oxetanes,⁷ cyclopentanones,⁸ and cyclopentanes.⁹ Many natural products and compounds which exhibit interesting biological activity contain the vinyl sulfide moiety.^{4,10}

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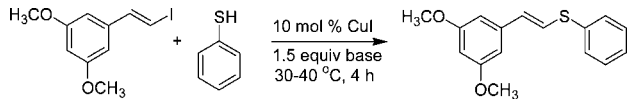
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Table 1. Optimization of the Reaction Conditions


catalyst	solvent	base	HPLC yield (%)
CuI	DMF	K ₃ PO ₄	0
CuI, phen ^a (1:2)	toluene	K ₃ PO ₄	45
CuI/phen ^a /PPh ₃ (1:1:2)	toluene	K ₃ PO ₄	65
CuI, L3 (1:1)	toluene	K ₃ PO ₄	63
CuI, L3 (1:2)	toluene	K ₃ PO ₄	68
CuI, L3 (1:2)	<i>i</i> PrOH	K ₃ PO ₄	72
CuI, L3 (1:2)	DME	K ₃ PO ₄	63
CuI, L3 (1:2)	DMF	K ₃ PO ₄	99
CuI, L3 (1:2)	DMA	K ₃ PO ₄	64
CuI, L3 (1:2)	1,4-dioxane	K ₃ PO ₄	72
CuI, L3 (1:2)	DMF	CS ₂ CO ₃	93
CuI, L3 (1:2)	DMF	K ₂ CO ₃	91
CuI, L3 (1:1)	DMF	K ₃ PO ₄	94

^a phen = 1,10-phenanthroline.

Due to the importance of vinyl sulfides, a number of methods in regard to their synthesis have been reported, each with their respective limitations.^{3,11–15} The most important catalytic process for the preparation of vinyl sulfides has been reported by Venkataraman and co-workers and employs a Cu(I) catalytic system.³ However, this process requires the use of air- and moisture-sensitive Cu catalysts, which must be used in a glovebox. In addition, the reaction requires the use of harsh reaction conditions (high reaction temperatures, i.e., 115 °C; and long reaction times, i.e., ~4 h) in order to go to completion, incompatible with many substrates. These harsh reaction conditions have proven to be inefficient for electron rich aryl vinyl iodides in coupling reactions. For

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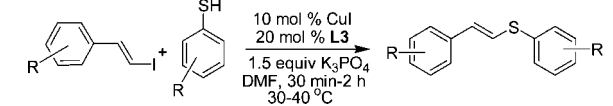
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Table 2. Copper-Catalyzed Cross-Coupling of Various *E*-Arylvinyl Iodides with Aromatic Thiols


entry	thiol	product	yield ^{a,b} (%)
1			96
2			97
3			97
4			95
5			84
6			96 ^c
7			84 ^c
8			95 ^c
9			96 ^c
10			98
11			87
12			84

^a Isolated yields, the average of at least two runs. ^b The starting aryl vinyl iodides contained ~ 9–12% *Z*-isomer; this led to ~ 9–12% of the *cis*-isomer, reflected in the overall yield. ^c Treatment with TBAF·THF provided the desired phenol.

example, 3,5-dimethoxyphenyl vinyl iodide gave approximately 35% of the 3,5-dimethoxyphenylacetylene as a byproduct when 1,10-phenanthroline was used in combination with triphenylphosphine (Table 1).¹⁰ Initially, 3-hydroxy-5-methoxystyrylphenyl thioether, a potent antibacterial agent active against drug-resistant strains of tuberculosis and anthrax surrogates,¹⁰ and its 3,5-dimethoxy analogues were prepared using the catalytic conditions of Venkataraman (Table 1). This system proved to be inefficient for the corresponding electron-rich aryl vinyl iodides. A significant

amount of arylacetylenes (approximately 30–35%) were observed as byproducts in the reaction mixture. Arylacetylene formation has been reported in Cu-catalyzed cross-coupling reactions of unfunctionalized aryl vinyl iodides using nitrogen based bidentate ligands, although this system was successfully applied to nitrogen and oxygen nucleophiles.^{1f}

However, the scope and functional group tolerance of these cross-coupling reactions had not been fully explored. Therefore, it was felt that a copper-based process might be readily extended to the synthesis of vinyl sulfides, including the cases where the aforementioned problems existed. A potential solution would

Table 3. Copper-Catalyzed Cross-Coupling of Various *E*-Arylvinyl Iodides with Heterocyclic Thiols

$\text{R}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{I} + \text{Het}-\text{SH} \xrightarrow[2-4 \text{ h}]{\substack{10 \text{ mol \% CuI} \\ 20 \text{ mol \% L3} \\ 1.5 \text{ equiv K}_3\text{PO}_4 \\ \text{DMF, 40-60 }^\circ\text{C}}} \text{R}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{S}-\text{Het}$			
entry	vinyl iodide	product	yield ^{a,b} (%)
1			97
2			93
3			92 ^d
4			87 ^{c,d}
5			90 ^c
6			86 ^c

^a Isolated yields, the average of at least two runs. ^b The starting aryl vinyl iodides contained ~ 9–12% *Z*-isomer; this led to ~ 9–12% of the *cis*-isomer, reflected in the overall yield. ^c Reaction mixture was heated for 8 h. ^d Treatment with TBAF·THF provided the desired phenol.

be to employ an alternative Cu-catalytic system which would take place under very mild conditions. By taking advantage of mild reaction conditions, the scope of the reaction could be extended, permitting the use of a wide variety of functional groups. The catalytic system required should be both inexpensive and easily handled under atmospheric conditions. Herein, a mild, stereo- and regiospecific copper-based process for the cross-coupling of vinyl iodides with thiols is reported. A broad substrate scope provided good to excellent yields with the catalytic system developed here.

The 3,5-dimethoxyphenyl vinyl iodide and thiophenol were used as the prototypical substrate combination for preliminary

Table 4. Copper-Catalyzed Cross-Coupling of Various *E*-Aryl Vinyl Iodides with Alkyl Thiols

$\text{R}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{I} + \text{Alkyl}-\text{SH} \xrightarrow[2-4 \text{ h}]{\substack{10 \text{ mol \% CuI} \\ 20 \text{ mol \% L3} \\ 1.5 \text{ equiv K}_3\text{PO}_4 \\ \text{DMF, 40-50 }^\circ\text{C}}} \text{R}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{S}-\text{Alkyl}$			
entry	vinyl iodide	product	yield ^{a,b} (%)
1			93
2			90 ^c
3			96 ^d
4			93
5			90 ^c

^a Isolated yields, the average of at least two runs. ^b The starting aryl vinyl iodides contained ~ 9–12% *Z*-isomer; this led to ~ 9–12% of the *cis*-isomer, reflected in the overall yield. ^c Reaction mixture was heated for 8 h. ^d Treatment with TBAF·THF provided the desired phenol.

optimization conditions. The optimized reaction conditions utilized 10 mol % of Cu(I), 20 mol % of *cis*-1,2-cyclohexanediol (**L3**), and 1.5 equiv of K₃PO₄ in reagent grade DMF (without drying or degassing), as illustrated in Table 1. Moreover, DME, *i*-PrOH, and 1,4-dioxane proved to be inefficient solvent systems at lower temperature; they required longer reaction times and produced a significant amount of alkyne byproduct. The formation of arylacetylenes was observed under many conditions in Table 1. The catalytic conditions with CuI and **L3** proved to be the best in the formation of the desired sulfides. This provided a very active catalyst, presumably due to the proper geometry of the copper complex.

These reaction conditions were applied to the coupling of various aryl vinyl iodides and aryl thiols, some of which were prone to yield a considerable amount of elimination byproduct with other catalytic systems. Thus, highly electron rich aryl vinyl iodides containing methoxy groups at the 3- and 5- positions gave coupling products in excellent yield, even with ortho-hindered functional groups (entries 1–5, Table 2). Deprotection of the silyl protected, phenolic vinyl iodides occurred at higher temperatures under the previously reported reaction conditions.³ In the latter case, isolation of the desired product had proven to be difficult. The silyl function remained intact under the newly developed catalytic system which provided the vinyl sulfides in high yield. Deprotection of the silyl group was then carried out in the same reaction vessel using TBAF·THF (entries

Table 5. Copper-Catalyzed Cross-Coupling of *E*-Cyclohexylvinyl Iodides with Various Thiols

entry	sulfide	product	yield ^{a,b} (%)
1			97
2			96
3			96
4			93
5			92

^a Isolated yields, the average of at least two runs. ^b The starting aryl vinyl iodides contained ~ 9–12% *Z*-isomer; this led to ~ 9–12% of the *cis*-isomer, reflected in the overall yield.

6–9, Table 2; entries 3–4, Table 3; entry 3, Table 4). Nitrile functionalized, electron-poor aryl vinyl iodides were also employed for the coupling reactions and these provided excellent yields of the sulfides under the same catalytic conditions (entries 10–12, Table 2; entries 5–6, Table 3; entries 4–5, Table 5).

Since many compounds of biological interest contain heterocycles,^{4,10} it was decided to subject heterocyclic thiols to the Cu-catalyzed cross-coupling reaction (Table 3). A range of heterocyclic thiols produced the desired sulfides in high yield. Relative to alkyl and aryl thiols, these coupling reactions were slower (4–6 h) and required slightly elevated temperatures (60 °C).

Alkyl thiols were also found to be effective nucleophiles under these reaction conditions with various aryl vinyl iodides (Table 4). Moreover, selective *S*-vinylation over *O*-vinylation was observed when 6-mercaptohexanol was used as the substrate (Table 4, entries 2 and 5).

The ability to couple alkyl vinyl iodides was also investigated with aryl, alkyl, and heterocyclic thiols. This proved to be an excellent catalytic system for alkyl vinyl iodides as well (Table 6).

The retention of regio- and stereochemistry in all products was observed in the cases of *E*-aryl vinyl iodides. To ensure the coupling reaction proceeded in a regio- and stereospecific fashion, the coupling reaction was investigated using *Z*-vinyl

Table 6. Copper-Catalyzed Cross-Coupling of *Z*-Ethyl-3-iodoacrylate with Various Thiols

entry	sulfide	product	yield ^{a,b} (%)
1			98
2			93
3			95
4			97
5			94

^a Isolated yields, the average of at least two runs.

iodide (ethyl *cis*-3-iodoacrylate) and various thiols. Analysis of the results indicated the catalytic system worked well for *Z*-vinyl iodides with aryl-, alkyl-, and heterocyclic thiols in excellent yields with complete retention of stereo- and regiochemistry (Table 6).

In summary, an efficient, regio- and stereospecific copper-catalyzed system has been developed for the synthesis of vinyl sulfides. This method is useful because of the mild reaction conditions, broad functional group tolerance, simplicity in operation, and low cost. Further investigation of the utility of this catalytic system is currently in progress and will be reported in due course.

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