

Synthesis of Vinyl Sulfides by Copper-Catalyzed Decarboxylative C–S Cross-Coupling

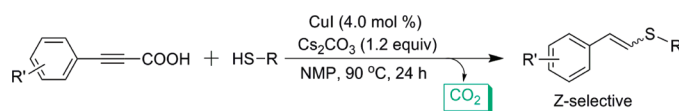
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ABSTRACT



A novel method for the synthesis of vinyl sulfides by the decarboxylative cross-coupling of arylpropionic acids with thiols using copper(I) salts as catalysts has been developed. In the presence of CuI and Cs₂CO₃, a variety of thiols reacted with arylpropionic acids to afford the corresponding vinyl sulfides in good to excellent yields with high stereoselectivity for Z-isomers.

The utility of vinyl sulfides has increased enormously over the past several years. Vinyl sulfides can be used as complementary building blocks to carbonyl compounds¹ and Michael acceptors² for synthesis of many polymeric materials,³ natural products,⁴ and synthetic reagents.⁵ Conventional approaches to the synthesis of vinyl sulfides include the

addition of thiols to alkynes under free-radical⁶ or metal-catalyzed conditions,⁷ Wittig olefination,⁸ and direct nucleophilic substitution through use of vinyl halides.⁹ Despite their usefulness, these approaches either require harsh reaction

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conditions, costly starting materials, and solvents or lack stereocontrol at the double bond geometry.

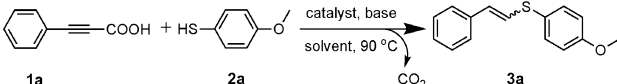
Numerous methods have been developed for the stereoselective synthesis of (*E*)-vinyl sulfides.¹⁰ In contrast, it has been challenging to prepare *Z*-isomers.¹¹ In 2005, Kondoh et al.¹² reported the synthesis of (*Z*)-1-alkenyl sulfides via a cesium-catalyzed hydrothiolation of alkynes in the presence of 2,2,6,6-tetramethylpiperidine-*N*-oxyl as a radical inhibitor. However, this synthetic strategy is only applicable to alkylthiols. More recently, Wang et al.¹³ have reported the synthesis of (*Z*)-1-alkenyl sulfides via a copper-catalyzed hydrothiolation of alkynes with diaryl disulfides, but the reaction requires large amounts of rongalite (4 equiv) as the radical initiator.

Recently, coupling reactions initiated by the decarboxylation of carboxylic acids have shown great promise in the field of synthetic chemistry.¹⁴ In particular, we have shown that a broad range of aryl sulfides can be prepared through decarboxylative C–S cross-coupling.¹⁵ Herein, we demonstrate a novel copper-catalyzed decarboxylative thiolation of

arylpropionic acids, resulting in stereoselective formation of (*Z*)-vinyl sulfides under mild reaction conditions.

Phenylpropionic acid (**1a**) and 4-methoxybenzenethiol (**2a**) were used as the substrates to screen and optimize reaction conditions. Copper(I) complexes generally gave significantly higher yields of the product than copper(II) source (Table 1).

Table 1. Decarboxylative C–S Cross-Coupling under Different Conditions^a



entry	catalyst (mol %)	base	solvent	yield of 3a ^b (%)
1		KF	NMP	<5
2	CuI (20)	K ₂ CO ₃	DMSO	57
3	CuI (4)	K ₂ CO ₃	DMSO	74
4	CuI (4)	K ₂ CO ₃	NMP	88
5	CuI (4)	K ₂ CO ₃	PEG	77
6	CuI (4)	K ₂ CO ₃	DMF	35
7	CuI (4)	K ₂ CO ₃	toluene	0
8	CuI (4)	K ₂ CO ₃	dioxane	5
9	CuI (4)	KHCO ₃	NMP	77
10	CuI (20)	KF	NMP	10
11	CuI (4)	piperidine	NMP	30
12	CuI (4)	TEA	NMP	5
13	CuI (4)	Cs₂CO₃	NMP	99(96)
14	CuCN (4)	Cs ₂ CO ₃	NMP	85
15	CuCl (4)	Cs ₂ CO ₃	NMP	80
16	CuBr (4)	Cs ₂ CO ₃	NMP	82
17	CuCl ₂ (4)	Cs ₂ CO ₃	NMP	35
18	CuCO ₃ ·Cu(OH) ₂ (4)	Cs ₂ CO ₃	NMP	5
19	Cu(OTf) ₂ (4)	Cs ₂ CO ₃	NMP	40

^a All of the reactions were carried out with phenylpropionic acid **1a** (0.5 mmol) and 4-methoxybenzenethiol **2a** (0.75 mmol) in the presence of a metal catalyst, NMP (3 mL), and base (1.2 equiv) at 90 °C for 24 h under air atmosphere. ^b GC yield. Isolated yield is in parentheses.

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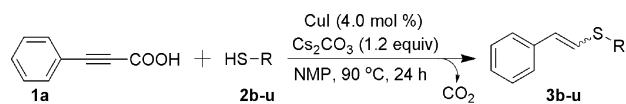
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The amount of CuI can be decreased down to 4.0 mol %. Different bases were screened, and the combination of cesium carbonate with CuI afforded the best conversion efficiency (Table 1, entry 13). In contrast to our previously reported synthesis of aryl sulfides,¹⁵ we observe that palladium(II) is not needed and milder reaction conditions are possible.

Under the optimal reaction conditions, a wide range of thiols including aromatic, benzylic, and aliphatic thiols were examined to react with phenylpropionic acid via decarboxylative cross-coupling reactions. The results are summarized in Table 2. We observed that in the presence of the phenylpropionic acid all thiols afforded *anti*-Markovnikov coupling products in good to excellent yields with high stereoselectivity for *Z*-isomers. The arylthiols with electron-rich and electron-deficient aromatic moieties were effectively converted to the corresponding vinyl sulfides. Importantly, the decarboxylative coupling reactions are tolerant of a broad range of functional groups including ethers, amines, alcohols, halides, and nitrogen-containing heterocycles. The functional group tolerance should enable further derivatization of the as-synthesized vinyl sulfides (**3k.o–s**) through cross-coupling reactions such as Suzuki–Miyaura, Sonogashira, and Heck reactions.

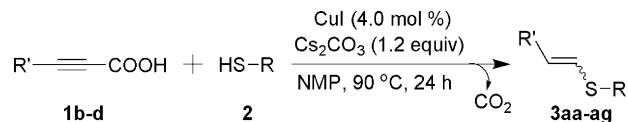
Table 2. Decarboxylative Cross-Coupling of Phenylpropionic Acid with Thiols^a

entry	thiols 2	product 3	yield[%] ^b , [Z:E] ^c
1	H ₃ C(H ₂ C) ₁₁ -SH 2b		78 [83:17]
2	H ₃ C(H ₂ C) ₇ -SH 2c		95 [88:12]
3	H ₃ C(H ₂ C) ₃ -SH 2d		93 [88:12]
4	2e		90 [79:21]
5	2f		80 [90:10]
6	2g		89 [90:10]
7	2h		90 [90:10]
8	2i		95 [90:10]
9	2j		95 [80:20]
10	2k		75 [85:15]
11	2l		87 [84:16]
12	2m		90 [90:10]
13	2n		95 [90:10]
14	2o		82 [93:07]
15	2p		88 [100:0]
16	2q		81 [92:08]
17	2r		94 [94:06]
18	2s		80 [85:15]
19	2t		92 [90:10]
20	2u		81 [94:06]

^a All of the reactions were carried out with phenylpropionic acids (0.5 mmol) and thiols (0.75 mmol) in the presence of CuI (4.0 mol %) and Cs₂CO₃ (1.2 equiv) in 3 mL of NMP at 90 °C under air atmosphere. ^b Yields of isolated products are the average of at least two experiments. ^c The Z/E ratio was based on the analysis of ¹H NMR spectra.

To expand the scope of the general reaction conditions further, we carried out decarboxylative C–S cross-coupling

via different aryl-substituted alkynyl carboxylic acids (Table 3). All alkynyl carboxylic acids were converted into the

Table 3. Decarboxylative Cross-Coupling of Substituted Phenylpropionic Acids with Thiols^a

entry	R'	product 3	yield[%] ^b , [Z:E] ^c
1	<i>p</i> -Br-C ₆ H ₄ 1b		90 [30:70]
2	<i>p</i> -Cl-C ₆ H ₄ 1c		93 [44:56]
3	<i>o</i> -H ₃ C-C ₆ H ₄ 1d		95 [100:0]
4	1b		94 [68:32]
5	1c		95 [51:49]
6	1b		89 [70:30]
7	1c		94 [58:42]

^a All of the reactions were carried out with acids (0.5 mmol) and thiols (0.75 mmol) in the presence of CuI (4.0 mol %) and Cs₂CO₃ (1.2 equiv) in 3 mL of NMP at 90 °C under air atmosphere. ^b Yields of isolated products are the average of at least two experiments. ^c The Z/E ratio was based on the analysis of ¹H NMR spectra.

corresponding alkenyl sulfides in excellent yields. However, alkynyl carboxylic acids with electron-withdrawing substituents in the *para* position led to low stereoselectivity (entries 1, 2, and 4–7). In stark contrast, introduction of an electron-donating group in the *ortho*-position resulted in the quantitative formation of the corresponding Z-isomer (entry 3).

In summary, we have disclosed a copper-based decarboxylative cross-coupling method for the synthesis of vinyl sulfides with high stereoselectivity for Z-isomers. This method is important not only for expanding our understanding of the decarboxylative reaction but also for providing a convenient synthetic pathway for facile synthesis of biologically or pharmaceutically relevant vinyl sulfide compounds. Further investigations of the substrate scope of this transformation and the reaction mechanism are currently in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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