

# An aqueous and recyclable copper(I)-catalyzed route to $\alpha$ -sulfenylated carbonyl compounds from propargylic alcohols and aryl thiols†

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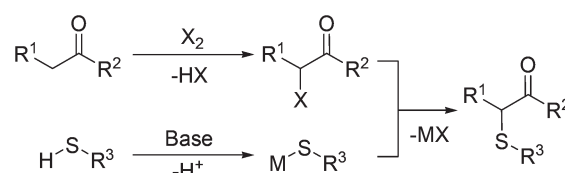
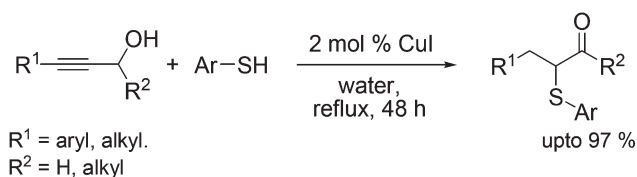
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A highly efficient one-step copper(I)-catalyzed method for the synthesis of  $\alpha$ -sulfenylated carbonyl compounds from propargylic alcohols and aryl thiols in aqueous media is described. A variety of  $\alpha$ -sulfenylated carbonyl compounds can be synthesized in good to excellent yields. The catalyst has been successfully recycled up to 4 times without any loss of activity in an aqueous medium.

The formation of C–S bonds represents a key step to the synthesis of a wide variety of biologically active molecules, functional materials and synthetic reagents.<sup>1–4</sup> In particular,  $\alpha$ -sulfenylated carbonyl compounds are chemical building blocks which can also be found in several pharmaceutically active molecules.<sup>2</sup> While the metal catalyzed C–O and C–N bond forming reactions have been widely explored,<sup>5</sup> the formation of C–S bonds has been less investigated,<sup>6</sup> perhaps due to poisoning of transition metal catalysts by thiols.

Traditionally,  $\alpha$ -sulfenylated carbonyl compounds are synthesized *via* the reaction of an  $\alpha$ -halogenated precursor with sulphide anions (Scheme 1).<sup>3</sup> The reaction of a carbonyl compound with sulfenylating agents is an alternative traditional method for the synthesis of  $\alpha$ -sulfenylated carbonyl compounds.<sup>4</sup> We have recently reported a new strategy for the synthesis of  $\alpha$ -sulfenylated carbonyl compounds using a gold catalyst in 1,2-dichloroethane as a solvent.<sup>7,8</sup> We herein report a copper catalyzed<sup>9,10</sup> synthesis of  $\alpha$ -sulfenylated carbonyl compounds from readily available propargylic alcohols and aryl thiols using water as the reaction medium (Scheme 2).<sup>11</sup> The catalyst has been recycled successfully up to 4 times without any significant loss of its catalytic activity.

4-Phenyl-3-butyne-2-ol (**1a**) and thiophenol (**2a**) were chosen as model substrates for the optimization of the reaction conditions. Various reaction parameters such as the nature of the

Scheme 1 Traditional synthesis of  $\alpha$ -sulfenylated carbonyl compounds.Scheme 2 CuI mediated synthesis of  $\alpha$ -sulfenylated carbonyl compounds.

catalyst, catalyst loading, and the reaction temperature were studied (Table 1).

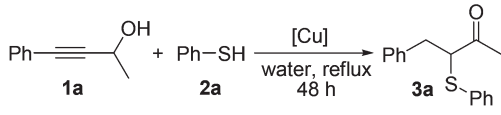
To make the synthetic protocol greener, we examined water as a reaction solvent and, gratifyingly, it provided an excellent yield of the desired product. Water was found to be superior compared to traditional organic solvents such as acetonitrile, toluene, 1,2-dichloroethane and nitromethane (see ESI† for details). Different copper(I) halides such as CuCl, CuBr and CuI were screened, among which CuI was found to be the best catalyst providing an excellent yield of the desired product **3a** in aqueous media (Table 1, entries 1–3). Furthermore, the activity of CuI was compared with that of the copper(I) trifluoromethanesulfonate/benzene complex which gave a lower yield of **3a** (Table 1, entries 3 and 4). The catalyst loading was studied in the range of 1 to 5 mol% where 2 mol% of catalyst loading was found to be sufficient for this transformation (Table 1, entries 3 and 8–10).

To investigate the temperature effect, the reaction was carried out at temperatures ranging from 70 °C to reflux (Table 1, entries 3, 11 and 12). Under the optimised reaction conditions, the reaction between **1a** (1 mmol) and **2a** (1.5 mmol) was run at reflux in the presence of 2 mol% CuI in

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**Table 1** Optimization of reaction conditions<sup>a</sup>


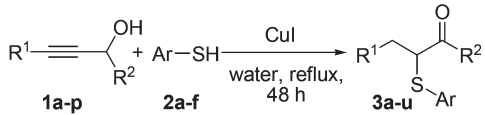
Entry	Catalyst	Equiv. of 2a	Catalyst loading (mol%)	Yield <sup>b</sup> (%)
1	CuCl	1.5	2.0	Traces
2	CuBr	1.5	2.0	89
3	CuI	1.5	2.0	97
4	Cu(I)OTf-Benzene Complex	1.5	2.0	Traces
5	Cu(OAc) <sub>2</sub>	1.5	2.0	—
6	CuI	1.2	2.0	79
7	CuI	1.0	2.0	60
8	CuI	1.5	0.0	—
9	CuI	1.5	1.0	71
10	CuI	1.5	5.0	97
11 <sup>c</sup>	CuI	1.5	2.0	Trace
12 <sup>d</sup>	CuI	1.5	2.0	84

<sup>a</sup> Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol) and Cu-catalyst (2 mol%), at reflux in 2.0 mL of water for 48 h. <sup>b</sup> Conversion based on <sup>1</sup>H NMR analysis. <sup>c</sup> The reaction was run at 70 °C. <sup>d</sup> The reaction was run at 90 °C.

2 mL of water as solvent for 48 h to produce the desired product **3a** in 97% yield (Table 1, entry 3).

To test the substrate scope, we examined the transformation between a variety of propargylic alcohols **1a–p** and aromatic thiols **2a–f** under the optimized reaction conditions (Table 2). Both secondary (**1a–c**) and primary (**1d**) aromatic propargylic alcohols reacted with **2a** to furnish the corresponding α-sulfenylated aldehyde and ketone products **3a–d** in excellent yields (Table 2, entries 1–4). The electronic character of the propargylic alcohols did not influence the outcome of the reaction when water was used as the solvent (Table 2, entries 5–12). Importantly, alcohols having a strong electron withdrawing *p*-COMe (**1i**, **1k**) or electron donating *p*-OMe (**1l**) group at the phenyl ring also tolerated the reaction conditions to furnish the corresponding products in moderate to good yields (Table 2, entries 9, 11, and 12). Alcohols with terminal triple bonds were unreactive under the given reaction conditions.

We investigated the effect of substituents at the *para*-position of the phenyl ring of aryl thiols under the optimized reaction conditions (Table 2, entries 13–17). It was found that the reaction of *para*-bromo (**2b**) and *para*-chloro (**2c**) thiophenols with **1a** proceeded to generate the products **3m** and **3n** in moderate yields (Table 2, entries 13 and 14). With *para*-fluoro thiophenol (**2d**), 90% yield of the product **3o** was achieved under the given reaction conditions (Table 2, entry 15). The corresponding gold(i)-catalyzed reaction in 1,2-dichloroethane generated 48% of **3o** in our previous report, showing advantages of the current Cu-catalyzed aqueous system.<sup>7</sup> Electron donating substituents such as -isopropyl (**2e**) and -methoxy (**2f**) in the *para* position of the phenyl ring of aryl thiols generated the desired products in 73% and 64% yield respectively under the optimized reaction conditions (Table 2, entries 16

**Table 2** α-Sulfenylation of propargylic alcohols by aryl thiols<sup>a</sup>


Entry	1	R <sup>1</sup>	R <sup>2</sup>	2	Ar	3	Yield <sup>b</sup> (%)
1	<b>1a</b>	Ph	Me	<b>2a</b>	Ph	<b>3a</b>	94
2	<b>1b</b>	Ph	Et	<b>2a</b>	Ph	<b>3b</b>	92
3	<b>1c</b>	Ph	<sup>i</sup> Pr	<b>2a</b>	Ph	<b>3c</b>	86
4	<b>1d</b>	Ph	H	<b>2a</b>	Ph	<b>3d</b>	96
5	<b>1e</b>	<i>p</i> -Me-Ph	Me	<b>2a</b>	Ph	<b>3e</b>	83
6	<b>1f</b>	<i>p</i> -Ph-Ph	Me	<b>2a</b>	Ph	<b>3f</b>	90
7	<b>1g</b>	<i>m,p</i> -Di-Cl-Ph	Me	<b>2a</b>	Ph	<b>3g</b>	91
8	<b>1h</b>	1-Naph	Me	<b>2a</b>	Ph	<b>3h</b>	95
9	<b>1i</b>	<i>p</i> -COMe-Ph	Me	<b>2a</b>	Ph	<b>3i</b>	85
10	<b>1j</b>	<i>p</i> -CF <sub>3</sub> -Ph	H	<b>2a</b>	Ph	<b>3j</b>	90
11	<b>1k</b>	<i>p</i> -COMe-Ph	H	<b>2a</b>	Ph	<b>3k</b>	73
12	<b>1l</b>	<i>p</i> -OMe-Ph	H	<b>2a</b>	Ph	<b>3l</b>	64
13	<b>1a</b>	Ph	Me	<b>2b</b>	<i>p</i> -Br-Ph	<b>3m</b>	74
14	<b>1a</b>	Ph	Me	<b>2c</b>	<i>p</i> -Cl-Ph	<b>3n</b>	77
15	<b>1a</b>	Ph	Me	<b>2d</b>	<i>p</i> -F-Ph	<b>3o</b>	90
16	<b>1a</b>	Ph	Me	<b>2e</b>	<i>p</i> - <sup>i</sup> Pr-Ph	<b>3p</b>	73
17	<b>1a</b>	Ph	Me	<b>2f</b>	<i>p</i> -OMe-Ph	<b>3q</b>	64
18 <sup>c</sup>	<b>1m</b>	Et	Me	<b>2a</b>	Ph	<b>3r</b>	67
19 <sup>d</sup>	<b>1n</b>	Cyclopentyl	Me	<b>2a</b>	Ph	<b>3s</b>	73
20 <sup>d</sup>	<b>1o</b>	Cyclohexyl	Me	<b>2a</b>	Ph	<b>3t</b>	75
21 <sup>d,e</sup>	<b>1p</b>	Ph-CH <sub>2</sub> -CH <sub>2</sub>	Me	<b>2a</b>	Ph	<b>3u</b>	81

<sup>a</sup> Reaction conditions: **1** (1 mmol), **2** (1.5 mmol) and CuI (2 mol%), water (2.0 mL) for 48 h at reflux. <sup>b</sup> Yields refer to isolated yields. <sup>c</sup> 3 Equiv. of **1j** was used with respect to **2a** and the yield was calculated with respect to **2a**. <sup>d</sup> 3 Equiv. of **2a** was used with respect to **1** and the yields were calculated with respect to **1**. <sup>e</sup> The reaction was run for 72 h.

and 17). This protocol was also successfully applied to propargylic alcohols having different aliphatic groups at R<sup>1</sup>-position (**1m–1p**) which provided good to excellent conversions to the desired products **3r–3u** (Table 2, entries 18–21). Aliphatic thiols were unreactive under the optimized reaction conditions.

To investigate the scalability of the reaction, the transformation of **1a** and **2a** was scaled up to 5 g of alcohol. Gratifyingly, the reaction proceeded to generate **3a** in 90% yield after 48 hours. We would like to investigate whether the catalyst loading could be decreased in the future.

In order to investigate the greener and economical aspects of the developed catalytic system, a recyclability study was carried out for the α-sulfenylation reaction (Fig. 1). The catalyst was efficiently recycled through four consecutive cycles without any loss in catalytic activity. After each cycle, the aqueous reaction mixture was extracted using reusable ethyl acetate to remove all traces of the product or reactants. The resulting aqueous solution containing the CuI catalyst was directly used for the next catalytic cycle.

The reaction proceeded *via* the formation of a diastereomeric mixture of intermediate **4** (Scheme 3) (*Z*:*E* = 7:2).<sup>12</sup> We were able to isolate and fully characterise intermediate **4** during the course of the reaction. Interestingly, CuI did not catalyse the transformation of intermediate **4** to **3d** alone.



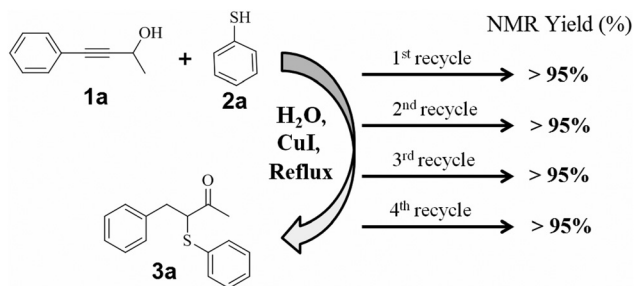
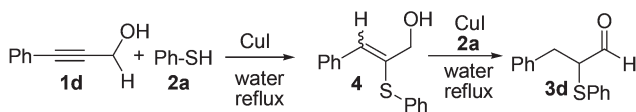
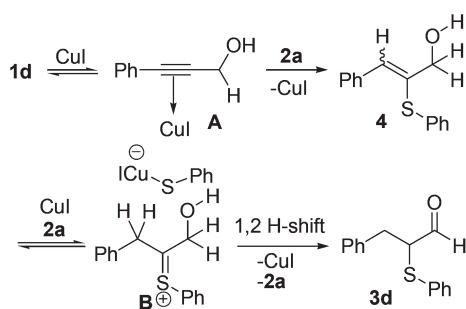


Fig. 1 Catalyst recyclability.



Scheme 3 Intermediate **4** formed in the  $\text{CuI}$  catalysed reaction of **1d** and **2a**.



Scheme 4 Proposed mechanism.

Instead, a combination of  $\text{CuI}$  and a catalytic amount of **2a** was required for the isomerization of **4** to **3d**. A possible explanation is that a coordination between  $\text{CuI}$  and **2a** acidifies the thiol proton that protonates the double bond of intermediate **4**, thus promoting the 1,2-hydride shift.

A plausible mechanism has been proposed in Scheme 4 similar to that previously reported for the gold mediated synthesis of  $\alpha$ -sulfenylated carbonyl compounds.<sup>7</sup> Copper(i) coordinates to the triple bond of **1d** to form a complex **A**. Thiophenol **2a** regioselectively attacks the  $\beta$ -position of the triple bond to form intermediate **4**. A  $\text{CuI}$  coordinated **2a** protonates **4** in intermediate **B**. This protonation promotes the 1,2-hydride transfer and generates **3d** (Scheme 4).

## Conclusions

An efficient and environmentally benign route to  $\alpha$ -sulfenylated carbonyl compounds catalysed by copper iodide catalyst in aqueous media has been developed. In this protocol, aryl thiols and either aromatic alcohols with different electron donating and withdrawing substituents at the phenyl ring or aliphatic alcohols are transformed to generate the  $\alpha$ -sulfenylated carbonyl compounds in good to excellent yields.

The reaction is scalable and the catalyst in aqueous phase can be easily recycled.

## Experimental

### Representative experimental procedure for the synthesis of 4-phenyl-3-(phenylthio)butan-2-one (**3a**)

$\text{CuI}$  (4 mg, 2 mol%) was weighed and transferred to a 5 mL vial containing a magnet under a nitrogen atmosphere. The cap of the vial was closed tightly and 2 mL of degassed water followed by alcohol **1a** (145  $\mu\text{L}$ , 1 mmol) and benzenethiol **2a** (154  $\mu\text{L}$ , 1.5 mmol) were added to the vial by a syringe. The reaction mixture was stirred using a magnetic stirrer at reflux for 48 h. After allowing the mixture to cool to room temperature, the reaction mixture was extracted with ethyl acetate (3  $\times$  15 mL). The combined organic phase was washed with water and brine, dried with anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by silica-gel (100–200 mesh) column chromatography using a 3% (v/v) ethyl acetate–pentane solution to afford the desired product **3a** (240 mg, 0.94 mmol, 94%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.20 (s, 3H, H-1), 3.00 (dd,  $J$  = 6.9 Hz, 14.4 Hz, 1H, H-4), 3.19 (dd,  $J$  = 8.4 Hz, 14.1 Hz, 1H, H-4), 3.90 (dd,  $J$  = 6.9 Hz, 8.4 Hz, 1H, H-3), 7.18–7.37 (m, 10H, H-arom) ppm.  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 28.1, 36.9, 59.0, 127.1, 128.5, 128.8, 129.4, 133.0, 133.3, 138.3, 204.5 ppm.

### Catalyst recyclability

The reaction was carried out as mentioned above using **1a** (145  $\mu\text{L}$ , 1 mmol), **2a** (154  $\mu\text{L}$ , 1.5 mmol) and  $\text{CuI}$  (4 mg, 2 mol%). The reaction mixture was cooled to room temperature after 48 h and was extracted by ethyl acetate (3  $\times$  5 mL). The recovered aqueous layer containing the catalyst (catalyst particles are suspended in aqueous layer) was washed with ethyl acetate (3  $\times$  5 mL) to remove all traces of the product or reactants present. The aqueous layer containing the catalyst was then directly used as the solvent for the next run of the catalyst recyclability experiment. The same procedure was followed for consecutive recycling. The combined organic phase obtained in each run was concentrated under reduced pressure.  $^1\text{H}$  NMR of the crude reaction mixture was checked using toluene as an internal standard and the conversions were determined by comparing the chemical shift of aromatic methyl protons of the toluene internal standard at 2.31 ppm with that of H-3 proton of the product **3a** at 3.90 ppm.

The recyclability of the catalyst used was checked up to 4 times and  $>95\%$  formation of **3a** was observed for all the runs.<sup>13</sup>

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