# Copper-catalyzed Oxidative Olefination of Thiols Using Sulfones and Phosphorous Ylides

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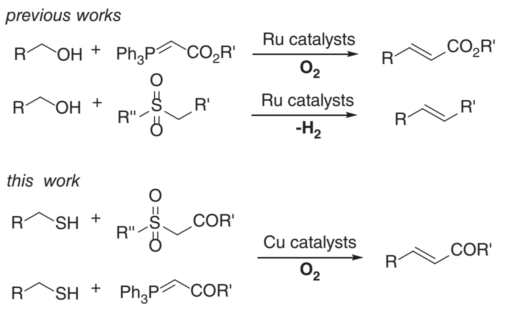
Copper-catalyzed one-pot conversion of thiols to olefins was conducted under aerobic conditions. Thiols were oxidized to generate thioaldehydes, which reacted with sulfones or phosphorous ylides to form the corresponding olefins. The formation of thiosulfonates and phosphorous sulfides confirms that these olefination protocols proceed via thioaldehyde-sulfone and thioaldehyde-ylide adducts.

**Keywords:** Copper, Oxidation, Olefination, Wittig, Julia

## Introduction

Olefination of carbonyl compounds is an efficient and convenient method to provide synthetically useful olefins; therefore, a variety of olefination methods such as Wittig, Horner–Wadsworth–Emmons, Peterson, Julia olefination reactions, and the olefination using Tebbe's reagent or titanium metals (McMurry coupling) have been developed.[1] Furthermore, carbonyl compounds generated *in situ* by oxidation of alcohols and dehydrogenation of alcohols have been used for such olefination reactions to directly generate olefins from alcohols (Scheme 1).[2–4] To promote catalytic and economical processes, oxygen is used as the oxidant for the oxidative olefination. Under nonoxidative conditions, dehydrogenation was applied to generate aldehydes from alcohols. Ruthenium complexes that are relatively expensive are commonly used as aerobic oxidation and dehydrogenation catalysts in the one-pot oxidation followed by olefination[4]; therefore, development of more economical catalysts is highly required.

Our research group recently reported copper-catalyzed oxidative coupling of thiols and amines/alcohols under aerobic conditions.[5] During the reaction, transient thioaldehydes are assumed to form; these compounds might behave similar to aldehydes during olefination.[6] The utilization of thioaldehydes as synthetic building blocks has not received significant attention because thioaldehydes are generally synthesized from specific starting materials under limited reaction conditions, *e.g.*, photoreaction of β-keto sulfides, 1,5-sigmatropic rearrangement of thiosulfinates, 1,2-elimination of sulfenyl chloride, and the thermolysis of trithianes.[7] Compared with the previous methods, our conditions provide thioaldehydes from thiols using relatively low-cost copper catalysts and economical oxygen. In this study, we present the direct conversion of thiols to a variety of olefins in good yields using sulfones and phosphorous ylides (Scheme 1).



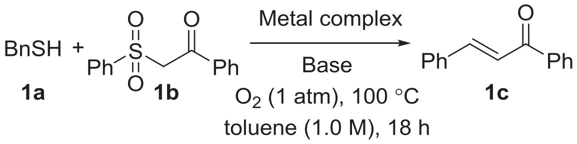
**Scheme 1.** Olefin formation via tandem oxidation–olefination protocols.

## Experimental

**Representative Procedure for the Reaction of Thiols and Sulfones.** A mixture of benzyl mercaptan **1a** (87 μL, 0.75 mmol), copper bromide (II) (1.1 mg, 0.005 mmol), 1,5,7-triazabicyclo[4,4,0]dec-5-ene (53.2 mg, 0.375 mmol), and 1-phenyl-2-(phenylsulfonyl)ethanone **1b** (65.1 mg, 0.25 mmol) in toluene (1 M, 0.25 mL) was taken in a 5 mL round bottom flask and stirred at 100 °C for 18 h under oxygen atmosphere. The reaction mixture was evaporated and purified by flash silica gel column chromatography using 1% ether/hexane to obtain **1c** (38.2 mg, 73%).

**Representative Procedure for the Reaction of Thiols and Phosphorous Ylides.** A mixture of benzyl mercaptan **1a** (116 μL, 1 mmol), copper chloride (II) (1.3 mg, 0.01 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (75 μL, 0.5 mmol), and phosphorous ylide **5b** (174.2 mg, 0.5 mmol) in toluene (0.5 M, 1 mL) was taken in a 5 mL round bottom flask and stirred at 100 °C for 18 h under oxygen atmosphere. The reaction mixture was evaporated and purified by flash silica gel column chromatography using 1% ether/hexane to obtain **7c** (64.1 mg, 73%).

**Table 1.** Oxidative olefination of **1a** using sulfone **1b**.



| Entry | Metal complex | Base | Yield[a](%) |
|---|---|---|---|
| 1 | $CuBr_2$ (2 mol %) | TBD (1 equiv) | 20 |
| 2 | $CuBr_2$ (2 mol %) | TBD (1.5 equiv) | 73 (29[b], 73[c]) |
| 3 | $CuBr_2$ (2 mol %) | TBD (2 equiv) | 29 |
| 4 | $CuCl_2$ (2 mol %) | TBD (1.5 equiv) | 41 |
| 5 | CuBr (2 mol %) | TBD (1.5 equiv) | 64 |
| 6 | $Cu(OTf)_2$ (2 mol %) | TBD (1.5 equiv) | 68 |
| 7 | $FeCl_3{\cdot}6H_2O$ (2 mol %) | TBD (1.5 equiv) | 54 |
| 8 | — | TBD (1.5 equiv) | 43 |
| 9 | $CuBr_2$ (2 mol %) | DBU (1.5 equiv) | 52 |
| 10 | $CuBr_2$ (2 mol %) | KO$^t$Bu (1.5 equiv) | 14 |
| 11 | $CuBr_2$ (2 mol %) | — | 5 |

[a] Isolated yield.
[b] The reaction was run under 1 atm of nitrogen.
[c] 5 mol % of $CuBr_2$

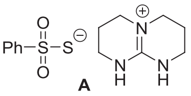
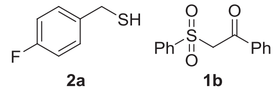
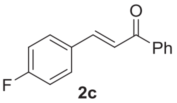
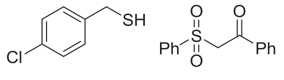
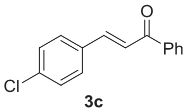
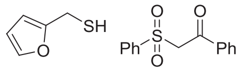
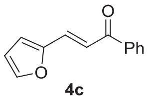
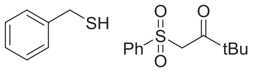
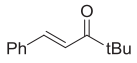
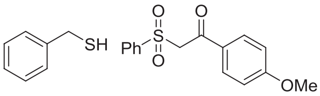
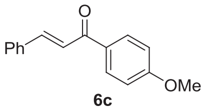
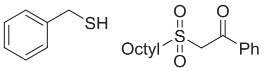
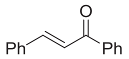


**Table 2.** Examples of the coupling of thiols and sulfones.

| Entry | Reactants | Products[a] |
|---|---|---|
| 1 |  **2a** **1b** |  **2c** 64%[b] |
| 2 |  **3a** **1b** |  **3c** 75%[b] |
| 3 |  **4a** **1b** |  **4c** 69%[b] |
| 4 |  **1a** **2b** |  **5c** 63%[a] |
| 5 |  **1a** **3b** |  **6c** 69%[b] |
| 6 |  **1a** **4b** |  **1c** 57%[b] |

[a] The reactions were run under the conditions of entry 2 (Table 1).
[b] Isolated yield.

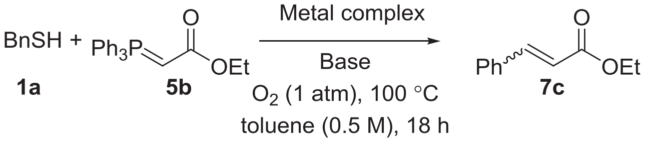
## Results and Discussion

The results of the optimization of the formation of olefin **1c** are listed in Table 1. Benzyl mercaptan **1a** and sulfone **1b** were exposed to copper-catalyzed oxidative olefination conditions involving $CuBr_2$ and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) to afford the (*E*)-form of chalcone **1c** in a 20% yield (entry 1). Increasing the amounts of TBD to 1.5 equivalents (equiv) increased the yield to 73% (entry 2). Under a nitrogen atmosphere, product formation was not efficient (29% yield, entry 2). With increased amounts of $CuBr_2$ (5 mol %), the yield of **1c** was not changed (73%, entry 2). Further increasing the TBD loading to 2 equiv was detrimental to the yield (29% yield, entry 3). $CuCl_2$, CuBr, and $Cu(OTf)_2$ and $FeCl_3{\cdot}6H_2O$ were tested as catalysts and gave lower yields than $CuBr_2$ (entries 4–7). In the absence of metal complexes, **1c** formed in a 43% yield (entry 8). In the presence of other organic and inorganic bases, the yield did not increase (entries 9 and 10). In the absence of base, **1c** was obtained in a 5% yield, implying that the base is critical to the nucleophilicity of **1b** (entry 11). Phenyl thiosulfonate TBDH$^+$ **A** was isolated as a byproduct of this reaction.[8]

Subsequent to optimization, various thiols and sulfones were exposed to a solution of $CuBr_2$ (2 mol %) and TBD (1.5 equiv) to afford the desired olefin products (Table 2). *p*-Fluoro and *p*-chloro-substituted benzyl thiols **2a** and **3a**, respectively, reacted with **1b** to afford **2c** and **3c** in 64 and 75% yields, respectively (entries 1 and 2). Furyl thiol **4a** participated in the reaction to give **4c** in a 69% yield (entry 3). Octyl thiol was subjected to the reaction conditions, but the desired olefin was not obtained. To investigate the substituents other than phenyl, *tert*-butyl-substituted sulfone **2b** was subjected to the reaction conditions to afford **5c** in a 63% yield (entry 4). Electron-rich OMe-substituted phenyl sulfone **3b** reacted with **1a** to afford **6c** in a 69% yield (entry 5). To compare the reactivities of the sulfones, octyl-substituted sulfone **4b** was subjected to the reaction conditions to form **1c** in a 57% yield, which was slightly lower than that obtained using **1b** (entry 6). In addition to sulfones containing a carbonyl group, dimethylsulfone was checked to show no product formation.

Oxidative olefination of **1a** with phosphorous ylide **5b** was performed under listed conditions in Table 3. A combination of $CuCl_2$ catalyst (2 mol %) and TBD (1 equiv) promoted oxidative olefination of **1a** in a 56% yield (entry 1). Changing the base to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) increased the yield of **7c** to 73%, and *Z*-isomer was observed as a minor product (entry 2). In contrast to oxidative olefination using sulfone **1b**, no product was isolated under a nitrogen atmosphere (entry 2). With 5 mol % of $CuCl_2$, the yield of **7c** was decreased to 67% (entry 2). Increasing or decreasing the amount of bases did not improve the yield of **7c** (entries 3 and

**Table 3.** Oxidative olefination of **1a** using phosphorous ylide **5b**.



| Entry | Metal complex | Base | Yield[a] (%) | (*E*):(*Z*) ratio |
|---|---|---|---|---|
| 1 | $CuCl_2$ (2 mol %) | TBD (1 equiv) | 56 | (*E*)-isomer only |
| 2 | $CuCl_2$ (2 mol %) | DBU (1 equiv) | 73 (0[b], 67[c]) | 1.00:0.18 |
| 3 | $CuCl_2$ (2 mol %) | DBU (1.5 equiv) | 66 | 1.00:0.17 |
| 4 | $CuCl_2$ (2 mol %) | DBU (0.5 equiv) | 67 | 1.00:0.19 |
| 5 | $CuCl_2$ (2 mol %) | — | 42 | 1.00:0.29 |
| 6 | $CuBr_2$ (2 mol %) | DBU (1 equiv) | 70 | 1.00:0.16 |
| 7 | $Cu(OTf)_2$ (2 mol %) | DBU (1 equiv) | 68 | 1.00:0.18 |
| 8 | CuCl (2 mol %) | DBU (1 equiv) | 62 | 1.00:0.14 |
| 9 | $FeCl_3 \cdot 6H_2O$ (2 mol %) | DBU (1 equiv) | 62 | 1.00:0.08 |
| 10 | — | DBU (1 equiv) | 55 | (*E*)-isomer only |
| 11 | CuBr (2 mol %) | DBU (1 equiv) | 73 | 1.00:0.16 |

[a] Isolated yield.

[b] The reaction was run under 1 atm of nitrogen.

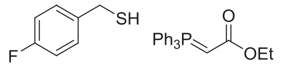
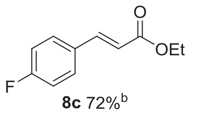
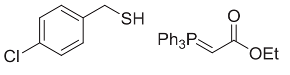
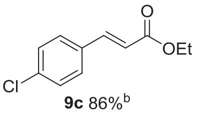
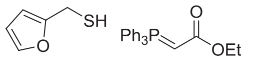
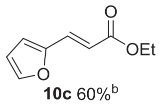
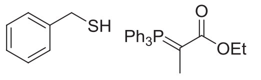
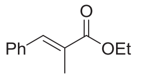
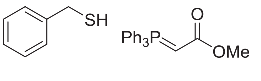
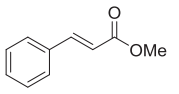
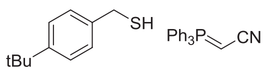
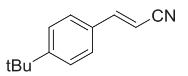
[c] 5 mol % $CuCl_2$ $Ph_3P{=}S$.
B

4). In the absence of bases, **7c** was isolated in a 42% yield (entry 5). Compared with the reactions using sulfone **5b**, oxidative olefination using phosphorous ylide **5b** appeared to be less sensitive to the amount of base, because ylide **5b** is sufficiently basic not to require additional base for increased nucleophilicity. Other copper catalysts (*i.e.*, $CuBr_2$, $Cu(OTf)_2$, and CuCl) showed similar catalytic activities and afforded **7c** in 70, 68, and 62% yields, respectively (entries 6–8). $FeCl_3 \cdot 6H_2O$ catalyzed the reaction; however, the yield was lower than those of the copper-catalyzed reactions (entry 9). In the absence of metal catalyst, **7c** formed in a 55% yield (entry 10). Phosphorous sulfide **B** was isolated as a byproduct of this reaction.[9]

The optimized reaction conditions for the coupling of benzyl mercaptan **1a** and phosphorous ylide **5b** were applied to diverse thiols and phosphorous ylides, as shown in Table 4. Fluoro- and chloro-substituted thiols **2a** and **3a**, respectively, reacted with **5b** to afford the desired α,β-unsaturated esters **8c** and **9c** in 72 and 86% yield, respectively (entries 1 and 2). Furyl thiol was converted to the corresponding unsaturated ester, **10c**, in a 60% yield (entry 3). As an aliphatic thiol example, octyl thiol was tested, but desired products were not obtained. Sterically hindered methyl-substituted phosphorous ylide **6b** reacted with **1a** to form α-substituted α,β-unsaturated ester **11c** in an 83% yield (entry 4). Ylides possessing methyl-ester and nitrile groups also participated in oxidative olefination to form the corresponding products **12c** and **13c**, respectively, albeit in slightly reduced yields (entries 5 and 6).

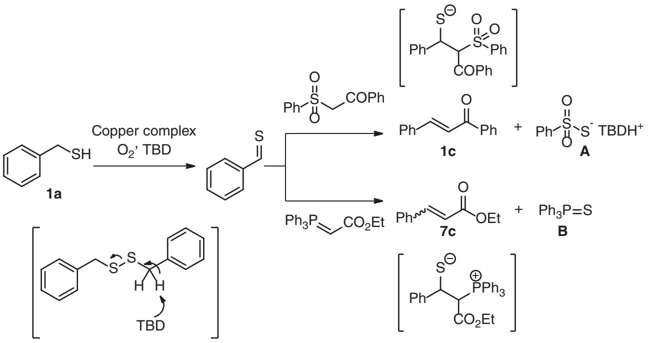
We proposed a possible reaction mechanism, which is shown in Scheme 2. As we published earlier,[5]

**Table 4.** Examples of the coupling of thiols and phosphorous ylides.

| Entry | Reactants | Products[a] |
|---|---|---|
| 1 |  <br>**2a** **5b** |  <br>**8c** 72%[b]<br>*E*:*Z* = 1.00:0.18 |
| 2 |  <br>**3a** **5b** |  <br>**9c** 86%[b]<br>*E* only |
| 3 |  <br>**4a** **5b** |  <br>**10c** 60%[b]<br>*E* only |
| 4 |  <br>**1a** **6b** |  <br>**11c** 83%[b]<br>*E* only |
| 5 |  <br>**1a** **7b** |  <br>**12c** 60%[b]<br>*E*:*Z* = 1.00:0.12 |
| 6 |  <br>**5a** **8b** |  <br>**13c** 45%[b]<br>*E*:*Z* = 1.00:1.14 |

[a] The reactions were run under the conditions of entry 2 (Table 3).

[b] Isolated yield.



**Scheme 2.** Plausible reaction mechanism for the formation of **1c** and **7c**.

thiobenzaldehydes can form *via* the deprotonation of dibenzyldisulfide, which is formed from **1a**.[10] Oxidation can be accelerated by a copper catalyst and oxygen. Thiobenzaldehydes react with either sulfones or phosphorous ylides to afford corresponding olefin **1c** and **7c**, respectively. The byproducts of each reaction account for the reaction mechanism that includes the intermediates described in Scheme 2.

## Conclusion

We reported the first example of copper-catalyzed one-pot aerobic oxidation of thiols followed by olefinations with sulfones and phosphorous ylides. The thiols underwent direct oxidation to afford thioaldehydes, which underwent Julia-type and Wittig-type olefination with sulfones and phosphorous ylides, respectively. Low-cost copper catalysts enhanced the oxidation of thiols, and the use of appropriate amounts of organic bases appears to be critical for obtaining a high yield of olefin products. Isolation of the byproducts of each reaction supported the proposed reaction mechanism.

**Acknowledgments.** This study was supported by the Korea Research Foundation (Nos 2009-0094046 and 2013008819) and a Korea CCS R&D Center (KCRC) grant from the Korea Government (Ministry of Education, Science and Technology; No. 2014M1A8A1049294).

**Supporting Information.** Experimental procedures and spectra of **1c–13c**.

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