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# Copper-catalyzed C–C direct cross-coupling: an efficient approach to phenyl-2-(phenylthiophenyl)-methanones†

Qi Zhang, Wei Wang, Chong Gao, Rong-Rong Cai and Run-Sheng Xu *

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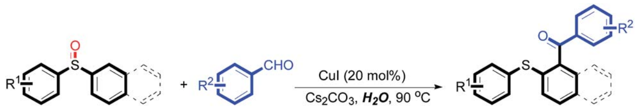
An efficient copper-catalyzed C–C bond direct cross-coupling reaction has been developed. Starting from diaryl sulfoxides and aromatic aldehydes, versatile phenyl-2-(phenylthiophenyl)-methanones were efficiently synthesized with high tolerance of functional groups under moderate conditions in water. This new methodology provides an economical and environmentally friendly approach toward C($sp^2$)–C($sp^2$) bond formation.

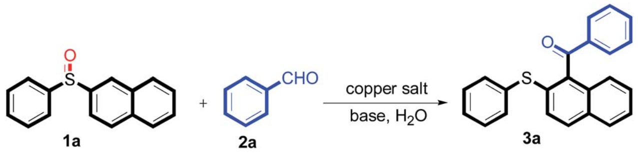
Transition-metal catalyzed direct cross-coupling reactions enable efficient preparation of multifunctional complex molecules, playing an essential role in the development of natural products, pharmaceuticals and functional materials.[1–5] Over the past few decades, nitrogen[6] and oxygen[7] group directed C–C bond coupling reactions *via* C–H bond activation have made great progress. Sulfur groups have a high electron density and are easy to modify, and have a non-maximal advantage in C–C bond direct cross-coupling.[8] However, the application of sulfur group-directed C–C cross-coupling reactions remains a formidable challenge.[9] One major problem is that regarding the competition between the sulfur atom and the reaction site, the coordination of the sulfur atom with the transition metal is very stable.[10] Namely, the transition metals are more inclined to lose their catalytic activity. Therefore, the development of a more efficient strategy of sulfur directed C–H functionalization is still highly desirable.

Modern green synthetic chemistry is now well-established in the design and realization of organic synthesis, because it is seriously concerned with the environment and sustainable development.[11] Among the challenges currently facing synthetic chemists is the development of efficient and environmentally friendly chemical processes for the synthesis of complex molecules, especially required in the area of drug discovery and natural product synthesis.[12] Here, we report a practical method for the environmentally friendly and highly selective Cu-catalyzed C–C bond direct cross-coupling of diaryl sulfoxides with aromatic aldehydes. Versatile phenyl-2-(phenylthiophenyl)-methanones were efficiently synthesized with high tolerance of functional groups under moderate conditions in water. This new methodology provides an efficient and economical approach toward C($sp^2$)–C($sp^2$) formation.



The reaction conditions were screened based on a model reaction of 2-benzenesulfinyl-naphthalene **1a** with benzaldehyde **2a** in water (Table 1). Initially, the experimental results demonstrated that Cu(I) salts have higher catalytic activities than Cu(II) salts (entries 1–3). Besides, those results

Table 1 Optimization of the model reaction[a]



**1a** **2a** **3a**

| Entry | Copper salt | Base | **1a : 2a** | **3a**[b] [%] |
|---|---|---|---|---|
| 1 | Cu(OAc)$_2$ | Cs$_2$CO$_3$ | 1 : 1 | 16 |
| 2 | CuSO$_4$ | Cs$_2$CO$_3$ | 1 : 1 | 45 |
| 3 | CuBr$_2$ | Cs$_2$CO$_3$ | 1 : 1 | nr |
| 4 | CuBr | Cs$_2$CO$_3$ | 1 : 1 | 54 |
| 5 | CuI | Cs$_2$CO$_3$ | 1 : 1 | 79 |
| 6 | CuI | Na$_2$CO$_3$ | 1.2 : 1 | nr |
| 7 | CuI | K$_3$PO$_4$ | 1.2 : 1 | 43 |
| 8 | CuI | Cs$_2$CO$_3$ | 1.2 : 1 | 66[c] |
| 9 | CuI | Cs$_2$CO$_3$ | 1.2 : 1 | 73[d] |
| 10 | CuI | Cs$_2$CO$_3$ | 1.2 : 1 | 82 |
| 11 | CuI | Cs$_2$CO$_3$ | 1.2 : 1 | 71[e] |

[a] Unless otherwise noted, reaction conditions were **1a** (0.3 mmol), **2a** (0.3 mmol), copper salt (20 mol%), Cs$_2$CO$_3$ (2 equiv.), H$_2$O (4 mL), 90 °C for 10 h. [b] Isolated yield. [c] At 80 °C. [d] At 100 °C. [e] In CH$_3$CN.

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*Department of Biology and Environment, Jiyang College of Zhejiang A&F University, Hangzhou 311800, Zhejiang, China. E-mail: 20140041@zafu.edu.cn*

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Table 2 Copper-catalyzed C–C bond direct cross-coupling of 2-benzenesulfinyl-naphthalenes with aromatic aldehydes[a]

Table 2 (Contd.)

| Entry | 1 | 2 | 3 | Yield[b] [%] |
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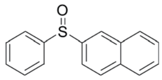
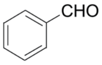
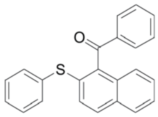
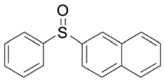
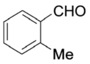
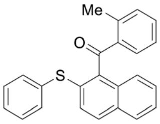
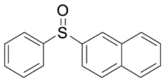
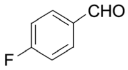
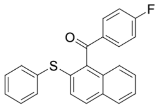
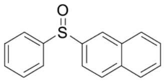
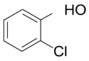
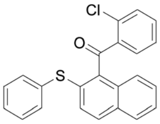
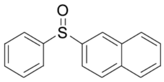
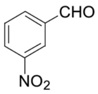
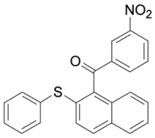
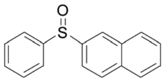
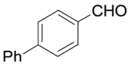
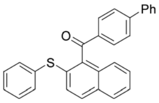
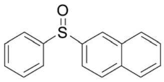
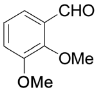
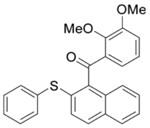
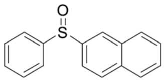
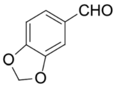
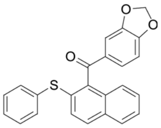
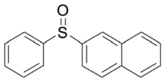
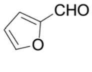
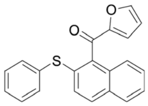
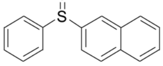
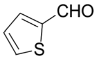
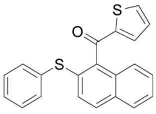
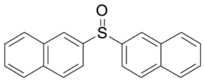
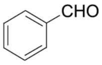
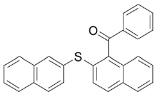
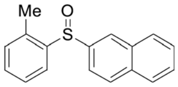
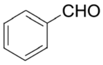
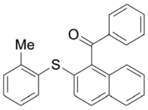
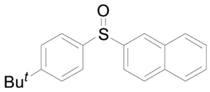
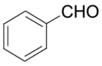
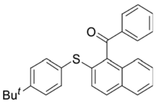
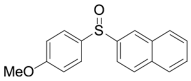
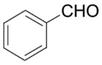
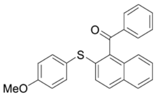
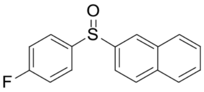
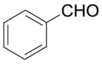
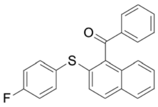
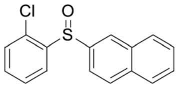
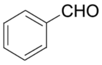
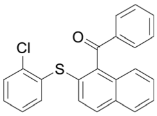
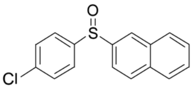
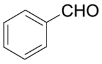
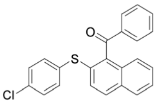
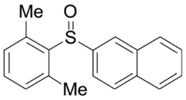
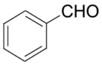
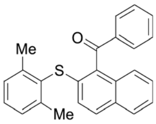
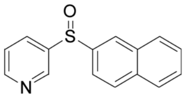
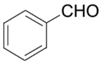
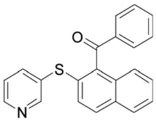
| 1 |  |  |  3a | 82 |
| 2 |  |  |  3b | 79 |
| 3 |  |  |  3c | 86 |
| 4 |  |  |  3d | 83 |
| 5 |  |  |  3e | 91 |
| 6 |  |  |  3f | 80 |
| 7 |  |  |  3g | 77 |
| 8 |  |  |  3h | 78 |
| 9 |  |  |  3i | 85 |
| 10 |  |  |  3j | 84 |
| 11 |  |  |  3k | 83 |
| 12 |  |  |  3l | 87 |
| 13 |  |  |  3m | 86 |
| 14 |  |  |  3n | 88 |
| 15 |  |  |  3o | 75 |
| 16 |  |  |  3p | 79 |
| 17 |  |  |  3q | 70 |
| 18 |  |  |  3r | 81 |
| 19 |  |  |  3s | 80 |

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| Entry | 1 | 2 | 3 | Yield$^b$ [%] |
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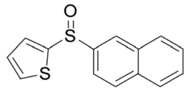
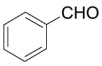
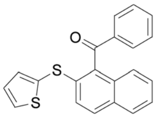
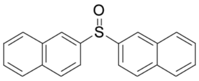
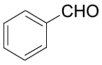
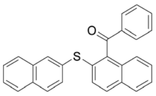
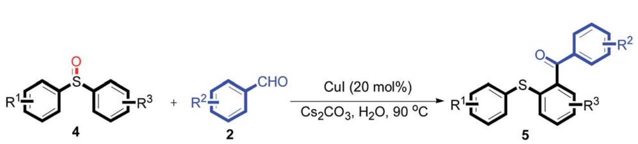
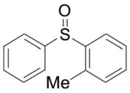
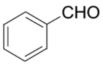
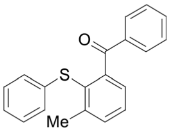
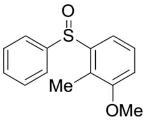
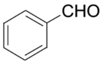
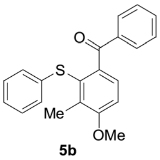
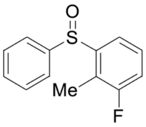
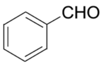
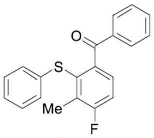
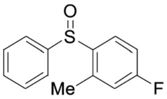
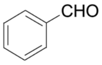
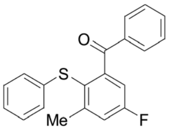
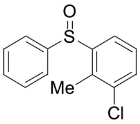
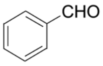
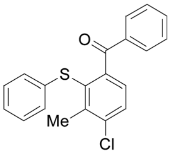
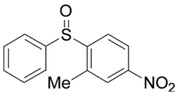
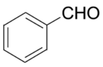
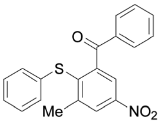
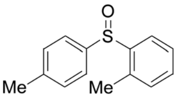
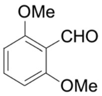
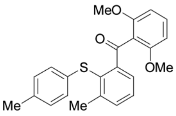
| 20 |  |  |  3t | 83 |
| 21 |  |  |  3u | 77 |

[a] Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), CuI (20 mol%), $Cs_2CO_3$ (2 equiv.), in $H_2O$ (4 mL) at 90 °C for 10 h. [b] Isolated yield.

Table 3 Copper-catalyzed C–C bond direct cross-coupling of diphenyl sulfoxides with aromatic aldehydes[a]



| Entry | 4 | 2 | 5 | Yield$^b$ [%] |
|---|---|---|---|---|
| 1 |  |  |  5a | 79 |
| 2 |  |  |  5b | 78 |
| 3 |  |  |  5c | 80 |
| 4 |  |  |  5d | 82 |
| 5 |  |  |  5e | 83 |
| 6 |  |  |  5f | 85 |
| 7 |  |  |  5g | 80 |

[a] Reaction conditions: **4** (0.36 mmol), **2** (0.3 mmol), CuI (20 mol%), $Cs_2CO_3$ (2 equiv.), $H_2O$ (4 mL), 90 °C for 10 h. [b] Isolated yield.

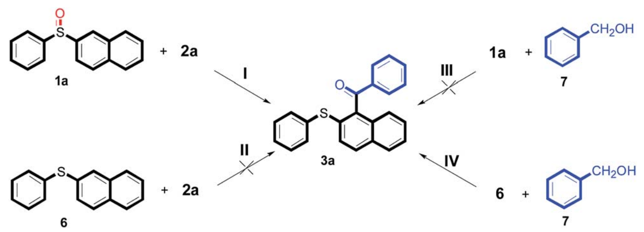
demonstrated that the reaction temperature is an important parameter whereby the desired product was formed in 66% yield at 80 °C (entry 8) and 73% yield at 100 °C (entry 9). Meanwhile, we observed that this reaction also proceeds smoothly in organic solvent, such as $CH_3CN$ (entry 11). However, the product yield was lower than that in water. Finally, the desired product **3a** was formed in 82% yield under the optimum reaction conditions employing CuI (20 mol%) and $Cs_2CO_3$ (2 equiv.) at 90 °C (entry 10).

With the optimized conditions in hand, the reaction scope was next investigated. A wide array of 2-benzenesulfinyl-naphthalenes **1** and aromatic aldehydes **2** gave the desired products in good to excellent yields (Table 2). It was found that both the electron-donating and electron-withdrawing 2-benzenesulfinyl-naphthalenes **1** reacted smoothly with aromatic aldehydes **2** to give the desired compounds. 2-Benzenesulfinyl-naphthalenes **1** bearing electron-donating groups showed better activity than **1** bearing electron-withdrawing groups. Aromatic aldehydes **2** bearing electron-withdrawing groups showed better activity than **2** bearing electron-donating groups. Heteroatom aromatic aldehydes also gave the desired product (entries 9 and 10).

Furthermore, we turned our attention to other diaryl sulfoxides (Table 3). To our delight, diphenyl sulfoxides also smoothly gave the desired products in 79–85% yield. Diphenyl sulfoxides **4** bearing electron-donating groups (entry 6, 85% nitro group) showed better activity than those bearing electron-withdrawing groups (entry 2, 78% MeO group).

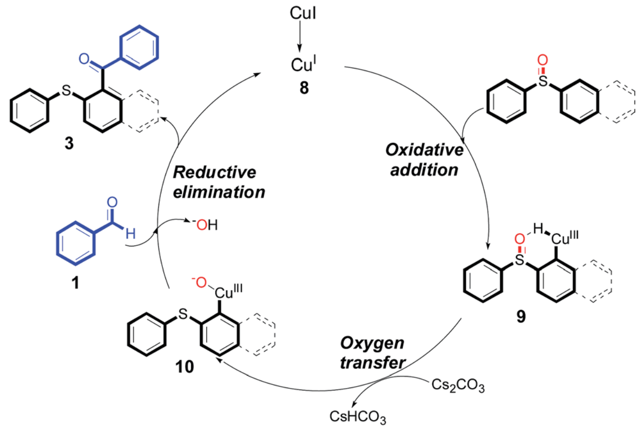
To obtain the preliminary details of the reaction mechanism, some additional reactions were done (Scheme 1). At first, the model reaction (Scheme 1I) was conducted in three other parallel reactions (Scheme 1II, III and IV). However, the results showed that only 2-phenylsulfanylnaphthalene **6** reacted with phenylmethanol **7** promoted by hydrogen peroxide under our standard conditions, successfully obtaining the target product **3a** in 67% yield (Scheme 2IV), indicating that diaryl sulfoxide was the necessary substrate for this reaction.

Many precedents from the literature have proved that sulfoxides are good directing groups[13] and oxidants[14] in C–H bond functionalization reactions. Based on the above results, a reaction mechanism was proposed (Scheme 2). At the beginning of



**I** **1a** (0.36 mmol), **2a** (0.3 mmol), CuI (20 mol%), $Cs_2CO_3$ (2 equiv), $H_2O$ (4 mL), **3a** (82%).
**II** **6** (0.36 mmol), **2a** (0.3 mmol), CuI (20 mol%), $Cs_2CO_3$ (2 equiv), $H_2O$ (4 mL), **3a** (0%).
**III** **1a** (0.36 mmol), **7** (0.3 mmol), CuI (20 mol%), $Cs_2CO_3$ (2 equiv), $H_2O$ (4 mL), **3a** (0%).
**IV** **6** (0.36 mmol), **7** (0.3 mmol), CuI (20 mol%), $Cs_2CO_3$ (2 equiv), $H_2O_2$ (50%, 5 mL), **3a** (67%).

Scheme 1



Scheme 2 A plausible reaction mechanism.

the reaction, an intermediate **9** was formed from CuI with diaryl sulfoxides by oxidative addition step.[15] There was a six-membered ring in the intermediate **9** which was very favorable for the intramolecular oxidation reaction, namely the oxygen transfer step. Next, intermediate **9** produced intermediate **10** by intramolecular oxygen transfer.[16] Finally, intermediate **10** reacted with aromatic aldehyde **1** to furnish the desired product **3** and meanwhile concomitantly generated Cu(I), which re-entered the catalytic cycle.

## Conclusions

In summary, an efficient copper-catalyzed C–C bond direct cross coupling of diaryl sulfoxides with aromatic aldehydes has been developed. Employing this methodology, various phenyl-2-(phenylthiophenyl)-methanone derivatives were efficiently synthesized under mild conditions in water. This new methodology provides an economical and environmentally friendly approach toward $C(sp^2)$–$C(sp^2)$ formation. Finally, a plausible reaction mechanism of the Cu(I)/Cu(III) catalytical cycle was proposed.

## Notes

### General procedure for preparation of 3 and 5

A mixture of 2-benzenesulfinyl-naphthalene **1a** (90.7 mg, 0.36 mmol), benzaldehyde **2a** (69 mg, 0.3 mmol), CuI (38.0 mg, 20 mol%) and $Cs_2CO_3$ (326.5 mg, 2 equiv.) in $H_2O$ (4 mL) was stirred in $N_2$ at 90 °C for 10 h. After completion of the reaction, the mixture was quenched with saturated salt water (10 mL), and then the solution was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried by sodium sulfate. The pure product phenyl-(2-phenylsulfanylnaphthalen-1-yl)-methanone **3a** (83.7 mg, 82% yield) was obtained by flash column chromatography on silica gel, washed with 4 : 1 cyclohexane/ethyl acetate.

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