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Copper-catalyzed C–S direct cross-coupling of thiols with 5-arylpena-2,4-dienoic acid ethyl ester[†]

Rongrong Cai, Zhuoda Zhou, Qianqian Chai, Yueer Zhu and Runsheng Xu  *

A selective copper (Cu)-catalyzed C–S bond direct cross-coupling of thiols with 5-arylpena-2,4-dienoic acid ethyl ester was developed. Notably, various biologically active 5-phenyl-3-phenylsulfanylpena-2,4-dienoic acid ethyl ester derivatives were efficiently synthesized under moderate conditions. Finally, a plausible Cu(i)/Cu(iii) reaction mechanism was proposed.

1 Introduction

As one of the most important compounds, organic thioethers are being widely applied in organic synthesis, the pharmaceutical industry, and functional materials.¹ C–H bonds functionalization has considerably progressed.² In theory, due to larger atomic radius and higher electron density, sulfur has more reactivity and is easy to modify (Scheme 1).³ In comparison with the state art of C–C coupling,⁴ acylation⁵ and amination,⁶ C–H bond direct thiolation has been seldom described in the literature. The main reason is that sulfur easily poisons transition metals.⁷ Therefore, developing more efficient strategies for C–H bond thiolation is still required.

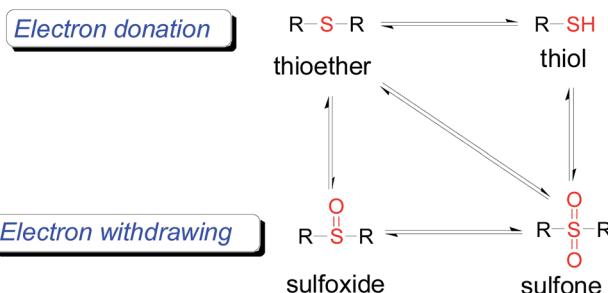
Selective C–H bond functionalization, either chemoselective or regioselective, has been long pursued.⁸ The progress on transition-metal catalyzed C–N and C–O cross-coupling has been prompted. However C–H bonds activated by alkenes is rarely reported.⁹ Considering the significance of diversifying synthetic strategies, we focused our interest on sulfur-directed C–H bond functionalization.¹⁰ 5-Arylpenta-2,4-dienoic acid ethyl esters is an excellent scaffold which ubiquitous in natural biological products, the pharmaceutical chemistry and functionalized materials.¹¹ However, the earlier reported synthetic methods have many disadvantages, such as low efficiency, inconvenience, and requiring harsh conditions. Efficient synthetic methods of 5-phenylpena-2,4-dienoic acid ethyl esters are still required. Due to the functional group tolerance and economic attractiveness, copper catalysts have been extensively used in C–H bonds functionalization.¹² Herein, we report a selective copper-catalyzed C–S bond direct cross-coupling reaction of thiols with 5-arylpena-2,4-dienoic acid ethyl ester. In this reaction,

various biological activity 5-aryl-3-phenylsulfanylpena-2,4-dienoic acid ethyl ester derivatives were efficiently synthesized under moderate conditions. Finally, a plausible reaction mechanism was proposed.

2 Results and discussion

The reaction conditions were screened based on a model reaction of thiophenol **1a** with 5-arylpena-2,4-dienoic acid ethyl ester **2a**. These reactions are mainly based on the use of the enaminone ligand, which was previously discovered in our laboratory as an effective ligand for the C–N coupling of Ullmann reactions between aryl halides and various azoles.¹⁰ At the beginning, various structurally similar enaminone ligands **L1–L9** were investigated (Scheme 2). The yields increased by changing the substituent R to R'. Additionally, other enaminone ligands, such as **L7**, **L8**, and **L9**, were observed to be less effective. Analyzing the results, **L4** was considered the best ligand.

Furthermore, other reaction parameters were optimized (Table 1). Experimental results demonstrated that the Cu(i) salt resulted in a higher yield than the Cu(ii) salt (entries 1–4). Additionally, the results also demonstrated that the reaction temperature was as an important parameter. The desired

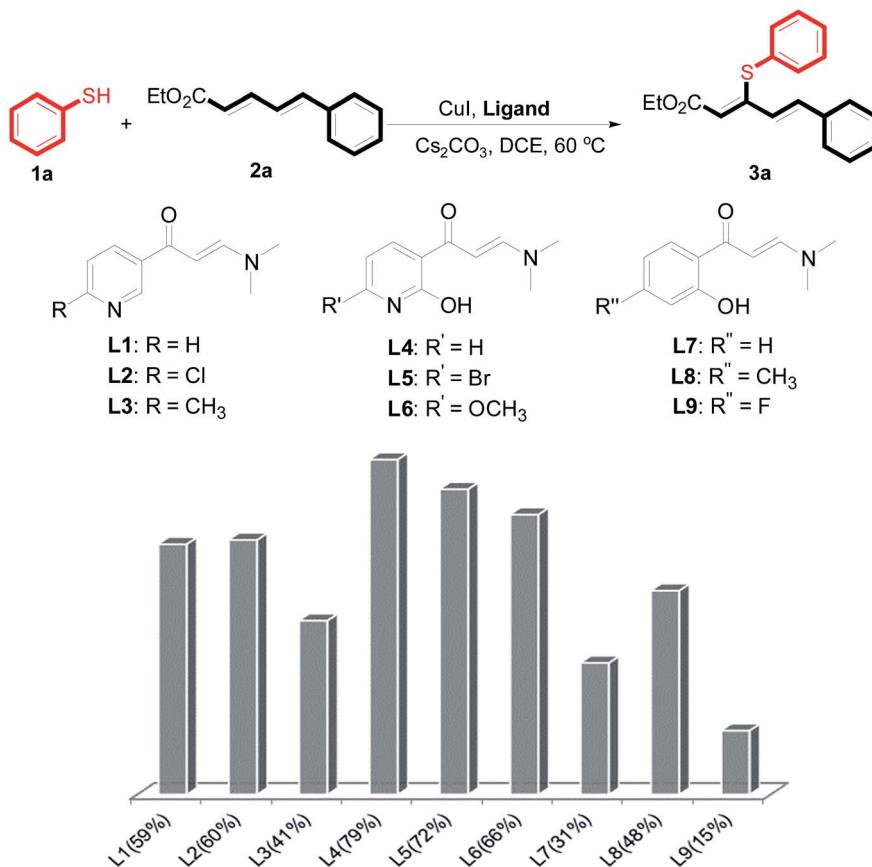


Scheme 1 Conversions of sulfur-containing groups.

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

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Scheme 2 Ligand performance in copper-catalyzed C–S direct cross coupling.

Table 1 Optimization of the model reaction^a

Entry	Copper salt	Base	1a : 2a	3a ^b (%)
1	Cu(OAc) ₂	Cs ₂ CO ₃	1 : 1	15
2	CuSO ₄	Cs ₂ CO ₃	1 : 1	42
3	CuBr ₂	Cs ₂ CO ₃	1 : 1	NR
4	CuBr	Cs ₂ CO ₃	1 : 1	53
5	CuI	Cs ₂ CO ₃	1 : 1	79
6	CuI	Na ₂ CO ₃	1 : 1.2	NR
7	CuI	K ₃ PO ₄	1 : 1.2	41
8	CuI	Cs ₂ CO ₃	1 : 1.2	63 ^c
9	CuI	Cs ₂ CO ₃	1 : 1.2	75 ^d
10	CuI	Cs ₂ CO ₃	1 : 1.2	81
11	CuI	Cs ₂ CO ₃	1 : 1.2	NR ^e

^a Unless otherwise noted, reactions conditions were 1a (0.3 mmol), copper source (10 mol%), L5 (10 mol%), Cs₂CO₃ (2 equiv.), DCE (4 mL), 60 °C for 24 h, in N₂. ^b Isolated yield. ^c At 50 °C. ^d At 70 °C.

^e Absence of the ligand.

product had a 63% yield at 50 °C (entry 8) and a 75% yield at 70 °C (entry 9). Furthermore, the reaction in the absence of the ligand did not occur (entry 11). Finally, the desired product 3a was formed with 81% yield when used the catalyst system L4 with CuI at 60 °C (entry 10).

Under the optimized conditions, the reaction scope was next investigated. A wide array of aryl thiols 1 and 5-arylpena-2,4-

dienoic acid ethyl esters 2 were obtained as the productivity with good to excellent yields (Table 2). We found that both the electron-donating and electron-withdrawing aryl thiols 1 reacted smoothly with 5-arylpena-2,4-dienoic acid ethyl esters 2. The aryl thiols 1 bearing electron-donating groups showed better activity than those with electron-withdrawing groups. 5-Arylpenta-2,4-dienoic acid ethyl esters 2 bearing electron-withdrawing groups showed better activity than those bearing electron-donating groups. The C=C configuration of the 5-arylpena-2,4-dienoic acid ethyl esters 2 was retained in the corresponding products.

Next, we focused on other thiols (Table 3). Aliphatic thiols worked well in this reaction. The corresponding products were isolated with 76–88% yields. The C=C configuration of the 5-phenylpena-2,4-dienoic acid ethyl esters 2 were also retained in corresponding products.

There were two reasons of the ester group essential for the regioselectivity in those reactions. First, ethyl ester was more common and more meaningful than other alkyl esters in the field of synthetic industry and functional materials. Secondly, ethyl ester had better coordination ability than other alkyl ester. Based on the above results, a reaction mechanism was proposed (Scheme 3). After the coordination of CuI with L4, a corresponding intermediate 6 was generated.¹³ Next, an intermediate 7 was formed from intermediate 6 with aryl thiols through a ligand exchange step. Next, intermediate 7

Table 2 Copper-catalyzed C–S direct cross-coupling of aryl thiols with 5-arylpenta-2,4-dienoic acid ethyl ester^a

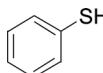
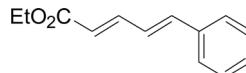
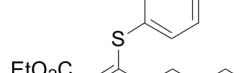
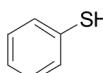
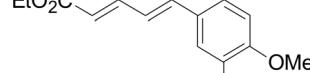
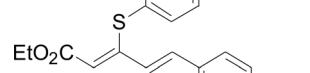
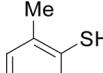
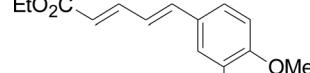
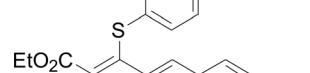
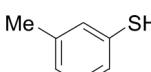
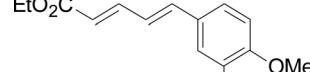
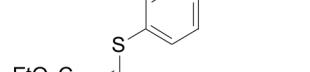
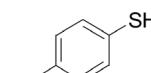
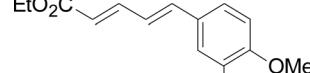
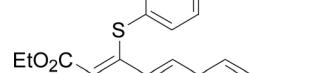
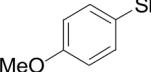
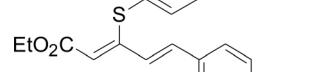
Entry	1	2	3	Yield ^b (%)
1				81
2				76
3				85
4				82
5				83
6				89

Table 2 (Contd.)

7				78
8				77
9				73
10				72
11				69
12				68



Table 2 (Contd.)

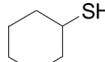
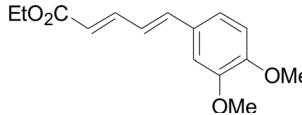
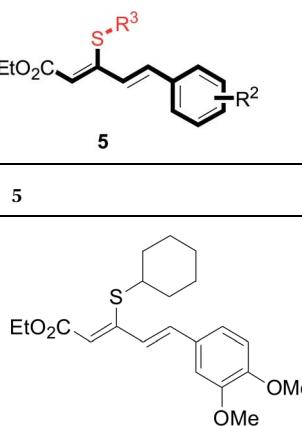
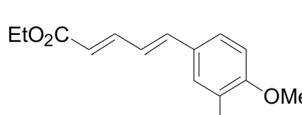
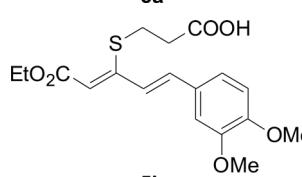
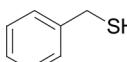
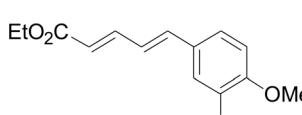
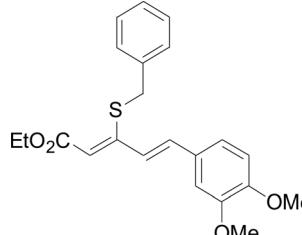
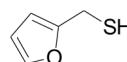
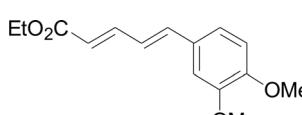
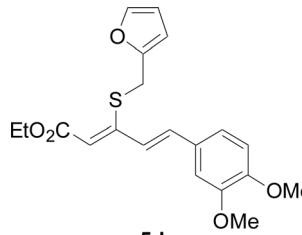
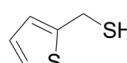
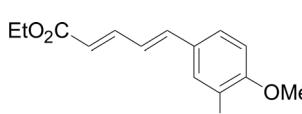
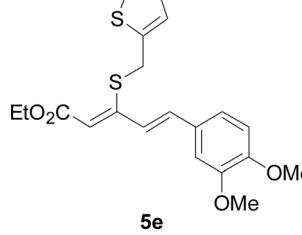
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^a Reactions conditions: **1** (0.3 mmol), **2** (0.36 mmol), CuI (10 mol%), **L4** (10 mol%), Cs₂CO₃ (2 equiv.), in DCE (4 mL) at 60 °C for 24 h, in N₂.

^b Isolated yield.



Table 3 Copper-catalyzed C–S direct cross-coupling of aliphatic thiols with 5-arylpena-2,4-dienoic acid ethyl ester^a

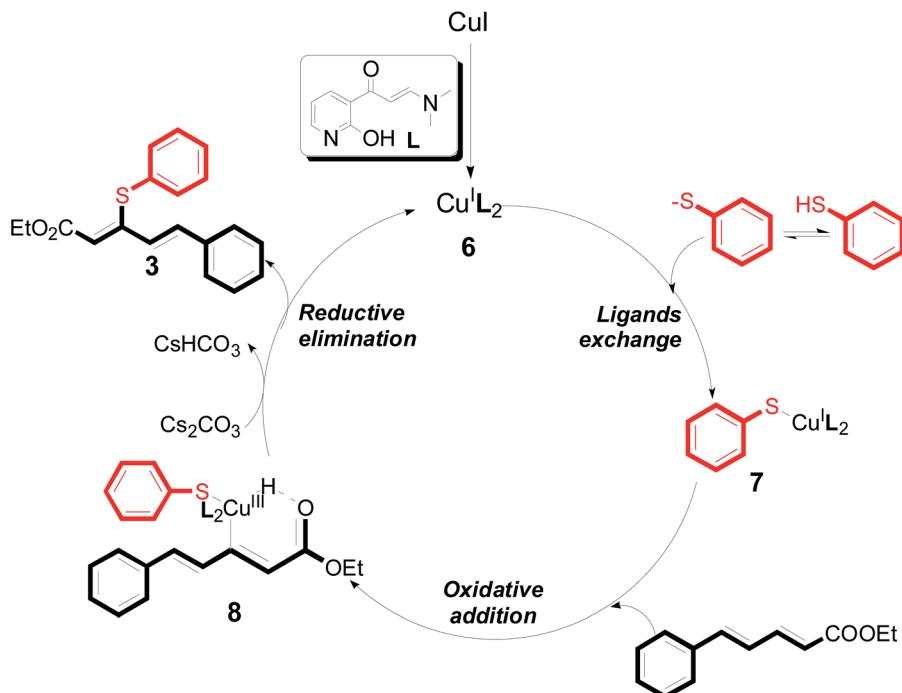
Entry	1	4	5	Yield ^b (%)
1				88
2				81
3				76
4				85
5				83

^a Reactions conditions: 4 (0.3 mmol), 2 (0.36 mmol), CuI (10 mol%), L4 (10 mol%), Cs₂CO₃ (2 equiv.), DCE (4 mL), 60 °C for 24 h, in N₂. ^b Isolated yield.

reacted with 5-arylpena-2,4-dienoic acid ethyl esters to produce intermediate 8 *via* an intermolecular oxidative addition. Finally, intermediate 8 furnished the desired product 3 and concomitantly generated intermediate 6, which re-entered

the catalytic cycle. Furthermore, the specific reaction mechanism is still under study *via* high-resolution electrospray ionisation mass spectrometry (HR-ESI-MS) and density functional theory (DFT).





Scheme 3 A plausible reaction mechanism.

3 Conclusions

In conclusion, a selective copper-catalyzed C-S bond direct cross-coupling of thiols with 5-arylpena-2,4-dienoic acid ethyl esters was developed. Using this methodology, various biological activity 5-aryl-3-phenylsulfanylpena-2,4-dienoic acid ethyl ester derivatives were efficiently synthesized. The process used inexpensive catalysts and under mild conditions. The reaction mechanism of the Cu(I)/Cu(III) catalysis cycle was proposed.

4 Experimental section

4.1. General procedure for preparation of L1-L10

Dimethylformamide dimethylacetal (DMFDA) (10 mmol, 1.19 g) and 1-pyridin-3-yl-ethanone (10 mmol, 1.21 g) were dissolved in *p*-xylene (2 mL). And the mixture was refluxed during a period of 5 to 12 hours, during which time the formation of yellow precipitate. The precipitate was filtered out and washed with petroleum ether three times. The solid was vacuum-dried, and 1.65 g (yield 94%) of a yellow solid was obtained **L1** 3-dimethylamino-1-pyridin-3-yl-propenone. ¹H NMR (500 MHz, ⁶DMSO): δ 14.51 (s, 1 H), 7.92–7.90 (t, J = 7.5 Hz, 2 H), 7.37–7.34 (s, J = 7.8 Hz, 1 H), 6.83 (d, J = 2.0 Hz, 1 H), 5.98–5.95 (d, J = 12 Hz, 1 H), 3.19 (s, 3 H), 2.98 (s, 3 H); ¹³C NMR (125 MHz, ⁶DMSO): δ 191.1, 163.6, 134.9, 129.9, 121.2, 119.1, 118.7, 90.4, 46.1, 38.6.

4.2. General procedure for preparation of 3 and 5

A mixture of benzenethiol **1a** (33.0 mg, 0.3 mmol), 5-phenylpena-2,4-dienoic acid ethyl ester **2a** (72.7 mg, 0.36 mmol), CuI (5.7 mg, 10 mol%), 3-dimethylamino-1-(2-hydroxypyridin-3-yl)-propenone **L4** (5.8 mg, 10 mol%) and

Cs₂CO₃ (195.6 mg, 2 equiv.) in DMSO (4 mL) was stirred under a N₂ atmosphere. After the reaction mixture was stirred at 60 °C for 24 h, it was allowed to cool to ambient temperature. Then the mixture was quenched with saturated salt water (10 mL), and the solution was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried by sodium sulfate and concentrated *in vacuo*. The pure product 5-phenyl-3-phenylsulfanylpena-2,4-dienoic acid ethyl ester **3a** (75.3 mg, 81% yield) was obtained by flash column chromatography on silica gel.

4.2.1 5-Phenyl-3-phenylsulfanylpena-2,4-dienoic acid ethyl ester (3a). 75.3 mg, 81% yield; yellow solid; mp 111–113 °C; ¹H NMR (500 MHz, CDCl₃): δ 8.41 (dd, 1 H, J = 15.9 Hz, 0.8 Hz), 8.20 (d, 2 H, J = 8.9 Hz), 7.57 (d, 2 H, J = 8.9 Hz), 7.50–7.55 (m, 2 H), 7.30–7.43 (m, 4 H), 6.73 (m, 1 H), 5.90 (m, 1 H), 4.23 (q, 2 H), 1.35 (t, 3 H); ¹³C NMR (125 MHz, CDCl₃): 160.8 (C), 145.9 (C), 142.8 (C), 140.7 (C), 136.9 (CH), 133.7 (CH), 129.0 (CH), 127.5 (CH), 126.8 (CH), 125.8 (CH), 122.4 (CH), 121.3 (CH), 120.1 (CH), 58.6 (CH₂), 11.3 (CH₃); ESI-HRMS *m/z*: calcd for C₁₉H₁₉O₂S⁺ [M + H]⁺: 311.1100; found 311.0997.

4.2.2 3-Cyclohexylsulfanyl-5-(3,4-dimethoxyphenyl)pena-2,4-dienoic acid ethyl ester (5a). 99.4 mg, 88% yield; yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 8.19 (dd, 1 H, J = 16.1, 0.8 Hz), 7.25 (d, 1 H, J = 16.1 Hz), 7.05–7.13 (m, 2 H), 6.84 (d, 1 H, J = 12.3 Hz), 5.71 (s, 1 H), 4.19 (q, 2 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.14–3.25 (m, 1 H), 2.02–2.14 (m, 2 H), 1.76–1.86 (m, 2 H), 1.60–1.70 (m, 1 H), 1.37–1.54 (m, 5 H), 1.26–1.36 (m, 3 H); ¹³C NMR (125 MHz, CDCl₃): δ 165.5 (C), 154.0 (C), 150.0 (C), 149.1 (C), 136.1 (CH), 129.5 (C), 123.1 (CH), 121.4 (CH), 111.4 (CH), 111.1 (CH), 109.7 (CH), 59.9 (CH₂), 55.94 (CH₃), 55.91 (CH₃), 44.0 (CH), 32.7 (CH₂), 26.0 (CH₂) 25.9 (CH₂), 14.5 (CH₃); ESI-HRMS *m/z*: calcd for C₂₁H₂₉O₄S⁺ [M + H]⁺: 377.1781; found 377.1778.



Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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