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PII: S0040-4020(16)31115-2

DOI: 10.1016/j.tet.2016.10.056

Reference: TET 28197

To appear in: *Tetrahedron*

Received Date: 26 July 2016

Revised Date: 17 October 2016

Accepted Date: 22 October 2016

Please cite this article as: Liu W, Zhao Y, Yi F, Chen J, Palladium(II)/copper(I)-catalyzed sequential C–H arylation and oxidative C–N bond cleavage of aryl sulfonamino acids: Efficient one-pot synthesis of primary biaryl sulfonamides, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.10.056.

## Graphic abstract

Palladium(II)/copper(I)-catalyzed sequential C-H arylation and oxidative C-N bond cleavage of aryl sulfonamino acids: efficient one-pot synthesis of primary biaryl sulfonamides

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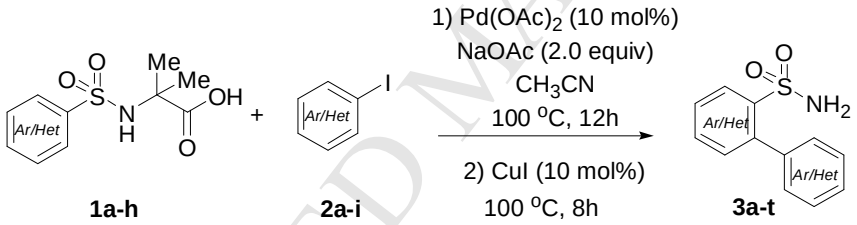

# Palladium(II)/copper(I)-catalyzed sequential C-H arylation and oxidative C-N bond cleavage of aryl sulfonamino acids: efficient one-pot synthesis of primary biaryl sulfonamides

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**Abstract:** A versatile strategy for the one-pot synthesis of primary biaryl-based sulfonamides has been developed *via* a tandem process consisting of palladium-catalyzed C-H arylation and subsequent copper-catalyzed oxidative C-N bond cleavage of aryl sulfonamino acids. Both electron-withdrawing and electron-donating functionalities can be introduced into the *ortho* positions of arenes bearing a variety of substituents. The amio acid moiety not only acts as a directing group but also as an ammonia synthetic equivalent. Importantly, the directing group was smoothly removed in the presence of catalytic CuI by using air as a sole oxidant.

**Keywords:** Palladium(II), copper(I), one-pot, C-H arylation, primary biaryl sulfonamides

## 1 Introduction

Sulfonamides are common motifs in many drugs and medicinal compounds and play a significant role in their bioactivity since the development of sulfa antibiotics in the 1930s.[1] Common drugs such as glibenclamide,[2] sultiame,[3] and COX-II inhibitors Piroxicam,[4] Ampiroxiam,[5] and Celecoxib[6] containing a sulfonyl moiety, which displays potential activity across a variety of biological targets (**Figure 1**). Recently, biaryl-based sulfonamides represent a significant class of promising bioactive compounds for drug discovery, for example, compound **MK-996** and their analogues **L-159,894** are a series of new potent angiotensin II antagonists for treating hypertension,[7] **BPBTS** represents a

structurally novel and potent sodium channel blocker.[8] Conventionally, the biaryl-based sulfonamides are synthesized *via* palladium-catalyzed Suzuki and Stille cross-coupling reactions.[9] However, these tactics rely on strategically installed metal-active groups and such starting materials require additional steps to prepare them from feedstock chemical sources.

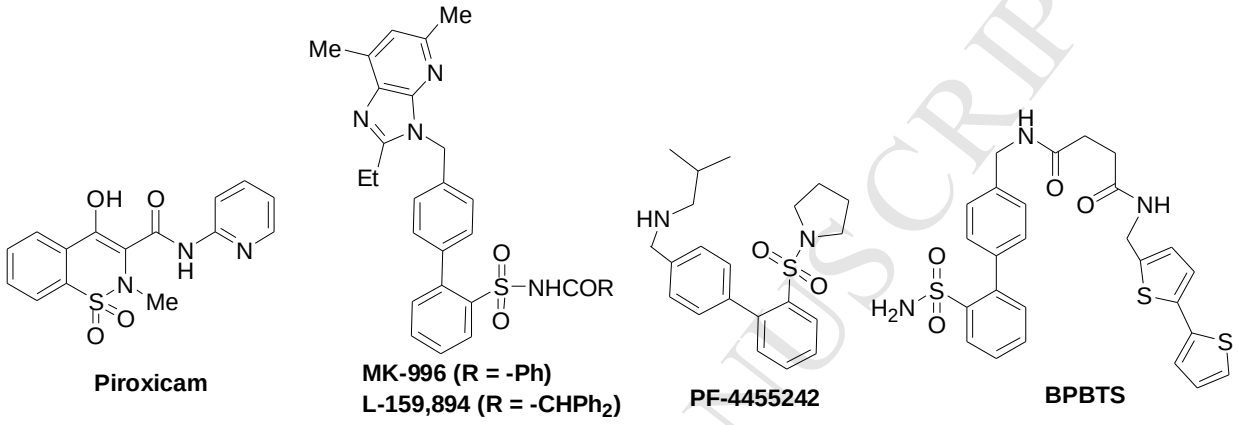



**Figure 1** Selected bioactive biaryl-based sulfonamide skeletons

Transition metal-catalyzed C-H activation/functionalization is a fascinating synthetic strategy for the construction of new chemical bonds. The past decades have witnessed considerable progress in the construction of C-C and C-hetero bonds and represent a useful method for the modification of organic molecules in terms of atom and step economy.[10] However, due to the ubiquity of C-H bonds in organic molecules, the presence of a nearby directing group (DG) is usually required in order to direct positioning of a metal catalyst so that specific C-H bond activation occurs. Based on this strategy, a variety of directing groups (such as oxygen, nitrogen and sufur containing)-assisted C-H bond activation is frequently used to realize regio- and chemoselective transformations of selected C-H bonds.[11] However, the sulfonamide-assisted C-H activation is not well explored.[12] Recently, Yu and co-workers successfully developed a kind of different Pd-catalyzed sulfonamide C-H functionalization reactions using $SO_2NHC_6F_5$ as a directing grouping.[13] More recently, Li and co-workers established a Rh(III)-catalyzed *ortho* C-H olefination of aryl sulfonamide directed by the

$SO_2NHAc$ group.[14] In spite of these significant progresses, developing a more practical traceless C-H activation-based one-pot synthetic protocol for the synthesis for primary biaryl sulfoamides is still desirable.

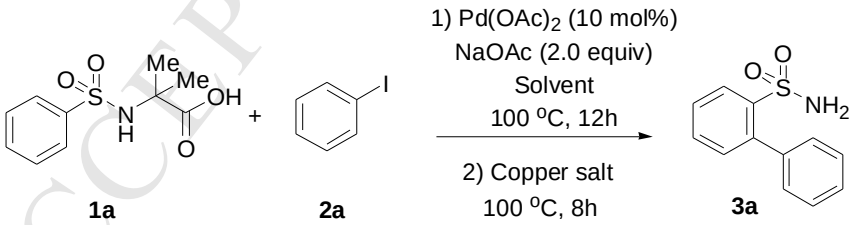
Recently, we first reported a Pd-catalyzed *mono*-selective C-H arylation of aryl sulfonamides in water by using an amino acid moiety as a bidentate directing group to afford the biaryl-based sulfonamide derivatives, and the amino acid auxiliary were removed with a 30 mol % amount of CuO as catalyst.[15] However, the C-H arylation reaction and removal of the directing group were conducted in different reaction system. In order to improve synthetic efficiency,[16] we attempt to explore a novel traceless C-H activation-based synthetic protocol for the synthesis for the primary biaryl-based sulfonamides derivatives. Herein, we report the preliminary result of an efficient one-pot palladium(II)/copper(I)-catalyzed sequential C-H arylation and oxidative C-N bond cleavage of aryl sulfonamino acids to afford primary biaryl sulfoamides.

## 2. Results and discussion

Initially, the N-arylsulfonyl amino acids **1a**, and aryl iodide **2a** was used to optimize the reaction conditions (Table 1). We began our investigation by screening various solvents and copper sources. Expectably, the C-H arylation reaction can smoothly take place in the presence of $Pd(OAc)_2$/NaOAc and using $H_2O$ as the solvent. However, only trace amount of primary biaryl sulfonamide **3a** were detected when 2.0 equiv of CuO was added (Table, entry 1). When DMSO was used as the solvent, the yield of primary biaryl sulfonamide **2a** increased to 48% (Table, entry 2). Then, various copper salts were screened; we found that $CuCl_2$ and $CuBr_2$ only deliver the moderate yields (Table 1, entries 3-4). Interestingly, CuI can afford the desired product in 57% yield (Table, entry 5). Other copper salts such as $Cu(OAc)_2$, $CuSO_4$ were also studied, but gave poor results (Table 1, entries 6-7). Next, a multitude of solvents were screened in the presence of CuI, DMF provided the desired product in

59% (Table 1, entry 8). Remarkably, the use of $CH_3CN$ dramatically improved the catalytic efficiency, and 87% yield was obtained (Table 1, entry 9). However, the yield of **2a** decreased, affording **2a** in 41%, 44% and 47% yields, respectively using EtOAC, DCE and Dioxane as the solvent (Table 1, entries 10-12). We found that protic solvent such as AcOH were inferior and only 29% yield was obtained (Table 1, entry 13). Whereas, xylene and dioxane were ineffective and only trace amount of the product were obtained (Table 1, entries 14, 15). It was worth mentioning that the first C-H arylation performed well in the above mentioned reactions. Finally, results of solvents and copper salts screening indicated that $CH_3CN$ and CuI was still the best choice, respectively (Table 1, entry 9). The amount of CuI was also screened; we found that 0.1 equiv of CuI were sufficient, affording the desired product in 86% yield under air (Table 1, entry 18). However, a drop in yield was observed when the amount of CuI was reduced to 0.05 equiv (Table 1, entry 19). Therefore, the optimized conditions employed CuI (0.1 equiv) as the catalyst in $CH_3CN$ by using air as a sole oxidant (Table 1, entry 9).

**Table 1.** Optimization of one-pot palladium(II)/copper(I)-catalyzed sequential C-H arylation and oxidative C-N bond cleavage of aryl sulfonamino acids[a]




| Entry | Solvent | Additive | Yield[b] (%) |
|---|---|---|---|
| 1 | $H_2O$ | CuO | trace |
| 2 | DMSO | CuO | 48 |
| 3 | DMSO | $CuCl_2$ | 35 |

| | | | |
|---|---|---|---|
| 4 | DMSO | $CuBr_2$ | 46 |
| 5 | DMSO | CuI | 57 |
| 6 | DMSO | $Cu(OAc)_2$ | 42 |
| 7 | DMSO | $CuSO_4$ | 44 |
| 8 | DMF | CuI | 59 |
| 9 | MeCN | CuI | 87 |
| 10 | EtOAC | CuI | 41 |
| 11 | DCE | CuI | 44 |
| 12 | Dioxane | CuI | 47 |
| 13 | AcOH | CuI | 29 |
| 14 | Xylene | CuI | trace |
| 15 | Hexane | CuI | trace |
| 16[c] | MeCN | CuI | 87 |
| 17[d] | MeCN | CuI | 87 |
| 18[e] | MeCN | CuI | 86 |
| 19[f] | MeCN | CuI | 62 |

[a] Reaction conditions: step 1: **1a** (0.25 mmol), **2a** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), NaOAc (0.5 mmol), 100 ℃, solvent (0.5 mL), 12h; step 2: copper source (2.0 equiv), 100 ℃, 8h.

[b] Isolated yield.

[c] 1.0 equiv of CuI.

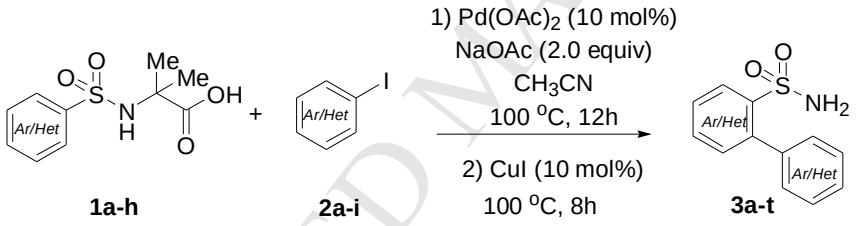
[d] 0.5 equiv of CuI.

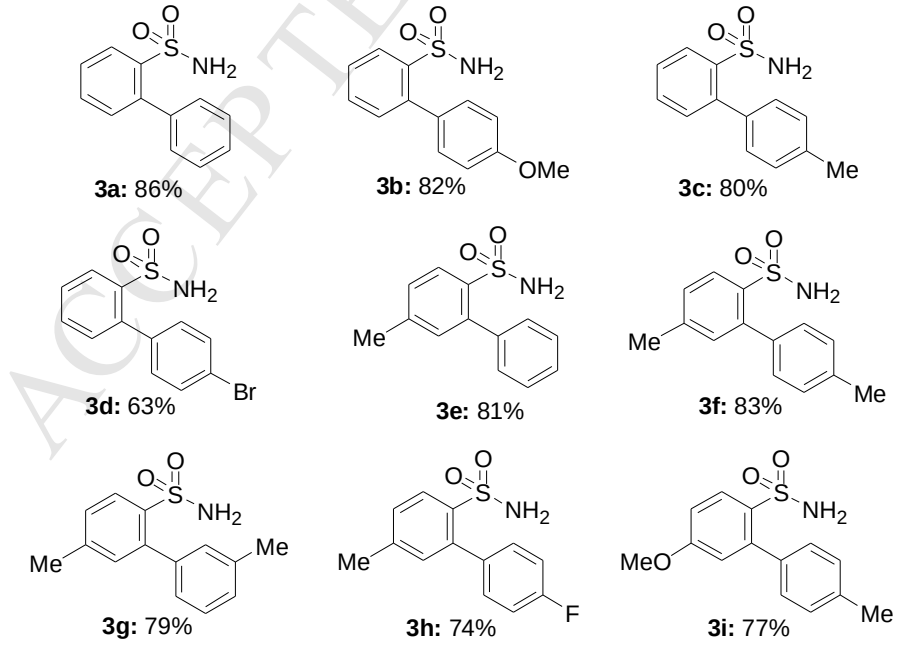
[e] 0.1 equiv of CuI.

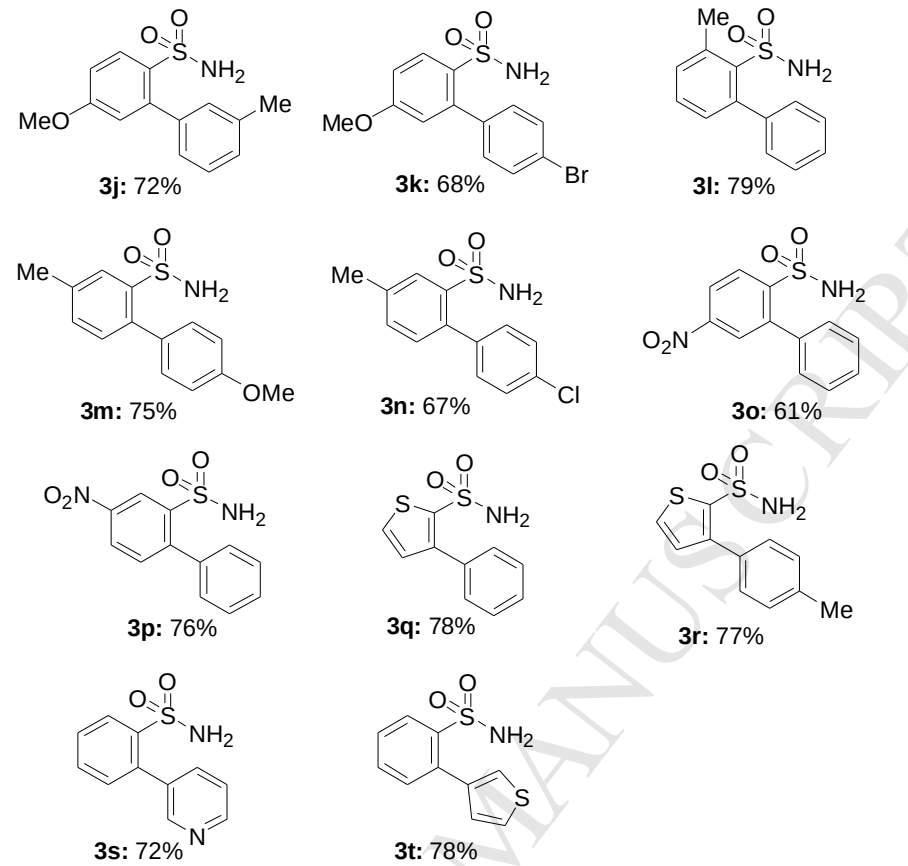
[f] 0.05 equiv of CuI.

Having established the optimal conditions, we next examined the substrate scope of N-arylsulfonyl amino acids **1**, and aryl iodide **2** (Table 2). Firstly, the substrate scope of aryl iodides was examined. We found that the arenes of aryl iodides **2** with both electron-donating and electron-withdrawing groups could smoothly react to afford the desired products **3b-d** in good to high yields. For example, the substrates containing *p*-MeO, *p*-Me, and *p*-Br gave the corresponding primary biaryl sulfonamides **3b-d** in 82%, 80%, and 63% yields, respectively. Then, the reactions of N-arylsulfonyl amino acids **1** containing different groups on arenes were investigated, a broad range of N-arylsulfonyl amino acids **1** can participate in this reaction efficiently. For example, the substrates **1** bearing *p*-Me, and *p*-MeO groups in aromatic ring afforded the corresponding products in high yields

**Table 2** Substrate scope of N-arylsulfonyl amino acids and aryl iodides[a,b]



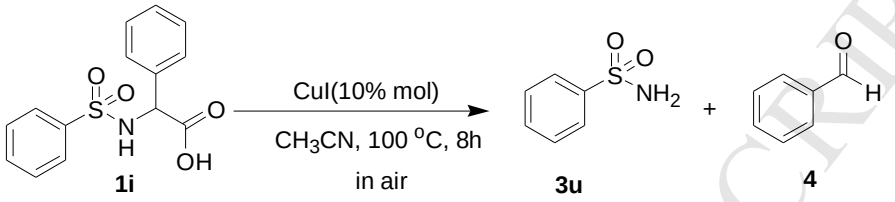



[a] Reaction conditions: step 1: **1** (0.25 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), NaOAc (0.5 mmol), 100 °C, $CH_3CN$ (0.5 mL), 12h; step 2: CuI (0.1 equiv), 100 °C, 8h.

[b] Isolated yield.

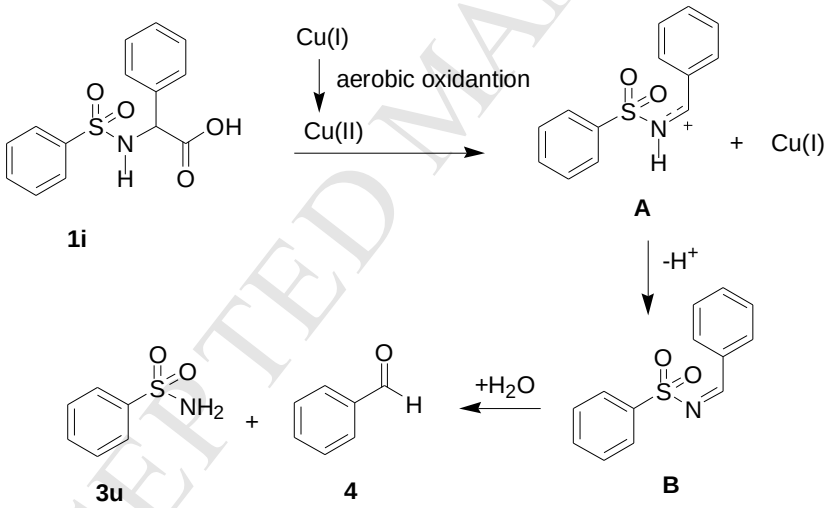
(products **3e-3k**). As for different substitution patterns of arenes of substrates **1**, *ortho*- and *meta*-substituted substrates all worked well to give the desired products. For example, substrate **1d** bearing an *ortho*-substituent such as Me proceeded well, and offered 79% isolated yield (product **3l**). Substrate **1e** with a MeO group in *meta*-position reacted smoothly with various aryl iodides and gave the corresponding products **3m**, and **3n** in 75%, and 67% yields, respectively. Substrates **1** containing an electron-withdrawing group such as $NO_2$ in either *meta*- or *para*-positon were less efficient in present catalysis system. Fortunately, satisfactory yields were obtained when AgOAc (2.0 equiv) was used in place of NaOAc (products **3o, 3p**). We were delighted to find that heterocyclic substrate **1h**

also react with various aryl iodides and afford the products **3q**, and **3r** in good yields. The reaction also preceded well with heterocyclic coupling partners, for example, 3-iodopyridine **2h** and 3-iodothiophene **2i** gave the desired products **3s**, and **3t** in good yields, respectively. Unfortunately, an attempt to employ the *ortho*-substituted aryl iodides failed to yield the expected product.




**Scheme 1**. Preliminary mechanistic studies

To aid understanding of the reaction mechanism, the substrate **1i** was carried out in the optimal reactions; the desired product **3u** and benzaldehyde **4** could be obtained in 97% yield (**Scheme 1**).




**Scheme 2.** Plausible reaction mechanism

On the basis of the results obtained and previous reports, a plausible reaction mechanism is proposed as shown in **Scheme 2**. Initially, Cu(I) was oxidized into Cu(II) intermediate by air, and then the **1i** underwent the Cu-catalyzed oxidative decarbonylation reactions to generate the corresponding iminium intermediate **A** and simultaneously release $CO_2$. The imine intermediate **B** is delivered after deprotonation. Finally, the imine **B** was hydrolyzed to afford the primary aryl sulfonamide **3u** and

benzaldehyde **4**. Lastly, the Cu(I) generated in the previous step could undergo further oxidation with air, regenerating Cu(II) to resume the catalytic cycle.

## 3. Conclusion

In conclusion, we have developed a straightforward route to the synthesis of primary biaryl sulfonamides via palladium (II)/copper(I)-catalyzed sequential C-H arylation and oxidative C-N bond cleavage of aryl sulfonamino acids. This reaction utilized N-sulfonyl amino acid as a directing group and showed excellent regio-selectivity and high reaction activity. Furthermore, the amino acid moiety could be sequentially removed in one pot reaction by adding CuI as the catalyst and air as a sole oxidant. The realization of such an approach enriches the methods for the preparation of the primary biaryl sulfonamides. Further investigations to study the mechanism of this reaction and transition-metal-catalyzed C–H activation/functionalization of the analogous substrates are in progress in our laboratory.

## 4. Experimental section

### 4.1. General

All reactions were performed under air, $Pd(OAc)_2$ was purchased from Acros. AgOAc, AgOTf, and $Ag_2CO_3$ were purchased from Alfa Aesar. Other reagents were commercially available and were used directly without further purification unless otherwise specified. All the solvents were directly used unless otherwise specified. $^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 M Hz) spectra were recorded on an AVANCE III Bruker 400 M Hz spectrometer. Chemical shifts are reported in (ppm) down field from tetramethylsilane with reference to solvent signals [$^1$H NMR: *d*-DMSO (2.50); $^{13}$C NMR: *d*-DMSO (40.00)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak, coupling constant (Hz), integration and assignment. Flash column

chromatography was performed over silica gel (230-400 mesh) purchased from Qindao Puke Co., China. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. High-resolution mass spectral (HRMS) data were recorded on Bruker APEX IV Fourier transform ion cyclotron resonance mass spectrometer using electrospray ionization (ESI).

**4.1.1 General Procedure for Palladium(II)/Copper(I)-Catalyzed Sequential C-H Arylation and Oxidative C-N Bond Cleavage of Aryl Sulfonamino Acids**

A mixture of aryl sulfonamide **1** (0.25 mmol), aryl iodide **2** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), NaOAc (0.5 mmol), and $CH_3CN$ (0.5 mL) was placed in a 25 mL Schlenk tube with a rubber plug. The tube was heated at 100 $^oC$ for 12h. At this point, the reaction mixture was cooled to room temperature, and the CuI (0.025 mmol) was added. The reaction mixture was reheated to 100 ℃ for an additional 8h, and the product was extracted with EtOAc (3×5 mL). Combined organic layers were dried over $Na_2SO_4$, concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 5/1) to afford the desired product **3**.

**Acknowledgements**

We are grateful for the financial support of the Science and Technology Planning Project of Jiangxi Province, China (20142BAB203007).

**Supplementary data**

Compounds **3** characterization data, copies of $^1H$ and $^{13}C$ spectra.

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