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# CuI/Oxalic Diamide-Catalyzed Cross-Coupling of Thiols with Aryl Bromides and Aryl Chlorides

**Chia-Wei Chen,[a] Yi-Ling Chen,[a] Daggula Mallikarjuna Reddy,[a] Kai Du,[a] Chao-En Li,[a] Bo-Hao Shih,[a] Yung-Jing Xue,[a] and Chin-Fa Lee*[a]**

**Abstract:** We report a general copper-catalyzed cross-coupling of thiols with aryl bromides and aryl chlorides by using *N*-aryl-*N*’-alkyl oxalic diamide (**L3**) or *N*,*N*’-dialkyl oxalic diamide (**L5**) as the ligands. Remarkably, this is the first copper-catalyzed coupling of thiols with unactivated aryl chlorides. Furthermore, this system features broad substrate scope and good tolerance of functional groups. Importantly, the oxalic diamides are stable and can be prepared easily from commerciall available cheap starting materials.

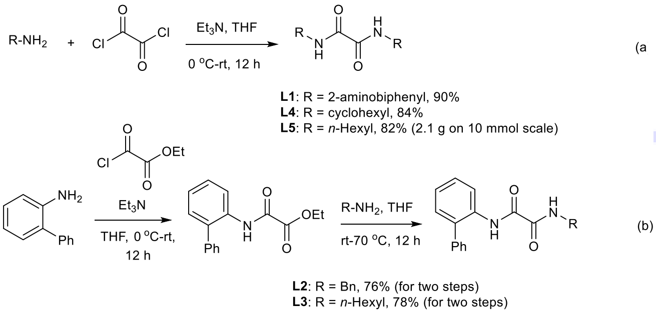
**Keywords:** oxalic diamide • ary bromide • aryl chloride • thiol • thioethe

## Introduction

Thioethers are an important class of motifs present in numerous bioactive molecules, organic synthesis and materials science.[1-4] Therefore, the synthesis of thioethers has received considerable attention during the past decades.[1-14] Transition-metal-catalyzed coupling reaction of aryl halides with thiols is a powerful strategy for the preparation of thioethers.[5-14] Migita and co-workers first reported the cross-coupling reaction of aryl halides and thiols by using $Pd(PPh_3)_4$ as a catalyst.[6a] Many nice works have later been achieved under palladium catalysis.[6b,6c,7] Catalytic systems based on other transition metals such as nickel[8], cobalt,[9] iron,[10] rhodium,[11] gold,[12] manganese[13] and iridium[14] have also been introduced for C-S bond cross-coupling reaction. Most of these catalytic systems however suffer from several limitations, such as high cost and high toxicity of catalysts and ligands. Although aryl chloride is the most attractive aryl halide for metal-catalyzed cross-coupling reactions, however, aryl chloride is less reactive than aryl bromides and iodides.[15] Palladium is the most prominent catalyst for the coupling of thiols with aryl chlorides.[7]

Copper salt has commonly applied for C-S cross-coupling reactions because of its low cost.[16-18] Aryl iodides,[16] aryl bromides[17] and activated aryl chlorides[18] are well-known in this area. Unactivated aryl chloride has not been well developed for the coupling with thiols through copper catalysis. Therefore, the development of a general coppe catalyzed coupling of thiols with aryl chlorides is highly desirable.

Recently, Ma and co-workers reported the copper-catalyze amination[19,20] and etherification[21,22] of aryl chlorides by using oxali diamide as ligand. Oxalic diamides are stable, and can be easily prepare from cheap commercially available oxalyl chloride [for symmetrica Scheme1, (a)] or ethylchlorooxalate [for unsymmetrical, Scheme 1, (b with amines .[19,22] As part of our ongoing interest in C-S bond formin reaction,[11b,13,16f-j,23] we herein report a general copper-catalyzed cross coupling reaction of thiols with aryl bromides and aryl chlorides Interestingly, *N*,*N*’-diaryl oxalamide is less reactive than *N*,*N*’-dialky oxalic diamide and *N*-aryl-*N*’-benzyl oxalic diamide for coupling wit aryl bromides. Surprisingly, *N*,*N*’-dialkyl oxalic diamide (**L5**) is powerful ligand for copper-catalyzed coupling of thiols with ary chlorides. To the best of our knowledge, this is the first general metho for copper-catalyzed thioetherification of aryl chlorides.



Scheme 1. Synthesis of oxalic diamides.

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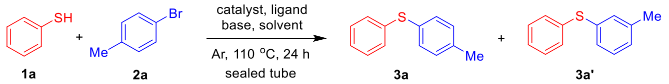
## Results and Discussion

Initially, thiophenol (**1a**) and 4-bromotoluene (**2a**) were chosen as model substrates to optimize the reaction conditions. When *N,N'*-bis(2-biphenyl) oxalic diamide, **L1** was used as a ligand, the target was obtained in 17% yield (Table 1, entry 1). When *N*-aryl-*N*'-benzyl oxalic diamide, **L2** was employed as a ligand, the desired product was afforded in 94% yield (Table 1, entry 2). Encouraged by this result, we then examined other oxalic diamides (**L3**-**L5**, Table 1, entries 3-5). Interestingly, *n*-hexyl-substituted oxalic diamides **L3** and **L5** showed excellent reactivity for this coupling reaction (Table 1, entries 3 and 5, respectively). When hexyl was replaced by bulkier cyclohexyl ligand (**L4**), the yield of the product was dropped to 49% (Table 1, entry 4). Replacing CuI with other catalysts such as $Cu_2O$, $CuCl_2$, CuBr and CuCl gave little inferior results compared with CuI (Table 1, entries 6-9). When DMSO, DMF and NMP were used as solvents, products **3a** and **3a'** in different ratio were detected (Table 1, entries 10-12), the formation of **3a'** suggests a benzyne intermediate was involved.[16h] We next used different bases for this system, bases such as KOMe, $Cs_2CO_3$, $K_3PO_4$ and NaO*t*Bu gave the product **3a** in lower yields (Table 1, entries 13-16). A lower yield was obtained when the loading of ligand was decreased to 5 mol% (Table 1, entry 17). Trace amount of product was detected when the reaction was carried out in the absence of ligand (Table 1, entry 18). Shorter reaction times diminished the product yield to 78% yield (Table 1, entry 19).

Scheme 2 summaries the copper-catalyzed C-S coupling reaction. A variety of *para*-substituted aryl bromides bearing either electron-donating or electron-withdrawing groups were coupled with thiophenol to afford the coupling products **3b**-**3g** in good to excellent yields. Aryl bromides with *ortho*- and *meta*-substituents were also worked to provide thioethers **3h**-**3j** in good yields. Importantly, **3h** was obtained as the sole product in 95% yield by using **L5** as a ligand, however, the regio-isomer **3h'** (through benzyne) was observed when **L3** was used as a ligand. When 1-naphthyl bromide was used as a coupling partner, **3k** was obtained in 74% yield. Aryl bromides with bulky groups such as *tert*-butyl at 3- and 5-positions were tolerated and afforded the thioethers **3j** and **3l** in good yields. Heterocycles such as 3-bromopyridine and 3-bromothiophene were also successfully coupled with thiophenol, gave the corresponding thioethers (**3m** and **3n**) in excellent yields.

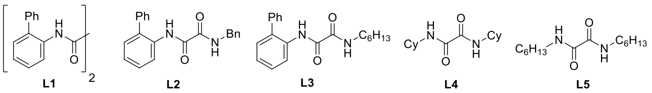
Since the performance of **L5** is better than **L3** in Scheme 2, we decided to use **L5** as a ligand to survey the coupling reaction of other aryl thiols with aryl bromides, the results are summarized in Scheme 3. A variety of *para*-substituted aryl thiols consisting of either electron-donating or electron-withdrawing groups were worked smoothly with aryl bromides to afford the targets **3a**, **3e**, **3f** and **3o** in 56-95% yields. Sterically hindered aryl thiols such as 2-methylthiophenol and 2-chlorothiophenol were successfully coupled with bromobenzene and delivered the desired products **3i** and **3p** in high yields. Remarkably, unprotected 2-aminothiophenol was reacted with bromobenzene to provide **3q** in 91% yield. 1-naphthylthiol was coupled with bromobenzene to obtain **3k** in almost quantitative yield. Heterocycles such as pyridine-2-thiol was coupled with bromobenzene to give thioether (**3r**) in 92% yield. Aryl bromides with electron-rich and electron-deficient were also conducted with various aryl thiols to afford the corresponding thioethers **3s**-**3u** in good yields. In general, alkyl thiol is less reactive than aryl thiol for copper-catalyzed C-S bond formation.[23b] A 10% of product **5a** was isolated when 2-methyl-1-propanethiol reacted with bromobenzene at 110 ºC. To our delight, a 74% yield was achieved when the reaction was performed at 135 °C employing 2.5 equiv of base. Several of alkyl thiols including linear, cyclic and branched thiols were reacted with aryl bromides to give the thioethers in good to excellent yields (Scheme 4).

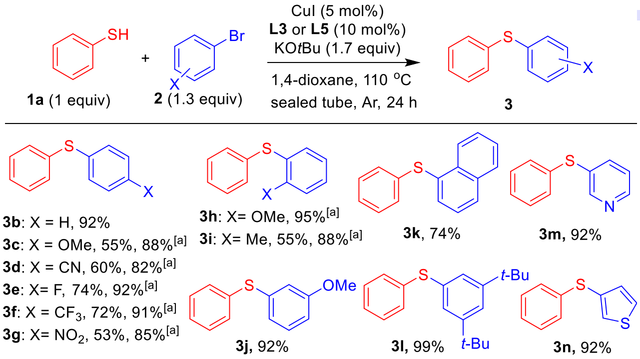
Table 1. Reaction conditions optimization.[a,b]



| Entry | Catalyst | Ligand | Base | Solvent | Yield of **3a** |
|---|---|---|---|---|---|
| 1 | CuI | L1 | KO*t*Bu | 1,4-dioxane | 17 |
| 2 | CuI | L2 | KO*t*Bu | 1,4-dioxane | 94 |
| 3 | CuI | L3 | KO*t*Bu | 1,4-dioxane | 99 |
| 4 | CuI | L4 | KO*t*Bu | 1,4-dioxane | 49 |
| 5 | CuI | L5 | KO*t*Bu | 1,4-dioxane | 98 |
| 6 | $Cu_2O$ | L3 | KO*t*Bu | 1,4-dioxane | 96 |
| 7 | $CuCl_2$ | L3 | KO*t*Bu | 1,4-dioxane | 95 |
| 8 | CuBr | L3 | KO*t*Bu | 1,4-dioxane | 95 |
| 9 | CuCl | L3 | KO*t*Bu | 1,4-dioxane | 93 |
| 10 | CuI | L3 | KO*t*Bu | DMSO | 99[c] |
| 11 | CuI | L3 | KO*t*Bu | DMF | 95[d] |
| 12 | CuI | L3 | KO*t*Bu | NMP | 41[e] |
| 13 | CuI | L3 | KOMe | 1,4-dioxane | 45 |
| 14 | CuI | L3 | $Cs_2CO_3$ | 1,4-dioxane | trace |
| 15 | CuI | L3 | $K_3PO_4$ | 1,4-dioxane | 12 |
| 16 | CuI | L3 | NaO*t*Bu | 1,4-dioxane | 20 |
| 17 | CuI | L3 | KO*t*Bu | 1,4-dioxane | 72[f] |
| 18 | CuI | - | KO*t*Bu | 1,4-dioxane | trace |
| 19 | CuI | L3 | KO*t*Bu | 1,4-dioxane | 78[g] |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.3 equiv), catalyst (5 mol%), ligand (1 mol%), base (1.7 equiv) and solvent (1.5 mL) under atmosphere of argon at 110 ºC f 24 h. [b] Isolated yields. [c] Ratio of **3a** and **3a'** is 1:1. [d] Ratio of **3a** and **3a'** is 8:2. [ Ratio of **3a** and **3a'** is 8:2. [f] 5 mol% of **L3** used. [g] Reaction run for 12 h. 1,4-Dioxa = 1,4-dioxacyclohexane; DMSO = dimethyl sulfoxide; DMF = *N*,*N*-dimethylformamid NMP = *N*-methyl-2-pyrrolidone.





Scheme 2. Scope of aryl bromides to couple with thiophenol. [a] Using **L5** as ligan Yields of the isolated products are given. See the Supporting Information for details.

We next turned our attention to the challenging cross-couplin reaction of aryl chlorides with thiols. 4-Chlorotoluene (**6a**) and thiophen (**1a**) were selected as the substrates to study the optimized reaction conditions. As shown in Table 2, only 15% of product was observed (Table 2, entry 1) when the reaction was performed under the best conditions used for aryl bromides. To our delight, when reaction temperatures increased to 120 °C and 135 °C, as a result, yields of the product **3a** were improved to 48% and 67% (Table 2, entries 2 and 3, respectively). After screening ligands (entries 4-7) and bases (entries 8-10), **L5** and KO*t*Bu were found to be the best ligand and base. Increased amount of KO*t*Bu to 2.5 equiv, resulted the formation of **3a** and **3a'** in

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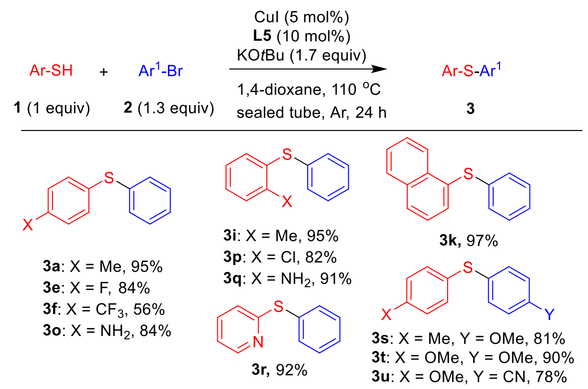
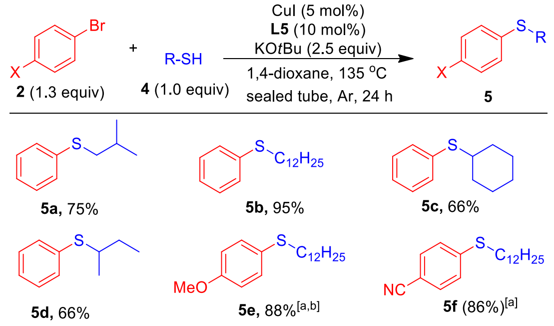
65:35 ratio in 91% yield. (Table 2, entry 11). To our delight, **3a’** was inhibited when the reaction was performed in toluene (Table 2, entry 12).

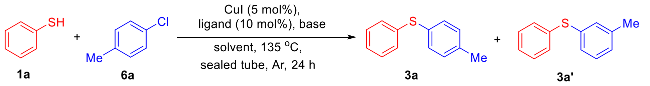


Scheme 3. Scope of aryl bromides with thiophenols. Yields of the isolated products are given. See the Supporting Information for details.



Scheme 4. Scope of aryl bromides with alkyl thiols. Yields of the isolated products are given. [a] At 110 °C. [b] Ratio of 5e and 5e’ is 9:1. See the Supporting Information for details.

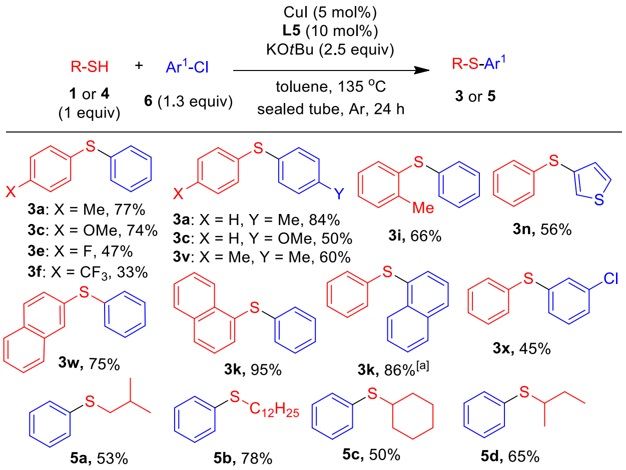
Table 2. Reaction conditions optimization.[a,b]



| Entry | Ligand | Base (equiv.) | Solvent | Yield of **3a** |
|---|---|---|---|---|
| 1 | **L5** | KO*t*Bu (1.7) | 1,4-dioxane | 15[c] |
| 2 | **L5** | KO*t*Bu (1.7) | 1,4-dioxane | 48[d] |
| 3 | **L5** | KO*t*Bu (1.7) | 1,4-dioxane | 67 |
| 4 | **L1** | KO*t*Bu (1.7) | 1,4-dioxane | NR |
| 5 | **L2** | KO*t*Bu (1.7) | 1,4-dioxane | NR |
| 6 | **L3** | KO*t*Bu (1.7) | 1,4-dioxane | 15 |
| 7 | **L4** | KO*t*Bu (1.7) | 1,4-dioxane | NR |
| 8 | **L5** | LiO*t*Bu (1.7) | 1,4-dioxane | NR |
| 9 | **L5** | NaO*t*Bu (1.7) | 1,4-dioxane | trace |
| 10 | **L5** | $Cs_2CO_3$ (1.7) | 1,4-dioxane | NR |
| 11 | **L5** | KO*t*Bu (2.5) | 1,4-dioxane | 91[e] |
| 12 | **L5** | KO*t*Bu (2.5) | toluene | 84 |

[a] Reaction conditions: 1a (1.0 mmol), 6a (1.3 equiv), CuI (5 mol%), ligand (10 mol%), base and solvent (1.5 mL) under atmosphere of argon at 135 °C for 24 h. [b] Isolated yields. [c] Reaction performed at 110 °C. [d] Reaction performed at 120 °C. [e] Ratio of 3a and 3a’ is 65:35.

With the optimized conditions established, we then explored the substrate scope of the reaction (Scheme 5). Functional groups such as fluoro, trifluoromethyl, chloro and thiophene are all suitable as coupling partners. When electron-rich thiols were conducted with aryl chlorides, the corresponding thioethers were delivered in good yields, whereas aryl chlorides coupled with electron-deficient thiols such as 4-fluoro thiophenol and 4-trifluoromethyl thiophenol, the products were obtained in moderate yields. Not only aryl thiols but also alkyl thiols successfully coupled with aryl chlorides and gave the products (**5**) in good yields.



Scheme 5. Scope of aryl chlorides with thiols. Yields of the isolated products are give [a] Ratio of 3k and 3w is 8:2. See the Supporting Information for details.

## Conclusion

In conclusion, we have developed a general copper/oxalic diamid catalytic system for the coupling reaction of thiols with aryl bromides an aryl chlorides. There are several advantages to this system: (1) oxali diamides are stable, and can be easily prepared from cheap startin materials; (2) Functional groups including fluoro, trifluorometh unprotected amine, chloro and heterocycles are all tolerated by th reaction conditions employed; (3) sterically substrates were also prove to be good coupling partners. Studies on the mechanism and applicatio of this catalytic system are in progress.

## Experimental

**General information:** all commercial chemicals were used as received excep where noted. All Cu-catalyzed experiments were performed under a atmosphere of argon using standard sealed tube unless otherwise stated. Flas chromatography was performed on Merck silica gel 60 (230–400 mesh). NM spectra were recorded on a Varian Unity Inova-600 or a Varian Mercury-40 instrument using $CDCl_3$ as a solvent. Chemical shifts are reported in parts pe million (ppm) and referenced to the residual solvent resonance. Couplin constant (J) are reported in hertz (Hz). Standard abbreviations indicatin multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd double of doublet, q = quartet, m = multiplet, b = broad. Melting points (M.P were determined using a Büchi 535 apparatus and are reported uncorrecte GC-MS analyses were performed on a GC-MS analysis on Agile Technologies 5977A GC equipped with Agilent 7890B MS. High-resolutio mass spectra were carried out on a Jeol JMS-HX 110 spectrometer by th services at the National Chung Hsing University. Ligands **L1-L3** and **L5** we prepared following the literature procedure.[22,24]

**Analysis:** NMR spectra were recorded on a Varian Unity Inova-600 or Varian Mercury-400 instrument using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Coupling constant (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, q = quartet, quin = quintet, m = multiplet, b = broad. GC-MS analysis were performed on a Agilent Technologies 5977A GC equipped with Agilent 7890B MS. High-resolution mass spectra were carried out on a Jeol JMS-HX 110 spectrometer by the services at the National Chung Hsing University.

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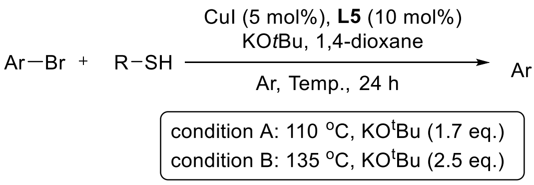
**General procedure for Table 1**

A 5 mL sealable tube equipped with a Teflon-coated magnetic stir bar was charged with catalyst (5 mol%), ligand (10 mol%) and base (1.7 equiv). The tube was then evacuated and backfilled with argon (this sequence was repeated three times), and 4-bromotoluene (0.160 mL, 1.3 mmol), thiophenol (0.102 mL, 1.0 mmol) and solvent (1.5 mL ) were then added into the tube via syringe. The reaction mixture was stirred at 110 °C in an oil bath for 24 h. After cooling to room temperature, the crude product was diluted with ethyl acetate (~40 mL), and filtered through silica gel pad. Then the filtrate was concentrated *in vacuum*. The residue was purified by flash chromatography ($SiO_2$, hexane) to yield **3a**.

**The representative example of Table 1**

**Phenyl(*p*-tolyl)sulfane (3a)**:[25] Following the condition A, using 4-bromotoluene (0.160 mL, 1.3 mmol), CuI (9.5 mg), **L5** (25.4 mg), KO*t*Bu (0.186g, 1.7 mmol), thiophenol (0.102 mL, 1.0 mmol) and dioxane (1.5 mL), then purified by column chromatography ($SiO_2$, hexane) to provide **3a** as a yellow liquid (196 mg, 98% yield). $^1H$ NMR (400 MHz, CDCl3): δ 2.28 (s, 3H), 7.06-7.13 (m, 3H), 7.17-7.28 (m, 6H); $^{13}C$ NMR (100 MHz, CDCl3): δ 21.0, 126.2, 128.9, 129.6, 129.9, 131.2, 132.2, 137.0, 137.4.

**General procedure for Table 2-4 and Table 6:**



**Condition A:** A 5 mL sealable tube equipped with a Teflon-coated magnetic stir bar was charged with CuI (9.5 mg), **L5** (25.4 mg), (hetero)aryl halide (if solid) (1.3 mmol), thiolphenol (if solid) (1.0 mmol) and KO*t*Bu (1.7 mmol for condition A, 2.5 mmol for condition B). The tube was then evacuated and backfilled with argon (this sequence was repeated three times), and (hetero)aryl halide (if liquid) (1.3 mmol), thiolphenol (if liquid) (1.0 mmol) and solvent (1.5 mL dioxane ) were then added into the tube via syringe. The reaction mixture was stirred at 110 °C (condition A) or 135 °C (condition B) in an oil bath for 24 h. After cooling to room temperature, the crude product was diluted with ethyl acetate (~40 mL), and filtered through silica gel pad. Then the filtrate was concentrated *in vacuum*. The residue was purified by flash chromatography (eluting with ethyl acetate/hexane) to afford the corresponding thioethers.

**Condition C (for all aryl chlorides):** A 5 mL sealable tube equipped with a teflon-coated magnetic stir bar was charged with CuI (9.5 mg), **L5** (25.4 mg), (hetero)aryl halide (if solid) (1.3 mmol), thiolphenol (if solid) (1.0 mmol) and KO*t*Bu (2.5 mmol). The tube was then evacuated and backfilled with argon (this sequence was repeated three times), and (hetero) aryl halide (if liquid) (1.3 mmol), thiolphenol (if liquid) (1.0 mmol) and toluene (1.5 mL) were then added into the tube via syringe. The reaction mixture was stirred at 135 °C in an oil bath for 24 h. After cooling to room temperature, the crude product was diluted with ethyl acetate (~40 mL), and filtered through silica gel pad. Then the filtrate was concentrated *in vacuum*. The resulting residue was purified by flash chromatography (eluting with ethyl acetate/hexane) to afford the corresponding thioethers.

## Acknowledgements

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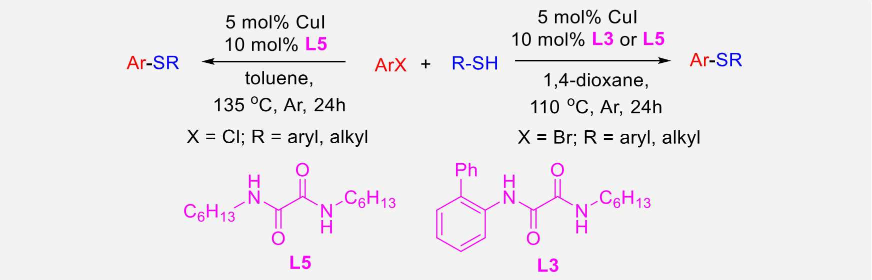
## Cross-Coupling Reactions

*Chia-Wei Chen, Yi-Ling Chen, Daggula Mallikarjuna Reddy, Kai Du, Chao-En Li, Bo-Hao Shih, Yung-Jing Xue and Chin-Fa Lee**

**CuI/Oxalic Diamide Catalyzed Cross-Coupling of Thiols with Aryl bromides and Aryl Chlorides**



We report a general copper-catalyzed cross-coupling of thiols with aryl bromides and aryl chlorides by using *N*-aryl-*N'*-alkyl oxalic diamide (**L3**) or *N,N'*-dialkyl oxalic diamide (**L5**) as the ligands. Both aryl- and alkyl thiols can be coupled with unactivated aryl bromides and unactivated aryl chlorides to give the desired products in good yields. Furthermore, this system features broad substrate scope and good tolerance of functional groups. Importantly, the oxalic diamides are stable and can be prepared easily from commercially available cheap starting materials.

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# Supporting Information

## CuI/Oxalic Diamide-Catalyzed Cross-Coupling of Thiols with Aryl Bromides and Aryl Chlorides

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## NMR spectra for new compounds

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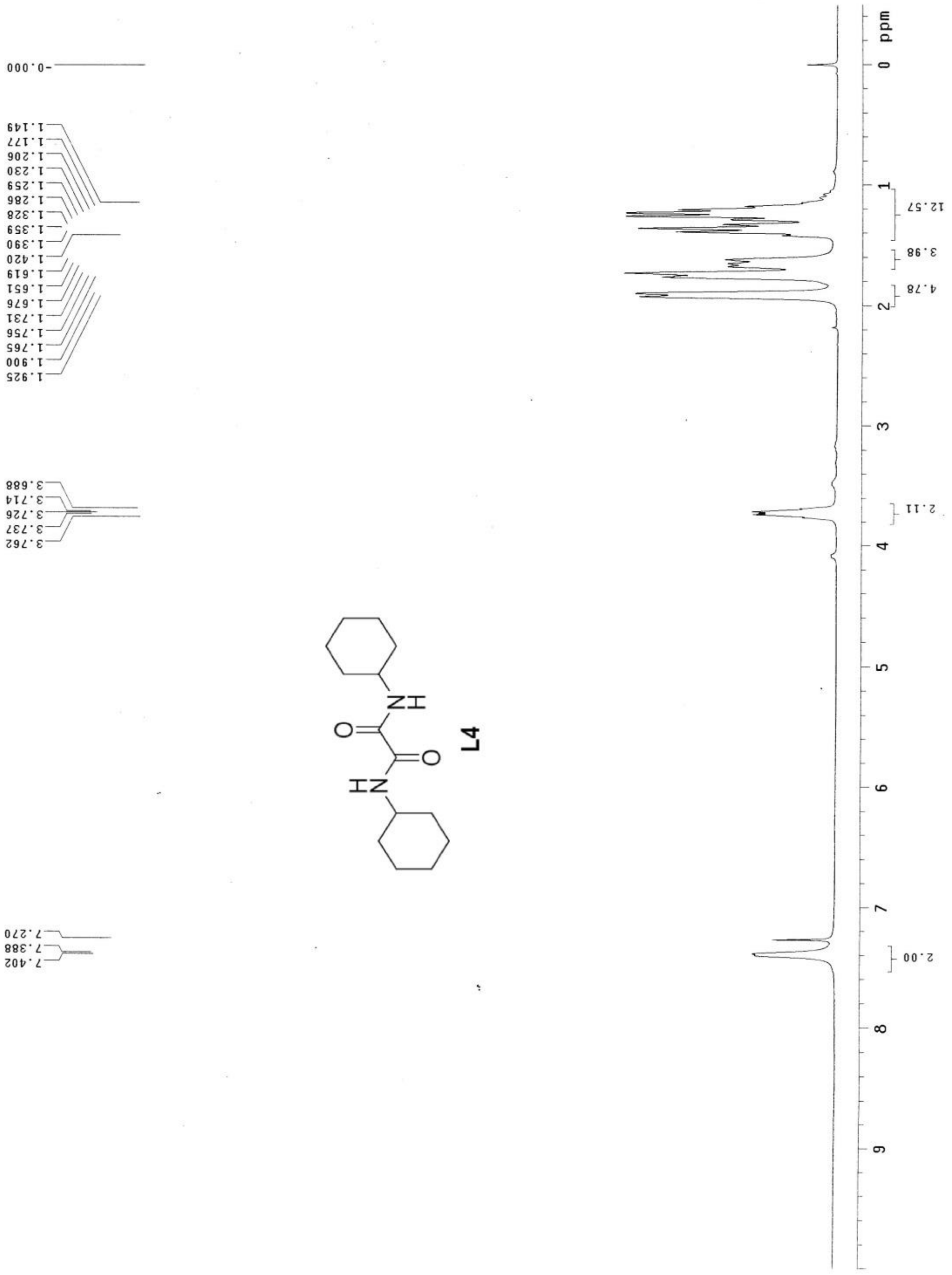

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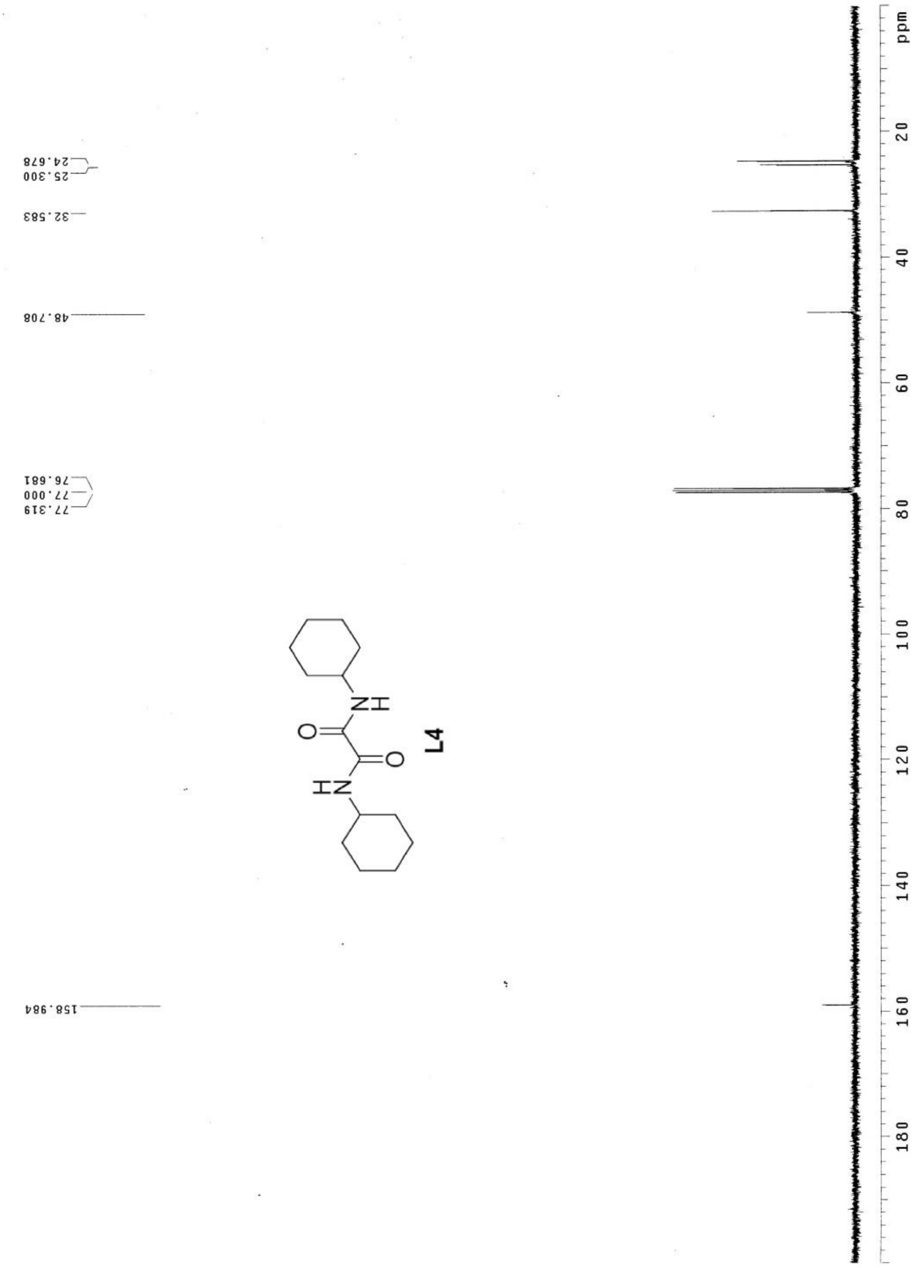

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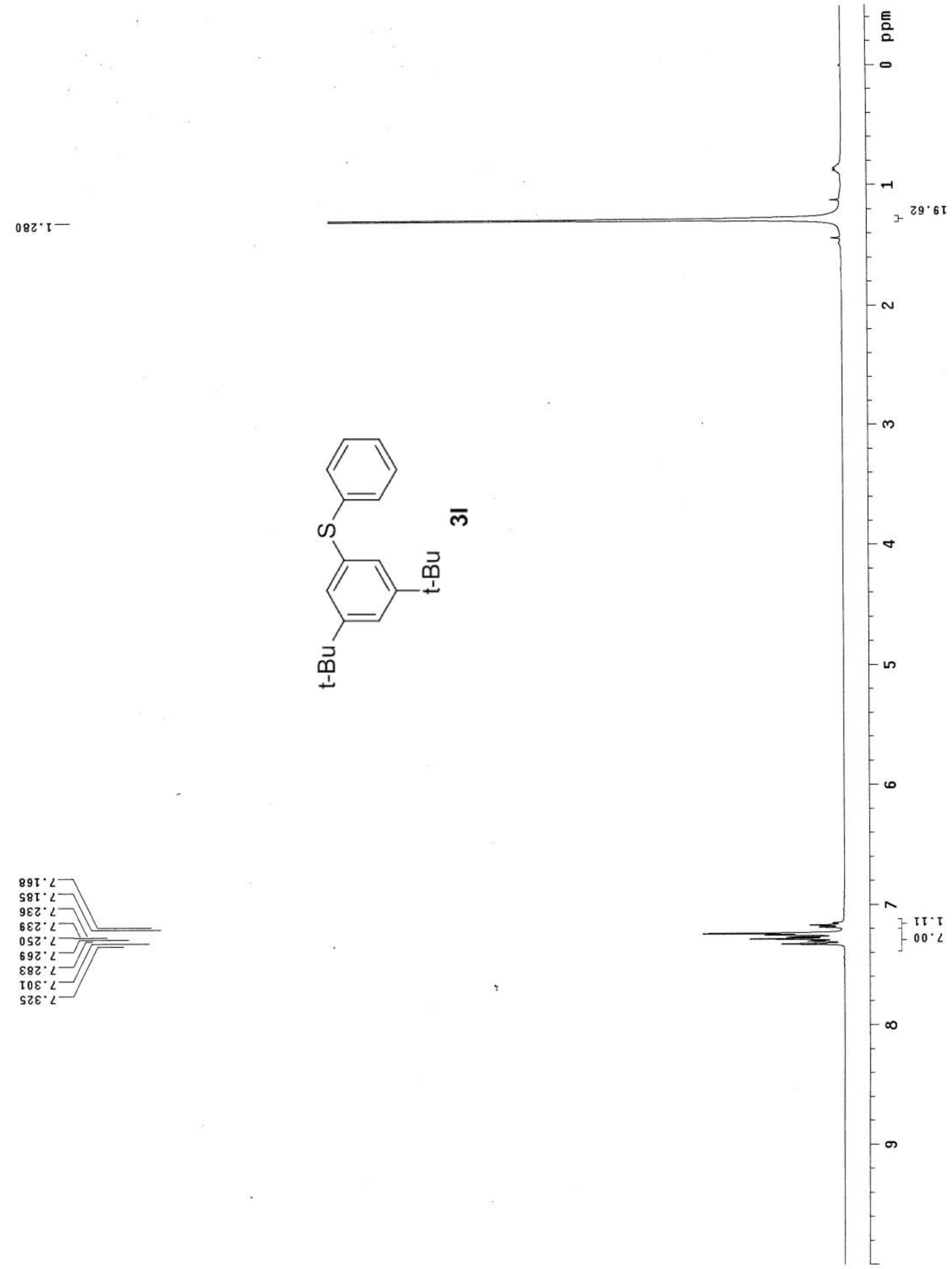

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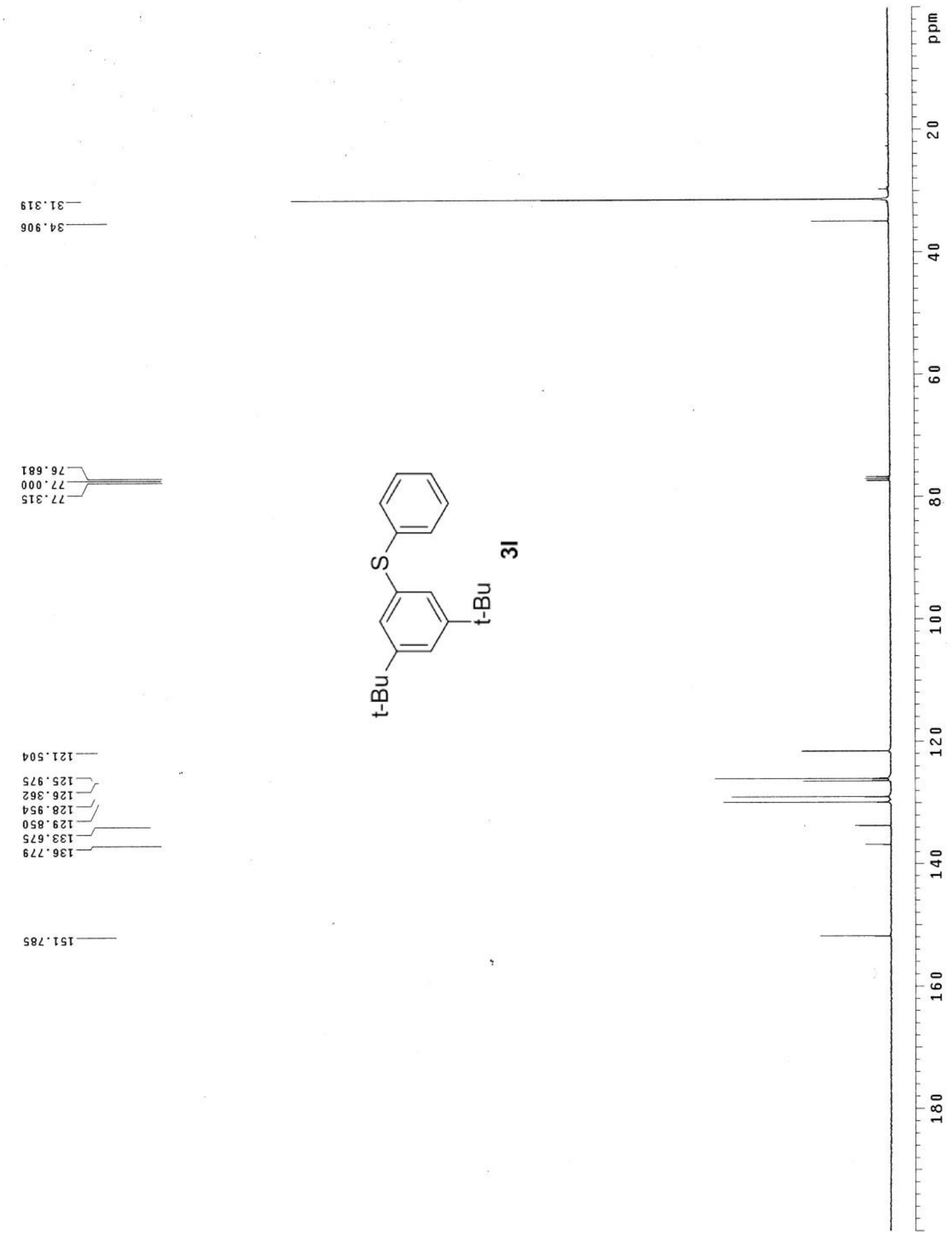

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