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A mild and efficient copper-catalyzed coupling of aryl iodides and thiols using an oxime–phosphine oxide ligand

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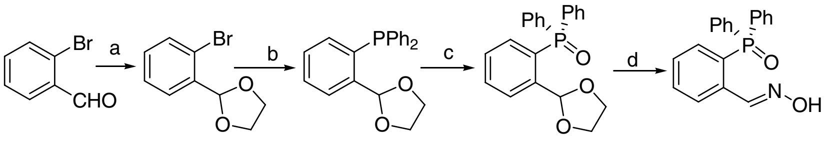
Abstract—A mild and efficient copper-catalyzed system for the coupling of aryl iodides and thiols was developed using a readily prepared and highly stable oxime–phosphine oxide ligand. Good to excellent yields were obtained.

Aryl sulfides are valuable intermediates in organic synthesis and are of great importance to the pharmaceutical industry.[1] Transition metal-catalyzed or -mediated arylation of thiols is a direct and powerful method to form these products. Although palladium-catalyzed C–S bond formation has achieved some good results,[2] the use of copper catalysts for this transformation is still attractive from an industrial perspective. Traditional copper-mediated couplings between thiols and aryl halides have required the use of copper salts in greater than stoichiometric amounts, polar solvents such as HMPA, and high temperatures around 200 °C.[3] Recently, along with the development of the research on mild copper-catalyzed aromatic carbon–heteroatom bond formations, copper-catalyzed C–S bond formation has received attention[3b,4] and some efficient ligands have been developed for this transformation, including phosphazene P_2-Et base,[5] neocuproine,[6] ethene glycol,[7] and amino acids such as *N*-methylglycine and *N*,*N*-dimethylglycine.[8] Though some progress has been made, copper-catalyzed thioether formations are less fruitful than the formations of aryl-nitrogen and aryl-oxygen.[4] Therefore, the development for more efficient and mild catalyst systems for copper-catalyzed arylation of thiols is still desirable.

Our group has embarked on a programme aiming at the development of ligands that are of low-cost and easily prepared[9,10] and have found that Cu_2O/oxime–phosphine oxide[10] can efficiently catalyze the coupling of aryl iodides with alkyl amines or N–H heterocycles. After these discoveries, we found that the copper-mediated system based on the oxime–phosphine oxide ligand could also be used to catalyze the C–S bond formation. Herein, we reported a mild and highly efficient copper-catalyzed coupling of aryl iodides and thiols using a readily prepared and highly stable oxime–phosphine oxide ligand.

The synthesis of oxime–phosphine oxide **5** was somewhat modified based on our previous procedure.[10,11] Intermediate **4** was easily prepared from commercially available and low-cost crude material **1** by conventional methods.[10,12] Ligand **5** was conveniently obtained without the need of an additional step to isolate the hydrolysis product of **4** (Scheme 1).



Scheme 1. Reagents and conditions: (a) TsOH, ethylene glycol, toluene, reflux; (b) *n*-BuLi, Et_2O, −78 °C, 3–4 h, Ph_2PCl, RT, 14 h; (c) H_2O_2, CH_2Cl_2, RT, 1 h; (d) TsOH, C_2H_5OH, H_2O, $NaHCO_3$, $NH_2OH{\cdot}HCl$.

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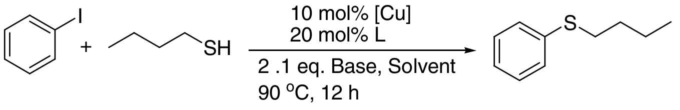
Table 1. Screening of the reaction conditions[a]



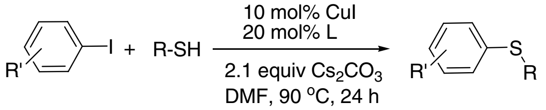
Entry	[Cu]	Solvent	Base	Yield[b] (%)
1	Cu_2O	Toluene	Cs_2CO_3	60
2	Cu_2O	DMF	Cs_2CO_3	96
3	Cu_2O	CH_3CN	Cs_2CO_3	89
4	Cu_2O	Dioxane	Cs_2CO_3	77
5	Cu_2O	DMF[c]	Cs_2CO_3	97
6	Cu_2O	DMF[c]	K_2CO_3	88
7	Cu_2O	DMF[c]	K_3PO_4	93
8	Cu_2O	DMF[c]	$K_3PO_4{\cdot}3H_2O$	95
9	Cu_2O	DMF[c]	KOH	85
10	Cu_2O	DMF[c]	KOAc	3
11	Cu_2O	DMF[c]	NaO*t*-Bu	63
12	Cu_2O	DMF[c]	Et_3N	4
13	CuI	DMF[c]	Cs_2CO_3	96
14	CuBr	DMF[c]	Cs_2CO_3	97
15	CuCl	DMF[c]	Cs_2CO_3	98
16	CuCN	DMF[c]	Cs_2CO_3	87
17	Cu Powder	DMF[c]	Cs_2CO_3	86

[a] Reaction conditions: 0.5 mmol PhI, 0.6 mmol *n*-butanethiol, 10 mol % [Cu], 20% ligand **5**, 1.05 mmol base, 0.5 mL solvent, 90 °C, 12 h.
[b] GC yield using *n*-dodecane as the internal standard.
[c] Reagent-grade DMF was degassed.

With the ligand **5** in hand, iodobenzene and *n*-butanethiol were used as model substrates for the subsequent screening experiments (Table 1).[13] Polar solvents were better than less polar solvents (entries 1–4). Reagent-grade DMF (degassed) gave similar result to newly distilled DMF (entry 5). K_3PO_4, $K_3PO_4{\cdot}3H_2O$, K_2CO_3 and Cs_2CO_3 were found to be effective bases for this coupling, while strong bases KOH and NaO*t*-Bu and organic base Et_3N gave bad results (entries 6–12). In addition, copper sources played a somewhat small role in the efficiency (entries 13–17). Although CuI provided somewhat lower yield than CuCl, we chose to focus on the use of CuI due to its stability to air. Therefore, Cs_2CO_3, CuI and degassed DMF were used in the following experiment.

To expand the scope of our catalyst system, a number of aryl iodides and thiols were employed (Table 2).[13] Good

Table 2. Coupling of aryl iodides with alkyl thiols or aryl thiols[a]



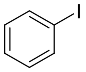
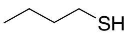
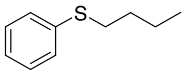
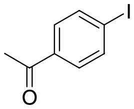
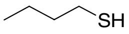
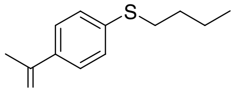
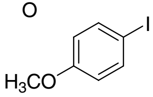
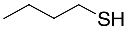
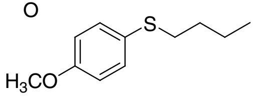
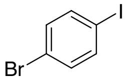
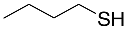
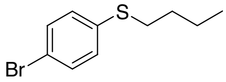
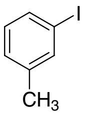
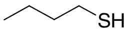
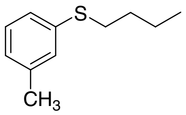
Entry	ArI	R–SH	Product	Yield[b] (%)
1				98[c]
2				86
3				92
4				80[d]
5				98[c]

Table 2 (*continued*)

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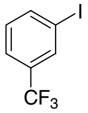
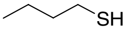
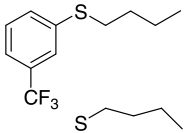
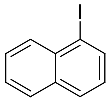
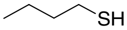
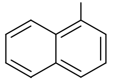
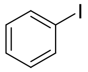
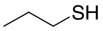
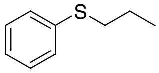
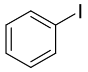
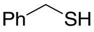
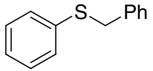
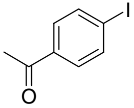
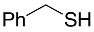
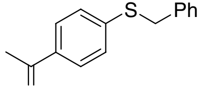
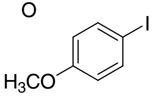
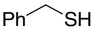
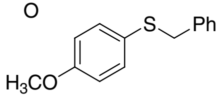
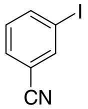
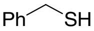
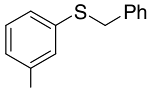
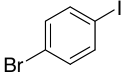
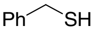
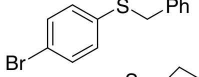
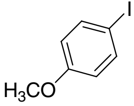
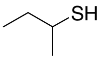
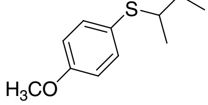
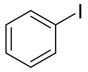
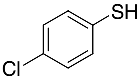
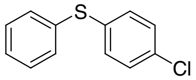
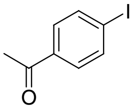
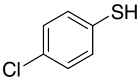
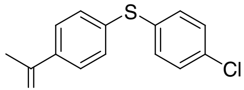
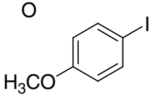
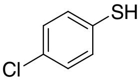
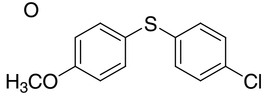
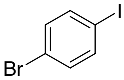
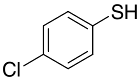
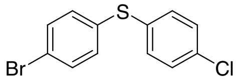
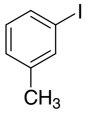
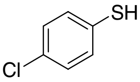
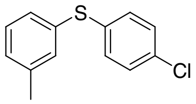
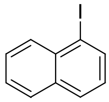
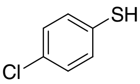
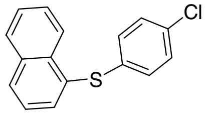
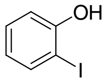
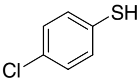
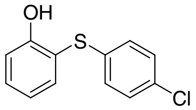
6				94[e]
7				98
8				87
9				98
10				89
11				89
12				84[f]
13				86
14				50
15				89
16				88
17				98
18				94
19				85
20				98
21				88[f]

[a] Reaction conditions: 1.0 mmol ArI, 1.2 mmol RSH, 0.1 mmol CuI, 0.2 mmol Ligand **5**, 2.1 equiv Cs_2CO_3, 1.0 mL DMF (degassed), 90 °C.

[b] Isolated yield.

[c] DMF was distilled from $CaCl_2$.

[d] K_3PO_4 as the base.

[e] Yield of the corresponding sulfone obtained after oxidation of sulfide with *m*-CPBA.

[f] Toluene as solvent, 100 °C, 29 h.

to excellent yields were observed with primary alkyl thiols (entries 1–13). Methoxy, trifluoromethyl, cyano, methyl, bromo, acetyl and hydroxyl groups were all tolerated on the aryl iodide component. When secondary alkyl thiol was employed as substrate, low yield was obtained (entry 14). 4-Chlorothiophenol was also found to be an effective nucleophile under these reaction conditions (entries 15–21).

In summary, we have developed a mild and efficient copper-catalyzed cross-coupling reaction between aryl iodides and thiols using a readily prepared and highly stable oxime-functionalized phosphine oxide ligand. Good to excellent yields were obtained. Many functional groups, especially the hydroxyl group, were tolerated. Although this method is restricted to the coupling of aryl iodides, the readily available ligand with excellent stability and high efficiency makes this protocol of potentially practical utility in many cases. Further studies to expand the application of this method to other catalytic reactions are currently under way.

Acknowledgements

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11. Procedure for the preparation of ligand **5**: Intermediate **3** was prepared from crude material **1** according to the literature.[12] 2-[2-(diphenylphosphinyl)phenyl]-1,3-dioxolane **4** was synthesized according to the method based on our previously reported procedure.[10] Intermediate **4** (2.37 g, 6.77 mmol) was dissolved in EtOH (60 mL). TsOH (36.2 mg, 0.21 mmol) was dissolved in H_2O (20 mL) and was added into the above solution of **4**. After the reaction mixture was refluxed for 12 h, $NaHCO_3$ (17.67 mg, 0.21 mmol) was added and the mixture was cooled to room temperature. Hydroxylamine hydrochloride (848.68 mg, 12.3 mmol) was dissolved in H_2O (20 mL), and $NaHCO_3$ (1.23 g, 14.64 mmol) added with stirring. The resulting aqueous solution of hydroxylamine was added into the hydrolysis solution of **4**. After stirring for 15 min, many white solids precipitated from the solution. The mixture was continued to be stirred overnight. The white solid was filtered, washed with water and CH_3OH and recrystallized from CH_3OH to give ligand **5** (1.75 g) in 80% yield. ^1H NMR (400 MHz, DMSO): δ 7.04–7.09 (m, 1H), 7.44–7.64 (m, 12H), 8.01–8.07 (m, 1H), 8.80 (s, 1H), 11.49 (s, 1H). ^{13}C NMR (100 MHz, DMSO): δ 126.2, 126.3, 128.7, 128.9, 129.0, 130.0, 131.0, 131.4, 131.5, 131.9, 132.3, 132.9, 133.0, 136.7, 146.3. ^{31}P NMR: δ 29.7. HRMS (APCI) calcd for $C_{19}H_{17}NO_2P$ $(M+H^+)$: 322.0991, found: 322.0975.
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13. General procedure for copper-catalyzed arylation of thiols: CuI (19.6 mg, 0.10 mmol), ligand (64.4 mg, 0.20 mmol), Cs_2CO_3 (692.0 mg, 2.1 mmol) and aryl iodides (if solid, 1.0 mmol) were weighed in air and transferred into a dried Schlenk tube. The tube was evacuated and backfilled with argon (3 cycles). Aryl iodides (if liquid, 1.0 mmol), degassed reagent-grade DMF (1.0 mL) and thiols (1.2 mmol) were injected to the tube successively by micro-syringe at RT. The tube was sealed and stirred in an oil bath (preheated to 90 °C) for the required time period. After cooling to RT, H_2O (3 mL) and Et_2O (5 mL) were added. The aqueous layer was extracted by Et_2O $(10\ mL \times 4)$. The combined organic layers were washed with saturated brine, dried over Na_2SO_4. Solvent was removed in vacuo, and the residue was further purified by flash column chromatography on silica to afford the desired product.