以羰基磷氧化物为配体的铜催化的 C-S 偶联反应

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摘要: 以邻溴苯甲醛为原料合成了一系列的羰基磷氧化物, 用作铜催化的 C-S 偶联反应的新配体. 在较温和的反应条件下可成功催化碘代芳烃或溴代芳烃与硫醇的偶联反应, 收率最高达 99%.

关键词: 铜; 羰基磷氧化物; 碳硫成键反应; 偶联反应; 碘代芳烃; 硫醇

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Cu-Catalyzed Coupling of Aryl Iodides with Thiols Using Carbonyl-Phosphine Oxide Ligands

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Abstract: A series of carbonyl-phosphine oxide ligands were synthesized from 2-bromophenylaldehyde and used in Cu-catalyzed C-S coupling reactions. Aryl iodide and aryl bromide reacted with thiols efficiently upon catalysis under mild reaction conditions and a yield of up to 99% was obtained.

Key words: Cu; carbonyl-phosphine oxide; carbon-sulfur bond formation; cross-coupling reaction; iodide aryl; thiol

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Sulfide ethers are backbones in a very important class of organic compounds that play a significant role in a number of chemical, material, and pharmaceutical industries [1-8]. For this reason the formation of C-S bonds is a subject of interest in organic chemistry. However, the traditional Ullmann-type C-S cross-coupling reaction which involves the condensation of thiols with aryl halides usually requires harsh conditions such as more than stoichiometric amounts of copper salts and temperatures above 200 °C. In 1980, Migita and co-workers [9] reported a palladium catalyzed C-S cross-coupling of aryl halides with thiols to overcome these difficulties and this resulted in C-S bond formation receiving plenty of interest. Over the past few years, several transition metals such as palladium [10,11], nickel [12,13], cobalt [14], and iron [15] have been used for this purpose. However, the development of traditional Cu-catalyzed Ull-

mann-type C-S cross-coupling reactions is still attractive because of the low price and the minor toxicity of copper.

Over the last few years several Cu-catalyzed processes have been developed in which the C-S coupling reaction was accelerated by special ligands such as phosphazene [16], ethylene glycol [17,18], neocuproine [19,20], N-methylglycine [21], the tripod ligand [22], benzotriazole [23], 1,2-diaminocyclohexane [24,25], β -ketoester [26], L-proline [27], BINAM [28], catechol violet [29], and o-aminophenol [30]. Recently, we developed an oxime-phosphine oxide ligand [31], which was used in Cu-catalyzed C-N and C-S cross-coupling reactions and good results were obtained. The phosphine oxide was an important functional group in these catalytic processes. To develop more efficient phosphine-oxide ligands we synthesized a series of ligands that contain a phosphine-oxide and

Scheme 1. Synthesis of the studied ligands.

carbonyl groups and these were applied to the Cu-catalyzed C–S cross-coupling reaction. Excellent yields of up to 99% were observed.

In the first stage, we synthesized the carbonyl phosphine-oxide ligands **1a–1c**, as shown in Scheme 1. 2-Bromophenylaldehyde (**2**) was used as a starting material to synthesize **3** as described by Xu et al. [32], which was reacted with the Grignard reagent to synthesize **4**. **1a** and **1b** were obtained by the oxidation of **4**. **1c** was synthesized by the oxidation of **6**, which was obtained by the reaction of **5** with lithium diphenylphosphide. To determine the best ligand, the coupling of iodobenzene and *n*-butylthiol was selected as a model reaction (Table 1). It was exciting to find that all carbonyl phosphine-oxide ligands were useful for the C–S coupling reaction giving high yields and the best result was obtained when using **1b** as ligand.

Table 1 Ligand screening for Cu catalyzed C–S cross-coupling

Entry	Ligand	Yield ^a (%)
1	1a	89
2	1b	92
3	1c	91

Reaction conditions: 0.5 mmol iodobenzene, 0.6 mmol *n*-butyl thiol, 0.05 mmol Cu catalyst, 0.05 mmol ligand, 2 mmol base, 80 °C, 12 h.

^aGC yield using *n*-dodecane as the internal standard.

The reaction was screened using several bases, solvents, and Cu sources and the results are summarized in Table 2. Preliminary results show that Cs₂CO₃ was a superior base compared with Na₂CO₃, K₂CO₃, and K₃PO₄. The solvent effect was then investigated and polar solvents gave better results in this reaction while CH₃CN was found to be the best solvent. The Cu sources were also evaluated and CuBr, CuCl, Cu₂O, and Cu were found to be inferior to CuI. Therefore, the best reaction conditions are CuI/**1b**/Cs₂CO₃/CH₃CN/80°C.

With the optimized reaction conditions in hand, various aryl iodides and thiols were applied to this reaction to explore its scope. As shown in Table 3, both iodides with either an electron-donating group or an electron-withdrawing group were tolerated to give the corresponding thioethers in very high yields. Sterically hindered aryl iodides such as 2-methylphenyl iodide and 2-hydroxyphenyl iodide readily coupled with *n*-butyl thiol (entries 5 and 6). Aryl iodides bearing an additional halogen atom in the aryl ring could convert exclusively to the desired product without being affected by the chloro or fluoro groups (entries 12, 13, and 15). Moreover, the reaction showed chemoselectivity for the thiol, for example, C–S coupling was preferred in the presence of amino and hydroxyl groups (entries 3 and 6).

The reactivity of aryl bromides was also evaluated (Table 3, entries 19 and 20), and aryl bromides with electron-withdrawing groups afforded the products in good yields whereas no reaction took place when electron-donating aryl bromides were used.

Table 2 Effect of Cu source, bases, and solvents

Entry	[Cu source]	Solvent	Base	Yield ^a (%)
1	CuI	CH ₃ CN	Cs ₂ CO ₃	92
2	CuI	CH ₃ CN	Na ₂ CO ₃	—
3	CuI	CH ₃ CN	K ₂ CO ₃	37
4	CuI	CH ₃ CN	K ₃ PO ₄	63
5	CuI	DMF	Cs ₂ CO ₃	72
6	CuI	DMSO	Cs ₂ CO ₃	69
7	CuI	toluene	Cs ₂ CO ₃	3
8	CuBr	CH ₃ CN	Cs ₂ CO ₃	87
9	CuCl	CH ₃ CN	Cs ₂ CO ₃	87
10	Cu	CH ₃ CN	Cs ₂ CO ₃	84
11	Cu ₂ O	CH ₃ CN	Cs ₂ CO ₃	91

Reaction conditions: 0.5 mmol iodobenzene, 0.6 mmol *n*-butyl thiol, 0.05 mmol Cu catalyst, 0.05 mmol ligand **1b**, 2 mmol base 80 °C, 12 h. ^aGC yield using *n*-dodecane as the internal standard. DMF—dimethylformamide; DMSO—dimethyl sulphoxide.

Table 3 Coupling of aryl iodides with thiols

Entry	Aryl iodide	Thiol	Product	Yield ^a (%)
1				99
2				98
3				99
4				98
5				82
6				73
7				99
8				77
9				99
10				88
11				95
12				81
13				98
14				95
15				97
16				92
17				87
18				60
19				94
20				91

Reaction conditions: 0.5 mmol iodobenzene, 0.6 mmol *n*-butyl thiol, 0.05 mmol Cu catalyst, 0.05 mmol ligand **1b**, 2 mmol base 80 °C, 12 h.^aIsolated yield.

In summary, a series of carbonyl phosphine-oxide ligands **1a–1c** was synthesized and used in the Cu-catalyzed coupling reaction of aryl iodides with thiols in good to excellent yields. Further studies to extend the application of this method to other catalytic reactions are currently under way.

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