Cite this article as: Chin. J. Catal., 2011, 32: 1129-1132.



SHORT COMMUNICATION

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

WANG Haolong, WAN Boshun*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China

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

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 Ullmann-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 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 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



Scheme 1. Synthesis of the studied ligands.

Received 1 April 2011. Accepted 5 May 2011.

^{*}Corresponding author. Tel: +86-411-84379260; Fax: +86-411-84379223; E-mail: bswan@dicp.ac.cn

Copyright © 2011, Dalian Institute of Chemical Physics, Chinese Academy of Sciences. Published by Elsevier BV. All rights reserved. DOI: 10.1016/S1872-2067(10)60243-4

Table 1 Ligand screening for Cu catalyzed C-S cross-coupling					
+	n-BuSH CuI/Ligand Cs ₂ CO ₃ /CH ₃ CN	s ^{-n-Bu}			
Entry	Ligand	Yield ^a (%)			
1	1 a	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.

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.

The reaction was screened using several bases, solvents, and Cu sources and the results are summarized in Table 2. Preliminary results show that Cs_2CO_3 was a superior base compared with Na_2CO_3 , K_2CO_3 , and K_3PO_4 . 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

Table 2 Effect of Cu source, bases, and solvents							
	I S´ ^{<i>n</i>-Bu}						
		[Cu]/1c	, j				
	+ n-BuS	H Base/Solve	ent				
Entry	[Cu source]	Solvent	Base	Yield ^a (%)			
1	CuI	CH ₃ CN	Cs_2CO_3	92			
2	CuI	CH ₃ CN	Na ₂ CO ₃	_			
3	CuI	CH ₃ CN	K_2CO_3	37			
4	CuI	CH ₃ CN	K_3PO_4	63			
5	CuI	DMF	Cs_2CO_3	72			
6	CuI	DMSO	Cs_2CO_3	69			
7	CuI	toluene	Cs_2CO_3	3			
8	CuBr	CH ₃ CN	Cs_2CO_3	87			
9	CuCl	CH ₃ CN	Cs_2CO_3	87			
10	Cu	CH ₃ CN	Cs_2CO_3	84			
11	Cu ₂ O	CH ₃ CN	Cs_2CO_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.

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

Table 3	Coupling	of aryl	iodides	with	thiols
---------	----------	---------	---------	------	--------

I		s ^{-R'}
R I + R'SH	Cul/1b Cs ₂ CO ₃ /CH ₃ CN	$R = \frac{1}{1!}$

Entry	Aryl iodide	Thiol	Product	Yield ^a (%)	Entry	Aryl iodide	Thiol	Product	Yield ^a (%)
1	MeO	SH SH	MeO-S-n-Bu	99	11	NC	SH SH	NC S-n-Bu	95
2	Me	SH SH	Me S-n-Bu	98	12	F	SH SH	FS-n-Bu	81
3	H ₂ N	SH SH	H ₂ N-S-n-Bu	99	13	Cl	SH SH	Cl S=n-Bu	98
4	Me	SH SH	Me S-n-Bu	98	14		SH SH	S-n-Bu	95
5	I Me	SH SH	S-n-Bu Me	82	15		SH SH	Cl-S-n-Bu	97
6	ССС	SH SH	S-n-Bu OH	73	16	I	F—————————————————————————————————————	FS	92
7		SH SH	S ^{-n-Bu}	99	17	I	MeO-SH	MeO-	87
8	F ₃ C	SH SH	F ₃ C-S-n-Bu	77	18	I	——————————————————————————————————————		60
9	Ac	SH SH	Ac-S-n-Bu	99	19	NC	SH SH	NC	94
10	MeOOC	SH SH	MeOOC———————————————————————————————————	88	20	MeOOC	SH SH	MeOOC	91

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.

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.

References

- Jones D N. In: Barton D H, Ollis D W eds. Comprehensive Organic Chemistry. Vol. 3. New York: Pergamon, 1979. 33
- 2 Tiecco M. Synthesis-stuttgart, 1988: 749
- 3 Rayner C M. Contemp Org Synth, 1996, 3: 499
- 4 Baird C P, Rayner C M. J Chem Soc, Perkin Trans 1, 1998: 1973
- 5 Procter D J. J Chem Soc, Perkin Trans 1, 1999: 641
- 6 Procter D J. J Chem Soc, Perkin Trans 1, 2000: 835
- 7 Procter D J. J Chem Soc, Perkin Trans 1, 2001: 335
- 8 Herradura P S, Pendola K A, Guy R K. Org Lett, 2000, 2: 2019
- 9 Migita T, Shimizu T, Asami Y, Shiobara J I, Kato Y, Kosugi M. Bull Chem Soc Jpn, 1980, 53: 1385
- 10 Fernández-Rodríguez M A, Shen Q L, Hartwig J F. Chem Eur J, 2006, 12: 7782
- 11 Fernández-Rodríguez M A, Shen Q, Hartwig J F. J Am Chem Soc, 2006, 128: 2180
- 12 Zhang Y, Ngeow K N, Ying J Y. Org Lett, 2007, 9: 3495
- 13 Jammi S, Barua P, Rout L, Saha P, Punniyamurthy T. Tetrahe-

dron Lett, 2008, 49: 1484

- 14 Wong Y C, Jayanth T T, Cheng C H. Org Lett, 2006, 8: 5613
- 15 Correa A, Carril M, Bolm C. Angew Chem, Int Ed, 2008, 47: 2880
- 16 Palomo C, Oiarbide M, Lopez R, Gomez-Bengoa E. Tetrahedron Lett, 2000, 41: 1283
- 17 Kwong F Y, Buchwald S L. Org Lett, 2002, 4: 3517
- 18 Enguehard-Gueiffier C, Thery I, Gueiffier A, Buchwald S L. Tetrahedron, 2006, 62: 6042
- 19 Gujadhur R K, Bates C G, Venkataraman D. Org Lett, 2001, 3: 4315
- 20 Bates C G, Gujadhur R K, Venkataraman D. Org Lett, 2002, 4: 2803
- 21 Deng W, Zou Y, Wang Y F, Liu L, Guo Q X. Synlett, 2004: 1254
- 22 Chen Y J, Chen H H. Org Lett, 2006, 8: 5609
- 23 Verma A K, Singh J, Chaudhary R. Tetrahedron Lett, 2007, 48: 7199
- 24 Rout L, Sen T K, Punniyamurthy T. Angew Chem, Int Ed, 2007, 46: 5583
- 25 Ranu B C, Saha A, Jana R. Adv Synth Catal, 2007, 349: 2690
- 26 Carril M, SanMartin R, Dominguez E, Tellitu I. *Chem Eur J*, 2007, **13**: 5100
- 27 Lv X, Bao W. J Org Chem, 2007, 72: 3863
- 28 Prasad D J C, Naidu A B, Sekar G. Tetrahedron Lett, 2009, 50: 1411
- 29 Basu B, Mandal B, Das S, Kundu S. *Tetrahedron Lett*, 2009, **50**: 5523
- 30 Feng Y, Wang H F, Sun F F, Li Y M, Fu X M, Jin K. Tetrahedron, 2009, 65: 9737
- 31 Zhu D, Xu L, Wu F, Wan B. Tetrahedron Lett, 2006, 47: 5781
- 32 Xu L, Zhu D, Wu F, Wan B. Tetrahedron, 2005, 47: 6553