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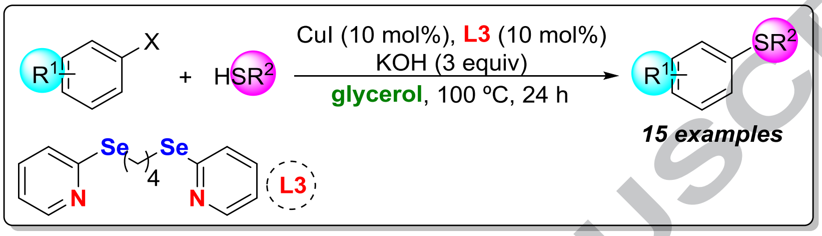

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Bis(2-pyridyl)diselenoethers as versatile ligands for copper-catalyzed C-S bond formation in glycerol

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ABSTRACT

In this work, we described a simple and efficient general methodology for CuI/ bis(2-pyridyl)diselenoether-catalyzed C–S coupling reactions of aryl halides with thiols using glycerol as an environmentally friendly solvent. The products were obtained in moderate to excellent yields. The performance of CuI/**L3**-catalyzed C–S coupling reactions in glycerol is comparable to the related cross-coupling reactions in common organic solvents using transition-metal salts as catalyst. The use of the system CuI/**L3**/glycerol related in this work offers the possibility of performing the reaction in the absence of toxic organic solvents, expensive metals and using ultrasound as an alternative energy source.

1. Introduction

The C–S cross-coupling reaction is a powerful means for the preparation of numerous compounds that are biological, chemical, material or pharmaceutical interest.[1] Several drugs currently used for the treatment in therapeutic areas such as cancer, inflammation and HIV contain aryl sulfides as the functional group.[2] In organic chemistry, the use of transition-metal-catalyzed C-S bond formation is a very important way to prepare these compounds and catalysts such as Co, Pd, Fe, In and Cu are the most employed for this purpose.[3] Among them, Cu is predominantly attractive due to its special redox properties, polarizability, easy handling, low cost and toxicity in comparison to other metal catalysts.[4]

Recently, several classes of ligands including phosphazene, ethylene glycol, neocuproine, 1,2-diamino derivatives, between others, rationalized such as bidentate ligands containing nitrogen and/or oxygen as copper chelating atoms, have been found to accelerate the C–S bond-forming reactions.[5] The most accepted explanation for this behavior is that the use of ligands may increase the solubility of copper salts in the solvents.[6]

Still, recent advances in this field have described the use of transition metal-catalyzed C-H activation for the construction of C-S bonds,[7] the use of Bunte-salts as thiol surrogate,[8] synthesis of sulfide containing-fluorine[9] and others.[10]

In view of these previous results, selenium-containing nitrogen ligands appear as an alternative to previous described copper/ligand system for synthetic organic chemistry. In this field, recent reports have described its use as chiral ligands for asymmetric catalysis on the construction of stereoselective new C-C bonds.[11] Still, the use of organoselenium compounds have been shown as catalyst in organic transformations, such as the selective addition of thiols to α,β-unsaturated carbonyl compounds.[12]

On the other hand, the development of green methodologies from renewable resources has grown because of the extensive use of solvents in chemical industries and the impact of these on the environment, health and safety.[13] Glycerol, an organic waste generated by the biodiesel industry, has been recently proposed by Gu and Jérôme as a valuable green solvent.[14] The current availability of glycerol on a large scale and low cost, combined with its intrinsic properties, *i.e.* no toxicity, no flammability, obtained from renewable sources and biodegradability, makes it an ideal candidate to develop greener synthetic processes.[15] Recently, glycerol has proved to be an efficient solvent in many organic reactions, including Suzuki-Miyaura cross-coupling reactions,[16] *N*-arylation of amines,[17] metal and base-free synthesis of arylselanyl anilines[18] and C-S bond forming reaction using vinyl bromides and disulfides.[19]

In the light of these previous results and our recent interest on the chemistry of bis(2-pyridyl)diselenide,[20] we synthesized three bis(2-pyridyl) diselenoethers containing one **L1**, three **L2** and

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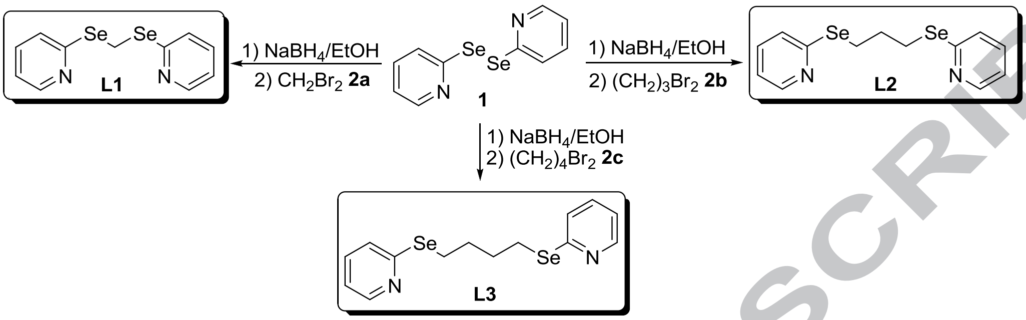
four **L3** methylene groups between the selenium atoms and investigated its potential use as ligands in CuI-catalyzed C-S cross-coupling reactions in the presence of glycerol as a renewable solvent.

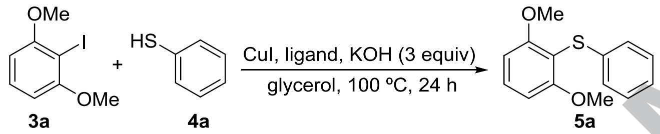
2. Results and Discussion

For this purpose, initially we investigated a simple method to synthesize the ligands (**L1**, **L2** and **L3)** by reacting the bis(2-pyridyl)diselenide[21a] **1** with sodium borohydride using ethanol as solvent, to generate *in situ* two equivalents of the desired 2-pyridylselenolate, followed by the addition of the corresponding dibromoalkanes **2** (Scheme 1).[21b]



Scheme 1. General scheme for the synthesis of ligands **L1**, **L2** and **L3**.

Table 1. Optimization conditions for CuI/L-catalyzed C-S cross coupling reaction.[a]



Entry	CuI (mol%)	Ligand - (mol%)	Yield (%)
1	10	**L1** – 10	94
2	10	**L2** – 10	89
3	10	**L3** – 10	95
4	10	**L1** – 5	83
5	10	**L3** – 5	85
6	5	**L1** – 10	49
7	5	**L3** – 10	85
8	10	-	55
9	-	**L3** – 10	N.R.
10	-	-	N.R.

[a]Reaction conditions: Aryliodide **3a** (1.0 mmol), benzenethiol **4a** (1.5 mmol), CuI, ligand, KOH (3 equiv), glycerol (10 mL), Argon, 100 ºC, 24 h.

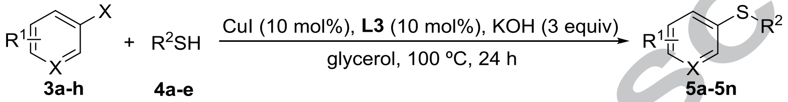
With these ligands in hands, 1-iodo-2,6-dimethoxybenzene **3a** and benzenethiol **4a** were selected as model substrates to evaluate the catalytic activity of the bis(2-pyridyl)diselenoethers ligands/copper iodide system and the reactions are described in table 1. The C-S cross coupling reaction was initially examined employing 10 mol% of CuI and 10 mol% of the ligands **L1**, **L2** and **L3**, using 3 equivalents of KOH as base in glycerol as solvent at 100 ºC for 24 hours (Table 1, entries 1-3). These preliminary results showed that the highest ligand efficiency can be associated to the ligands containing one **L1** and four **L3** methylene groups between the selenium atoms that furnished the desired (2,6-dimethoxyphenyl)(phenyl)sulfide **5a** in 94 and 95% yield, respectively. Based on these results, we reduced the Cu/ligand catalytic system to 5 mol% to compare the efficiency of **L1** and **L3**, however, a lower isolated yield was observed in both cases (Table 1, entries 4 and 5). When only the catalytic amount of CuI was reduced to 5 mol%, it was observed a better result for the ligand **L3** compared to ligand **L1** (Table 1, compare entries 7 and 6). These observations suggest the possibility to form different catalytic species on the reaction media. One possibility described in the literature[22] is the formation of polymeric complexes between CuI and nitrogen-based ligands, which could have a catalytic activity increased if compared to the monomeric species. Based on it, we believe that the **L3**, which present the longer carbon chain between the selenium atoms, showed the highest catalytic activity when coordinated to copper, because of it better ability to form a polymeric complex. On the other hand, at higher concentrations of the ligands, the possibility to generate a stable monomer or dimer copper complex increase, mainly for **L1**, which could reduce the reactivity of the metal. In order to demonstrate the necessity for the use of ligands on this cross-coupling reaction, a control experiment was conducted in the absence of ligands and only 55% yield for the product **5a** was obtained (Table 1, entry 8). Still, no reaction was observed suppressing the copper iodide or the catalytic system Cu/ligand (Table 1, entry 9 and 10).

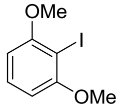
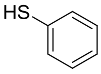
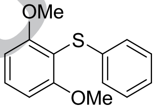
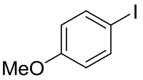
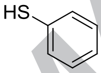
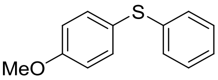
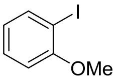
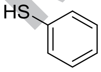
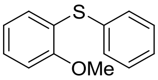
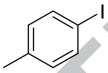
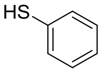
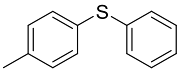
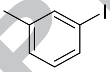
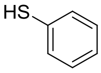
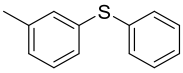
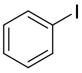
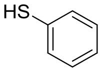
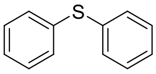
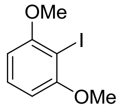
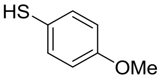
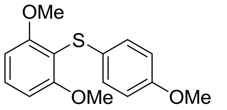
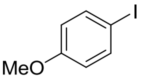
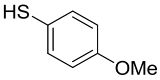
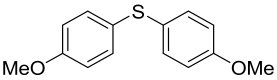
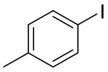
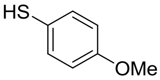
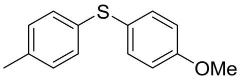
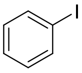
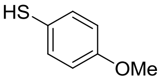
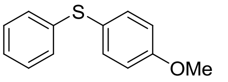
Analysis of the results described in table 1 showed that the optimal condition for the C–S cross-coupling reaction between 1-iodo-2,6-dimethoxybenzene **3a** and benzenethiol **4a** in glycerol as solvent is using 10 mol% of CuI and 10 mol% of **L3** at 100 °C (Table 1, entry 3).

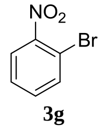
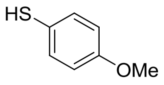
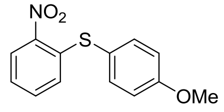
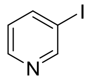
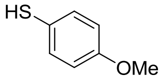
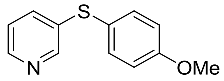
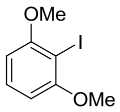
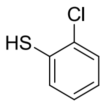
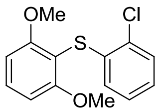
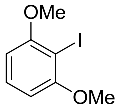
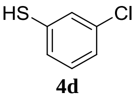
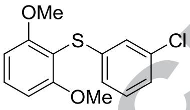
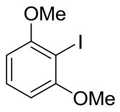
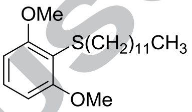
In order to demonstrate the efficiency of this C-S cross-coupling reaction using glycerol as solvent, we explored the generality of our method extending the coupling reaction to other aryl halides **3** as well to other thiols **4** and the results are summarized in table 2. As shown in table 2, groups attached to the aryl halide such as electron rich, -neutral and –poor were cross-coupled efficiently under these conditions and produced the bis(aryl) sulfides **5** in moderate to excellent yields (Table 2, entries 1-15). For example, reactions of aryl iodides containing *orto, meta* or *para*-methoxy and -methyl substituents furnished the desired products in 79 to 99% yield (Table 2, entries 1–6). Comparing entries 1, 2, 3 and 6 in table 2, none steric influence could be observed to this cross-coupling reaction based on the presented results, aryl iodides **3a**, **3b** and **3c** containing *o*- and *p*-methoxy groups furnished the desired sulfides in comparable yields with the non-substituted iodobenzene **3f**. Besides, when electron rich or electron poor groups were used directly attached to the arylthiol **4**, good to excellent yields were obtained for the sulfides and the reaction does not seems to be clearly influenced to electronic effects (Table 2, entries 7-14). Thiol-containing methoxy **4b** or chloro **4c**, **4d** groups were satisfactorily used to give the respective products **5g**, **5l** and **5m** (Table 2, entries 7, 13 and 14). Still, it is important to mention that a good result was obtained using the aryl bromide **3g**, showing the versatility of this reaction not only for iodides (Table 2, entry 11). The methodology was also extended to the heteroaryl iodide **3h** and the 3-(4-methoxyphenylthio)pyridine **5k** was obtained in 93% isolated yield after 24 hours (Table 2, entry 12). Finally, when the alkyl 1-dodecanothiol **4e** was employed in the presence of 1-iodo-2,6-dimethoxybenzene **3a** in a catalytic system of CuI / **L3** (10 mol% each), the (2,6-dimethoxyphenyl)(dodecyl)sulfide **5n** was readily synthesized in 62% (Table 2, entry 15).

A plausible mechanism can be proposed for this CuI-catalyzed C-S cross-coupling reaction of aryl halides and thiols in the presence of bis(2-pyridyl)diselenoether ligand **L3** (Scheme 1). Based on literature,[23] the mechanism suggests that the reaction occurs by an oxidative addition of the aryliodide **4** to the active copper specie **a** to generate the intermediated **b**. The reaction of intermediate **b** with the thiol **5** afford the intermediate **c**, which can provide the C-S cross-coupling product by reductive elimination. The role of the bis(2-pyridyl)diselenoether ligand **L3** in the reaction can be either to promote the oxidative addition of ArX to the Cu(I) specie or to stabilize the high-valent Cu(III) intermediate.[23c]

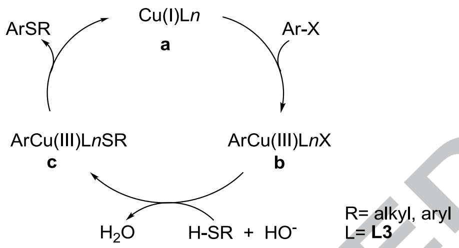
Table 2. CuI/**L3**-catalyzed C–S cross-coupling reaction of aryl halides with thiols using glycerol as solvent.[a]



Entry	Aryl halide **3**	Thiol **4**	Product **5**	Yield (%)
1	 **3a**	 **4a**	 **5a**	95
2	 **3b**	 **4a**	 **5b**	87
3	 **3c**	 **4a**	 **5c**	79
4	 **3d**	 **4a**	 **5d**	99
5	 **3e**	 **4**[a]	 **5e**	87
6	 **3f**	 **4**[a]	 **5f**	78
7	 **3a**	 **4b**	 **5g**	83
8	 **3b**	 **4b**	 **5h**	90
9	 **3d**	 **4b**	 **5i**	84
10	 **3f**	 **4b**	 **5b**	93

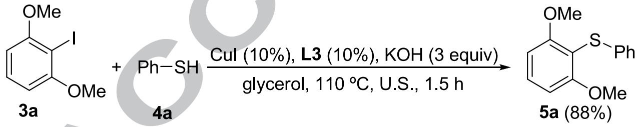
11	 **3g**	 **4b**	 **5j**	77
12	 **3h**	 **4b**	 **5k**	93
13	 **3a**	 **4c**	 **5l**	88
14	 **3a**	 **4d**	 **5m**	99
15	 **3a**	$HS(CH_2)_{11}CH_3$ **4e**	 **5n**	62

[a]Reaction conditions: Arylhalide **3** (1.0 mmol), thiol **4** (1.5 mmol), KOH (3.0 mmol), CuI (10 mol%), **L3** (10 mol%), glycerol (10 mL), 100 °C, under Argon.



Scheme 2. Proposed catalytic cycle.

Finally, exploring the possibility of perform the C-S cross-coupling reaction employing a non-conventional energy source and becoming the current methodology still greener, an ultrasound probe was used. By the same reaction conditions described before, the bis(aryl) sulfide **5a** could be obtained in 88% yield after only 1 hour and 30 minutes (Scheme 3).



Scheme 3. The use of ultrasound to accelerate the C-S cross-coupling reaction.

3. Conclusion

In conclusion, we have developed a simple and efficient general methodology for CuI-catalyzed C–S cross-coupling reaction of aryl halides with thiols using glycerol as solvent in the presence of bis(2-pyridyl)diselenoether **L3** as an ideal ligand. The methodology allows the use of a broad scope of aryl iodides and thiols, including aryl, heteroaryl and alkyl groups, and the products are obtained in moderate to excellent yields. The results showed that the performance of CuI/**L3**-catalyzed C–S cross-coupling reactions in glycerol was comparable to the performance of CuI in common toxic and non-environmentally friend organic solvents. Glycerol is greener and safer than common organic solvents that combined with the use of CuI/**L3**, related in this work, still offers the possibility of performing the reaction in the absence of expensive metals and using the ultrasound to accelerate this process.

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Supplementary Material

Supplementary data (experimental procedures and spectral data) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.