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PAPER

Glycerol as a recyclable solvent for copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl boronic acids†

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We describe herein the use of glycerol as the solvent in the copper-catalyzed cross-coupling reaction of diaryl diselenides with arylboronic acids using CuI and DMSO as additive. This cross-coupling reaction was performed with diaryl diselenides and arylboronic acids bearing electron-withdrawing and electron-donating groups, affording the corresponding diaryl selenides in good to excellent yields. The glycerol–CuI mixture can be directly reused for further cross-coupling reactions.

Introduction

The versatility and applicability of organoselenium compounds in organic chemistry is widely described in a great number of reviews[1] and books.[2] Organoselenium compounds are attractive molecules because of their use as ionic liquids[3] and in asymmetric catalysis,[1b–d] their fluorescent properties[4] and because of their interesting biological activities.[5] Diaryl selenides are certainly the organoselenium compounds most studied and a large number of methodologies have been reported to prepare these compounds.[2] In some cases, the described methodologies need long reaction times, harsh reaction conditions, stoichiometric or greater amount of metallic reagents and sometimes the products are only generated in moderate yields.[2]

To overcome these limitations, much attention has recently been focused to develop catalytic systems to reduce the environmental impact of these methodologies. Thus, metal-catalyzed reactions of diaryl diselenides with aryl halides or aryl boronic acids has become a versatile tool for the synthesis of symmetrical or unsymmetrical diaryl selenides.[6] A great number of studies have focused on the use of copper, palladium, iron, indium, rhodium, ruthenium and nickel-based catalytic systems for this purpose.[6] Most of these systems involve a homogeneous process and specific ligands, which in some cases may increase the cost and limit the scope of any applications.[6] Recently, diaryl selenides were synthesized by a copper catalyzed process through C_{Ar}–Se bond formation under mild reaction conditions from aryl iodides or bromides and diphenyl diselenide.[7] In that work, the solvent CH_3CN acts as ligand for copper(I) iodide and no external ligand was required.

More examples concerning the role of the solvent in these reactions have been described. In studies using DMSO, it was observed that this molecule not only acts as solvent, but also as the oxidant of the active metal species in the catalytic cycle.[8] Furthermore, developing greener catalytic systems that are economical, free of external ligands and that would produce the desirable diarylselenides in high yields, are still highly sought after.

In this context, the development of green methodologies from renewable resources has gained much interest recently because of the extensive use of solvents in chemical industries, and of the predicted disappearance of fossil oil.[9] The desirable characteristics for a green solvent include low flammability, high availability, biodegradability and ideally can be obtained from renewable sources.[10] With the increase in biodiesel production world-wide, the market saturation of glycerol, a side product of biodiesel production, is inevitable.[11] The use of glycerol[12] and their eutetics[13] as a sustainable solvents for green chemistry was recently studied. Heck and Suzuki cross-couplings, ring closing metathesis of diolefins, multicomponent reactions, asymmetrical reduction and cycloisomerization of (*Z*)-enynols into furans, are some examples of the use of glycerol as solvent in organic reactions.[12] Recently, glycerol has proved an efficient solvent in the cross-coupling reaction of diaryl diselenides with (*Z*)- or (*E*)-vinyl bromides catalyzed by CuI. In this study, the glycerol/catalyst mixture was directly reused for further cross-coupling reactions.[14]

Results and discussion

In this sense and due to our interest in green protocols correlated to the organochalcogen chemistry,[15] we describe here the use of glycerol as solvent in the copper-catalyzed cross-coupling reaction of diaryl diselenides with arylboronic acids by CuI as catalyst and using DMSO as additive (Scheme 1).

We initially focused our attention on the optimization of the reaction conditions for the synthesis of 4-methoxyphenyl-phenyl selenide **3a** starting from diphenyl diselenide **1a** and 4-

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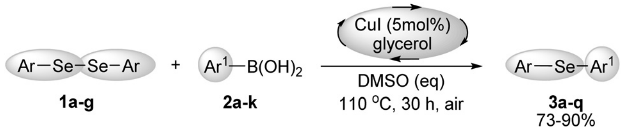
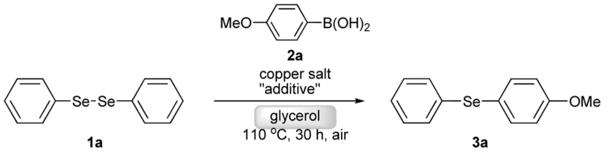


Scheme 1 General scheme of the reaction.

Table 1 Reaction conditions optimization using arylboronic acid **2a**[a]



Entry	Copper salt (mol%)	Additive (1 eq.)	Yield of **3a**[b] (%)
1	CuO NPs (5%)	—	30
2	CuI (5%)	—	32
3	CuI (5%)	DMSO	90
4	CuO NPs (5%)	DMSO	78
5[c]	CuI (5%)	DMSO	91
6[d]	CuI (5%)	DMSO	10
7	CuI (5%)	DMF	31
8	CuI (5%)	CH_3CN	29
9	CuI (5%)	H_2O	32
10	CuI (5%)	Mg	27
11	CuI (5%)	Zn	23
12	CuCl (5%)	DMSO	54
13	$CuCl_2$ (5%)	DMSO	47
14	$Cu(OAc)_2$ (5%)	DMSO	51
15	CuI (10%)	DMSO	92
16	CuI (3%)	DMSO	69
17	CuI (1%)	DMSO	55

[a] Reactions are performed in the presence of compounds **1a** (0.25 mmol) and **2a** (0.5 mmol) in glycerol (0.5 mL), at 110 °C for 30 h in open atmosphere. [b] Yields are given for isolated product. [c] Reaction using 0.75 mmol of **2a**. [d] Reaction using 10 mol% of DMSO.

methoxyphenylboronic acid **2a** in glycerol (Table 1). Experimental procedures recently published to accomplish these cross-coupling reactions needed the use of copper salts at temperatures over 100 °C.[8a,16] For this reason, we started studying the reaction of substrates **1a** and **2a** in the presence of CuO nanoparticles (CuO NPs) (5 mol%) using glycerol as solvent at 110 °C in open atmosphere. Under this condition, the desired product **3a** was obtained in only 30% after 30 hours (Table 1, entry 1). A similar result was obtained when we change the copper reagent CuO NPs to CuI (Table 1, entry 2).

Aiming to improve the yield of product **3a**, a mixture of diphenyl diselenide **1a**, arylboronic acid **2a** in glycerol was reacted in open atmosphere for 30 hours, applying different copper salts and additives. To our satisfaction, product **3a** was obtained in 90% using 5 mol% of CuI using 1.0 eq. of DMSO (Table 1, entry 3). We observed that the use of stoichiometric DMSO as additive was important for the reaction success. Substrates **1a** and **2a** were reacted in glycerol using a range of additives, such as, DMSO, DMF, CH_3CN, H_2O, Mg and Zn, and the corresponding product **3a** was obtained in best yields in the reactions using DMSO (Table 1, entries 3 *vs.* 7–11). Recent studies show that the DMSO acts as oxidant of the activity metal species in these cross-coupling reactions and might be reduced into dimethylsulfide under the reaction conditions.[8] In our experiment, dimethyl sulfide could be observed in small amounts in gas chromatography analysis.

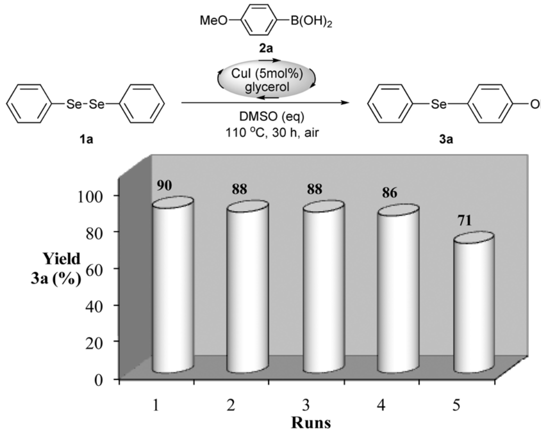


Fig. 1 Reuse of catalytic system glycerol–CuI.

A great decrease in the yield of product **3a** was observed when the reaction was performed using 10 mol% of DMSO (Table 1, entry 6). When the reactions were carried out using other copper salts, such as, CuCl, $CuCl_2$ and $Cu(OAc)_2$ or using reduced amounts of CuI (3 and 1 mol%), product **3a** was obtained in lower yields compared to reactions using 5 mol% of CuI (Table 1, entries 12–17 *vs.* 3).

In an optimized reaction, diphenyl diselenide **1a** (0.25 mmol), 4-methoxyphenyl boronic acid **2a** (0.5 mmol), CuI (5 mol%) and DMSO (0.5 mmol) were dissolved in glycerol (0.5 mL). The heterogeneous reaction mixture was stirred for 30 hours at 110 °C under atmospheric air affording 4-methoxyphenyl-phenyl selenide **3a** in 90% yield.

After reaction optimization, a study regarding the recovering and reusing of glycerol was performed. Subsequent to the formation of product **3a**, the reaction mixture was diluted and extracted with a mixture of hexane/ethyl acetate 95 : 5 (3 × 3 mL). The upper phase was dried and the solvent evaporated. The inferior, glycerol phase, was dried under vacuum and directly reused. However, only traces of compound **3a** were obtained. In view of this result, we performed two different studies. Initially, after the first reaction, we added CuI (5 mol%) on the recovered glycerol phase and performed the reuse. This protocol was not efficient and product **3a** was not formed. In a further study, after the first reaction, we added DMSO (0.5 mmol) on the recovered glycerol phase and to our satisfaction the desired product **3a** was obtained in 88%. After these experiments, we proceeded the reuse study adding new DMSO portions (0.5 mmol) in all runs, according Fig. 1. It was observed that a good level of efficiency was maintained even after being reused three times. Diaryl selenide **3a** was obtained in 90%, 88%, 88% and 86% yields after successive cycles. After four runs, the efficiency of glycerol was decreased and the yield of compound **3a** was 71%.

After that, the scope of our methodology was evaluated by reacting other arylboronic acids **2b–k** with diphenyl diselenide **1a** (Table 2). The results shown in Table 2 reveal that the reaction worked well with a range of substituted arylboronic acids, affording good yields of the products. The reactions are not

Table 2 Synthesis of diarylselenides **3a–q** using glycerol as solvent[a]

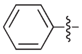
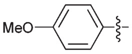
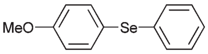
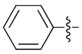
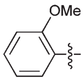
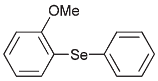
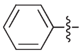
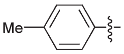
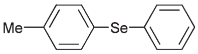
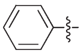
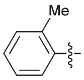
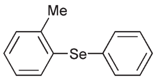
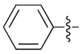
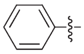
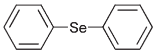
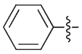
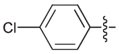
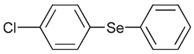
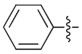
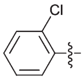
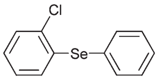
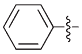
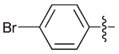
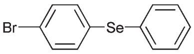
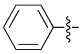
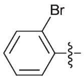
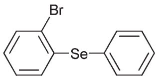
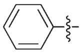
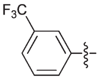
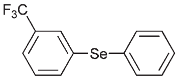
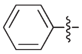
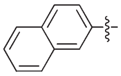
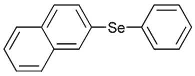
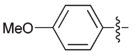
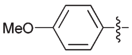
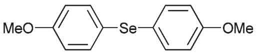
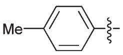
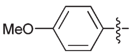
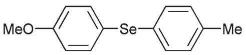
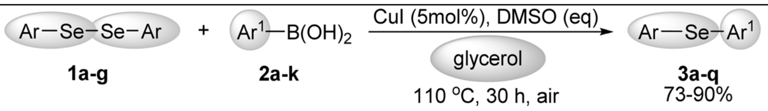
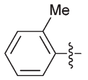
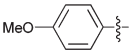
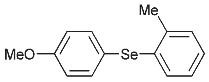
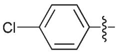
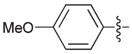
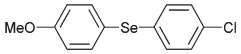
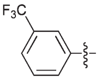
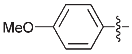
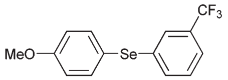
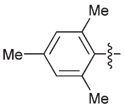
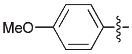
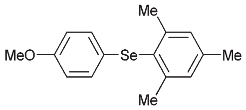
Entry	Ar	Ar^1	Product [ref.]	Isolated Yield (%)
1	 **1a**	 **2a**	 **3a**[16a]	90
2	 **1a**	 **2b**	 **3b**[16a]	85
3	 **1a**	 **2c**	 **3c**[16a]	90
4	 **1a**	 **2d**	 **3d**[16a]	83
5	 **1a**	 **2e**	 **3e**[16a]	90
6	 **1a**	 **2f**	 **3f**[16a]	87
7	 **1a**	 **2g**	 **3g**[16a]	86
8	 **1a**	 **2h**	 **3h**[16a]	86
9	 **1a**	 **2i**	 **3i**[17]	82
10	 **1a**	 **2j**	 **3j**[18]	77
11	 **1a**	 **2k**	 **3k**[19]	73
12	 **1b**	 **2a**	 **3l**[20]	82
13	 **1c**	 **2a**	 **3m**[16a]	80

Table 2 *(Contd.)*



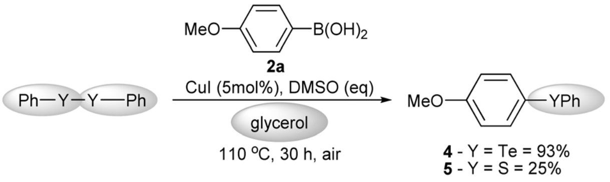
Entry	Ar	Ar^1	Product $^{[ref.]}$	Isolated Yield (%)
14	 **1d**	 **2a**	 **3n**[16a]	80
15	 **1e**	 **2a**	 **3o**[16a]	89
16	 **1f**	 **2a**	 **3p**[21]	79
17	 **1g**	 **2a**	 **3q**[15f]	76

[a] Reactions are performed in the presence of diaryl diselenide (0.25 mmol), arylboronic acid (0.5 mmol), CuI (5 mol%), DMSO (0.5 mmol), glycerol (0.5 mL), at 110 °C for 30 hours in open atmosphere.

sensitive to the electronic effect of the aromatic ring in the arylboronic acid. According the results, arylboronic acids containing electron-donating (OMe, Me), electron-withdrawing (Cl, Br) and electron-neutral group at the aromatic ring gave good yields of desired diaryl selenides (Table 2, entries 1–9). Differentiation in the reactivity between bromine and boron atoms of boronic acid can be seen by coupling of boronic acids **2h** and **2i** with diphenyl diselenide **1a**. In these cases, only the coupling products **3h** and **3i** were obtained in 86% and 82% yield respectively, without by-products (Table 2, entries 8–9). In our methodology, the bromine substituent was not affected. A slight decrease in the yield was observed using 3-trifluoromethyl group attached in the aromatic ring at boronic acid partner (Table 2, entry 10). Reaction performed with 2-naphthylboronic acid **2k** furnished the respective product **3k** in satisfactory yield (Table 2, entry 11).

Later, the possibility of performing these reactions with other diaryl diselenides **1b–g** was also investigated. A range of diaryl diselenides containing electron-donating and electron-withdrawing groups at the aromatic ring were efficiently coupled with 4-methoxyphenylboronic acid **2a**, affording the respective diarylselenides **3l–p** in good yields (Table 2, entries 12–16). We observed that steric effects had little influence on the coupling reaction and dimesityl diselenide gave the desired product **3q** in 76% yield (Table 2, entry 17).

In addition, under the optimized reaction conditions, the possibility of performing the reaction with other diphenyl dichalcogenides was also investigated. Thus, 4-methoxyphenylboronic acid **2a** was efficiently coupled with diphenyl ditelluride, affording the respective diaryltelluride **4** in excellent yield. However, when the arylboronic acid **2a** reacted with diphenyl disulfide, low yield of diarylsufide **5** was obtained (Scheme 2).



Scheme 2 Reaction with diphenyl ditelluride and diphenyl disulfide.

Conclusions

In conclusion, glycerol has proved to be an efficient solvent for the synthesis of diaryl selenides by cross-coupling reactions of diaryl diselenides with aryl boronic acids using a catalytic amount of CuI and DMSO as additive, under open atmosphere at 110 °C. This cross-coupling reaction affords the corresponding products in good to excellent yields and a range of diaryl diselenides and arylboronic acids were coupled. In addition, catalytic system glycerol–CuI can be easily recovered and utilized for further cross-coupling reactions, specially appropriated to green chemistry concept. Studies toward the mechanism insight and the role of DMSO in this reaction are in progress in our laboratory.

Experimental

General

The reactions were monitored by TLC carried out on Merck silica gel (60 F_{254}) by using UV light as visualizant agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. NMR spectra were recorded with Bruker DPX 200 and DPX 400 (200 and 400 MHz) instrument using $CDCl_3$ as solvent and calibrated using tetramethylsilane as internal standard. Chemical shifts are reported in δ ppm relative to $(CH_3)_4Si$ for ^1H and $CDCl_3$ for ^{13}C NMR. Coupling constants (J) are reported in Hertz. Mass spectra (MS) were measured on a Shimadzu GCMS-QP2010 mass spectrometer.

General procedure for the cross-coupling using glycerol

To a round-bottomed flask containing organic diselenide (0.25 mmol), aryl boronic acid (0.5 mmol), CuI (0.025 mmol; 0.0048g), was added glycerol (0.5 mL) and DMSO (0.5 mmol). The reaction mixture was allowed to stir at 110 °C for 30 hours. After this time, the solution was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with water (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The obtained products were purified by flash chromatography on silica gel using hexane or a mixture of ethyl acetate/hexane as the eluent. The spectral data of obtained compounds are in agreement with those described in literature.

Recycling of glycerol

The aforementioned procedure was used with diphenyl diselenide **1a** (0.25 mmol), 4-methoxyphenylboronic acid **2a** (0.5 mmol), CuI (0.025 mmol; 0.0048 g), DMSO (0.5 mmol) and glycerol (0.5 mL). After the reaction was complete, the reaction mixture was washed with a mixture of hexane/ethyl acetate (95 : 5) (3 × 3 mL) and the upper organic phases were separated from glycerol. The product was isolated according procedure above. The resulting glycerol phase was dried under vacuum and reused for further reactions without previous purification.

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