Recent advances in copper-catalyzed C-S cross-coupling reactions

Asha Sujatha, Anns Maria Thomas, Amrutha P Thankachan,
and Gopinathan Anilkumar*

School of Chemical Sciences, Mahatma Gandhi University, Kottayam, Kerala 686 560, India
Email: anilgi1@yahoo.com

DOI: http://dx.doi.org/10.3998/ark.5550190.p008.779

Abstract

Copper-catalyzed cross-coupling reactions offer a powerful tool for the formation of carbon-heteroatom bonds. Copper catalysis has an indisputable advantage over the other catalytic systems due to its low cost and the use of readily accessible and stable ligands. Among the various copper-catalyzed coupling reactions, C-S bond forming reactions have gained much attention due to its applications in the synthesis of molecules having biological and pharmaceutical impact. This review illustrates the current strategies and applications of Cu-catalyzed C-S cross coupling reactions.

Keywords: copper, catalysis, coupling, C-S cross-coupling, ligands, transition metal catalysis

---

Table of Contents

1. Introduction

Thioethers are important class of compounds that are in great demand as intermediates in the synthesis of numerous compounds having biological and therapeutic applications and molecular precursors of material interest.[1-4] The transition metal catalyzed cross-coupling reactions offer a powerful strategy for the construction of aryl-sulfur bonds. This approach involves the coupling of organic halides with thiols. Despite the importance of this reaction protocol in organic synthesis, transition metal catalyzed thioetherification received lesser attention, compared to other carbon-heteroatom bond forming reactions. The strong chelating property of sulfur causes catalyst poisoning, rendering the catalytic reaction ineffective. However, recently there has been considerable progress in the area of transition metal catalyzed organosulfur chemistry.

Migita *et al.* used $Pd(PPh_3)_4$ as a catalyst for the coupling reaction between aryl iodides and bromides with thiols under mild conditions.[5] Many other Pd based catalytic systems have also been developed, which are based on bidentate phosphines or diverse organophosphane derivatives.[6-9] But these systems have limitations since they require the preparation and use of PR_3 ligands which are not eco-friendly. Catalytic systems based on other transition metals such as nickel[10-13], cobalt[14] and iron[15] have also been studied. These catalytic systems also suffer from certain disadvantages like metal toxicity, low turnover numbers etc. But there is much interest in the development of copper based catalytic systems because of the low cost of Cu and use of readily accessible and stable ligands. Many attractive Cu-catalyzed coupling processes have been reported by various research groups. However, the Cu-catalyzed C-S coupling alone has not been reviewed yet, although it has been sparsely discussed with other carbon-heteroatom coupling reactions.[16-20] This review highlights the existing strategies for copper-catalyzed C-S bond forming reactions and covers the literature from 2004-2014.

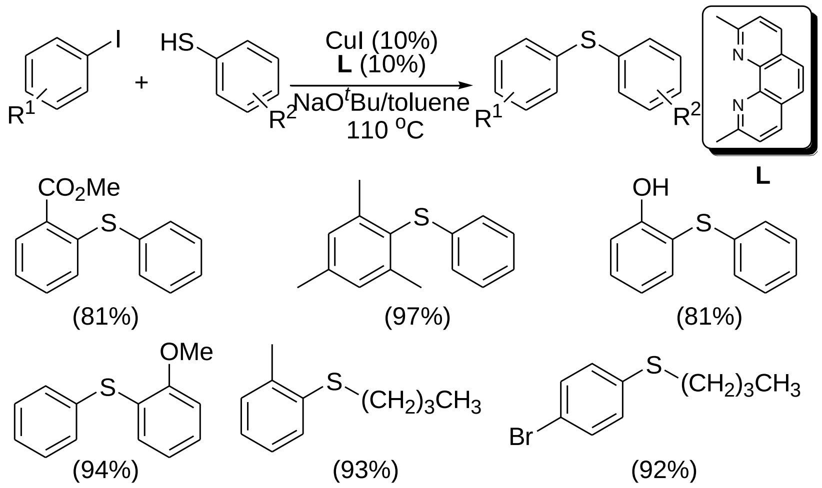
The classical Cu-catalyzed reaction between thiols and aryl halides required stoichiometric amounts of copper salts, polar solvents and high temperature.[21] In recent years there is an upsurge of reports on C-S bond formation using various ligands such as phosphazene P_2-Et base, neocuproine etc., primarily due to the high stability and low cost of copper.

2. Different Catalytic Systems

In this review we classify the catalyst systems according to the nature of the ligand present in the complex

2.1. Cu-Nitrogen complexes

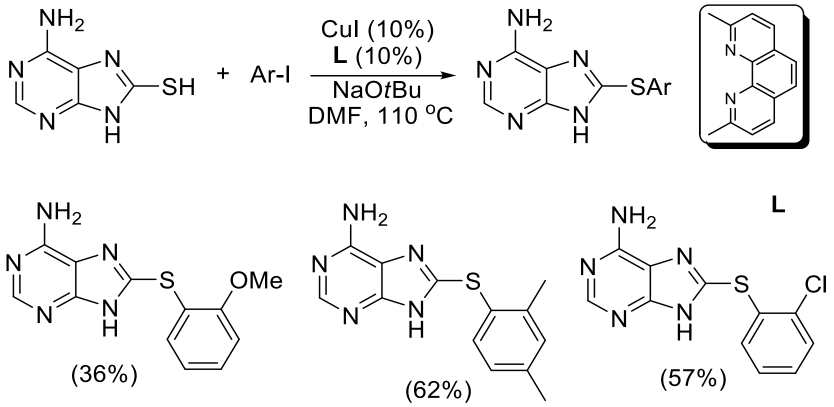
Venkataraman *et al*. have used CuI-neocuproine (2,9-dimethyl-1,10-phenanthroline) complex for the coupling of aryl iodides with aryl and alkyl thiols in presence of NaO^tBu in toluene at 110 ^oC, affording the products in excellent yields (Scheme 1).[22]



Scheme 1. Cu-catalyzed synthesis of sulfides using neocuproine as ligand.

Electron-rich aryl iodides gave better yields in this reaction. The substituents on the *o*-position of the aryl iodide or thiol did not affect the rate of the reaction.

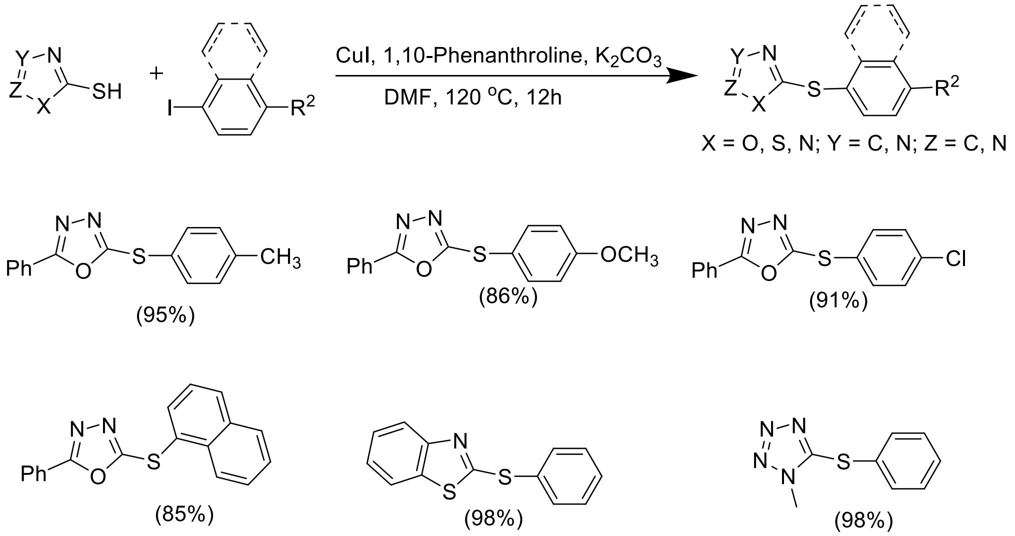
Chiosis *et al*. used the CuI-neocuproine system for S-arylation of 8-mercaptoadenine with aryl iodides in DMF at 110 °C (Scheme 2).[23]



Scheme 2. Cu-catalyzed S-arylation of 8-mercaptoadenine using neocuproine as ligand.

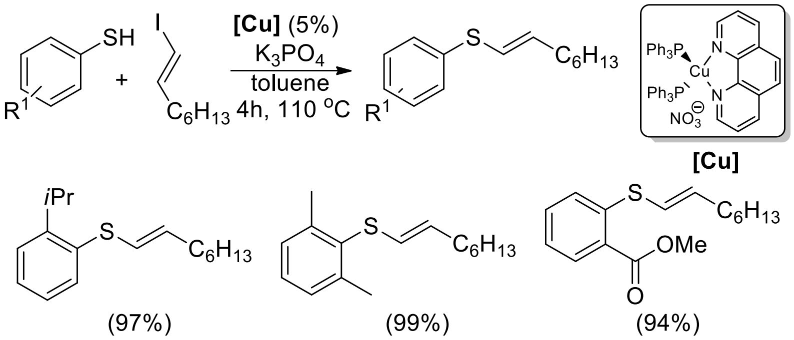
Electron-withdrawing and electron donating groups as well as ortho substituents on the aryl iodide are tolerated in the reaction affording moderate yields of the thioether.

A copper-catalyzed cross-coupling of heterocyclic thiols with aryl iodides was reported by Niu *et al*.[24] The reaction was carried out in the presence of CuI, 1,10-phenanthroline and K_2CO_3 in DMF at 120 ºC, affording the heterocyclic sulfides in high selectivities and yields. (Scheme 3)



Scheme 3. CuI-catalyzed carbon-sulfur bond formation of heterocyclic thiols with aryl iodides.

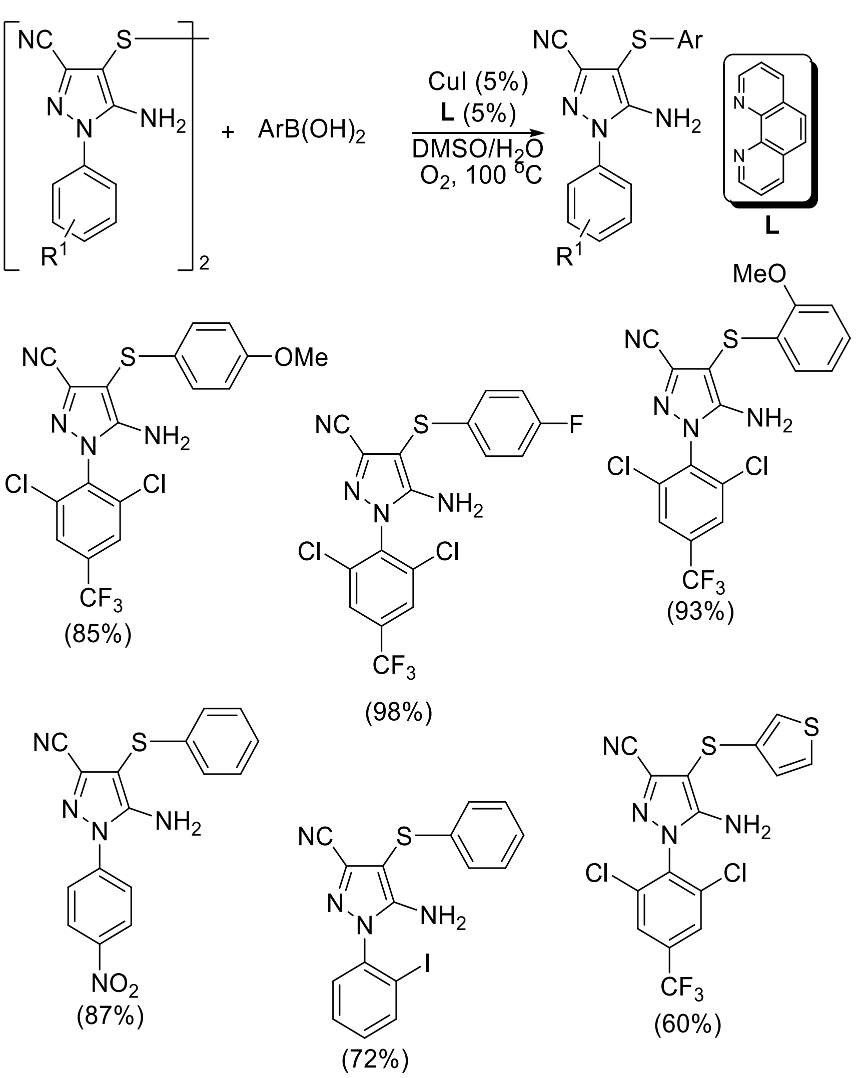
Vinyl sulfides were synthesized in good to excellent yields from vinyl iodides and thiols under CuI-catalysis using 5 mol% [Cu(phen)$(PPh_3)_2$]NO_3 and K_3PO_4 in toluene at 110 ºC (Scheme 4).[25]



Scheme 4. Cu-catalyzed synthesis of vinyl sulfides using [Cu(phen)$(PPh_3)_2$]NO_3 catalyst.

Electronic and steric effects of the substituents on the thiol did not affect the rate of the reaction. Heterocyclic thiols also gave excellent yields.

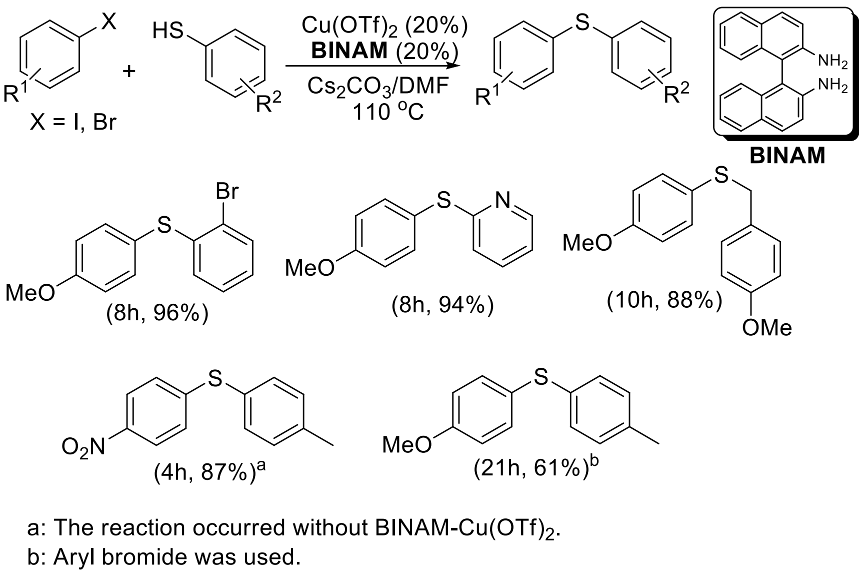
Cu-catalyzed S-arylation of dipyrazolyl disulfides with organoboronic acids in presence of CuI and 1,10-(phen) in DMSO-H_2O afforded good to excellent amount of the products (Scheme 5).[26]



Scheme 5. Cu-catalyzed S-arylation of dipyrazolyl disulfides with organoboronic acids.

Electron rich and electron poor aryl boronic acids afforded good yields of the products. However alkylboronic acids are found to be unsuitable for this transformation. A number of functional groups such as Me, OMe, F, Cl, CF_3, NO_2, CO_2H, on the arylboronic acid are tolerated in the reaction.

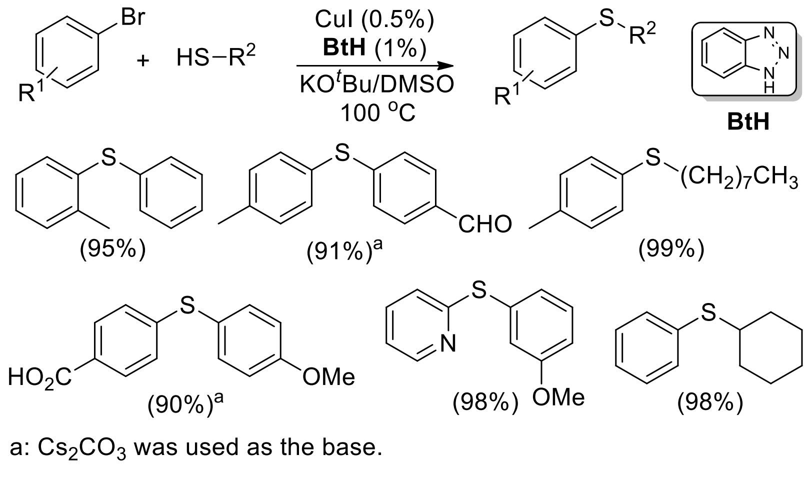
Sekar *et al*. synthesized diarylthioethers from thiols and aryliodides in presence of BINAM-$Cu(OTf)_2$ complex and Cs_2CO_3 in DMF at 110 °C (Scheme 6).[27] The reaction was unaffected by the position of substituents on the aryl iodide.



Scheme 6. Cu-catalyzed synthesis of sulfides using BINAM ligand.

Electron donating and weakly electron withdrawing groups on aryl chloride failed to give the thioether and aryl halides containing strong electron withdrawing groups afforded the thioether product by nucleophilic substitution reaction in the absence of BINAM-Cu catalyst.

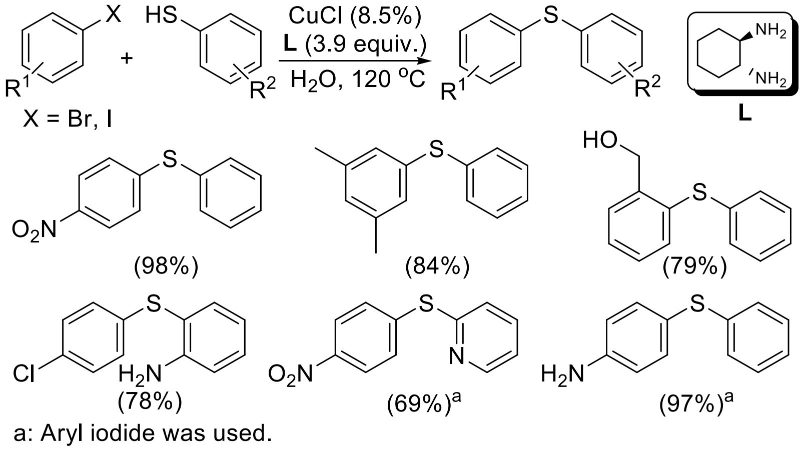
Benzotriazole was also found to be an efficient ligand for C-S coupling reactions.[28] Aryl iodides and aryl bromides coupled with aryl thiols and alkyl thiols in presence of 0.5 mol% CuI and 1 mol% benzotriazole in DMSO at 100 ºC affording the sulfides in >90% yield (Scheme 7). Aryl bromides required only 80 ºC for the reaction to get good yields.



Scheme 7. Cu-catalyzed synthesis of sulfides using benzotriazole as ligand.

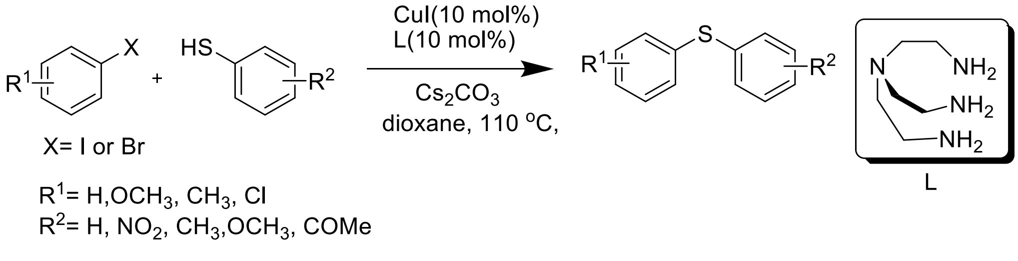
A variety of functional groups were found to be compatible with the reaction.

An environmentally benign diaryl thioether coupling in water has been reported recently.[29] Under the optimized reaction conditions, aryl thiol and aryl iodide or aryl bromide were heated in water at 120 ºC in the presence of CuCl and *trans*-1,2-diaminocyclohexane (Scheme 8). A large variety of functional groups, both electron donating and electron withdrawing as well as free NH_2 and –OH on the aryl iodide partner and aryl thiol partner were found to be compatible with the reaction.



Scheme 8. Cu-catalyzed synthesis of sulfides using *trans*-1,2-diaminocyclohexane ligand in water.

Steric effects arising from *o*-substitution has not shown much influence on the product yield. Aryl bromides are also good substrates for this reaction but restricted to those containing electron withdrawing groups like NO_2, Ac, CF_3 and F. To accommodate electron rich aryl bromides, an *in situ* halogen exchange (Br-I) was carried out on 4-bromoaniline in presence of CuCl, diamine and NaI in water followed by treatment with thiol and diamine, which led to the product (phenyl 4-aminophenyl sulfide) in good yield (84%). The green coloured aqueous solution obtained after removing the product could be further used for three consecutive reaction cycles without isolation and reactivation of the catalyst and without any loss of activity.

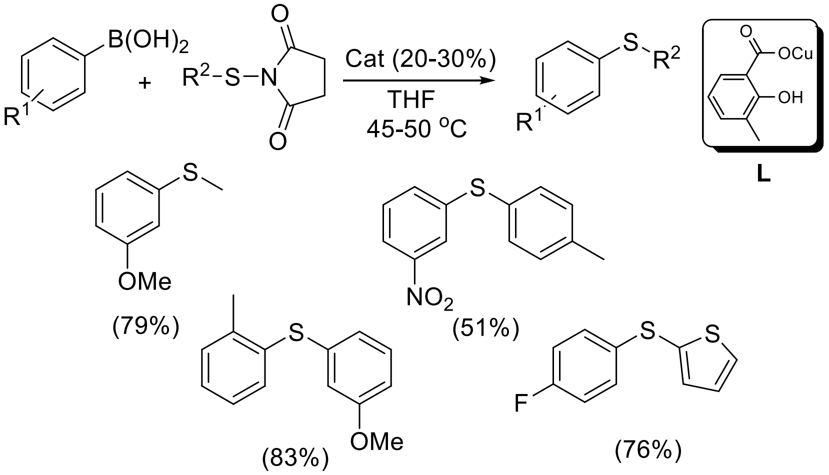


Scheme 9. Cu-catalyzed coupling of thiol with aryl halide using tris-(2-aminoethyl)amine ligand.

Shingare and co-workers developed an efficient methodology for the copper-catalyzed C-S cross-coupling reactions of aryl halides with thiols using a tripodal ligand, tris-(2-aminoethyl)amine.[30] (Scheme 9)

2.2. Cu-oxygen complexes

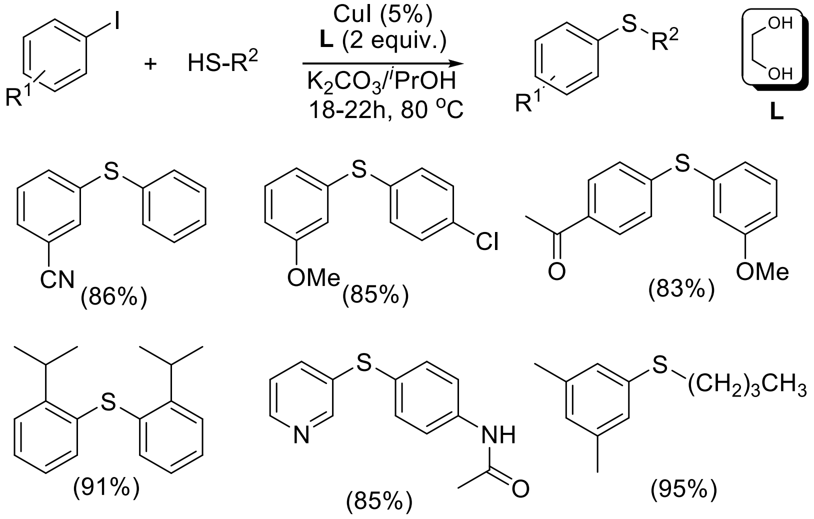
Liebeskind and coworkers reported a mild synthesis of thioethers *via* Cu(I) catalyzed coupling of boronic acids with *N*-thioimides in good yields (Scheme 10).[31] In a typical reaction, two equivalents of boronic acid reacted with *N*-(alkyl, aryl or heteroaryl thio)imides in presence of 20-30 mol% Cu^1-3-methylsalicylate (CuMeSal) in THF at 45-50 ºC, yielding the corresponding thioethers in good yields.



Scheme 10. Cu-catalyzed synthesis of diaryl sulfides using CuMeSal catalyst.

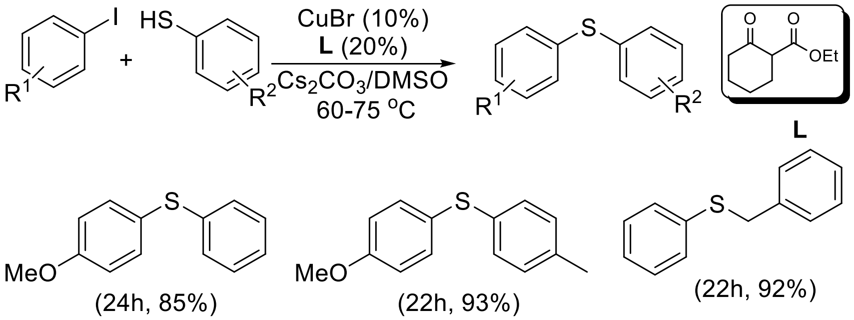
A variety of functional groups in the phenylboronic acid such as methoxy, nitro, CF_3, fluoro etc. were tolerated in the reaction. Notably, functional groups sensitive to reducing conditions (eg. NO_2) were unaffected in this reaction.

At the same time, Buchwald and Kwong reported a simple thioether formation protocol from aryl iodides and aryl/alkyl thiols using CuI, ethyleneglycol and K_2CO_3 in isopropanol at 80 ºC (Scheme 11).[32] Functional groups such as cyano, nitro, keto, amino, hydroxyl, carboxylic acid, aldehyde, on the aryl iodide are compatible with the reaction. The reaction is also tolerant of steric hindrance as many *o*-substituted aryl iodides yielded the thioethers in excellent yields. Aliphatic thiols are also found to be efficient nucleophiles in this reaction. Buchwald then used the protocol in the coupling of 6-iodoimidazo[1,2-*a*]pyridine with thiophenols and obtained the products in moderate yields.[33]



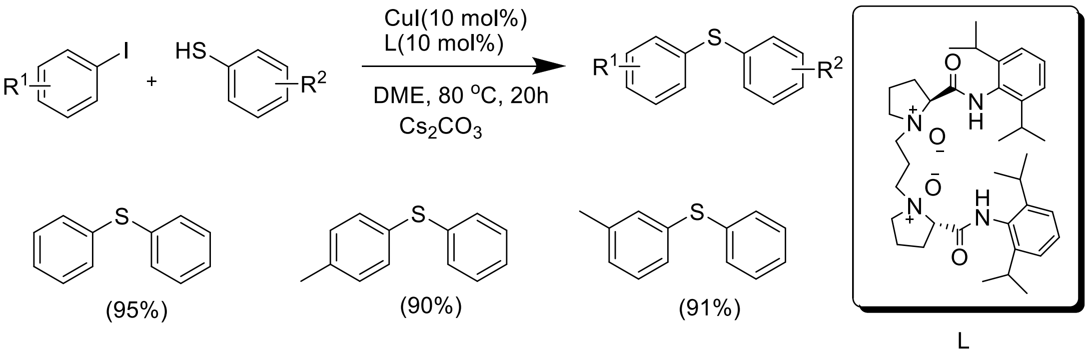
Scheme 11. Cu-catalyzed synthesis of sulfides using ethyleneglycol as ligand.

The β-ketoester used in C-N and C-O coupling reaction was also found to be an efficient ligand for C-S bond formation.[34] Aryl iodides containing electron donating and electron neutral groups reacted with electron rich and electron neutral thiols in the presence of CuBr, β-ketoester ligand and Cs_2CO_3 in DMSO at 60-75 °C affording very high yields of the corresponding diarylthioethers (Scheme 12).



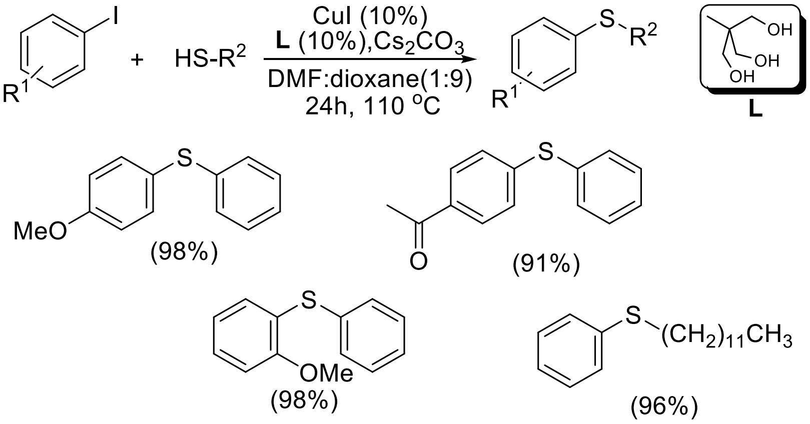
Scheme 12. Cu-catalyzed synthesis of sulfides using ethyl 2-oxocyclohexanecarboxylate.

The S-arylation reactions of thiols with aryl halides catalyzed by N,N′-dioxide/ CuI catalytic system was reported by Chen *et al*.[35] The reaction was carried out in presence of Cs_2CO_3 in DME at 80 °C.(Scheme 13)



Scheme 13. Cu-catalyzed S-arylation of thiols with aryl halides using N,N′-dioxide as ligand.

The tripodal ligand 1,1,1-tris(hydroxymethyl)ethane used in C-N and C-O coupling reaction was found to be efficient in the C-S coupling as well.[36] Aryl iodides reacted with aryl and alkyl thiols in presence of CuI, tripodal ligand and Cs_2CO_3 in DMF:dioxane (1:9) at 110 ºC affording the thioethers in excellent yields (Scheme 14).



Scheme 14. Cu-catalyzed synthesis of sulfides using the tripodal ligand 1,1,1-tris-(hydroxymethyl)ethane.

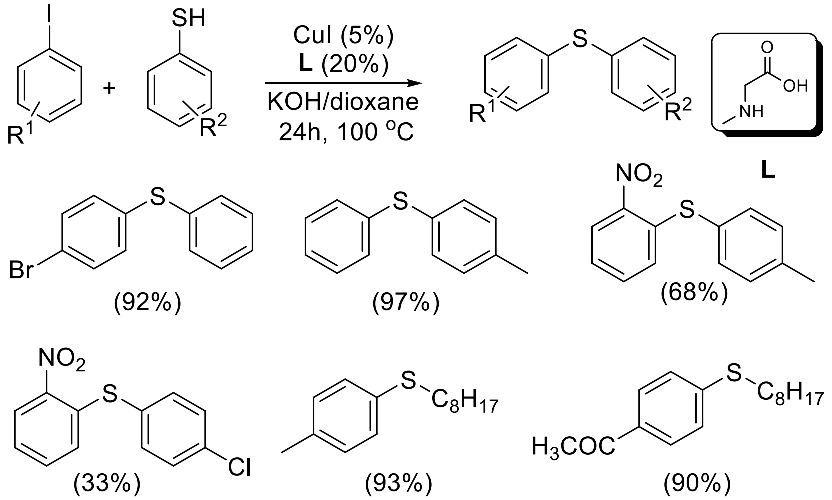
In the limited examples studied, methoxy and keto groups on the aryl iodide and methoxy and chloro on the aryl thiol were found to be compatible with the reaction.

Biologically active thioethers were synthesized by CuI catalyzed coupling of aryl or heteroaryl chlorides with aryl mercaptan using racemic trans-cyclohexane-1,2-diol.[37]

Basu *et al*. have used catechol violet as a ligand for the CuI catalyzed thioether formation in DMF at 70-90 ºC in which electron rich and electron deficient aryl iodides afforded good yields of the products.[38]

2.3. Cu–N and O bidentate ligand complexes.

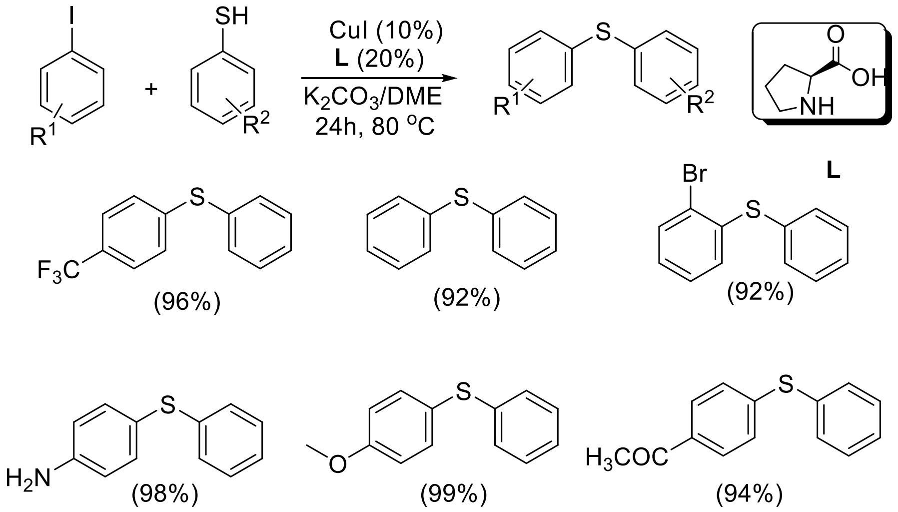
Guo *et al*. reported a thioether synthesis using CuI–*N*-methylglycine system in presence of KOH in dioxane at 100 ºC (Scheme 15).[39]



Scheme 15. Cu-catalyzed synthesis of sulfides using methylglycine as ligand.

Aryl iodides having electron donating or electron withdrawing groups gave very good yields with alkyl and aryl thiols. Aryl bromides also afforded the sulfide but the rate of reaction was low. The reaction could also be carried out in DMF solvent and with K_3PO_4 as base.

This procedure was then modified by Ma *et al*. using L-proline at lower temperature.[40] Thus aryl iodides reacted with aryl and alkyl thiols in presence of 10 mol% CuI, 20 mol% L-proline and K_2CO_3 (or K_3PO_4 for aliphatic thiols) in DME at 80 ºC affording excellent yields of the products.(Scheme 16)



Scheme 16. Cu-catalyzed synthesis of sulfides using L-proline as ligand.

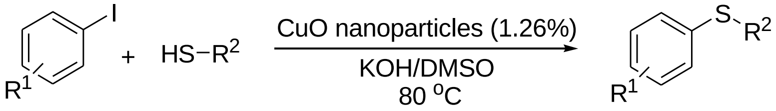
Both electron withdrawing and electron donating groups on the aryl iodide as well as *o*-substituted aryl iodides afforded very high yields of the thioether products with both aryl and alkyl thiols.

2.4. Cu nanoparticles

Cu nanoparticles have excellent catalytic activity because of their high surface to volume ratios. A ligand-free diaryl or aryl alkyl thioether formation was achieved between aryl iodides and aryl/alkyl thiols using Cu nanoparticles under microwave irradiation (120 ºC) in less than 10 min. in presence of K_2CO_3 in DMF.[41] Many functional groups including free NH_2 and OH were tolerated in the reaction. Substituents at the *ortho* position of the aryl iodide did not affect the reaction.

CuO nanoparticles are also found to be efficient catalyst for C-S bond formation.[42] Aryl and alkyl thiols underwent coupling reaction with aryl iodides in presence of 1.26 mol% CuO nanoparticles and KOH in DMSO at 80 ºC affording in most cases quantitative yields of the products in less than 10h (Table 1).

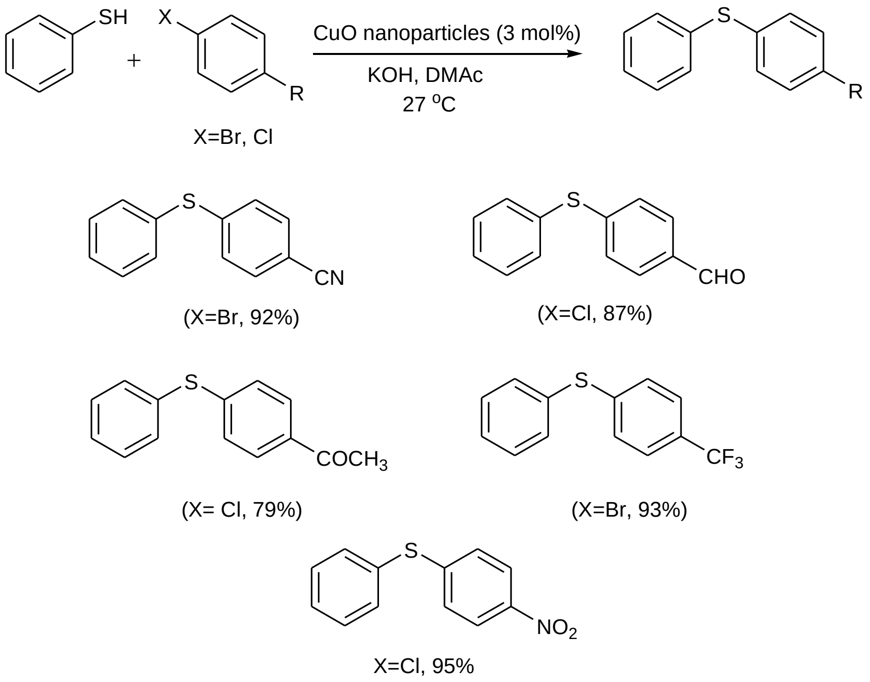
Table 1. CuO nanoparticle-catalyzed synthesis of aryl sulfides



Entry	Iodide: R^1	Thiol: R^2	Reaction time (h)	Yield (%)
1	H	C_6H_4OMe-*p*	9.5	99
2	H	$C_6H_4NO_2$-*p*	15	88
3	H	C_6H_4Br-*o*	9	90
4	H	$(CH_2)_5CH_3$	7	91
5	H	Ph	5	71
6	*p*-MeO	Ph	5	14
7	*p*-O_2N	Ph	5	83

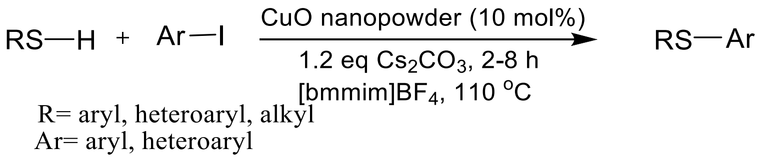
Electron donating groups on thiols were found to be more reactive than electron withdrawing groups. Electron withdrawing groups on the aryl iodides enhanced the yield of the sulfide product. The catalyst was found to be suitable for reuse up to three cycles without appreciable loss of activity.

Babu and Karvembu reported a nano CuO-catalyzed C-S cross coupling of aryl halides with thiophenol in presence of KOH as a base in dimethylacetamide (DMAc) at room temperature under ligand-free conditions (Scheme 17).[43]



Scheme 17. CuO nanoparticle-catalyzed S-arylation of thiophenols.

Another nano copper oxide catalyzed cross coupling reaction of thiols with aryl iodides in [bmmim]BF_4 was reported by Braga *et al* (Scheme 18).[44] Compared to the usual organic solvents, [bmmim]BF_4 exhibited more efficiency as it can be reused up to four successive runs.



Scheme 18. CuO nanoparticle-catalyzed S-arylation of thiols with aryl iodides.

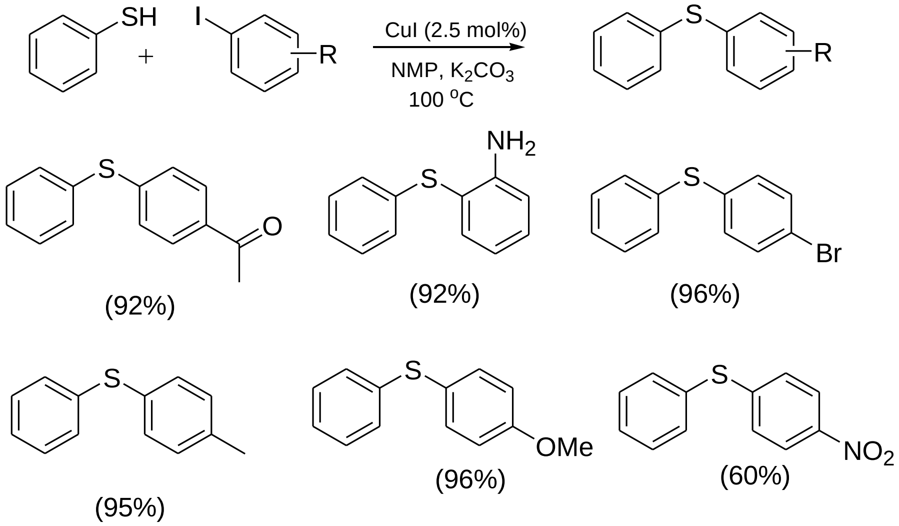
This reaction offers a strategy to obtain diaryl or alkyl aryl sulfides from aryl iodides and thiols using CuO nanopowder in ionic liquid as a reusable medium.

Kamal and coworkers developed a method for C-S bond forming reactions, catalyzed by copper oxide nanoparticles supported on graphene oxide, employing weak bases like triethyl amine.[45] A variety of aryl sulfides were synthesized using this strategy. The authors extended the scope of this method for the synthesis of symmetrical diaryl sulfides from thiourea and aryl iodides.

2.5. Ligand free catalytic systems

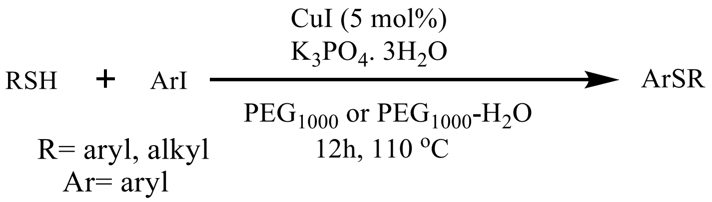
The general approach for Cu-catalyzed C-S cross coupling reactions is the use of a catalytic amount of copper salt, always in presence of a ligand and a base under relatively mild conditions. But in some cases the coupling can even be carried out under ligand-free conditions. The ligand-free catalytic procedures are interesting since it avoids the use of expensive and time consuming preparation of ligands.

van Koten and coworkers reported an efficient C-S bond forming reaction of aryl iodides and thiophenol under ligand free conditions.[46] The reaction was catalyzed by CuI in presence of K_2CO_3 base in *N*-methylpyrrolidinone at 100 ºC (Scheme 19). A variety of diaryl thioethers were synthesized with good functional group tolerance.



Scheme 19. Cu-catalyzed S-arylation of thiophenol with aryl iodides under ligand-free conditions.

Another ligand-free protocol for C-S coupling of thiols with aryl iodides was reported by Wang *et al*.[47] The reaction was catalyzed by CuI-PEG or CuI-PEG-H_2O system (Scheme 20). A variety of functionalized aryl sulfides were synthesized in excellent yields by this method. Both aryl thiols and aliphatic thiols reacted well with the aryl iodides.

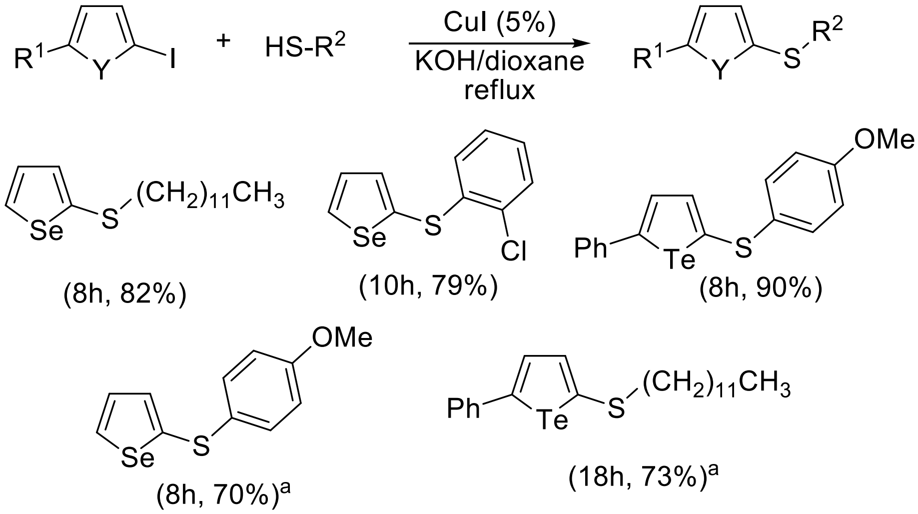


$$\text{RSH} + \text{ArI} \xrightarrow[\text{PEG}_{1000} \text{ or PEG}_{1000}\text{-H}_2\text{O, 12h, 110 °C}]{\text{CuI (5 mol\%), K}_3\text{PO}_4\text{. 3H}_2\text{O}} \text{ArSR}$$

R= aryl, alkyl
Ar= aryl

Scheme 20. CuI-PEG-catalyzed S-arylation of thiols with aryl iodides.

Thioether formation on 2-iodo and 2-bromo chalcogenophenes occurred smoothly on treatment of the chalcogenophenes with thiols in presence of catalytic CuI and KOH or K_3PO_4 in refluxing dioxane (Scheme 21).[48]

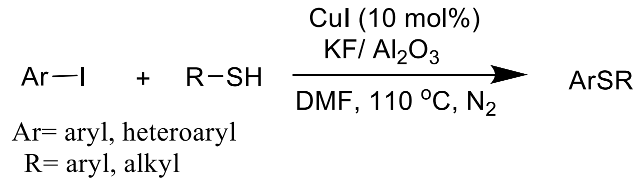


a: Bromo chalcogenophene was used with CuI(10%) and K_3PO_4.

Scheme 21. Cu-catalyzed synthesis of sulfides from 2-halochalcogenophenes.

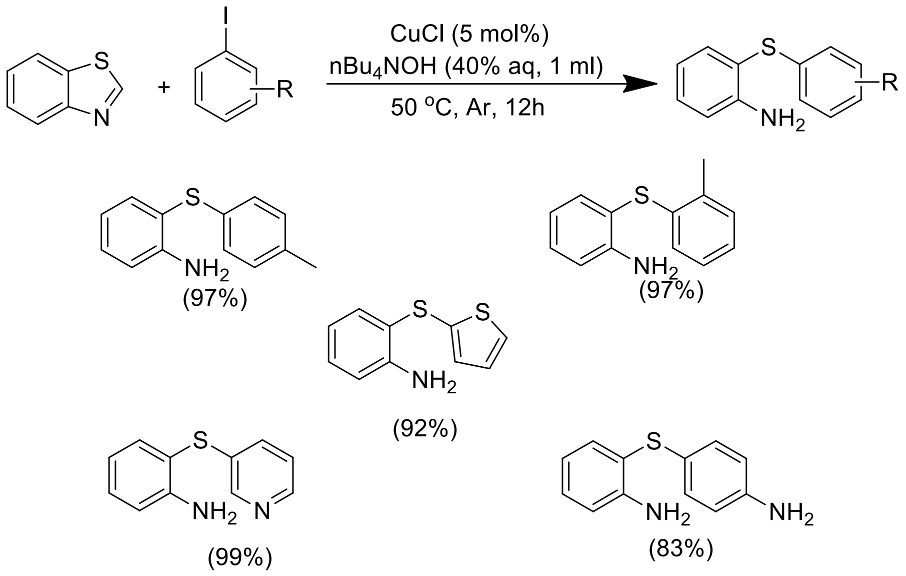
For iodochalcogenophenes, 5 mol% CuI and KOH base and for bromo derivatives, 10 mol% CuI and K_3PO_4 were found to be the best reagents. The reaction was found to be insensitive to the electronic nature of thiol and also the nature of the substitution at the ortho position. Notably, no ligand was used in this reaction.

Feng *et al*. explained a ligand-free copper-catalyzed C-S cross coupling of thiols with aryl iodide using KF/Al_2O_3 as base.[49] The reaction was carried out in DMF at 110 ºC (Scheme 22).



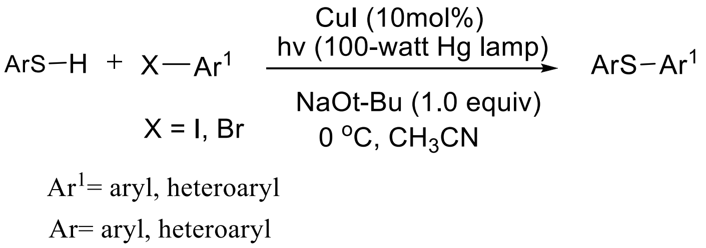
Scheme 22. Cu-catalyzed C-S cross coupling of thiols with aryl iodide using KF/Al_2O_3 as base.

Feng *et al*. also reported a ligand-free copper-catalyzed C-S cross coupling of benzothiazole with aryl iodides in aqueous solution to form 2-aminophenyl sulfide derivatives (Scheme 23).[50] The reactions were catalyzed by CuCl with tetrabutylammonium hydroxide as base and water as the solvent at 50 ºC.



Scheme 23. Cu-catalyzed C-S cross coupling of benzothiazole with aryl iodides.

Recently, Peters *et al*. reported the first photo-induced copper-catalyzed cross coupling reaction between aryl thiols and aryl halides *via* single electron transfer under mild conditions (0° C) (Scheme 24).[51] The inexpensive CuI was used as the precatalyst without the need of any ligand. This new strategy can be applied for the efficient cross coupling of a broad range of aryl thiols with a wide array of functionalized aryl halides.



$$\mathrm{ArS{-}H} + \mathrm{X{-}Ar^1} \xrightarrow[\substack{\text{NaOt-Bu (1.0 equiv)}\\ 0\ ^{\circ}\text{C, CH}_3\text{CN}}]{\substack{\text{CuI (10mol\%)}\\ h\nu\ \text{(100-watt Hg lamp)}}} \mathrm{ArS{-}Ar^1}$$

X = I, Br

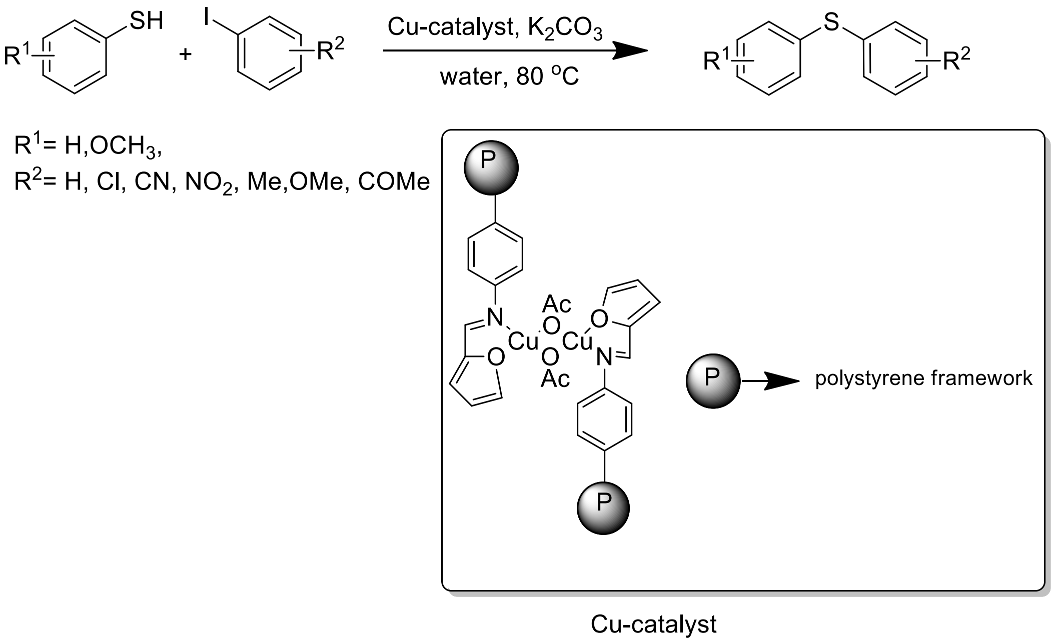
Ar^1= aryl, heteroaryl

Ar= aryl, heteroaryl

Scheme 24. Photo-induced Cu-catalyzed C-S cross coupling reaction of aryl thiols with aryl halides.

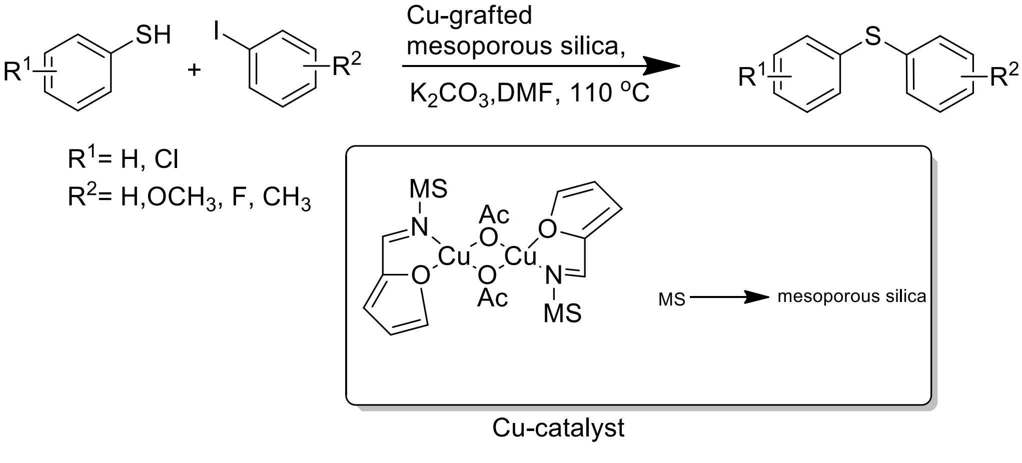
2.6. Supported Cu catalysts

Islam *et al*. reported the synthesis of a furfural functionalized polymer-amine grafted with copper which was used as an excellent catalyst for S-arylation reactions of various aryl halides with aryl thiols in water medium (Scheme 25).[52] The catalyst could be reused for several consecutive cycles with consistent catalytic activity.



Scheme 25. C–S coupling reaction catalyzed by polymer supported Cu-catalyst.

Bhaumik *et al.* synthesized a Cu(II)-grafted furfural functionalized mesoporous organosilica catalyst for the aryl-sulfur coupling reaction between different aryl iodides and thiophenol (Scheme 26).[53]



Scheme 26. C–S coupling reactions catalyzed by Cu-grafted functionalized mesoporous material.

A copper modified amine-functionalized zirconia which could be used as an efficient catalyst for C-S coupling reactions was developed by Parida and co-workers.[54] The amine functionalization provides a better loading and uniform distribution of the Cu particle in the zirconia surface. The catalyst shows good catalytic activity and recycling efficiency.

3. Mechanism

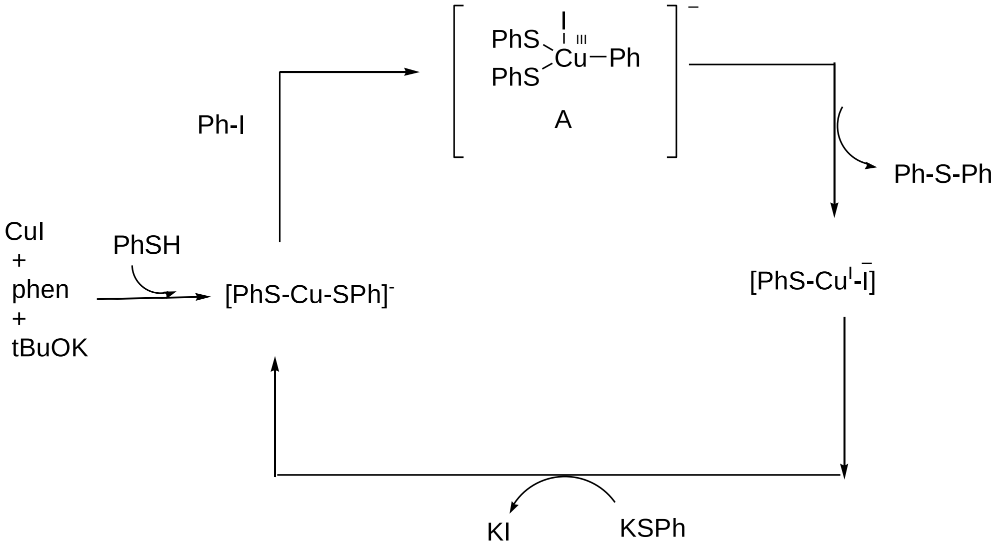
Although the mechanism of Cu-catalyzed C-N coupling has been extensively studied, the corresponding C-S bond formation has not received much attention.

The copper(I)-catalyzed Ullmann-type C-S coupling reaction generally consists of a ligand, a base and a copper salt. Better yields are obtained when a ligand was used in combination with a copper(I) catalyst indicating that the proposed intermediate of the reaction could be a Cu(I) complex chelated with the additive ligand.[55]

In the proposed mechanism of copper(I)-catalyzed C-S coupling reaction, the base deprotonates the thiol generating a thiolate, which may then replace the counter anion of the copper source and produce a copper complex Cu(I)L(SR) with the thiolate and the ligands.[56] An oxidative addition of the aryl halide (ArI) to the complex takes place to produce the intermediate Cu(III)LArI(SR). This intermediate regenerates the Cu(I)LI and the desired product ArSR by reductive elimination. Another proposed mechanism involves the oxidative addition of the aryl halide to form Cu(III)LArI followed by the substitution of the I- with the RS- to form Cu(III)LAr(SR).[57-60] However, the intermediates from the catalytic reaction has not been directly observed or isolated, and the mechanism of the catalytic reaction has not been well established so far.

An *in situ* electrospray ionization mass spectrometry (ESI-MS) study of the copper(I)-catalyzed Ullmann-type C-S coupling reaction under catalytic reaction condition was carried out by Shyu and coworkers.[61] Thus coupling reaction between iodobenzene and thiophenol was studied using catalytic CuI in presence of potassiun *tert*-butoxide as base and 1,10 phenanthroline as ligand in toluene at 120 °C for 6h. Complexes $[Cu(SPh)_2]^-$, $[Cu(SPh)I]^-$ and $K[Cu(SPh)_2(Ph)]^+$ were observed under the catalytic reaction conditions indicating that they are intermediates in the reaction. A reaction mechanism was proposed based on these observations (Scheme 27).

The reaction of thiophenol with potassium *tert*-butoxide and CuI generates the complex $[Cu(SPh)_2]^-$ which on reaction with iodobenzene produces the intermediate $[Cu(SPh)_2(Ph)I]^-$ through an oxidative addition reaction. Reductive elimination of diphenyl thioester generates $[Cu(SPh)I]^-$ which subsequently reacts with PhS^- to form $[CuSPh)_2]^-$ and completes the catalytic cycle.

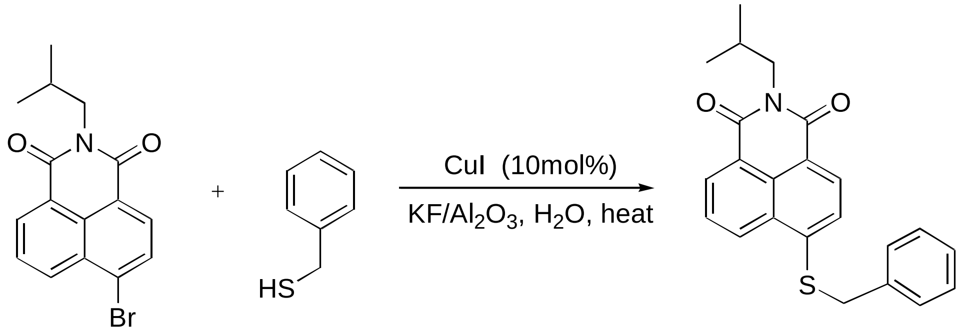


Scheme 27. The proposed mechanism for Cu-catalyzed C-S coupling by Shyu *et al.*

4. Applications

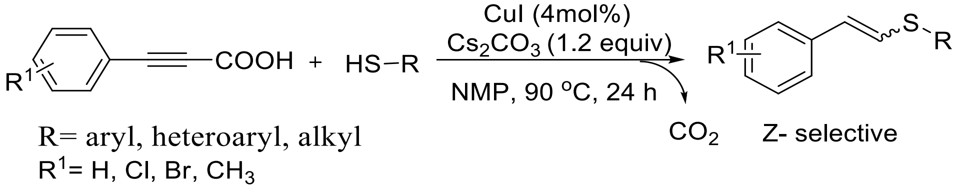
Carbon-heteroatom bond forming reactions have emerged as one of the most versatile and powerful tool in organic synthesis. The products of such transformations are often used as fine chemicals, pharmaceuticals, dyes and polymers. Many synthetic methodologies involving carbon-heteroatom coupling reactions have been developed. Among them, C-S bond forming reaction gained much attention since thioethers are of great significance due to their broad spectrum of therapeutic activities. The C-S bond forming reactions are widely used in pharmaceutical research, material synthesis and process development in industry and academia.

Bardajee demonstrated an efficient synthesis of fluorescent naphthalimide dyes *via* a CuI-catalyzed C-S cross coupling reaction between benzylthiol and 4-bromo-*N*-isobutylnaphthalimide (Scheme 28).[62] 1,8-Naphthalimide derivatives are highly fluorescent and photostable and they have wide range of applications as fluorescent synthetic polymers, liquid crystal additives, fluorescent markers in medicine and biology, as fluorescent solar energy collectors and in laser technology.



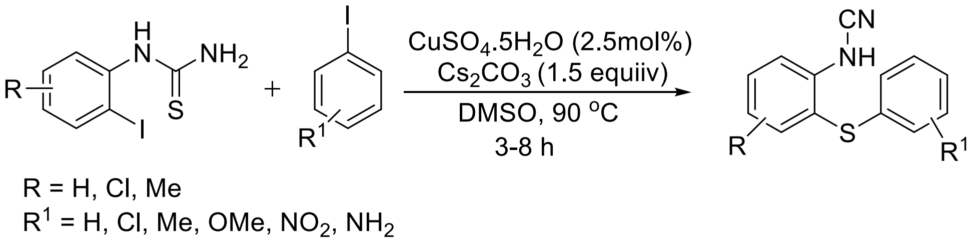
Scheme 28. Cu-catalyzed synthesis of a fluorescent naphthalimide derivative.

Nowadays the significance of vinyl sulfides has increased greatly, since they can be used as complementary building blocks to carbonyl compounds and Michael acceptors for the synthesis of many polymeric materials, natural products and synthetic reagents. Conventional methods for the synthesis of vinyl sulfides require harsh reaction conditions. Liu *et al*. developed a novel method for the synthesis of aryl sulfides *via* a Cu-catalyzed decarboxylative cross coupling of aryl propiolic acids with thiols (Scheme 29).[63] The reaction was catalyzed by CuI in presence of Cs_2CO_3. A broad range of thiols reacted with aryl propiolic acids to form the corresponding vinyl sulfides in good to excellent yields with high stereoselectivity for *Z*-isomers.



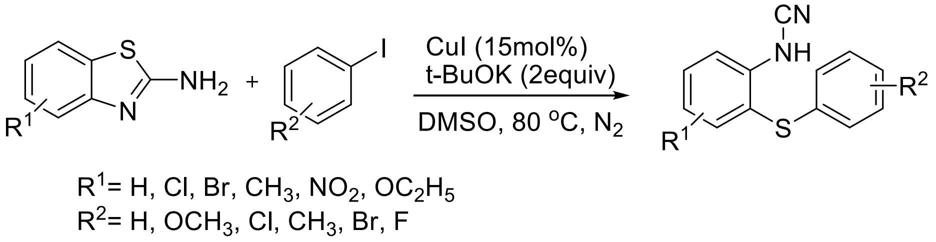
Scheme 29. Cu-catalyzed synthesis of vinyl sulfides.

Compounds containing a cyanamide functional group gained attention in synthetic organic chemistry because of their unique structure and reactivity.Punniyamurthy and coworkers reported a one- pot synthesis of 2-(arylthio)aryl cyanamides using cheap and air stable $CuSO_4.5H_2O$ as a catalyst by domino intra- and inter-molecular C-S cross coupling reactions of 2-(iodoaryl)thioureas with aryl iodides under ligand free conditions (Scheme 30).[64]



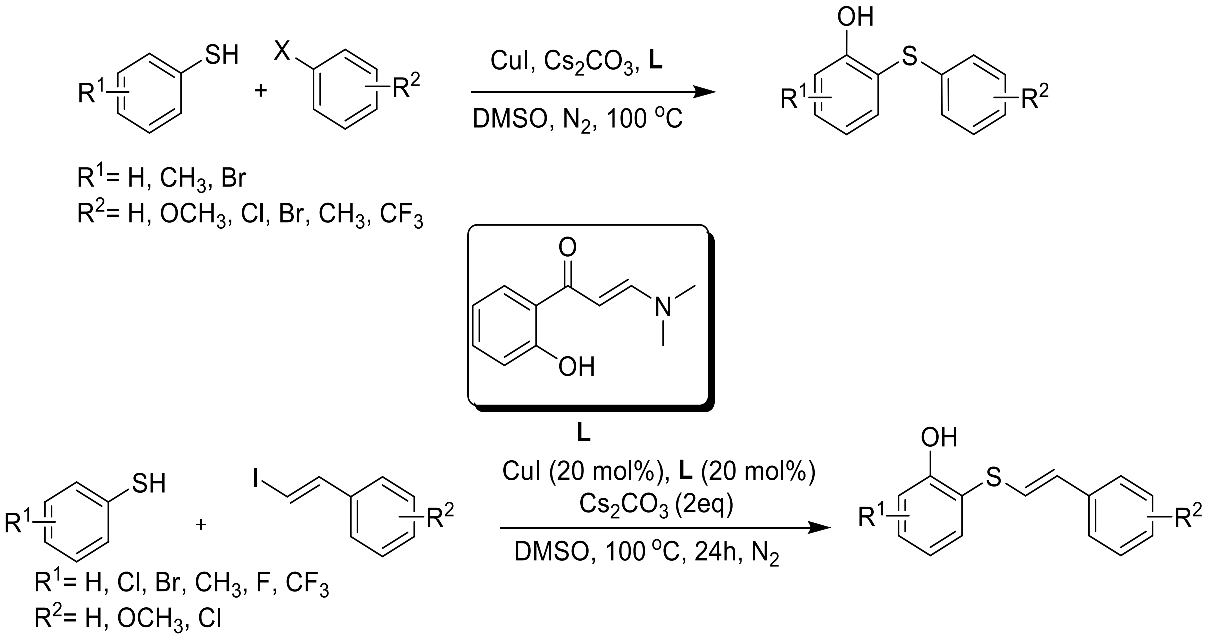
Scheme 30. Cu-catalyzed synthesis of 2-(arylthio)aryl cyanamides.

Another protocol for the synthesis of 2-(arylthio)aryl cyanamide derivatives was demonstrated by Shao *et al* (Scheme 31).[65] They synthesized the cyanamides *via* a copper-catalyzed domino C-S cross coupling of 2-aminobenzothiazoles with aryliodides. This reaction proceeded through an intermolecular C-S bond formation, associated with C-S bond cleavage followed by an intermolecular S-arylation under ligand free conditions.



Scheme 31. Cu-catalyzed synthesis of 2-(arylthio)aryl cyanamides.

Pan *et al*. synthesized 2-(phenylthio)phenols from simple phenols and aromatic halides by using dimethyl sulfoxide as the oxidant, via a tandem CuI catalyzed C-S coupling / C-H functionalization in presence of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one ligand.[66] This protocol was also applied to the regioselective copper(I) catalyzed C-H hydroxylation/ C-S coupling of aryl thiols with vinyl halides for the synthesis of 2-(styrylthio)-phenol derivatives.[67] (Scheme 32) The 2-(styrylthio)phenols have been employed in synthesis of many bioactive compounds.



Scheme 32. Cu-catalyzed C-H hydroxylation/ C-S coupling of aryl thiols with aryl and styryl halides.

5. Conclusions

This review highlights the recent developments in copper-catalyzed carbon-sulfur bond forming reactions. The C-S bond forming reactions serve as powerful tools in synthetic organic chemistry for the synthesis of various molecules that are of biological, pharmaceutical and material interest. Even though various other transition metals are used for catalyzing C-S cross coupling reactions, copper is found to be the most suitable one, as it is less toxic and inexpensive. This review also demonstrates the use of copper nanoparticles as an efficient catalyst for C-S cross coupling reactions.

Acknowledgements

GA thanks the Kerala State Council for Science, Technology and Environment (KSCSTE), Trivandrum (Order no. 341/2013/KSCSTE dated 15.03.2013) for financial support. AS and AMT thank the Council of Scientific and Industrial Research (CSIR, New Delhi) for Junior research fellowships. APT thanks the KSCSTE for a junior research fellowship.

References

1. Procter, D. J. *J. Chem. Soc., Perkin Trans*. 1 **2001**, 335–354. http://dx.doi.org/10.1039/b002081h
2. Kondo, T.; Mitsudo, T.-A. *Chem. Rev*. **2000**, *100*, 3205–3220, references therein. http://dx.doi.org/10.1021/cr9902749
3. Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. http://dx.doi.org/10.1016/S0040-4020(01)91791-0
4. Correa, A.; Bolm, C. *Adv. Synth. Catal*. **2007**, 349–2673.
5. Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 3657–3658. http://dx.doi.org/10.1246/bcsj.58.3657
6. Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397–7403. http://dx.doi.org/10.1016/j.tet.2004.05.044
7. Fernández-Rodrìguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem. Eur. J*. **2006**, *12*, 7782–7796, and references therein. http://dx.doi.org/10.1002/chem.200600949
8. Fernández-Rodrìguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 2180–2181. http://dx.doi.org/10.1021/ja0580340
9. Itoh, T.; Mase, T. *Org. Lett*. **2004**, *6*, 4587–4590. http://dx.doi.org/10.1021/ol047996t
10. Cristau, H. J.; Chabaud, B.; Chene, A.; Christol, H. *Synthesis* **1981**, 892-894.

http://dx.doi.org/10.1055/s-1981-29636

11. Yatsumonji, Y.; Okada, O.; Tsubouchi, A.; Takeda, T. *Tetrahedron* **2006**, *62*, 9981-9987. http://dx.doi.org/10.1016/j.tet.2006.08.001
12. Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495-3498. http://dx.doi.org/10.1021/ol071248x
13. Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484-1487. http://dx.doi.org/10.1016/j.tetlet.2007.12.118
14. Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613-5616. http://dx.doi.org/10.1021/ol062344l
15. Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880-2883. http://dx.doi.org/10.1002/anie.200705668
16. Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449. http://dx.doi.org/10.1002/anie.200300594
17. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428-2439. http://dx.doi.org/10.1055/s-2003-42473
18. Tekale, S. U.; Jadhav, V. B.; Pagore, V. P.; Kauthale, S. S.; Gaikwad, D. D.; Rajendra, P. P.; *Mini-Reviews in Organic Chemistry*. **2013**, 10, 281-301. http://dx.doi.org/10.2174/1570193X11310030007
19. Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev*. **2011**, *111*, 1596-1636. http://dx.doi.org/10.1021/cr100347k
20. Lee, C-F.; Liu, C.Y.; Badsara, S. S. *Chem. Asian J*. **2014, 9,** 706-722. http://dx.doi.org/10.1002/asia.201301500
21. Lindery, J. Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron* **1984**, *40*, 1433–1456.
22. Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett*. **2002**, *4*, 2803-2806. http://dx.doi.org/10.1021/ol0264105
23. He, H.; Llauger, L.; Rosen, N. ; Chiosis, G. *J. Org. Chem.* **2004**, *69*, 3230-3232. http://dx.doi.org/10.1021/jo049875c
24. Niu, L-F.; Cai,Y.; Liang,C.; Hui,X-P.; Xu, P-F. *Tetrahedron* **2011**, *67*, 2878-2881. http://dx.doi.org/10.1016/j.tet.2011.02.064
25. Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005-5008. http://dx.doi.org/10.1021/ol0477935
26. Luo, P-S.; Wang, F.; Li, J-H.; Tang, R-Y.; Zhong, P. *Synthesis* **2009**, 921-928.
27. Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett*. **2009**, *50*, 1411-1415. http://dx.doi.org/10.1016/j.tetlet.2009.01.022
28. Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett*. **2007**, *48*, 7199-7202. http://dx.doi.org/10.1016/j.tetlet.2007.07.205
29. Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Chem. Eur. J.* **2007**, *13*, 5100-5105.

http://dx.doi.org/10.1002/chem.200601737

30. Jogdand, N. R.; Shingare,B.B.; Shingare,M. S. *Tetrahedron Lett*. **2009**, *50*, 6092-6094.
http://dx.doi.org/10.1016/j.tetlet.2009.08.064
31. Savarin, C.; Srogl, J. ; Liebeskind, L. S. *Org. Lett*. **2002**, *4*, 4309-4312.
http://dx.doi.org/10.1021/ol026948a
32. Kwong, F. Y.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 3517-3520.
http://dx.doi.org/10.1021/ol0266673
33. Gueiffier, C. E.; Thery, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron*, **2006**, *62*, 6042-6049.
http://dx.doi.org/10.1016/j.tet.2006.04.007
34. Lv, X.; Bao, W.; *J. Org Chem*. **2007**, *72*, 3863-3867.
http://dx.doi.org/10.1021/jo070443m
35. Yang, H.; Xi, C.; Miao, Z.; Chen, R. *Eur. J. Org. Chem*. **2011**, 3353–3360.
http://dx.doi.org/10.1002/ejoc.201100274
36. Chen, Y-J.; Chen. H-H. *Org. Lett*. **2006**, *8*, 5609-5612.
http://dx.doi.org/10.1021/ol062339h
37. Bagley, M. C. ; Davis, T.; Dix, M. C.; Fusillo, V.; Pigeaux, M.; Rokicki, M. J.; Kipling, D. *J. Org. Chem*. **2009**, *74*, 8336-8342.
http://dx.doi.org/10.1021/jo9017155
38. Basu, B.; Mandal, B.; Das, S.; Kundu, S. *Tetrahedron Lett*. **2009**, *50*, 5523-5528.
http://dx.doi.org/10.1016/j.tetlet.2009.07.076
39. Deng, W.; Zou, Y.; Wang, Y-F.; Liu, L.; Guo, Q-X. *Synlett* **2004**, 1254-1258.
40. Zhang, H.; Cao, W.; Ma, D. *Synth. Commun*. **2007**, *37*, 25-35.
http://dx.doi.org/10.1080/00397910600977533
41. Ranu, B. C.; Saha, A.; Jana, R. *Adv. Synth. Catal*. **2007**, *349*, 2690-2696.
http://dx.doi.org/10.1002/adsc.200700289
42. Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem. Int. Ed*. **2007**, *46*, 5583-5586.
http://dx.doi.org/10.1002/anie.200701282
43. Babu, S. G.; Karvembu, R. *Tetrahedron Lett*. **2013**, *54*, 1677–1680.
http://dx.doi.org/10.1016/j.tetlet.2013.01.063
44. Schwab, R. S.; Singh, D.; Alberto, E. E.; Piquini, P.; Rodrigues, O. E. D.; Braga, A. L. *Catal. Sci. Technol*. **2011**, *1*, 569-573.
http://dx.doi.org/10.1039/c1cy00091h
45. Kamal, A.; Srinivasulu, V.; Murty, J. N. S. R. C.; Shankaraiah, N.; Nagesh, N.; Reddy, T.S.; Rao, A.V.S.; *Adv. Synth. Catal*. **2013**, *355*, 2297–2307.
http://dx.doi.org/10.1002/adsc.201300416
46. Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem*. **2008**, *73*, 5625–5628.
http://dx.doi.org/10.1021/jo800491k
47. She, J.; Jiang, Z.; Wang, Y. *Tetrahedron Lett*. **2009**, *50*, 593–596.

http://dx.doi.org/10.1016/j.tetlet.2008.11.082

48. Zeni, G. *Tetrahedron Lett*. **2005**, *46*, 2647-2651.
http://dx.doi.org/10.1016/j.tetlet.2005.02.102

49. Feng, Y-S.; Li, Y-Y.; Tang, L.; Wu, W.; Xu, H-J. *Tetrahedron Lett*. **2010**, *51*, 2489-2492.
http://dx.doi.org/10.1016/j.tetlet.2010.02.155

50. Feng, Y-S.; Qi, H-X.; Wang, W-C.; Liang, Y-F.; Xu, H-J. *Tetrahedron Lett*. **2012**, *53*, 2914-2917.
http://dx.doi.org/10.1016/j.tetlet.2012.04.004

51. Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc*. **2013**, *135*, 9548−9552.
http://dx.doi.org/10.1021/ja404050f

52. Islam, M. S.; Salam, N.; Mondal, P.; Roy, A. S.; Ghosh. K.; Tuhina, K. *J. Mol. Catal. A: Chem*. **2014**, *387*, 7–19.
http://dx.doi.org/10.1016/j.molcata.2014.02.007

53. Mondal, J.; Modak, A.; Dutta, A.; Bhaumik, A. *Dalton Trans.* **2011**, *40*, 5228–5235.
http://dx.doi.org/10.1039/c0dt01771j

54. Mallick, S.; Rana, S.; Parida, K. *Dalton Trans*. **2011**, *40*, 9169–9175.
http://dx.doi.org/10.1039/c1dt10951k

55. Haldón, E.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. *Organometallics* **2009**, *28*, 3815‑3821.
http://dx.doi.org/10.1021/om900119r

56. Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev*. **2004**, *248*, 2337‑2364.
http://dx.doi.org/10.1016/j.ccr.2004.09.014

57. Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett*. **2007**, *48*, 7199–7202.
http://dx.doi.org/10.1016/j.tetlet.2007.07.205

58. Rout, L.; Saha, P.; Jammi,S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, *4*, 640-643.
http://dx.doi.org/10.1002/ejoc.200700978

59. Xu, H-J.; Zhao, X-Y.; Deng, J.; Fu, Y.; Feng, Y-S. *Tetrahedron Lett.* **2009**, *50*, 434–437.
http://dx.doi.org/10.1016/j.tetlet.2008.11.029

60. Feng,Y.; Wang, H.; Sun, F.; Li, Y.; Fu, X.; Jin, K. *Tetrahedron* **2009**, *65*, 9737‑9741.
http://dx.doi.org/10.1016/j.tet.2009.09.085

61. Cheng, S-W.; Tseng, M-C.; Lii, K-H.; Lee, C-R.; Shyu, S-G. *Chem. Commun.* **2011**, *47*, 5599–5601.
http://dx.doi.org/10.1039/c1cc11067e

62. Bardajee, G. R. *Tetrahedron Lett.* **2013**, *54*, 4937–4941.
http://dx.doi.org/10.1016/j.tetlet.2013.07.010

63. Ranjit, S.; Duan, Z.; Zhang, P.; Liu, X. *Org. Lett.* **2010**, *12*, 4134-4136.
http://dx.doi.org/10.1021/ol101729k

64. Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. *Org. Lett*. **2010**, *12*, 84-87.
http://dx.doi.org/10.1021/ol9024088

65. Shao, Y-L.; Zhang, X. H.; Han, J. S.; Zhong, P. *Phosphorus, Sulfur, Silicon, Relat. Elem.* **2013**, *188*, 1137-1146. http://dx.doi.org/10.1080/10426507.2012.755973

66. Xu, R-S.; Wan, J-P.; Mao, H.; Pan,Y-J. *J. Am. Chem. Soc*. **2010**, *132*, 15531–15533. http://dx.doi.org/10.1021/ja107758d

67. Xu, R-S.;Yue, L.; Pan, Y-J. *Tetrahedron* **2012**, *68*, 5046-5052. http://dx.doi.org/10.1016/j.tet.2012.04.048

Authors' Biographies

Asha Sujatha was born in Kerala, India, in 1988. She received her B.Sc. degree from M.G University (Assumption College, Changanassery) in 2009 and her M.Sc. degree from School of Chemical Sciences, Mahatma Gandhi University in 2011. Currently, she is doing her doctoral research under the guidance of Dr. G Anilkumar in School of Chemical Sciences, Mahatma Gandhi University, working in the area of Cu-catalyzed Sonogashira coupling reaction.

Anns Maria Thomas was born in Kerala, India, in 1988. She obtained her B.Sc. degree from Mahatma Gandhi University (Pavanatma College, Murickassrey) in 2009 and her M.Sc. degree from School of Chemical Sciences, Mahatma Gandhi University in 2011. Currently she is doing her doctoral research in Cu-catalysed coupling reaction under the guidance of Dr. G. Anilkumar in School of Chemical Sciences, Mahatma Gandhi University.

Amrutha P Thankachan was born in Kerala, India, in 1988. She obtained her B.Sc. degree from Mahatma Gandhi University (C M S College, Kottayam) in 2009 and her M.Sc. degree from School of Chemical Sciences, Mahatma Gandhi University in 2011. Currently she is doing her doctoral research under the guidance of Dr. G. Anilkumar in School of Chemical Sciences, Mahatma Gandhi University.

Gopinathan Anilkumar was born in Kerala, India and took his Ph. D in 1996 from Regional Research Laboratory (CSIR), Trivandrum with Dr. Vijay Nair. He did his postdoctoral studies at University of Nijmegen, The Netherlands (with Professor Binne Zwanenburg), Osaka University, Japan (with Professor Yasuyuki Kita), Temple University, USA (with Professor Franklin A. Davis) and Leibniz-institüt für Katalyse e.V, Rostock, Germany (with Professor Matthias Beller). He was a senior research scientist at AstraZeneca, Bangalore. Currently he is

Associate Professor at the School of Chemical Sciences, Mahatma Gandhi University. His research interests are in the areas of organic synthesis, medicinal chemistry and catalysis, particularly on Ruthenium, Iron, Zinc and Copper catalyzed reactions.